Guidelines for the management of

**Absolute cardiovascular disease risk**

An initiative of the National Vascular Disease Prevention Alliance
About the National Vascular Disease Prevention Alliance

The National Vascular Disease Prevention Alliance (NVDPA) is an alliance of four leading and well-known Australian charities: Diabetes Australia, the National Heart Foundation of Australia, Kidney Health Australia and the National Stroke Foundation.

In 2000, these four charities began to work together to reduce the burden of cardiovascular disease in Australia. Much of the work of the NVDPA to date has been to promote the use of an ‘absolute risk’ approach to predicting risk of cardiovascular disease.

The NVDPA advocates to government and professional bodies for a health system that supports an absolute risk approach. The NVDPA aims to raise awareness among health professionals to use absolute risk assessment in their everyday practice.
Guidelines for the management of Absolute cardiovascular disease risk

National Vascular Disease Prevention Alliance

Disclaimer
This document is a general guide to appropriate practice, to be followed subject to the circumstances, clinician's judgement and patient's preferences in each individual case. The guidelines are designed to provide information to assist decision making and are based on the best available evidence at the time of development. The relevance and appropriateness of the information and recommendations in this document depend on individual circumstances. Moreover, the recommendations and guidelines are subject to change over time. While all care has been taken in preparing the content of this material, the National Vascular Disease Prevention Alliance and the funding body expressly disclaims and accepts no responsibility for any undesirable consequences arising from relying on the information or recommendations contained herein.

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Further information and resources are available from:
www.diabetes.org.au
www.kidney.org.au
www.heartfoundation.com.au
www.strokefoundation.com.au

Publication approval

These guidelines were approved by the Chief Executive Officer of the National Health and Medical Research Council (NHMRC) on 27 April 2012, under Section 14A of the National Health and Medical Research Council Act 1992. In approving these guidelines the NHMRC considers that they meet the NHMRC standard for clinical practice guidelines. This approval is valid for a period of 5 years.

NHMRC is satisfied that they are based on the systematic identification and synthesis of the best available scientific evidence and make clear recommendations for health professionals practising in an Australian health care setting. The NHMRC expects that all guidelines will be reviewed no less than once every five years.

This publication reflects the views of the authors and not necessarily the views of the Australian Government.
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In Australia, 64% of the adult population have three or more modifiable risk factors. As CVD is largely preventable, an approach focusing on comprehensive risk assessment will enable effective management of identified modifiable risk factors through lifestyle changes and, where needed, pharmacological therapy.

Absolute CVD risk in the context of these guidelines refers to the likelihood of a person experiencing a cardiovascular event within the next five years. These guidelines incorporate the previous Guidelines for the Assessment of Absolute Cardiovascular Disease Risk and provide additional guidance on the management of CVD risk in a primary prevention setting in all adults over 45 years of age (35 years for people of Aboriginal or Torres Strait Islander [A&TSI] decent).

Although the goal for management of absolute CVD risk is to reduce the level of absolute risk (AR) in the person, this is achieved by management of multiple individual risk factors. Individual risk factors such as blood pressure (BP) and lipid levels have been shown to have a continuous association with the risk of CVD events; therefore, moderate reductions in several risk factors may be more effective in reducing overall CVD risk than a major reduction in one factor. Decisions regarding management of risk are therefore made according to the individual’s AR level, while response to treatment is monitored by measurement of individual risk factors.

The algorithms and table on the next page provide a summary of the recommended assessment pathway, interventions, targets and follow-up.
Risk Assessment and Management Algorithm:
Adults aged 45 years and over without known history of CVD

**Already known to be at increased risk?**
Adults with any of the following conditions do not require absolute CVD risk assessment using the Framingham Risk Equation because they are already known to be at clinically determined high risk of CVD:**(EBR: Grade D)**
- Diabetes and age >60 years
- Diabetes with microalbuminuria (> 20 mcg/min or urinary albumin:creatinine ratio >2.5 mg/mmol for males, >3.5 mg/ mmol for females)
- Moderate or severe chronic kidney disease (persistent proteinuria or estimated glomerular filtration rate [eGFR] <45 mL/min/1.73 m²)
- A previous diagnosis of familial hypercholesterolaemia
- Systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg
- Serum total cholesterol >7.5 mmol/L

**Conduct formal absolute risk assessment**

**YES**
- **High:** greater than 15% risk of CVD within the next 5 years (includes clinically determined high risk) **(PP)**
  - Provide frequent and sustained lifestyle advice, support and follow-up **(CBR)**
  - Commence BP + lipid lowering therapy unless contraindicated or clinically inappropriate **(EBR: Grade B)**

- **Moderate:** 10-15% risk of CVD within the next 5 years **(PP)**
  - Provide lifestyle advice and support **(CBR)**

- **Low:** less than 10% risk of CVD within the next 5 years **(PP)**
  - Provide lifestyle advice **(CBR)**

**NO**

- Is one of the following present?
  - BP persistently ≥160/100 mmHg
  - Family history of premature CVD
  - South Asian, Middle Eastern, Maori or Pacific Islander peoples

**YES**
- Identify all other risk factors
- Continue with lifestyle intervention **(CBR)**
- Treat for BP and/or lipid lowering **(CBR)**

**NO**
- Monitor response **(PP)**
- Monitor and review risk at 3-6 months **(CBR)**
- Has risk improved?
  - **YES**
    - Continue with lifestyle intervention **(CBR)**
    - Monitor response **(PP)**
  - **NO**
    - Consider treating for BP and/or lipid-lowering **(CBR)**
    - Monitor response **(PP)**

**Review absolute risk according to clinical context** **(PP)**
- Review absolute risk in 6-12 months **(PP)**

**MONITOR ABSOLUTE RISK**
- Review absolute risk in 2 years **(PP)**
- Review absolute risk in 6-12 months **(PP)**
- Review absolute risk in 6-12 months **(PP)**

EBR: Evidence-based recommendation (Graded A-D) CBR: Consensus-based recommendation PP: Practice point
Risk Assessment and Management Algorithm:
Aboriginal and Torres Strait Islander adults aged 35 years and over without known history of CVD

**Already known to be at increased risk?**
Adults with any of the following conditions do not require absolute CVD risk assessment using the Framingham Risk Equation because they are already known to be at clinically determined high risk of CVD: **(EBR: Grade D)**
- Diabetes and age >60 years
- Diabetes with microalbuminuria (>20 mcg/min or urinary albumin/creatinine ratio >2.5 mg/mmol for males, >3.5 mg/mmol for females)
- Moderate or severe chronic kidney disease (persistent proteinuria or estimated glomerular filtration rate [eGFR] <45 mL/min/1.73 m²)
- A previous diagnosis of familial hypercholesterolaemia
- Systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg
- Serum total cholesterol >7.5 mmol/L
- Aboriginal and Torres Strait Islander adults aged over 74 **(CBR)**

**NO**

**CONDUCT FORMAL ABSOLUTE RISK ASSESSMENT**

**Calculate risk level using Framingham Risk Equation** **(EBR: Grade B):**
- Australian cardiovascular risk charts
- Web calculator www.cvdcheck.org.au

**YES**

**High:** greater than 15% risk of CVD within the next 5 years (includes clinically determined high risk) **(PP)**
- Provide frequent and sustained lifestyle advice, support and follow-up **(CBR)**
- Commence BP + lipid-lowering therapy unless contraindicated or clinically inappropriate **(EBR: Grade B)**

**Moderate:** 10-15% risk of CVD within the next 5 years **(PP)**
- Provide lifestyle advice and support **(CBR)**
- Identify all other risk factors
- Continue with lifestyle intervention **(CBR)**
- Treat for BP and/or lipid lowering **(CBR)**

**Low:** less than 10% risk of CVD within the next 5 years **(PP)**
- Provide lifestyle advice **(CBR)**
- Is BP persistently ≥160/100 mmHg? **(PP)**
- **YES**
  - Treat BP **(CBR)**
  - Continue with lifestyle advice **(CBR)**

- **NO**
  - Monitor response **(PP)**
  - **Review absolute risk according to clinical context** **(PP)**

**Review absolute risk in 6-12 months** **(PP)**

**Review absolute risk in 2 years** **(PP)**

EBR: Evidence-based recommendation (Graded A-D), CBR: Consensus-based recommendation, PP: Practice point
# Risk Management Summary

<table>
<thead>
<tr>
<th>CVD risk</th>
<th>Lifestyle</th>
<th>Pharmacotherapy</th>
<th>Targets</th>
<th>Monitoring</th>
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<tr>
<td><strong>High risk</strong></td>
<td>Frequent and sustained specific advice and support regarding diet and physical activity.</td>
<td>Treat simultaneously with lipid lowering and BP lowering unless contraindicated or clinically inappropriate.</td>
<td>BP: ≤140/90 mmHg in general or people with CKD; ≤130/80 mmHg in all people with diabetes; ≤130/80 mmHg if micro or macro albuminuria (UACR &gt; 2.5 mg/mmol in men and &gt;3.5 mg/mmol in women).</td>
<td>Adjust medication as required. Review of absolute risk according to clinical context.</td>
</tr>
<tr>
<td></td>
<td>Appropriate advice, support and pharmacotherapy for smoking cessation.</td>
<td>Aspirin not routinely recommended. Consider withdrawal of therapy for people who make profound lifestyle changes.</td>
<td>Lipids: TC &lt;4.0 mmol/L; HDL-C ≥1.0 mmol/L; LDL-C &lt;2.0 mmol/L; Non-HDL-C &lt;2.5 mmol/L; TG &lt; 2.0 mmol/L.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Advice given simultaneously with BP and lipid lowering drug treatment.</td>
<td></td>
<td>Lifestyle: Smoking cessation (if smoker); consume diet rich in vegetables and fruit, low in salt and saturated and trans fats; at least 30 mins physical activity on most or preferably every day of the week; limit alcohol intake.</td>
<td></td>
</tr>
</tbody>
</table>
| **Moderate risk**         | Appropriate, specific advice and support regarding diet and physical activity. | Not routinely recommended. Consider BP lowering and/or lipid lowering in addition to lifestyle advice if 3-6 months of lifestyle intervention does not reduce risk or:  
- BP persistently ≥160/100 mmHg  
- Family history of premature CVD  
- Specific population where the FRE underestimates risk e.g. A&TSI peoples, South Asian, Maori and Pacific Islander, Middle Eastern. |                                                                                  | Adjust medication as required. Review absolute risk every 6–12 months. |
|                           | Appropriate advice, support and pharmacotherapy for smoking cessation.    |                                                                                  |                                                                                  |                                                                            |
|                           | Lifestyle advice given in preference to drug therapy.                    |                                                                                  |                                                                                  |                                                                            |
| **Low risk**              | Brief, general lifestyle advice regarding diet and physical activity.     | Not routinely recommended. Consider BP lowering therapy in addition to specific lifestyle advice if BP persistently ≥160/100 mmHg. |                                                                                  | Adjust medication as required. Review absolute risk every 2 years.         |
|                           | Appropriate advice, support and pharmacotherapy for smoking cessation.    | Consider withdrawal of therapy for people who make profound lifestyle changes.   |                                                                                  | Blood test results within 5 years can be used.                              |

A&TSI: Aboriginal and Torres Strait Islander peoples; BP: blood pressure; CKD: Chronic Kidney Disease; DBP: diastolic blood pressure; FRE: Framingham Risk Equation; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; SBP: systolic blood pressure; TC: total cholesterol; TG: Triglycerides; UACR: urinary albumin:creatinine ratio
Summary of Recommendations

This section lists the recommendations presented in the guidelines together with the relevant section where the supporting evidence is discussed. Each recommendation is given an overall grading based on National Health and Medical Research Council (NHMRC) Levels of Evidence and Grades for Recommendations for Developers of Guidelines (2009). Where no robust evidence was available but there was sufficient consensus within the Expert Working Group (EWG), consensus-based recommendations (CBR) have been provided. Practice points (PP) were added where necessary, to provide practical guidance to facilitate the implementation of the guidelines. Where recommendations were developed in an AR paradigm, but based on relative risk (single risk factor) evidence, the expert panel carefully examined the literature before making and grading the recommendations. Consideration included any heterogeneity found between subgroups and the generalisability of the findings. The final grading of these recommendations was downgraded to account for the uncertainty of applying evidence from a relative risk approach to an AR paradigm. Some recommendations have been drawn from the Guidelines for the Assessment of Absolute Cardiovascular Disease Risk and have been included to provide context and a complete set of absolute CVD risk recommendations. These recommendations are dated (2009) to indicate that they were developed in a separate process. (See Scope for further details on recommendations from the Guidelines for the Assessment of Absolute Cardiovascular Disease Risk).

**Grading of evidence-based recommendations (EBR)**

<table>
<thead>
<tr>
<th>Grade of recommendation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Body of evidence can be trusted to guide practice</td>
</tr>
<tr>
<td>B</td>
<td>Body of evidence can be trusted to guide practice in most situations</td>
</tr>
<tr>
<td>C</td>
<td>Body of evidence provides some support for recommendation but care should be taken in its application</td>
</tr>
<tr>
<td>D</td>
<td>Body of evidence is weak and recommendation must be applied with caution</td>
</tr>
</tbody>
</table>

**Additional guidance**

| CBR | Consensus-based recommendations: developed by the guidelines expert working group when a systematic review of the evidence found either an absence of direct evidence which answered the clinical question or poor quality evidence, which was deemed not to be strong enough to formulate an evidence-based recommendation. |
| PP  | Practice points: developed by the guidelines expert working group where a systematic review had not been conducted but there was a need to provide practical guidance to support the implementation of the evidence-based and/or consensus-based recommendations. |
### Evidence-based recommendations

#### Assessment of CVD risk

<table>
<thead>
<tr>
<th>Clinically determined high risk</th>
<th>Grade</th>
</tr>
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<tbody>
<tr>
<td><strong>EBR 1:</strong> Adults with any of the following conditions do not require absolute cardiovascular risk assessment using the Framingham Risk Equation because they are already known to be at clinically determined high risk of CVD:</td>
<td>D¹⁰ (2009)</td>
</tr>
<tr>
<td>i. Diabetes and age &gt;60 years</td>
<td></td>
</tr>
<tr>
<td>ii. Diabetes with microalbuminuria (&gt;20 mcg/min or UACR &gt;2.5 mg/mmol for males, &gt;3.5 mg/mmol for females)</td>
<td></td>
</tr>
<tr>
<td>iii. Moderate or severe CKD (persistent proteinuria or eGFR &lt;45 mL/min/1.73 m²)</td>
<td></td>
</tr>
<tr>
<td>iv. A previous diagnosis of familial hypercholesterolaemia</td>
<td></td>
</tr>
<tr>
<td>v. SBP ≥180 mmHg or DBP ≥110 mmHg</td>
<td></td>
</tr>
<tr>
<td>vi. Serum TC &gt;7.5 mmol/L</td>
<td></td>
</tr>
</tbody>
</table>

#### General population aged 45–74 years

**EBR 2:** Absolute CVD risk assessment, using the Framingham Risk Equation to predict risk of a cardiovascular event over the next five years, should be performed for all adults aged 45–74 years who are not known to have CVD or to be at clinically determined high risk. B¹⁰ (2009)

#### Aboriginal and Torres Strait Islander adults aged 35–74 years

**EBR 3:** In Aboriginal and Torres Strait Islander adults aged 35–74 years who are not known to have CVD or to be at clinically determined high risk, absolute cardiovascular risk over the next five years should be calculated using the Framingham Risk Equation. Although the Framingham Risk Equation might underestimate risk in this population, available evidence suggests that this approach will provide an estimate of minimum cardiovascular risk. D²⁶ (2009)

#### Adults with diabetes

**EBR 4:** In adults with diabetes aged 60 years or less who are not known to have CVD or to be at clinically determined high risk, absolute cardiovascular risk over the next five years should be assessed using the Framingham Risk Equation. Although the Framingham Risk Equation might underestimate risk in this population, available evidence suggests that this approach will provide an estimate of minimum cardiovascular risk. C¹² (2009)

#### Adults who are overweight or obese

**EBR 5:** In adults who are overweight or obese and who are not known to have CVD or to be at clinically determined high risk, absolute cardiovascular risk over the next five years should be assessed using the Framingham Risk Equation. The results should be interpreted with the awareness that its predictive value has not been specifically assessed in this population. D¹⁰ (2009)

#### Treatment

**Lifestyle modification**

**EBR 6:** Weight loss should be recommended for people who are overweight or obese. B¹²⁴-¹²⁷

**EBR 7:** All adults should be advised to participate in at least 30 minutes of moderate activity on most days or preferably every day of the week. B¹³⁵-¹³⁹

**EBR 8:** All smokers should be advised to stop smoking. A¹⁴,¹⁴⁸

**Pharmacotherapy**

**EBR 9:** Aspirin or other antiplatelet therapy is not routinely recommended for primary prevention of CVD. B¹²³, 234, 237, 238, 242, 243
## Assessment of CVD risk

### For adults at high risk of CVD

| EBR 10: | Adults at high absolute risk of CVD should be simultaneously treated with lipid and blood pressure-lowering pharmacotherapy in addition to lifestyle intervention unless contraindicated or clinically inappropriate. | Grade: B 192, 195, 204, 206, 207 |

### Blood pressure-lowering therapy

| EBR 11: | Treatment should begin with any one of the following agents: | Grade: A 192, 199 |
| - ACE inhibitor | - Angiotensin receptor blocker | - Calcium channel blocker | - Low dose thiazide or thiazide-like diuretic. |

| EBR 12: | If monotherapy does not sufficiently reduce blood pressure add a second agent from a different pharmacological class. | Grade: A 192 |

### Lipid-lowering therapy

| EBR 13: | Statins should be used as first-line therapy. | Grade: A 206, 208, 209 |

| EBR 14: | If LDL-C levels are not sufficiently reduced on maximally tolerated dose of statin, one or more of the following may be added: | Grade: C 224-226, D 219, 223, D 218, 227 |
| - ezetimibe | - bile acid binding resin | - nicotinic acid. |

| EBR 15: | Where statins cannot be tolerated at all, one or more of the following can be used: | Grade: D 225, D 223, D 227-229 |
| - ezetimibe | - bile acid binding resin | - nicotinic acid. |

| EBR 16: | If triglyceride levels remain elevated, treatment with one of the following may be considered: | Grade: C 220-222, C 218, 227, C 230-232 |
| - fenofibrate (especially if HDL is below target) | - nicotinic acid | - fish oil. |

### Populations requiring special consideration

#### People with diabetes

| EBR 17: | Blood pressure-lowering therapy in people with diabetes should preferentially include an ACE inhibitor or angiotensin receptor blocker. | Grade: A 287, 298, 302, 303 |

| EBR 18: | If monotherapy does not sufficiently reduce blood pressure add one of the following: | Grade: B 299, 300, C 273, 299 |
| - Calcium channel blocker | - Low-dose thiazide or thiazide-like diuretic. |

#### People with chronic kidney disease (CKD)

| EBR 19: | Blood pressure-lowering therapy in people with CKD should begin with an ACE inhibitor or angiotensin receptor blocker. | Grade: A 302, 303 |
**Consensus-based recommendations**

### Assessment of CVD risk

#### General population aged over 74 years

**CBR 1:** In adults aged over 74, who are not known to have CVD or to be at clinically determined high risk, absolute cardiovascular risk over the next five years should be assessed using the Framingham Risk Equation. Calculation should be performed using the age of 74 years. Although the Framingham Risk Equation might underestimate risk in this population, available evidence suggests that this approach will provide an estimate of minimum cardiovascular risk.

#### Aboriginal and Torres Strait Islander adults aged over 74 years

**CBR 2:** Aboriginal and Torres Strait Islander adults aged over 74 years should be considered as being at high CVD risk.

### Treatment

#### For adults at moderate risk of CVD

**CBR 3:** Adults at moderate absolute risk of CVD should have their risk factors initially managed by lifestyle interventions. Pharmacotherapy for blood pressure and/or lipid lowering is not routinely recommended but may be considered if 3–6 months of lifestyle intervention does not reduce the individual’s risk factors.

**CBR 4:** Adults at moderate absolute risk of CVD may be treated with pharmacotherapy for blood pressure and/or lipid lowering in addition to lifestyle intervention if one or more of the following applies:
- Persistent blood pressure ≥160/100 mmHg
- Family history of premature CVD
- Aboriginal and Torres Strait Islander peoples
- Other populations where Framingham Risk Equation is known to underestimate risk (South Asians, Maori and Pacific Islanders, people from the Middle East).

#### For adults at low risk of CVD

**CBR 5:** Pharmacotherapy for blood pressure and lipid lowering is not routinely recommended for adults at low absolute risk of CVD.

**CBR 6:** Adults at low absolute risk of CVD who have persistent blood pressure ≥160/100 mmHg may be treated with blood pressure-lowering pharmacotherapy in addition to lifestyle intervention.

### Maximising the benefits of pharmacotherapy

**CBR 7:** Pharmacotherapy for blood pressure-lowering should aim towards the following targets while balancing the risks/benefits:
- ≤140/90 mmHg for adults without CVD (including those with CKD)
- ≤130/80 mmHg for adults with micro or macro albuminuria (UACR >2.5 mg/mmol in males and >3.5 mg/mmol in females)
- ≤130/80 mmHg for all adults with diabetes.

**CBR 8:** Pharmacotherapy for lipid lowering should aim towards the following targets while balancing the risks/benefits:
- TC <4.0 mmol/L
- HDL-C ≥1.0 mmol/L
- LDL-C <2.0 mmol/L
- Non HDL-C <2.5 mmol/L
- TG <2.0 mmol/L.
### Assessment of CVD risk

#### Conducting a comprehensive risk assessment

**PP 1 (2009):** In adults without known CVD, a comprehensive assessment of cardiovascular risk includes consideration of the following:

**Modifiable risk factors**
- Smoking status
- Blood pressure
- Serum lipids
- Waist circumference and Body Mass Index (BMI)
- Nutrition
- Physical activity level
- Alcohol intake.

**Non-modifiable risk factors**
- Age and sex
- Family history of premature CVD
- Social history including cultural identity, ethnicity and socioeconomic status.

**Related conditions**
- Diabetes
- Chronic Kidney Disease (albuminuria ± urine protein, eGFR)
- Familial hypercholesterolaemia
- Evidence of atrial fibrillation (history, examination, electrocardiogram).

#### Absolute CVD risk categories

**PP 2 (2009):** The following qualitative risk categories can be used to describe calculated absolute cardiovascular risk:
- **Low** risk corresponds to <10% probability of CVD within the next five years
- **Moderate** risk corresponds to 10–15% probability of CVD within the next five years
- **High** risk corresponds to >15% probability of CVD within the next five years.

#### All adults aged over 74 years

**PP 3:** In adults aged over 74 years, the decision to initiate therapy should be based on clinical judgement which takes into account:
- Likely benefits and risks of treatment
- Life expectancy, co-morbidities and quality of life
- Personal values.

#### Adults with depression

**PP 4:** Adults being assessed for CVD risk should also be assessed for depression (and other psychosocial factors). Cardiovascular risk assessment using the Framingham Risk Equation may underestimate risk in adults with depression.

#### Socioeconomic status

**PP 5 (2009):** A comprehensive assessment of cardiovascular risk involves consideration of socioeconomic deprivation, because it is an independent risk factor for CVD. Absolute risk of CVD calculated using the Framingham Risk Equation is likely to underestimate CVD risk in socioeconomically disadvantaged groups.

#### Atrial fibrillation (AF)

**PP 6 (2009):** In adults with AF (particularly those aged over 65 years), the increased risk of cardiovascular events and all-cause mortality, in addition to thromboembolic disease including stroke, should be taken into account when assessing cardiovascular risk.
Review of CVD risk

**PP 7 (2009):** Regular review of absolute cardiovascular risk is recommended at intervals according to the initial assessed risk level:
- **Low** – review every 2 years
- **Moderate** – review every 6–12 months
- **High** – review according to clinical context

**PP 8:** In adults at low absolute risk of CVD, blood test results within five years may be used for review of absolute cardiovascular risk unless there are reasons to the contrary.

### Treatment

**Lifestyle modification**

**PP 9:** All adults should be supported to follow the current *Dietary Guidelines for Australian Adults*.

**PP 10:** All smokers should be offered advice about methods to aid smoking cessation, including counselling services, and if assessed as nicotine dependent, nicotine replacement therapy or other appropriate pharmacotherapy should be used.

**PP 11:** All adults should be advised to follow the current *Australian guidelines to reduce health risks from drinking alcohol (2009)*.

**PP 12:** Adults at higher absolute risk of CVD should be given more frequent and sustained lifestyle advice, support and follow-up to achieve behavioural change.

### Blood pressure-lowering therapy

**PP 13:** If blood pressure is not responding to pharmacotherapy, reassess for:
- non-adherence
- undiagnosed secondary causes for raised blood pressure
- hypertensive effects of other drugs
- treatment resistance due to sleep apnoea
- undisclosed use of alcohol or recreational drugs
- unrecognised high salt intake (particularly in patients taking ACE inhibitors or angiotensin receptor blockers)
- ‘white coat’ raised blood pressure
- technical factors affecting measurement
- volume overload, especially with CKD.

**PP 14:** If dual therapy at higher doses does not sufficiently reduce blood pressure, add an additional agent.

**PP 15:** If combination therapy does not sufficiently reduce blood pressure, consider specialist advice.

**PP 16:** Treatable secondary causes for raised blood pressure should be considered before commencing blood pressure drug therapy.

**PP 17:** The following combinations should generally be avoided:
- potassium-sparing diuretic plus either ACE inhibitor or angiotensin receptor blocker
- beta-blocker plus verapamil.

### Lipid-lowering therapy

**PP 18:** Treatable secondary causes of dyslipidaemia should be considered before commencing lipid-lowering pharmacotherapy.

### Maximising the benefits of pharmacotherapy

**PP 19:** Adults who commence pharmacotherapy should have their medication adjusted as required and response assessed regularly (approximately 6–12 weekly) until sufficient improvement has been achieved or maximum tolerated dose has been reached.

**PP 20:** Reduction or withdrawal of pharmacotherapy may be considered in adults who make sustained lifestyle changes which significantly reduce their risk (e.g. smoking cessation, significant weight loss).
Cardiovascular disease (CVD), defined collectively in these guidelines as coronary heart disease (CHD), stroke and other vascular disease including peripheral arterial disease (PAD) and renovascular disease, is a leading cause of death and disability in Australia and in 2003 accounted for approximately 18% of the total burden of disease in Australia. In 2008, CVD accounted for over one-third (nearly 50,000) of deaths in Australia. It has a strong relationship with diabetes and chronic kidney disease (CKD) as these conditions share many risk factors and often co-exist.

In Australia, 90% of the adult population has at least one modifiable risk factor, while 64% have three or more modifiable risk factors. Although the rate of death due to CVD continues to decline in Australia, the total CVD burden is expected to increase over the next few decades due to the ageing population. The Guidelines for the Management of Absolute CVD Risk have been developed by the National Vascular Disease Prevention Alliance (NVDPA) in response to the burden of CVD in the Australian community. They recommend strategies for management of CVD risk in the primary prevention setting, in addition to providing guidance on assessment of CVD risk in all adults over 45 years of age (35 years for A&TSI peoples).

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Purpose

CVD remains the leading cause of mortality in Australia. These guidelines have been developed to consolidate a number of evidence-based guidelines for conditions with similar risk factors and management approaches, and provide clear guidance to prevent first-ever CVD events. They build on the NHMRC approved NVDPA Guidelines for the Assessment of Absolute Cardiovascular Disease Risk 2009, which introduced the concept of AR in the assessment of CVD risk.

Scope

The Guidelines for the Management of Absolute Cardiovascular Disease Risk make recommendations regarding the management of cardiovascular risk in Australian adults aged 45 years and over (35 years for A&TSI peoples) who have no previous history of CVD.

Correlation with the Guidelines for the Assessment of Absolute Cardiovascular Disease Risk (2009)

These guidelines build on the existing Guidelines for the Assessment of Absolute Cardiovascular Disease Risk by expanding the age range for absolute CVD risk assessment from 45 to 74 years (35 to 74 for A&TSI peoples) to include all adults aged 75 years and over in addition to providing guidance for the management of risk. All of the recommendations have been replicated in the new guidelines (dated 2009) to ensure completeness and provide context. Some minor wording changes have been made to ensure that the recommendations make sense within the context of the new guidelines e.g. replacement of the term ‘high risk’ with the term ‘clinically determined high risk’ to clarify how this risk was determined, and the addition of an upper age limit in some recommendations to clarify the age range.

Correlation with other guidelines


These guidelines do not apply to people with existing CVD, because they are already known to be at high risk of further CVD events. However, they should be considered in parallel with other existing Australian guidelines (some of which are noted within these guidelines and some of which were being updated as this document was being finalised) including:

Dietary Guidelines for Australian Adults. NHMRC 2003.


Australian Guidelines to Reduce Health Risks from Drinking Alcohol. NHMRC, Canberra 2009.


National Evidence-Based Guideline on Secondary Prevention of Vascular Disease in Type 2 Diabetes. (Currently being drafted - see Appendix 2 Section 6.1 for details of consultation between guideline development groups.)


Correlation with Pharmaceutical Benefits Scheme (PBS)

The timing of releasing a new clinical guideline and review and update of related items in the PBS is not currently aligned in Australia. Therefore in regard to pharmacotherapy recommendations within this guideline doctors should be mindful of current regulations that may apply where the cost of the medicine is subsidised by the Government (Schedule of Pharmaceutical Benefits).

Target audience

The Guidelines for the Management of Absolute CVD Risk are intended for use by general practitioners, Aboriginal health workers, other primary care health professionals and physicians. They are intended to provide health system policy makers with the best available evidence as a basis for population health policy.

Development

The Guidelines for the Management of Absolute CVD Risk build on the Guidelines for the Assessment of Absolute CVD Risk 2009 and incorporate information previously provided by specific risk factor guidelines. The guidelines have been developed according to the processes outlined in the document NHMRC Standards and Procedures for Externally Developed Guidelines (2007) under the direction of a multidisciplinary EWG (see Appendix 1). Details of the development methodology and consultation process are outlined in Appendix 2.

Revision of the guidelines

To maintain currency these guidelines will be reviewed and updated by 2016/7.

Funding body

The National Stroke Foundation received funding from the Australian Government Department of Health and Ageing (DoHA) to develop guidelines for the management of absolute cardiovascular disease risk on behalf of the NVDPA.
Multiple causal factors contribute to CVD. It has been estimated that 64% of Australians have three or more modifiable risk factors. Approximately 90% of the risk of myocardial infarction (MI) observed worldwide can be attributed to blood lipid abnormalities, smoking, raised BP, diabetes, abdominal obesity, psychosocial factors, physical inactivity and inadequate intake of fruits and vegetables.

Given that CVD is largely preventable, Australian and overseas primary care guidelines emphasise comprehensive risk assessment to enable effective management of identified modifiable risk factors through lifestyle changes (e.g. weight management, smoking cessation and increased physical activity) and pharmacological therapy (e.g. BP-lowering agents and lipid-modifying agents).

Absolute CVD risk in the context of these guidelines refers to the likelihood of a person experiencing a cardiovascular event within the next five years. The Guidelines for the Assessment of Absolute Cardiovascular Disease Risk 2009 focused on the assessment of absolute risk in those aged 45–74 years (35–74 years for A&TSI peoples) because many risk factors included in the FRE (e.g. high BP, high total cholesterol [TC]) become more prevalent with increasing age. In addition to providing guidance in the management of CVD risk, these new guidelines build on the assessment guidelines to include a discussion of AR assessment in the population aged greater than 74 years.

This chapter covers methods for assessment and review of CVD risk for adults aged 45 (35 for A&TSI peoples) and over. It incorporates the recommendations from the assessment guidelines and new recommendations for those aged 75 years and over. Evidence relating to the new recommendations is presented in detail in these guidelines. Evidence for the existing recommendations for assessment of CVD risk for people aged 45–74 years (or 35–74 years for A&TSI peoples) is summarised in this document to provide context for the recommendations. Further details on evidence relating to these recommendations can be found in the Guidelines for the Assessment of Absolute CVD Risk 2009.

1.1 Potential benefits of absolute CVD risk assessment

Individuals tend to develop clusters of risk factors. Assessment of CVD risk on the basis of the combined effect of multiple risk factors is more accurate than the use of individual risk factors, because the cumulative effects of multiple factors may be additive or synergistic. Individual risk factors such as BP and lipid levels have been shown to have a continuous association with the risk of CVD events, therefore, moderate reductions in several risk factors may be more effective in reducing overall CVD risk than a major reduction in one factor. This evidence forms the basis of the AR approach, where reduction of any of the key risk factors has an effect on the total risk score, regardless of the starting level of that risk factor. For example, Person A, who presents with a BP of 150/95 mmHg, may have a lower AR score than Person B, who has a BP of 140/90 mmHg but is a smoker and has an elevated lipid level. Person B is more likely to benefit from interventions to reduce risk than Person A because of the potential to reduce the overall absolute CVD risk.

There is emerging evidence that clinical decisions based on absolute CVD risk may lead to improved management of CVD risk. Access to absolute CVD risk assessments has been shown to increase prescribing of lipid-modifying drugs for high-risk people with diabetes and lead to improvement in lipid profiles and significant reductions in the risk of CHD. Modelling studies provide the most compelling current evidence that absolute CVD risk assessment in general practice is likely to improve CVD outcomes, compared with assessment of single risk factors. When applied to a reference population with known risk factors, a strategy based on targeting those at highest absolute CVD risk is
potentially more than twice as effective in reducing death from CHD than treating people with single risk factors (e.g. high TC level).22

At the population level, interventions targeting those at highest overall CVD risk are likely to achieve the best balance between preventing death and avoiding unnecessary treatment in those at lower risk.23, 24 For example, lipid-lowering treatment in people assessed to be at high risk on consideration of all risk factors present will potentially prevent twice as many deaths from CHD in a given population than treating only those with TC levels above a given arbitrary cut-point.22, 23 Therefore, accurate estimation of CVD risk, especially in people without known CVD, could play a complementary role with other strategies (e.g. to reduce salt and tobacco consumption) in delivering effective population preventive health programs. Since the mid-1990s, major guidelines for the prevention of CVD have moved from an approach based on identifying and correcting individual risk factors through the application of several separate guidelines, to a focus on the individual’s overall risk through multiple risk factor assessment.

1.2 Taking a clinical history

To ensure a comprehensive risk assessment, a clinical history should be routinely taken and should cover the information given in Practice Point 1. This includes the risk factors to be used for calculation of a risk score and other modifiable and non-modifiable risk factors to be considered in making a clinical judgement about the individual’s total CVD risk. Consideration of related conditions that could contribute to CVD risk, such as the presence of AF, should also be made. Readers are referred to an Australian evidence summary25 and international guidelines for a discussion of the general evidence related to AF assessment and management26-29 and current Australian guidelines for assessment and management of diabetes,12, 30 CKD31 and familial hypercholesterolaemia.32

1.3 Measuring Risk Factors

In order to estimate an individual’s absolute risk of CVD, the risk factors in Table 1 should be measured.

1.4 Assessing absolute CVD risk

To calculate an individual’s estimated 5-year absolute CVD risk use the Risk Assessment and Management Algorithm (Appendix 4) and the risk charts or online calculator at

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**Practice point**

**Conducting a comprehensive risk assessment**

PP 1 (2009): In adults without known CVD, a comprehensive assessment of CVD risk includes consideration of the following:

**Modifiable risk factors**
- Smoking status
- Blood pressure
- Serum lipids
- Waist circumference and BMI
- Nutrition
- Physical activity level
- Alcohol intake

**Non-modifiable risk factors**
- Age and sex
- Family history of premature CVD
- Social history including cultural identity, ethnicity and socioeconomic status

**Related conditions**
- Diabetes
- CKD (albuminuria ± urine protein, eGFR)
- Familial hypercholesterolaemia
- Evidence of AF (history, examination, electrocardiogram)
### Blood pressure

Absolute risk calculators have been developed using clinic BP measurements, therefore, if using ambulatory BP readings for risk assessment, clinicians should convert to the clinic equivalent using the appropriate tables (see National Heart Foundation and High Blood Pressure Research Council of Australia consensus statement 2012). For clinic BP measurement, the average of two seated BP measurements over two separate occasions should be used to calculate risk. The most recently recorded pre-treatment value can be adopted for individuals taking antihypertensive medication. Ambulatory BP measurement is a better predictor of outcomes than clinic BP measurements and therefore should be used to monitor BP lowering therapy.

### Serum lipids

A fasting lipid profile (TC, low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], non-high-density lipoprotein cholesterol [non-HDL-C], TC:HDL ratio and triglycerides) should be taken. A single TC:HDL ratio is used to calculate CVD risk. When a fasting sample is not possible, a non-fasting TC:HDL ratio may be used for an initial screening assessment of CVD risk, however treatment decisions should be made on the basis of fasting lipid levels.

### Plasma glucose

In order to screen for diabetes, an assessment of fasting plasma glucose is recommended. A value of ≤ 5.4 mmol/L indicates a normal level. A result of 5.5–6.0 mmol/L may be normal but some people will show diabetes or impaired glucose tolerance in an OGTT. A value of ≥ 6.1 mmol/L but ≤ 6.9 mmol/L is diagnostic of impaired fasting glucose and requires an OGTT to confirm diabetes or impaired glucose tolerance. A value of ≥ 7.0 mmol/L on two separate occasions is diagnostic of diabetes and does not require an OGTT.

When a fasting sample is not possible non-fasting glucose can be measured with further testing required if the result is ≥5.5 mmol/L. HbA1c can be used to diagnose diabetes with a level of ≥6.5% being diagnostic.

### Waist circumference and BMI

A BMI <25 kg/m² is desirable. Individuals with a BMI ≥25 kg/m² are classified as overweight and those with a BMI ≥30 kg/m² are obese and at increased risk of diabetes, CHD and stroke compared with individuals with normal BMI (< 25 kg/m²). A waist circumference, as a measure of central obesity, is a better predictor of CVD risk than BMI. A waist circumference of ≥94 cm in men (≥90 cm in Asian men) and ≥80 cm in women (≥80 cm in Asian women) is suggestive of central obesity.

### Left ventricular hypertrophy (LVH)

Echocardiography, if available, should be the test of choice to assess for LVH as it is more sensitive than electrocardiography. In the absence of echocardiography, electrocardiograms can be used.

### Renal function

Renal function should be estimated from GFR. An eGFR <60 ml/min/1.73m² is indicative of stage 3 CKD. Proteinuria is defined as urinary albumin:creatinine ratio (UACR) > 35 mg/mmol in females and >25 mg/mmol in males. Persistent proteinuria is defined as 2 positive measurements, 3 months apart. The preferred method for assessment of proteinuria in both diabetic and non-diabetic patients is UACR in a first void spot specimen. Where a first void specimen is not possible or practical, a random spot urine specimen for UACR is acceptable. A positive UACR test should be repeated to confirm persistence of albuminuria. CKD is present if two out of three tests (including the initial test) are positive. If the first positive UACR is a random spot (as it may be for opportunistic testing), then repeat test results should ideally be first morning void specimens.

### Smoking status

For the purposes of CVD risk assessment, a non-smoker is defined as someone who has never smoked or has given up smoking and has not smoked for ≥12 months.

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**Table 1: Risk factors that may be considered for absolute CVD risk assessment**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Measurement</th>
</tr>
</thead>
<tbody>
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<td><strong>Plasma glucose</strong></td>
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</tr>
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<td><strong>Smoking status</strong></td>
<td>For the purposes of CVD risk assessment, a non-smoker is defined as someone who has never smoked or has given up smoking and has not smoked for ≥12 months.</td>
</tr>
</tbody>
</table>

BMI: body mass index; CHD: coronary heart disease; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; OGTT: oral glucose tolerance test.
www.cvdcheck.org.au which are based on the FRE. The FRE has been validated to include age, sex, smoking status, diabetes, SBP, TC:HDL ratio and LVH as part of the equation. All other risk factors should be factored into the clinical judgement for decisions regarding the management of individual patients.

Descriptors of risk categories are arbitrary, with definitions of ‘moderate’ and ‘high’ risk varying between national and international guidelines. For the Australian context, the Guidelines for the Assessment of Absolute Cardiovascular Disease Risk (2009)\(^{10}\) defined the categories as in Practice point 2.

### Practice point

**Assessing absolute CVD risk**

**PP 2 (2009):** The following qualitative risk categories can be used to describe calculated absolute cardiovascular risk:

- **low** risk corresponds to <10% probability of CVD within the next five years
- **moderate** risk corresponds to 10–15% probability of CVD within the next five years
- **high** risk corresponds to >15% probability of CVD within the next five years

1.5 Assessment of CVD risk in different populations

1.5.1 Clinically determined high risk

Based on available published evidence and clinical consensus, certain groups can be assumed to be at high risk of cardiovascular events because of their clinical condition, and a calculation of absolute CVD risk is not considered necessary. This section applies to adults aged 45 and older (35 and older for A&TSI peoples) of any ethnic background who have been clinically determined to be at high risk.

#### Diabetes and age >60 years

In clinical practice it is both reasonable and expedient to make the assumption that all patients aged over 60 years with diabetes are at high CVD risk, given that numerical calculation of absolute CVD risk is unlikely to affect clinical management decisions significantly because intensive management of risk factors is generally indicated in this group. For instance, blood pressure-lowering drugs are indicated and cholesterol-lowering drugs are likely to be prescribed regardless of numerical risk.

#### Diabetes with microalbuminuria

The presence of microalbuminuria approximately doubles CVD risk,\(^{38-41}\) In clinical practice it is both reasonable and expedient to make the assumption that all adults with diabetes and microalbuminuria are at high CVD risk. Numerical calculation of absolute CVD risk is unlikely to affect clinical management decisions significantly, given that intensive management of risk factors is generally indicated in this group.

#### Moderate or severe CKD

Clinical studies indicate that people with moderate or severe CKD (defined as persistent proteinuria or eGFR < 45 mL/min/1.73 m\(^2\)) have an increased risk of developing CVD. This effect is independent of the presence of diabetes or pre-existing CVD.\(^{42, 43}\) The definition of moderate or severe CKD on which this recommendation is based represents a threshold midway between stage 3 and stage 4 CKD as defined by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative.\(^{44}\) Absolute CVD risk assessment based on the FRE is not suitable in this population because traditional risk factors have been shown to underestimate CVD events in people with CKD.

#### Familial hypercholesterolaemia

Familial hypercholesterolaemia (FH), a genetic disorder resulting in impaired cellular uptake of plasma LDL-C, is strongly associated with premature CHD. Most international guidelines for CVD risk management recommend that individuals with FH should be considered to be at high risk for CVD and receive treatment to reduce risk.\(^{14, 45, 46}\)
**SBP ≥180 mmHg or DBP ≥110 mmHg**

Extreme levels of risk factors are associated with high absolute CVD risk, regardless of other factors. Adults with severely elevated BP should be assessed as having high risk for CVD.

**Serum total cholesterol >7.5 mmol/L**

The Framingham Heart Study included few people with TC levels of 7.5 mmol/L or higher. Therefore, the FRE has not been validated in this group. Markedly elevated TC levels are commonly associated with FH, which is known to carry a high risk of CVD. Consistent with other international guidelines, it is reasonable to assume that markedly elevated TC indicates high CVD risk.

### 1.5.2 General population

There has been a natural evolution in research evaluating models to assess AR – comparing new and locally produced models with the original FRE or recalibrations of the FRE using local data. This section presents a brief summary of the evidence presented in the *Guidelines for the Assessment of Absolute Cardiovascular Disease Risk*, and a review of the more recent evidence for CVD risk assessment of adults. For details of the evidence relating to risk assessment models for people aged 45–74 years refer to the *Guidelines for the Assessment of Absolute Cardiovascular Disease Risk*.

Fourteen high-quality cohort studies that assessed AR in a mixed population (>18 years) with no history of CVD or diabetes were identified in the current literature review in addition to the 10 high-quality studies that were indentified in the literature review of the assessment guidelines. These 14 additional studies reported on the applicability to local populations of recalibrated versions of various risk calculation models including FRE, SCORE, UKPDS, CLEM, Qrisk, and locally generated models: 3C (France), GP (United Kingdom), India, and NIPPON DATA80 (Japan). A consistent finding from these studies is that regardless of the tool used to measure AR, recalibration using local, country-specific data can produce more accurate risk estimations. However, one study using recalibrated versions of FRE showed that although recalibration of risk calculation models to local data is a practical approach to estimation of CVD risk, the reliability and applicability of the data used for recalibration is of key importance.

In Australia, one new study was located, the purpose of which was to develop a parsimonious model to predict CHD and CVD deaths using individual components of the FRE plus measures of central obesity. Fifteen-year mortality data were assessed in 8,662 Australian adults in the National Heart Foundation Risk Factor Prevalence Survey of 1989, excluding those with a baseline history of heart disease. Smoking status, HDL-C and the TC:HDL-C ratio together with SBP were found to be significant predictors of CVD deaths. The obesity measures of waist circumference and waist-to-hip ratio were significant univariate predictors but BMI was not. In multivariable analyses, smoking status and waist-to-hip ratio were the only risk factors identified as key independent risk factors for coronary and cardiovascular-related deaths, although TC:HDL-C ratio contributed minimally to the prediction of CHD deaths. However, the FRE was found to have almost identical accuracy of risk prediction as the use of the waist-to-hip ratio plus smoking risk prediction model. These

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**Evidence-based recommendation**

<table>
<thead>
<tr>
<th>Clinically determined high risk</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EBR 1</strong>: Adults with any of the following conditions do not require absolute cardiovascular risk assessment using the Framingham Risk Equation because they are already known to be at clinically determined high risk of CVD:</td>
<td>D10 (2009)</td>
</tr>
<tr>
<td>i. Diabetes and age &gt;60 years</td>
<td></td>
</tr>
<tr>
<td>ii. Diabetes with microalbuminuria (&gt;20 mcg/min or UACR &gt;2.5 mg/mmol for males, &gt;3.5 mg/mmol for females)</td>
<td></td>
</tr>
<tr>
<td>iii. Moderate or severe CKD (persistent proteinuria or eGFR &lt; 45 mL/min/1.73m²)</td>
<td></td>
</tr>
<tr>
<td>iv. A previous diagnosis of familial hypercholesterolaemia</td>
<td></td>
</tr>
<tr>
<td>v. SBP ≥180 mmHg or DBP ≥110 mmHg</td>
<td></td>
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<tr>
<td>vi. Serum total cholesterol &gt;7.5 mmol/L.</td>
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</tbody>
</table>
results suggest that a model for predicting coronary and cardiovascular deaths that incorporates central obesity plus smoking would have similar efficacy as the FRE.

One study found that the locally calibrated version of the SCORE risk prediction tool was more accurate than the standard tool in populations aged 36–64 years.\(^6\) Another study in people aged 30–74 years validated a sex-specific multivariable risk factor algorithm that can predict risk based on traditional risk factors such as age, TC, HDL-C, SBP, treatment for hypertension, smoking and diabetes status.\(^5\) A comparison of the FRE and CLEM models in a population aged 30–67 years demonstrated reasonable discriminating ability for both models to predict risk in this age group.\(^5\)

Another recent study constructed a prediction algorithm for 30-year risk of cardiovascular events (e.g., coronary death, MI and stroke) using observational follow-up data from 4,506 participants from the Framingham Offspring cohort aged 20–59 years and free of CVD and cancer at baseline.\(^4\) After adjusting for competing risks of death, the 30-year event rates were 7.6% for women and 18.3% for men. Standard risk factors (male sex, SBP, antihypertensive treatment, TC and HDL-C, smoking and diabetes mellitus) measured at baseline, were significantly related to the incidence of CVD and remained significant when updated regularly. BMI was also associated positively with 30-year risk of CVD, but only in models that did not update risk factors.

Collectively, these results indicate that risk prediction models can be used to reasonably predict CVD risk in adult populations. The FRE, when compared to other absolute CVD risk assessment methods, has shown equivalent or higher predictive ability in non-diabetic cohorts. It remains the most thoroughly tested method of assessing absolute CVD risk in adults without a previous history of diabetes or CVD. The FRE has been found to overestimate or underestimate risk in some populations. There is no current support for the use of ancillary cardiac imaging such as coronary CT angiography to refine FRE based risk assessment and decisions to initiate therapy.

Many of the risk factors included in the FRE become more prevalent with increasing age. An analysis of the risk factors associated with chronic disease found that in Australia, the proportion of people with five or more risk factors for chronic disease (including CVD) was highest in the 45-64 and 65-84 year old age groups.\(^6\)

The lower and upper age limits presented by the Guidelines for the Assessment of Absolute CVD Risk were selected for several reasons. Firstly, the lower age limit of 45 years was consistent with Australian policy initiatives, such as the ‘45-year-old health check’ (Medicare Benefits Scheme item number 717). This program has now been updated to encourage preventative health checks for people between the ages of 45 and 49 years who are at risk of developing chronic disease (Medicare Benefits Scheme items 701, 703, 705 and 707). The lower age limit of 45 years is also aligned with existing clinical recommendations in Australia, such as the Royal Australian College of General Practitioners (RACGP) Guidelines for Preventative Activities in General Practice,\(^4\) which recommends assessment of lipid levels from 45 years. The upper age limit of 74 years was proposed because this was the upper age for the original Framingham Heart Study cohort.\(^6\)

The literature review found little strong evidence supporting CVD risk estimation in people aged 30 years or less and only limited evidence for those 30-45 years. Hence the original baseline age of 45 years (35 years for A&TSI peoples) was deemed appropriate. For people aged under 45 years clinicians should examine those with isolated, elevated single risk factors or a strong family history of CVD to rule out secondary causes and to determine if they fall into the clinically determined high risk category.

**Aged over 74 years**

The upper age limit of 74 years was proposed by the expert panel for the use of the FRE for routine assessment of absolute CVD risk because this was the upper age for the original Framingham Heart Study cohort. In the absence of robust data for risk estimation in this population, the FRE can provide an estimate of risk for this age group, which can be used to guide management decisions. Although age is a significant risk factor for CVD, age in itself is not a reason to initiate pharmacotherapy. Age alone should not be a contraindication to drug therapy, but consideration should be given to quality of life, co-morbidities and life expectancy. These issues should be discussed with the patient before making treatment decisions. Although older people gain a similar relative benefit from reduction of the levels of individual risk factors such as BP and lipids, they are more likely to benefit in absolute terms because of their much higher pre-treatment cardiovascular risk. Therefore, when assessing CVD risk in people aged 74 and older, FRE may be used as a guide to determine the level of risk by assuming an age of 74 years. While acknowledging that FRE may underestimate risk in that individual, the resulting score may be used to inform management decisions by discriminating between adults at moderate risk and those at high risk.
**Evidence-based recommendation**

<table>
<thead>
<tr>
<th>General population aged 45-74 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EBR 2:</strong> Absolute CVD risk assessment, using the Framingham Risk Equation to predict risk of a cardiovascular event over the next five years, should be performed for all adults aged 45–74 years who are not known to have CVD or to be at clinically determined high risk.</td>
</tr>
<tr>
<td><strong>Grade:</strong> B(2009)</td>
</tr>
</tbody>
</table>

**Consensus-based recommendation**

<table>
<thead>
<tr>
<th>General population aged over 74 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CBR 1:</strong> In adults aged over 74, who are not known to have CVD or to be at clinically determined high risk, absolute cardiovascular risk over the next five years should be assessed using the Framingham Risk Equation. Calculation should be performed using the age of 74 years. Although the Framingham Risk Equation might underestimate risk in this population, available evidence suggests that this approach will provide an estimate of minimum cardiovascular risk.</td>
</tr>
</tbody>
</table>

**Practice point**

<table>
<thead>
<tr>
<th>All adults aged over 74 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PP 3:</strong> In adults aged over 74 years, the decision to initiate therapy should be based on clinical judgement which takes into account:</td>
</tr>
<tr>
<td>• Likely benefits and risks of treatment</td>
</tr>
<tr>
<td>• Life expectancy, co-morbidities and quality of life</td>
</tr>
<tr>
<td>• Personal values</td>
</tr>
</tbody>
</table>

### 1.5.3 Aboriginal and Torres Strait Islander peoples

Aboriginal and Torres Strait Islander peoples have a high prevalence of risk factors for heart, stroke and vascular disease. The presence of these risk factors may contribute to the overall risk differently from the patterns observed in reference populations that are reported in the published evidence. People of Aboriginal and Torres Strait Islander background may experience more rapid disease progression than the reference population. They also have exceedingly high age-standardised mortality that has not shown the downward trend seen in the rest of the Australian community over the past 40 years. A literature search failed to locate any new data on this cohort. Therefore, the recommendations below are based on one published study from the *Guidelines for the Assessment of Absolute CVD Risk* and on expert opinion.

**Evidence-based recommendation**

<table>
<thead>
<tr>
<th>Aboriginal and Torres Strait Islander adults aged 35–74 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EBR 3:</strong> In Aboriginal and Torres Strait Islander adults aged 35–74 years who are not known to have CVD or to be at clinically determined high risk, absolute cardiovascular risk over the next five years should be calculated using the Framingham Risk Equation. Although the Framingham Risk Equation might underestimate risk in this population, available evidence suggests that this approach will provide an estimate of minimum cardiovascular risk.</td>
</tr>
<tr>
<td><strong>Grade:</strong> D(2009)</td>
</tr>
</tbody>
</table>
1.5.4 Populations requiring special consideration

Adults with diabetes

In adults with diabetes without known CVD, most risk equations developed in the general population underestimate risk. However, there is little evidence that risk scores developed in diabetic populations provide better estimates. Two high-quality studies were identified that each compared two methods of absolute CVD risk assessment. The FRE was compared with the UKPDS risk score in people participating in a small (n=428) UK general practice-based follow-up study conducted among men and women with diabetes aged 30–64 years.67 For the entire cohort, no statistically significant difference in predictive ability was found between the two methods. However, the area under the curve (AUC) for 10-year risk was numerically higher for the FRE than the UKPDS risk score for both men and women when data were analysed separately. The clinical implications of this finding are unclear.

A US study of 1,237 men and women with diabetes aged 45–64 years compared the predictive ability of traditional risk factors (e.g. age, race, TC, HDL-C, SBP) with the predictive ability of a combination of traditional and non-traditional factors (e.g. BMI, waist-to-hip ratio, serum lipoprotein(a), serum albumin, serum creatinine, white blood cell count, fibrinogen, factor VIII, physical activity, dietary lipid, left ventricular hypertrophy, carotid intima-media thickness).

The score based on a combination of traditional and non-traditional factors was a better predictor of 10-year absolute CVD risk than traditional factors alone, in both men and women.68 Other recent cohort studies have reported that the FRE underestimated risk in people with diabetes,69,70 consistent with the findings of the systematic review. Based on these findings, some investigators argue for the development of diabetes-specific CVD risk calculators.69 However, others have concluded that the development of separate risk prediction models for people with diabetes does not improve predictive ability and that the presence of diabetes alone should not be assumed to indicate a common level of high risk.71 Some investigators have proposed the use of the FRE with the addition of a constant calibration factor for diabetes.70

A more recent systematic review compared the FRE with observed events in people with type 1 diabetes, and found that, in general, the equation was a poor predictor of cardiovascular events.72 However, the authors noted that diabetes-specific risk scores need to be validated in other populations before they are widely adopted. In another recent study, the FRE, SCORE and UKPDS tools were compared in adults with and without diabetes.73 The FRE appeared to either underestimate or overestimate events, while the SCORE and UKPDS risk models, with the addition of non-traditional risk factors, proved more accurate for the assessment of AR.

Overall, current evidence supports the use of the FRE for calculation of CVD risk in the general population of adults with diabetes, despite evidence to show that it underestimates risk in this population.70,74 In people with diabetes aged over 60 years, a high risk of CVD events (>15% probability of a CVD event within five years) is likely, therefore numerical calculation of absolute CVD risk is not necessary in this group.

Consensus-based recommendation

Aboriginal and Torres Strait Islander adults aged over 74 years

CBR 2: Aboriginal and Torres Strait Islander adults aged over 74 years should be considered as being at high CVD risk.

Evidence-based recommendation

Populations requiring special consideration: adults with diabetes

EBR 4: In adults with diabetes aged 60 years or less who are not known to have CVD or to be at clinically determined high risk, absolute cardiovascular risk over the next five years should be assessed using the Framingham Risk Equation. Although the Framingham Risk Equation might underestimate risk in this population, available evidence suggests that this approach will provide an estimate of minimum cardiovascular risk.

Grade C10(2009)
Adults who are overweight or obese

No studies were identified that specifically evaluated the predictive ability of absolute CVD risk assessment in adults who are overweight or obese and without known CVD. Two meta-analyses from large observational studies have found a strong relationship between overweight and obesity and CVD mortality. Australian data are limited. Investigators in a multivariate analysis concluded that obesity (in this study, best measured by waist-to-hip ratio) is a dominant and independent predictive variable for CVD events and deaths in Australian men and women. In line with previous meta-analyses, a recent meta-analysis found the association of measures of obesity are generally accounted for by changes in BP, diabetes and lipid measures.

The most widely recognised indicator of overweight and obesity is BMI, measured as weight divided by height squared (kg/m²). Recently, several authors have proposed that CVD risk correlates better with other metrics that quantify abdominal (visceral) obesity, such as waist circumference or waist-to-hip ratio. NHMRC clinical practice guidelines for the management of overweight and obesity in adults recommend that waist circumference should be measured in combination with either BMI or weight, for those patients who wish to be measured. Definitions and targets based on data from European populations may not be appropriate for all ethno-cultural groups.

The FRE does not include measures of obesity. Hence, in the absence of evidence for the predictive ability of an absolute CVD risk assessment method in adults who are overweight or obese, it is reasonable to use the FRE in this group. Further details of assessment of those who are overweight or obese can be found in the Clinical Practice Guidelines for the Management of Overweight and Obesity in Adults.

Adults with depression

Clinical depression, social isolation and lack of quality social support have been shown to predict incident CHD and worsen its prognosis, independent of conventional risk factors such as smoking, raised lipids and elevated BP. Therefore, adults being assessed for CVD risk should also be assessed for depression and other psychosocial factors. This section reviews the evidence to support the assessment of depression in adults at risk of CVD.

Multiple cohort studies have found a similar strength of association between depression, social isolation or lack of quality social support and CHD compared with traditional risk factors. With minor depression, the risk of CHD increased one-to two-fold. However, with major depression there was a three-to five-fold increase in CHD risk. These results concur with the results of another meta-analysis involving 11 cohort studies in initially healthy subjects that found an overall increase in risk by 64% (RR 1.64, 95% CI 1.29–2.08, p<0.001). Another recent review of the relationship between depression and anxiety with chronic diseases found consistent evidence that depression is a risk factor for heart disease, stroke and diabetes. However, there is no evidence that treatment of depression reduces the risk of CVD events. Two systematic reviews, both in patients with established CHD, failed to demonstrate a link between cardiovascular outcomes and the treatment of depression. Both reviews concluded, however, that the lack of evidence should not detract from the need to address depression as a clinical issue in its own right.

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**Evidence-based recommendation**

<table>
<thead>
<tr>
<th>Populations requiring special consideration: adults who are overweight or obese</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBR 5: In adults who are overweight or obese and who are not known to have CVD or to be at clinically determined high risk, absolute cardiovascular risk over the next five years should be assessed using the Framingham Risk Equation. The results should be interpreted with the awareness that its predictive value has not been specifically assessed in this population.</td>
<td>Dº (2009)</td>
</tr>
</tbody>
</table>

**Practice point**

<table>
<thead>
<tr>
<th>Populations requiring special consideration: adults with depression</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>PP 4: Adults being assessed for CVD risk should also be assessed for depression (and other psychosocial factors). Cardiovascular risk assessment using the Framingham Risk Equation may underestimate risk in adults with depression.</td>
<td></td>
</tr>
</tbody>
</table>
Socioeconomic status

Measures of socioeconomic status are not included in the FRE, but are included in some more recent absolute CVD risk assessment methods. Socioeconomic deprivation should be considered in addition to calculated risk, because it is an independent risk factor for CVD.

Few data are available to quantify the effect of socioeconomic status on absolute CVD risk. Data from a study conducted in Scotland indicate that the FRE underestimated absolute CVD risk in socioeconomically deprived groups. No Australian studies have directly addressed this issue.

Socioeconomic deprivation has been associated with adverse cardiovascular outcomes in Australian adults (where socioeconomic disadvantage is measured according to the Index of Relative Socioeconomic Disadvantage, which takes into account social and economic characteristics of the geographical area such as low income, low educational attainment, high levels of public sector housing, high unemployment and jobs in relatively unskilled occupations). There is emerging evidence that the incorporation of social deprivation scores into absolute CVD risk assessment tools improves their predictive value. However, this approach has been tested only in specific populations and has not been validated in the Australian population. In the absence of a numerical formula for incorporating social deprivation into risk assessments for Australian adults, it is recommended that a subjective assessment of the effect of social status should be taken into account when assessing CVD risk.

Atrial fibrillation

Atrial fibrillation (AF) is an important marker (regardless of causality), not only of thromboembolic disease and stroke, but also of incident all-cause mortality, cardiovascular death, heart failure and possibly coronary events. AF is associated with an odds ratio for death of 1.5 for men and 1.9 in women, which does not vary by age, but most of the excess of mortality attributed to AF occurs early after the diagnosis.

The prothrombotic state imposed by AF predisposes individuals to stroke and thromboembolism, with an approximately five-fold greater risk than that of people without AF. Furthermore, the risk of stroke increases with increasing age, previous transient ischaemic attack (TIA) or stroke, raised BP, diabetes, impaired left ventricular function and a large left atrium.

The presence of AF should prompt a thorough investigation for other CVD risk factors. Readers are referred to an Australian evidence summary and international guidelines for a discussion of the general evidence related to AF management.

Practice point

Populations requiring special consideration: socioeconomic status

PP 5 (2009): A comprehensive assessment of cardiovascular risk involves consideration of socioeconomic deprivation, because it is an independent risk factor for CVD. Absolute risk of CVD calculated using the Framingham Risk Equation is likely to underestimate CVD risk in socioeconomically disadvantaged groups.

Practice point

Populations requiring special consideration: atrial fibrillation

PP 6 (2009): In adults with AF (particularly those aged over 65 years), the increased risk of cardiovascular events and all cause mortality, in addition to thromboembolic disease including stroke, should be taken into account when assessing cardiovascular risk.
Adults already receiving pharmacotherapy for single risk factors

Use of on-therapy measures for BP and cholesterol will inaccurately estimate AR for people already receiving lipid or blood pressure-lowering therapy. Therefore, it is recommended that the most recently recorded pre-treatment measure be used to estimate absolute CVD risk. Where this is not possible, clinicians should make decisions on intensification or withdrawal of pharmacotherapy or lifestyle interventions based on discussions with the patient and consideration of their individual context.

1.6 Review of CVD risk

Intervals for review of absolute CVD risk were determined after consideration of the recommendations of established preventive guidelines for general practice and of the likelihood that an individual's risk status will change over time. Reassessment of absolute CVD risk status should be undertaken when there is a reasonable expectation that it will affect clinical management decisions. In those at low risk, absolute CVD risk should be assessed approximately every two years or if individual risk factor status deteriorates. Another set of blood tests may not be necessary for assessment of people at low risk, i.e. assessment may be conducted with previous cholesterol or blood glucose levels if they have been taken within five years. The decision to conduct a blood test should be made by the clinician after taking into consideration the individual person's context, e.g. specific populations known to be at increased risk, or recent changes such as significant weight gain, uptake of smoking, or onset of menopause.

In a person assessed to be at moderate absolute CVD risk (10–15% probability of a cardiovascular event within five years), closer monitoring of risk is needed because risk level may become high in response to worsening status of one or more risk factors. In a person assessed to be at high absolute CVD risk (>15% probability of a cardiovascular event within five years), risk status is unlikely to be revised downward in the short term, although occasionally it may be reduced following reversal of modifiable risk factors (e.g. permanent smoking cessation). Reassessment of risk status will depend on the individual's clinical profile and the purpose of risk assessment (e.g. to encourage continued adherence to a treatment plan or to inform the decision to commence additional treatment).

The following intervals are intended only as a guide. Appropriate intervals at which an individual's absolute CVD risk should be reviewed will depend on clinical judgment.

<table>
<thead>
<tr>
<th>Practice point</th>
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<tbody>
<tr>
<td><strong>Review of CVD risk</strong></td>
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<tr>
<td><strong>PP 7 (2009):</strong> Regular review of absolute cardiovascular risk is recommended at intervals according to the initial assessed risk level:</td>
</tr>
<tr>
<td>• Low – review every 2 years</td>
</tr>
<tr>
<td>• <strong>Moderate</strong> – review every 6–12 months</td>
</tr>
<tr>
<td>• High – review according to clinical context</td>
</tr>
<tr>
<td><strong>PP 8:</strong> In adults at low absolute risk of CVD, blood test results within five years may be used for review of absolute cardiovascular risk unless there are reasons to the contrary.</td>
</tr>
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</table>
Chapter 2: Treatment

2.1 Lifestyle

This section covers treatment, including targets, for the management of CVD risk, and applies to all adults aged over 45 years (35 years for A&TSI peoples), irrespective of CVD risk level.

Lifestyle changes in nutrition, physical activity and smoking status typically show excellent cost-effectiveness in lowering the burden of disease, especially with respect to obesity, future diabetes and heart disease. However, there is an inherent difficulty in undertaking randomised controlled trials of lifestyle factors. For example, the diet of any individual is related to other lifestyle factors (e.g. smoking, exercise, etc.), and although randomised controlled trials are able to eliminate such bias, they are more difficult to conduct for lifestyle factors than those for pharmacotherapy. For that reason, data pertaining to lifestyle interventions is primarily from cohort and observational studies.

2.1.1 Nutrition, overweight and obesity

A number of behavioural characteristics, including nutrition, overweight and obesity, play an important role in the development of CVD. In Australia, the prevalence of overweight and obesity has been steadily increasing over the past 20–30 years. Data from 2004–05 indicate that about 2.5 million Australian adults were obese (19% of males and 17% of females aged 18 years and over), and a further 4.9 million adults were estimated to be overweight. This section reviews the relationship between nutrition, overweight, obesity and CVD.

Dietary advice

Dietary advice appears to be effective in bringing about modest beneficial changes in diet and CVD risk factors. In a recent review of 38 trials with a minimum follow-up period of three months, dietary advice (e.g. advice to decrease consumption of fat, saturated fatty acids, cholesterol, salt and/or increase consumption of fruit, vegetables, polyunsaturated fatty acids, monounsaturated fatty acids, fish, fibre and potassium) reduced total serum cholesterol by 0.16 mmol/L (95% CI 0.06–0.25) and LDL-C by 0.18 mmol/L (95% CI 0.1–0.27). Mean HDL-C levels and triglyceride levels were unchanged, however BP was reduced, SBP by 2.07 mmHg (95% CI 0.95–3.19) and DBP by 1.15 mmHg (95% CI 0.48–1.85). Dietary Guidelines for Australian Adults have been developed by the NHMRC and are currently being updated. Although the dietary guidelines have been developed for general health measures and not specifically for CVD prevention, the recommendations are consistent with the aim of CVD prevention. Referral for nutritional review and dietary counselling should be considered, depending on need. A brief guide to dietary advice is presented, along with other lifestyle advice, in Table 4.

Altering dietary fat: saturated fat

There is a strong, consistent and graded relationship between saturated fat intake, blood cholesterol and the occurrence of CVD. A review of 27 trials involving 18,196 participants examined the effect of a reduction or modification of dietary fats for at least six months on reducing serum cholesterol levels and on all-cause and cardiovascular mortality and morbidity. The review included trials of high (n=7), moderate (n=6) and low risk (n=14) participants. There was a trend towards protection from cardiovascular mortality (rate ratio 0.91, 95% CI 0.77–1.07), and significant protection from cardiovascular events (rate ratio 0.84, 95% CI 0.72–0.99). This effect was non-significant if studies at high risk of bias were removed.
However, there was stronger evidence of protection against cardiovascular events when trials with at least two years of follow-up were assessed (rate ratio 0.76, 95% CI 0.65-0.90).

**Altering dietary fat: n-3 fatty acids**

While the evidence for the benefits of fish oil is stronger in secondary prevention, the benefits also appear to translate to the primary prevention setting. Several large systematic reviews have reported lower rates of fatal coronary events and sudden death among people who regularly consume fish than among non-consumers. In a meta-analysis of observational studies including 222,364 individuals and an average follow-up period of 11.8 years, individuals with a higher intake of fish had lower CHD-related mortality compared with those who never consumed fish or ate fish less than once per month. The relative risks for CHD were 0.89 (95% CI 0.79–1.01) for fish intake 1–3 times per month, 0.85 (95% CI 0.76–0.96) for once per week, 0.77 (95% CI 0.66–0.89) for 2–4 times per week, and 0.62 (95% CI 0.46–0.82) for five or more times per week. Furthermore, each 20 g/d increase in fish intake was related to a 7% lower risk of CHD mortality (p for trend = 0.03).

However, conflicting results were reported in a 2006 meta-analysis of 48 randomised controlled trials and 26 cohort studies. In that analysis, the observational studies alone suggested that omega 3 fats reduced total mortality. The pooled results from the 48 randomised controlled trials showed no benefit of omega 3 fats on mortality or cardiovascular events in patients with existing CHD. Further high-quality trials are needed to confirm suggestions of a protective effect of n-3 fatty acids on cardiovascular health to prevent CVD.

**Salt intake**

There is now abundant evidence from epidemiological studies and clinical trials that increased levels of salt intake increases BP and therefore, the risk of stroke and CHD. A meta-analysis of 28 trials showed that BP could be significantly reduced in people with raised or normal BP levels, by a modest reduction of dietary salt over four or more weeks. A Cochrane review of salt restriction for the prevention of CHD cited too few cardiovascular events to make a clear conclusion. However, it did report that SBP and DBP were reduced in those given low sodium advice as compared with controls (SBP by 1.1 mmHg, 95% CI 1.8–0.4, DBP by 0.6 mmHg, 95% CI 1.5 to -0.3). Furthermore, people on anti-hypertensive medications were able to stop their medication more often on a reduced sodium diet as compared with controls, while maintaining similar BP control. Over 70% of the salt consumed comes from processed foods and is not related to the discretionary use of salt, therefore a reduction in the amount of salt in the diet would require reduction in the amount of salt used in food production.

**Vegetables and fruit**

Four systematic reviews examined the benefits of vegetable and fruit intake for the reduction of CVD risk. There is evidence from these reviews to support the notion that vegetable and fruit consumption is inversely associated with the risk of CVD. In one review of eight cohort studies, the pooled relative risk of stroke was 0.89 (95% CI 0.83–0.97) for individuals with 3–5 servings per day, and 0.74 (95% CI 0.69–0.79) for those with more than five servings per day, compared with those who had less than three servings of vegetables and fruit per day. Another report found that the risk of CHD decreased by 4% (RR 0.96, 95% CI 0.93–0.99, p=0.0027) for each additional portion of vegetables and fruit intake per day.

**Dairy products**

A detailed meta-analysis of the evidence on milk and dairy consumption and the incidence of vascular diseases and diabetes was recently published. The results provide evidence of an overall survival advantage from the consumption of milk and dairy foods. However, it should be noted that the meta-analysis did not differentiate between full fat and reduced fat products. The relative risk of stroke and/or heart disease in subjects with high milk or dairy consumption was 0.84 (95% CI 0.76–0.93) and 0.79 (95% CI 0.75–0.82) respectively, relative to the risk in those with low consumption.

**Wholegrain cereals**

Despite the evidence from observational studies that whole grains can have a beneficial effect on risk factors for CHD, a meta-analysis of 10 randomised controlled trials found no effect of wholegrain diets on CHD mortality or CHD events or morbidity. In eight of the included studies, the wholegrain component was oats. Pooled analysis of those studies demonstrated lower TC (-0.20 mmol/L, 95% CI -0.31 to -0.10, p=0.0001) and LDL-C (0.18 mmol/L, 95% CI -0.28 to -0.09, p<0.0001) with oatmeal foods. However, many of the trials were short-term, poor quality and had insufficient power.
Low glycaemic index diets

The glycaemic index (GI) is a physiological measure of the ability of a carbohydrate to affect blood glucose. Interest is growing in the low GI index for the clinical management of people at risk of or with established CHD. To date, however, the evidence from randomised controlled trials showing that low GI diets reduce CHD and CHD risk factors is weak. In a meta-analysis of 15 trials there was no evidence that low GI diets have an effect on LDL-C or HDL-C, triglycerides, fasting glucose or fasting insulin levels.120

Mediterranean diets

The Mediterranean diet is characterised by the traditional cooking style of countries bordering the Mediterranean Sea. The principle of the Mediterranean diet includes high levels of olive oil, legumes, unrefined cereals, fruits, vegetables, moderate consumption of dairy products (mostly as cheese and yogurt), moderate to high consumption of fish, low consumption of meat and meat products, and moderate wine consumption.

A systematic review of 12 observational studies with a total of 1,574,299 subjects followed from 3 to 18 years, demonstrated that adherence to a Mediterranean diet is associated with a significant improvement in health status, as seen by a significant reduction in overall mortality (RR 0.91, 95% CI 0.89–0.94), and mortality from CVD (RR 0.91, 95% CI 0.87–0.95).121

Other interventions

Several other interventions, including soya protein,122 phytosterols123 and selenium supplements,124 have been investigated for their potential benefits on CVD risk factors. In general, soya protein,122 phytosterols and soluble fibre123 may have modest hypocholesterolaemic effects, while there is insufficient evidence to determine the effect of selenium supplements on the prevention of CVD.124 More evidence is required before clear recommendations can be made regarding these interventions.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study details</th>
<th>Intervention</th>
<th>Results</th>
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<tbody>
<tr>
<td>Brunner et al (2007)99</td>
<td>Good quality SR (n=38 RCTs); 17,871 healthy adults. Median follow-up 10 months.</td>
<td>Dietary advice vs no advice or minimal advice</td>
<td>↓TC 0.16 mmol/L, ↓ LDL-C 0.18 mmol/L, ↓SBP 2.07 mmHg / DBP 1.15 mmHg after 3-24 months. Mean HDL-C levels and triglyceride levels unchanged.</td>
</tr>
<tr>
<td>Dickinson et al (2006)125</td>
<td>Good quality SR (n=105 RCTs); 6,805 adults with BP ≥140/85 mmHg. At least 8 weeks follow-up.</td>
<td>Lifestyle interventions vs control</td>
<td>Improved diet ↓SBP 5.0 mmHg; ↑ aerobic exercise ↓SBP 4.6 mmHg; ↓ alcohol ↓SBP 3.8 mmHg; sodium restriction ↓SBP 3.6 mmHg; and fish oil supplements ↓ 2.3 mmHg.</td>
</tr>
<tr>
<td>Dauchet et al (2005)108</td>
<td>Good quality SR (n=7 prospective cohort studies); 232,049 participants; 90,513 men, 141,536 women.</td>
<td>Vegetables and Fruit</td>
<td>↓ risk of stroke (RR 0.89, 95% CI 0.85-0.93) for each additional portion per day of fruit. ↓ risk of stroke (RR 0.95, 95% CI 0.92-0.97) for additional fruit and vegetables per day. Linear relationship between fruit or fruit and vegetables and stroke.</td>
</tr>
<tr>
<td>Dauchet et al (2006)109</td>
<td>Good quality SR (n=9 prospective cohort studies); 221,080; 91,379 men, 129,701 women.</td>
<td>Vegetables and Fruit</td>
<td>For each additional portion per day of vegetable and fruit ↓ risk CHD (RR 0.96, 95% CI 0.93-0.99). For each additional portion per day of fruit intake ↓ risk of CHD (0.93, 95% CI 0.89-0.96).</td>
</tr>
<tr>
<td>Reference</td>
<td>Study details</td>
<td>Intervention</td>
<td>Results</td>
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<tr>
<td>Elwood et al (2008)112</td>
<td>Fair quality SR (n=15 cohort studies).</td>
<td>Dairy</td>
<td>High vs low milk or dairy consumption ↓ stroke and/or CHD (RR 0.84, 95% CI 0.76-0.93 and RR 0.79, 95% CI 0.75-0.82 respectively). Limited data on full vs fat reduced products although the risk of IHD was halved in one large cohort of women with reduced fat products.</td>
</tr>
<tr>
<td>Flores-Mateo et al (2006)124</td>
<td>Moderate quality SR (n=31 studies). 14 cohort and 11 CCTs that measured selenium concentrations and six RCTs of selenium supplements.</td>
<td>Selenium supplements</td>
<td>In the 6 RCTs, there was no difference in CHD (RR 0.89, 95% CI 0.68-1.17).</td>
</tr>
<tr>
<td>Harland et al (2008)122</td>
<td>Good quality SR (n=30 RCTs); 2,913 adults with normal or mildly elevated cholesterolaemia.</td>
<td>Soya protein</td>
<td>The inclusion of modest amounts of soya protein (~25 g) into the diet of adults with normal-mild raised lipids resulted in small, but significant reductions in LDL-C, TC and triglycerides.</td>
</tr>
<tr>
<td>He et al (2004)103</td>
<td>Good quality SR (n=11 cohort studies); 222,364 participants. Mean follow-up 11.8 years.</td>
<td>Fish Intake</td>
<td>Compared with those who never ate fish or ate fish &lt;once a month, individuals with a higher intake of fish had lower CHD mortality. Each 20-g/d increase in fish intake was related to a 7% lower risk of CHD mortality.</td>
</tr>
<tr>
<td>He et al (2006)111</td>
<td>Good quality SR (n=8 cohort studies); 257,551 individuals. Average follow-up 13 years.</td>
<td>Vegetables and Fruit</td>
<td>Compared with individuals who had &lt;3 servings/day of vegetables and fruit: &gt;5 servings/day ↓ stroke (RR 0.74, 95% CI 0.69-0.79); 3-5 servings per day ↓ stroke (RR 0.89, 95% CI 0.83-0.97)</td>
</tr>
<tr>
<td>He et al (2007)110</td>
<td>Good quality SR (n=12 cohort studies); 278,459 individuals (9,143 CHD events). Median follow-up 11 years.</td>
<td>Vegetables and Fruit</td>
<td>Compared with individuals who had &lt;3 servings/day of vegetables and fruit: &gt;5 servings/day ↓ CHD (RR 0.83, 95% CI 0.77-0.89); 3-5 servings per day did not change CHD (RR 0.93, 95% CI 0.86-1.00; p=0.06)</td>
</tr>
<tr>
<td>Hooper et al (2001)101</td>
<td>Good quality SR (n=27 RCTs); 18,196 healthy adults. Follow-up periods were grouped into &lt;2 years and &gt;2 years.</td>
<td>Reduction or modification of dietary fats</td>
<td>↓ CVD events (RR 0.84, 95% CI 0.72-0.99). No difference in all-cause mortality (RR 0.98, 95% CI 0.86-1.12) or CV mortality (RR 0.91, 95% CI 0.77-1.07). Analysis of CVD events became non-significant on sensitivity analysis. Stronger results found for trials &gt;2 yrs.</td>
</tr>
<tr>
<td>Hooper et al (2004)107</td>
<td>Good quality SR (n=11 RCTs); 3,514 healthy adults reducing sodium intake over at least a six month period.</td>
<td>Salt reduction diet</td>
<td>Dietary salt reduction may lower BP by small amounts (e.g. ~1 mmHg SBP, &lt;1 mmHg DBP after one year). However reductions may be higher in people with higher BP.</td>
</tr>
<tr>
<td>Hooper et al (2006)105</td>
<td>Good quality SR (n=48 RCTs and 41 cohort studies); 36,913 participants in the RCTs. Mixed primary and secondary prevention.</td>
<td>Omega-3 fatty acids</td>
<td>No difference for all-cause mortality or CVD events.</td>
</tr>
<tr>
<td>Kelly et al (2004)120</td>
<td>Good quality SR (n=21 RCTs); 713 adults with existing CHD or who had at least one risk factor for CHD.</td>
<td>Low GI diet</td>
<td>Compared to high GI diets, there is no evidence that low GI diets have any effect on CHD outcomes, and only borderline reduction in LDL-C (-0.16 mmol/L, 95% CI -0.32-0.00, p=0.05).</td>
</tr>
<tr>
<td>Reference</td>
<td>Study details</td>
<td>Intervention</td>
<td>Results</td>
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<tr>
<td>Kelly et al (2007)</td>
<td>Good quality SR (n=10 RCTs); 738 adults with existing CHD or who had at least one risk factor for CHD. Minimum 4 weeks diet.</td>
<td>Wholegrain cereal diet</td>
<td>There is no evidence that wholegrain diets have an effect on CHD outcomes. In eight studies wholegrain (oats) ↓ TC (-0.20 mmol/L, p=0.0001) and ↓ LDL-C (0.18 mmol/L, p&lt;0.0001).</td>
</tr>
<tr>
<td>Sofi et al (2008)</td>
<td>Good quality SR (n=12 prospective cohort studies); 1,574,299 subjects with 3-18 years follow up.</td>
<td>Mediterranean diet</td>
<td>Greater adherence to a Mediterranean diet is associated with a ↓ in overall mortality (RR 0.91, 95% CI 0.89-0.94) and a ↓ in CVD mortality (RR 0.91, 95% CI 0.87-0.95).</td>
</tr>
<tr>
<td>Wang et al (2006)</td>
<td>Good quality SR (n=33 trials). 1,199, 246 participants. Primary prevention (1 RCT; 25 prospective cohort studies; 7 CCTs). Secondary prevention (14 RCTs; 1 prospective cohort study). All studies followed patients for &gt; 1 yr.</td>
<td>Fish oils / n-3 fatty acids</td>
<td>Increased consumption of n-3 fatty acids from fish or fish-oil supplements, but not of alpha-linolenic acid, ↓ all-cause mortality, cardiac and sudden death, and possibly stroke. The evidence for the benefits of fish oil is stronger in secondary than in primary-prevention settings.</td>
</tr>
</tbody>
</table>

BP: blood pressure; CCT: clinical controlled trial; CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease; DBP: diastolic blood pressure; GI: glycaemic index; HDL: high density lipoprotein; HR: hazard ratio; IHD: ischaemic heart disease; LDL: low density lipoprotein; RCTs: randomised controlled trials; RR: relative risk; SBP: systolic blood pressure; SR: systematic review; TC: total cholesterol.

**Practice point**

**Nutrition, overweight and obesity**

**PP 9:** All adults should be supported to follow the current Dietary Guidelines for Australian Adults.

**Weight loss**

There is evidence to support the promotion of weight loss interventions in people who are overweight or obese. Such interventions can favourably influence CVD risk factors such as BP and blood lipid levels. There is limited evidence that directly links weight loss with a reduction in cardiovascular events.

Four systematic reviews covering a range of weight loss interventions including, pharmacologic, diet, exercise, behaviour therapy and surgery were identified.126-129 The most recent assessed the effects of weight loss interventions versus placebo or no intervention across nine trials involving almost 2,000 participants.129 At 12 months, weight loss interventions resulted in significantly greater weight loss compared with controls (-3.0 kg, 95% CI -5.1 to -0.9, p=0.005). Weight loss interventions were also associated with significant reductions in TC (-0.36 mmol/L; 95% CI -0.75 to 0.04, p=0.008), and favourable (although not statistically significant) changes in LDL-C, HDL-C and triglycerides. This study also identified some evidence to indicate that weight loss could have an independent effect on cardiovascular events, showing a hazard ratio for recurrence of hypertension or cardiovascular events of 0.65 (95% CI 0.50-0.85) for weight loss compared with controls.130

These observations are supported by the results of other reviews where weight loss resulted in improvements in BP,126-128, 131, 132 lipid profiles126-128 and glucose.128 In general, the combination of physical activity and dietary advice provided the greatest benefit,126 while low carbohydrate and high protein diets were more effective than low fat diets in reducing weight and CVD risk factors at 12 months in one review.127
In another review of 84 studies, a weight loss of 10 kg was associated with a fall in TC of 0.25 mmol/L and a fall in DBP of 3.6 mmHg, while a weight loss of 10% was associated with a fall in SBP of 6.1 mmHg. Low fat diets were associated with the prevention of type 2 diabetes and improved control of elevated BP. These diets were associated with a weight loss after 12 months of 5.31 kg (95% CI -5.86 to -4.77 kg). Furthermore, intentional weight loss in women with obesity-related illnesses was associated with a reduced risk of death, CVD death, cancer and diabetes-related death – a result that was irrespective of the amount of weight lost. Men with general illness who lost weight intentionally appeared to have a reduced risk of diabetes related death, but there was no demonstrable effect on CVD mortality, and cancer mortality appeared increased.

In one study, participants randomised to the weight loss group demonstrated a BP reduction of 4.0/1.1 mmHg compared with a 0.8/0.8 mmHg change in the control group (p<0.001). The net effect of those reductions resulted in the discontinuation of antihypertensive medications in 93% of the weight loss group.

**2.1.2 Physical activity**

Physical activity is defined as any bodily movement produced by skeletal muscles that requires energy expenditure. Physical inactivity, including sitting time and leisure activity, is a growing public health problem and is associated with an increased risk of ill health and death, particularly relating to CVD. Regular physical activity reduces CVD risk in its own right, reduces CVD risk factors such as obesity and elevated blood pressure, improves the levels of HDL-C and helps protect against type 2 diabetes.

This section summarises the evidence for physical activity from systematic reviews and individual trials considered for the primary prevention of cardiovascular events.

**Physical activity as an independent risk factor**

Several meta-analyses provide evidence for a significant effect of physical activity on CVD risk, after controlling for other key risk factors. In general, these studies confirm an inverse relationship between physical activity and the risk of a cardiovascular event or all-cause mortality. Effect sizes for specific activities range from 30% to 40% relative risk reductions for CVD and 19% to 33% risk reductions for all-cause mortality.

One meta-analysis combined the results of 22 observational studies, involving 977,925 participants, and used a dose-response meta-regression model to estimate the relationship between non-vigorous physical activity and mortality. The results demonstrated a dose response-relationship for exercise duration: 2.5 hours/week (equivalent to 30 minutes daily of moderate intensity activity on five days a week) compared with no activity, was associated with a reduction in mortality risk of 19% (95% CI 15–24), while 7 hours/week of moderate activity compared with no activity reduced the mortality risk by 24% (95% CI 19–29). Furthermore, the largest benefit was found when moving from no activity to low levels of activity. The presence of a dose-response curve for exercise duration is consistent with results from other studies.

The evidence also suggests a dose-response relationship for exercise intensity. For example, one well conducted meta-analysis evaluated the results from 38 studies with 3–4 different intensities of regular physical activity. For studies with three activity categories (mildly, moderately and highly active), highly active men had a 22% lower risk of all-cause mortality (RR 0.78; 95% CI 0.72–0.84) compared with mildly active men (RR 0.81; 95% CI 0.75–0.90). Similarly, for women, the relative risk was 0.69 (95% CI 0.53–0.90) for those who were highly active, compared with 0.76 (95% CI 0.66–0.89) in the moderately active group. Similar results were observed when moderately active persons were compared with mildly active individuals (RR of 0.81 for men and 0.76 for women).

These results suggest that physical activity should include occupational and/or leisure time activity and incorporate

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**Evidence-based recommendation**

**Nutrition, overweight and obesity**

**EBR 6:** Weight loss should be recommended for people who are overweight or obese.

**Grade:** B

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EBR 6: Weight loss should be recommended for people who are overweight or obese.
accumulated bouts of moderate intensity activities such as brisk walking, cycling, taking public transport and household physical activity. Adults who are moderately active and are able to increase their activity should be encouraged to do so. This may involve changes to intensity, duration or frequency of activity. Any increase in activity should be done gradually irrespective of the level of fitness.

Effects of physical activity on other CVD risk factors

Several randomised controlled trials and meta-analyses provide evidence for a significant effect of physical activity on CVD risk factors. All forms of exercise appear to be effective, with a positive influence on CVD risk factors: lowering LDL-C and triglycerides, increasing HDL-C and insulin sensitivity, reducing body fat and lowering BP.

2.1.3 Smoking

There is overwhelming evidence that smoking has a strong, dose-dependent association with cardiovascular events, including CHD, stroke, peripheral arterial disease and cardiovascular death. Men who smoke are three times more likely to die aged 45–64 years, and twice as likely to die aged 65–84 years than non-smokers. The Nurse’s Health Study showed that female smokers had nearly 1.9 times the risk of total mortality from smoking than non-smokers. Passive smoking also increases the burden of CVD. Smoking cessation reduces these risks substantially, although the decrease is dependent on the duration of cessation. This section summarises the published evidence for smoking cessation for the primary prevention of cardiovascular events.

During the period of the literature search, one high-quality randomised controlled trial of smoking cessation and one secondary analysis of a longitudinal study were located. The randomised controlled trial assessed the effects of a smoking cessation program on long-term mortality among 5,887 middle-aged volunteers with asymptomatic airway obstruction. Intervention included a 10-week smoking cessation program, strong physician support and 12 group sessions using behaviour modification and nicotine gum, plus either ipratropium or a placebo inhaler. At five years, 21.7% of the intervention participants had stopped smoking compared with 5.4% of usual care participants. After up to 14.5 years of follow-up, all-cause mortality was significantly lower in the special intervention group than in the usual care group (8.83 per 1000 person-years vs. 10.38 per 1,000 person-years; p = 0.03). The hazard ratio for mortality in the usual care group compared with the special intervention group was 1.18 (95% CI 1.02–1.37).

Longitudinal data also support smoking cessation as an important primary prevention strategy. In England and Wales between 1981 and 2000, smoking prevalence in adults aged 25–84 years decreased from 43% to 28% in men and from 35% to 24% in women. Using that information and a validated mortality model to estimate the deaths prevented or postponed by changes in population smoking prevalence, the authors estimated that 29,460 deaths were prevented or postponed by the reduction in smoking prevalence.

The number of studies identified during the literature search was small. However, the recommendations presented here also take into account the results of literature prior to 2002. Specifically, one randomised controlled trial found that advice to change diet and smoking habits reduced the relative risk of CHD mortality after 23 years in men with high triglyceride concentrations (HR 0.56, 95% CI 0.34–0.93, p = 0.027). Men with normal triglyceride concentrations did not appear to achieve the same long-term benefit.

Five observational studies of over 293,000 patients support these results. In one study, cause-specific mortality was monitored for 50 years in 34,439 male British doctors. For those born between 1900 and 1909, the probabilities of dying in middle age (35–69) were 42% vs 24% (a two-fold death rate ratio) for smokers and non-smokers, respectively, but were 43% vs 15% (a three-fold death rate ratio) for those born in the 1920s. Cessation at age 60, 50, 40 or 30 years provided an approximate 3, 6, 9 or 10 additional years, respectively, of life expectancy.
Table 3: Effect of physical activity on CVD outcomes: summary of key evidence

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study details</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
</table>
| Hamer et al (2008) | Good quality SR (n=18 prospective cohort studies). 459,833 participants free   | Walking                       | For highest vs lowest walking category: ↘CVD events (HR 0.69, 95% CI 0.61-0.77)  
  ↘all-cause mortality (HR 0.68, 95% CI 0.59-0.78). Walking pace was a stronger independent predictor of overall risk compared with walking volume (48% vs 26% risk reductions, respectively). |
| Lollgen et al (2009)| Good quality SR (n=38 prospective cohort studies) Primary prevention. Study    | Physical activity              | All-cause mortality. Highly vs mildly active: Men (RR = 0.78, 95% CI 0.72-0.84); Women (RR 0.69, 95% CI 0.53-0.90. There is a dose-response curve from sedentary subjects to those with mild and moderate exercise. This association was similar for sex and age. |
| Orozco et al (2008)| Good quality SR (n=8 RCTs; 10 interventions) 5,095 participants at risk of     | Exercise or exercise and diet  | Exercise and diet interventions had a modest effect on blood lipids, and improved SBP and DBP by 4 mmHg, (95% CI -5 to -2) and 2 mmHg, (95% CI -3 to -1), respectively. Exercise alone or diet alone did not demonstrate these effects.                                      |
| Shaw et al (2008)  | Good quality SR (43 RCTs). 3,476 participants who are obese or overweight.     | Exercise + diet vs diet or no | Exercise + diet resulted in a greater weight reduction than diet alone (WMD - 1.0 kg; 95% CI -1.3 to -0.7). Exercise intensity increased the magnitude of weight loss (WMD -1.5 kg; 95% CI -2.3 to -0.7). Exercise alone ↓DBP (WMD -2 mmHg; 95% CI -4 to -1), ↓triglycerides (WMD - 0.2 mmol/L; 95% CI -0.3 to -0.1) and ↑fasting glucose (WMD - 0.2 mmol/L; 95% CI -0.3 to -0.1). |
| Shiroma et al (2010)| Fair quality review based on previous robust SR (n=54 prospective cohort       | Physical activity              | Compared with no activity, physical activity provides a significant and consistent benefit in the order of 30-40% risk reduction for CHD and CVD. Consistent benefit for sex, age and ethnicity. Higher intensity had greater effects than moderate intensity. |
| Thomas et al (2006)| Good quality SR (n=14 RCTs) 377 participants with type 2 diabetes mellitus.    | Aerobic, fitness or PRT exercise vs no exercise | Exercise significantly improves glycaemic control and reduces visceral adipose tissue and plasma triglycerides, but not plasma cholesterol, in people with type 2 diabetes even without weight loss. |
| Woodcock et al (2010)| Good quality SR (n=22 prospective cohort studies). 977,925 people (334,738 men | Light or moderate physical     | 2.5 h/week moderate intensity activity ↓risk of mortality by19% (95% CI 15-24), while 7 hr/ week of moderate activity ↓mortality risk by 24% (95% CI 19-29). Smaller effects found in trials of walking alone. |

CI: confidence interval, CHD: coronary heart disease; CV: cardiovascular; CVD: cardiovascular disease; DBP: diastolic blood pressure; PRT: progressive resistive training; RCT: randomised controlled trial; SBP: systolic blood pressure; WMD: weighted mean difference.
Another two case controlled studies involving 1,274 subjects and 3,372 controls indicated that smoking is associated with an increased risk of MI and CHD-related mortality, and a dose-response relationship exists between the total tar consumption per day and risk. The odds ratio for subjects smoking medium and high-tar-yield compared with low-tar-yield cigarettes was 1.86 (95% CI 1.21–2.87) and 2.21 (85% CI 1.47–3.34), respectively. The INTERHEART study demonstrated the dose-response relationship between number of cigarettes smoked and MI. People who smoked over 40 cigarettes per day were found to have an almost 10-fold relative risk of MI compared with non-smokers (OR 9.16, 99%CI 6.18–13.58).

Several Cochrane reviews have been undertaken related to different therapies for smoking cessation. Nicotine replacement therapy can increase smoking cessation by 50–70%. Some antidepressants, for example bupropion and nortriptyline, but not selective serotonin reuptake inhibitors, aid long-term smoking cessation. Varenicline, a nicotine receptor partial agonist, leads to a two-fold success rate compared with non drug quit attempts and appears to be more beneficial than bupropion. Tailored behavioural strategies via group or individual approach have demonstrated modest effects for smoking cessation. Strategies and support provided from a range of health professionals including physicians, community pharmacists or nurses are effective. Telephone counselling improved smoking cessation rates particularly when three or more call-backs were made. Other approaches using the internet may also be useful where tailored information is provided.

Overall, the evidence shows a dose dependent relationship between smoking and CVD events. A range of behavioural and support interventions have been shown to improve smoking cessation. Although there are several high-level reviews for interventions for smoking cessation, the literature was not systematically searched and hence the guidance is included as a practice point.

### 2.1.4 Alcohol

Alcohol has a complex role in Australian society. Most Australians drink alcohol, generally for enjoyment, relaxation and sociability, and do so at levels that cause few adverse effects. However, a substantial proportion of people drink at levels that increase their risk of alcohol-related harm. As such, alcohol is known to have both beneficial and harmful effects on the risk of cardiovascular events and the psychological consequences of the disease. The 2007 National Drug Strategy Household Survey indicated that approximately 10% of Australian adults have never had a full serve of alcohol and about 17% have not consumed alcohol in the past year. On the other hand, the number of Australians who drink daily and weekly was approximately 8% and 14%, respectively. This section summarises the evidence for alcohol consumption from systematic reviews and individual trials considered for the primary prevention of cardiovascular events.
Several systematic reviews of observational studies have consistently reported lower CVD mortality and CVD events with light to modest alcohol consumption.\textsuperscript{174-178} The most recent meta-analysis involving 84 observational studies (>2 million participants) found reduced relative risks for alcohol drinkers relative to non-drinkers for CVD mortality (21 studies; RR 0.75, 95% CI 0.70–0.80), incident CHD (29 studies; RR 0.71, 95% CI 0.66 to 0.77), CHD mortality (31 studies; RR 0.75, 95% CI 0.68–0.81), incident stroke (17 studies; RR 0.98, 95% CI 0.91–1.06) and stroke mortality (10 studies; RR 1.06, 95% CI 0.91–1.23).\textsuperscript{175} Dose-response analysis revealed that the lowest risk of CHD mortality occurred with 1–2 drinks a day, but for stroke mortality it occurred with ≤1 drink per day. Secondary analysis of all-cause mortality demonstrated lower risk for drinkers compared with non-drinkers (RR 0.87, 95% CI 0.83–0.92). Modest alcohol intake was found to lower stroke incidence and mortality, but, unlike the risk for CHD, the risk of all stroke subtypes increased significantly with heavier drinking.\textsuperscript{175, 179} It is also noted that the association of alcohol consumption differs by stroke subtype; there is a lower risk of ischaemic stroke but increased risk of haemorrhagic stroke.\textsuperscript{175} This is likely due to the fact that studies analysing the effect of alcohol on BP reported linear BP elevations at levels above 20 g/day for women and 30 g/day for men.\textsuperscript{174} A recent meta-analysis of 44 intervention studies (mix of random and non random studies) found alcohol significantly increased levels of HDL-C (pooled mean difference 0.094 mmol/L, 95% CI 0.064–0.123), apolipoprotein A1 (0.101 g/L, 95% CI 0.073–0.129) and adiponectin (0.56 mg/L, 95% CI 0.39–0.72). Alcohol decreased fibrinogen levels (−0.20 g/L, 95% CI −0.29 to −0.11), but did not affect triglyceride levels. Different study designs and beverage types demonstrated consistent findings.\textsuperscript{175} These biomarker studies provide indirect pathophysiological support for a protective effect of moderate alcohol use on CHD.

It is important to note that studies reported here focus on the link between alcohol intake and CVD only and do not consider other known detrimental effects of high alcohol consumption, including the risk of alcohol abuse. The results of the most recent meta-analysis generally reinforce the current national alcohol guidelines which recommend consuming light to moderate amounts of alcohol to prevent alcohol-related harm.\textsuperscript{171}

### Practice point

#### Alcohol

**PP 11:** All adults should be advised to follow the current Australian guidelines to reduce health risks from drinking alcohol (2009).

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### People with atrial fibrillation

Among 34,715 healthy middle-aged women (>45 years and free of AF at baseline) participating in the Women’s Health Study, consumption of up to two alcoholic beverages per day was not associated with an increased risk of incident AF. Heavier consumption of two or more drinks per day, however, was associated with a small but statistically significant increased risk of AF (hazard ratio 1.60, 95% CI 1.13–2.25).\textsuperscript{180}

### People with raised blood pressure

A cohort of the Physicians’ Health Study assessed total and CVD mortality among 14,125 men with raised BP who had reported to be either non-drinkers or rare drinkers, or light to moderate drinkers.\textsuperscript{181} During 75,710 person-years of follow-up, there were 1,018 deaths, including 579 from CVD. Compared with individuals who rarely or never drank alcoholic beverages, those who reported monthly, weekly and daily alcohol consumption, respectively, had multivariate adjusted relative risks for CVD mortality of 0.83 (95% CI 0.62–1.13), 0.61 (95% CI 0.49–0.77) and 0.56 (95% CI 0.44–0.71) (p<0.001 for linear trend). In the same groups, relative risks for total mortality were 0.86 (95% CI 0.67–1.10), 0.72 (95% CI 0.60–0.86) and 0.73 (95% CI 0.61–0.87), respectively (p<0.001 for linear trend). These results, which require confirmation in other large-scale studies, suggest that light to moderate alcohol consumption is associated with a reduction in risk of total and CVD-related mortality in hypertensive men.

### People with diabetes

Two systematic reviews assessing the effect of alcohol use on the incidence and complications of diabetes mellitus in adults were identified. In the first, the risks of fatal and total CHD were significantly lower in all three categories of alcohol consumers (<6, 6 to <18 and ≥18 g/day) than in non-consumers; relative risks ranged from 0.34 to 0.75.\textsuperscript{182} Similar results were reported in the second review: compared with no alcohol use, moderate consumption (1–3 drinks/day) was associated with a 33–56% lower incidence of diabetes and a 34–55% lower incidence of diabetes-related CHD.\textsuperscript{183} It is clear from these reviews and those noted above there is no difference in effect between those with or without diabetes.
2.1.5 Multiple lifestyle interventions

One Cochrane review and three trials using lifestyle change interventions to improve cardiovascular outcomes were located. In the Cochrane review, 55 trials using education or counselling with or without pharmacotherapy to reduce CVD risk factors were assessed. The trials were all more than six months in duration using counselling or education to modify more than one CVD risk factor in adults from general populations, occupational groups or specific risk factors (i.e. diabetes, hypertension, hyperlipidaemia, obesity) and all involved people aged 40 years or older with no evidence of CVD at baseline (trials with more than 25% participants with prior CVD were excluded). The interventions had some effect on risk factors, demonstrating reductions in SBP (53 trials; WMD -2.71 mmHg, 95% CI -3.49 to -1.93), DBP (53 trials; WMD -2.13 mmHg, 95% CI -2.67 to -1.58) and blood cholesterol (50 trials; WMD -0.24 mmol/L, 95% CI -0.32 to -0.16). In general, lifestyle intervention was ineffective for improving cardiovascular outcomes, including total mortality and CHD mortality (OR 1.00, 95% CI 0.96-1.05 and OR 0.99, 95% CI 0.92-1.07 respectively).

In several randomised controlled trials, intensive interventions to address lifestyle factors were used, while in another, motivational interviewing based on an AR profile was investigated. The group-based interventions resulted in modest improvements in body weight, waist circumference and BP, while motivational interviewing, used in the latter study demonstrated a small difference compared with controls in terms of 10-year Framingham risk profile. In that study, the effects on individual risk factors (e.g., BP, cholesterol and smoking) were generally modest where they occurred at all.

Collectively, this evidence indicates that for the general population, lifestyle interventions can modestly reduce the levels of individual CVD risk factors, but have not been consistently found to affect CVD outcomes. The reduction in number of CVD events by multiple lifestyle interventions appears to be related to the initial level of AR.

### Practice point

**General Lifestyle**

**PP 12:** Adults at higher absolute risk of CVD should be given more frequent and sustained lifestyle advice, support and follow-up to achieve behavioural change.

### Table 4: General lifestyle advice

<table>
<thead>
<tr>
<th>Lifestyle factor</th>
<th>Advice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet</td>
<td>Consume a varied diet rich in vegetables, fruits, wholegrain cereals, lean meat, poultry, fish, eggs, nuts and seeds, legumes and beans, and low-fat dairy products</td>
</tr>
<tr>
<td>Fats</td>
<td>Limit foods containing saturated and trans fats</td>
</tr>
<tr>
<td>Salt</td>
<td>Limit salt to &lt;6g/day (approximately 2300 mg sodium)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Limit alcohol intake to ≤2 standard drinks per day</td>
</tr>
<tr>
<td>Physical activity</td>
<td>At least 30 minutes physical activity on most or preferably every day of the week</td>
</tr>
<tr>
<td>Weight</td>
<td>Limit energy intake to maintain a healthy weight. Ideal weight should be BMI &lt;25 kg/m² and waist circumference &lt;94 cm in men (&lt;90 cm in Asian men) or &lt;80 cm in women (including Asian women)</td>
</tr>
<tr>
<td>Smoking</td>
<td>Stop smoking using counselling, and if required nicotine replacement therapy or other medication</td>
</tr>
</tbody>
</table>
2.2 Pharmacotherapy

2.2.1 Blood pressure-lowering therapy

Blood pressure-lowering reduces CVD risk

BP lowering using pharmacotherapy results in reduction in both total mortality and mortality from CHD and stroke. However, questions remain about which drugs to use, at what dose and whether BP should be reduced to a limited extent only – a treat to target approach – or reduced as far as possible. This section summarises the evidence for lowering BP from systematic reviews and individual trials considered for the primary prevention of cardiovascular events.

Two large systematic reviews of BP-lowering drugs versus placebo in people without a history of CVD demonstrate that pharmacological lowering of BP reduces the incidence of CHD events and strokes in the order of 20–25% and 30–45%, respectively. The first review analysed the results from 147 randomised trials of BP-lowering drugs in preventing CHD and stroke events. The preventive effect of BP-lowering therapies in people without a history of CVD, and those with and without high blood pressure was similar. For people without a history of CVD, active treatment resulted in a 10 mmHg reduction in SBP or 5 mmHg reduction in DBP, and led to a relative risk of CHD events of 0.79 (95% CI 0.72–0.86) and for stroke of 0.54 (95% CI 0.45–0.65).

In the second review, a quantitative assessment of elevated BP trials was performed to investigate to what extent lowering of SBP and DBP contributed to prevention of CVD. A total of 12,903 young (30–49 years of age) people, 14,324 old (60–79 years of age) and 1,209 very old (≥80 years of age) people were assessed. In the young, old and very old, the median follow-up period was 5.0, 3.9 and 3.8 years, respectively, and active treatment reduced SBP and DBP by a similar amount in each cohort. However, with increasing age, the ratio of DBP to SBP lowering significantly decreased from 0.55 (95% CI 0.46–0.64) in the young to 0.39 (95% CI 0.29–0.49) and 0.32 (95% CI 0.01–0.63) in the old and very old, respectively (p=0.004). Despite this, active treatment reduced all cardiovascular events and the risk of stroke and CHD events to a similar extent in all three age strata. In addition, active treatment reduced total mortality by 17% (95% CI 6–26; p=0.003) and cardiovascular mortality by 21% (95% CI 7–33; p=0.004) in old people. This was not the case in the young and very old groups (p>0.28), although this result was expected given the relatively short period of follow-up in young people and long period in the very elderly.

The HYVET trial examined the effects of a diuretic on people aged 80 or over with raised BP. This randomised trial found that treatment with a diuretic reduced the relative risk of fatal and non-fatal stroke, but not significantly (hazard ratio 0.70, 95% CI 0.49–0.91, p=0.06). The same study demonstrated significant reductions in all cause mortality (hazard ratio 0.79, 95% CI 0.65–0.95, p=0.02) and CVD events (hazard ratio 0.79, 95% CI 0.69–0.90, p=0.0004). Collectively, these data demonstrate that active treatment with BP-lowering therapies improves cardiovascular outcomes.

People with diabetes

In people with type 2 diabetes, BP-lowering therapy reduces CVD risk to an equal or greater extent than for the population without diabetes.

People with CKD

There is a growing body of evidence to suggest that people with CKD receive the same or similar benefits from BP-lowering therapy as those in the general population. Other evidence shows benefits of BP lowering in this population for cardiovascular events but not mortality. Much less evidence is available for people on maintenance dialysis; however, the available evidence suggests that treatment using agents that lower BP reduces cardiovascular morbidity and mortality. Treatment for BP lowering in people on dialysis is highly complex and specialist advice and management is usually required. While more studies are required, the possible risks and benefits of BP lowering should be considered for all people receiving dialysis.

Other considerations

The benefits of BP lowering using an AR approach have not been assessed. Meta-analysis clearly demonstrates reductions of CVD risk from lowering BP, which is consistent across all subgroups.

Is it also noted that BP lowering reduces important non-CVD related conditions such as heart failure, glaucoma and diabetic and non-diabetic nephropathy.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study details</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP Lowering Treatment Trialists’ Collaboration; Turnbull et al (2008) 198</td>
<td>Good quality SR (n=31 RCTs); 190,606 participants. Compared age groups &lt;65 and above 65. Mixed primary and secondary prevention.</td>
<td>Comparison of BP-lowering regimens against placebo or less intensive control</td>
<td>No difference in reductions in major CV events between age groups for any comparison. For each ↓5mmHg SBP, risk of CVD events ↓11.9% (5.3-18%) for those aged &lt;65 and ↓9.1% (3.6-14.3%) for those aged ≥65.</td>
</tr>
<tr>
<td>Law et al (2009) 192</td>
<td>Good quality SR (n=147 RCTs); 464,000 participants. 26 RCTs specifically with no history of CVD.</td>
<td>All BP lowering medications vs placebo or other class of drug</td>
<td>For a reduction of 10mmHg SBP or 5mmHg DBP: ↓CHD events (RR 0.79, 95% CI 0.72-0.86), ↓stroke (RR 0.54, 95% CI 0.45-0.65). Preventative effect similar in people with and without history of CVD. Effect is similar for all classes of blood pressure-lowering drugs (although CCBs slightly more effective for stroke prevention and BBs slightly less effective). CCBs ↓heart failure by 19% whereas for other classes ↓24%. Consistent RR for CHD (0.84) and stroke (0.70) irrespective of initial BP.</td>
</tr>
<tr>
<td>Wang et al (2005) 193</td>
<td>Good quality SR (n=10 RCTs). 12,903 young (30-49 yrs old) from 3 trials; 14,324 old (60-79 yrs) and 1209 very old (≥80 yrs old) from 8 trials. Limited to trials with available individual data. Combined primary and secondary trials.</td>
<td>All BP lowering medications vs placebo or no treatment</td>
<td>↓BP in young (8.3/4.6 mmHg), old (10.7/4.2 mmHg) and very old (9.4/3.2 mmHg). ↓17% all-cause mortality (p=0.003) and ↓21% CVD morality (p=0.004) in those 60-79 but not in the younger or older groups. No difference in CVD events for different ages but ↑absolute benefit with increasing age. Effects related to ↓SBP rather than DBP.</td>
</tr>
<tr>
<td>Wright et al (2009) 199</td>
<td>Good quality SR (n=24 RCTs; 28 arms). 58,040 people, 42,196 (72.7%) were primary prevention. Included trials had &gt;70% of people with BP &gt;140/90 mmHg at baseline and were for &gt;1 year duration.</td>
<td>All BP lowering medications vs placebo or other class of drug</td>
<td>Low-dose thiazides in ↓mortality (RR 0.89, 95% CI 0.83-0.96) and ↓CV events (RR 0.70, 95% CI 0.64-0.76). BBs ↓CV events (RR 0.89 95% CI 0.8-0.98) but not CHD or mortality. ACEi ↓mortality (RR 0.83, 95%CI 0.72-0.95) and CV events (RR 0.76, 95% CI 0.67-0.85). CBBs ↓CV events (RR 0.71, 95% CI 0.57 to 0.87) but not CHD or mortality. Moderate to high BP in primary prevention ARR 3.7-5.1 (NNT for 5 years 20-27); Mild BP in primary prevention ARR 0.75-0.82 (NNT 120); secondary prevention ARR 5.5 (NNT 18).</td>
</tr>
</tbody>
</table>

ACEi: ACE inhibitor; ARR: absolute risk reduction; BB: beta blocker; BP: blood pressure; CCB: calcium channel blocker; CI: confidence interval; CHD: coronary heart disease; CV: cardiovascular; CVD: cardiovascular disease; DBP: diastolic blood pressure; MI: myocardial infarction; NNT: number needed to treat; RCTs: randomised controlled trials; RR: relative risk; SBP: systolic blood pressure.
2.2.2 Lipid-lowering therapy

Lipid-lowering reduces CVD risk

High plasma cholesterol is a well-known, modifiable risk factor for CVD. A 10% increase in TC is associated with a 27% increase in the incidence of CHD, and the relationship persists, irrespective of smoking status, the presence or absence of elevated BP, or a history with or without vascular disease. Lipid lowering therefore plays an important role in the prevention of cardiovascular events.

Most of the cholesterol in blood plasma is carried by LDL-C and the strong relationship between TC and CVD suggests that LDL-C is a powerful risk factor. Moreover, the results of epidemiological studies, as well as trials with clinical endpoints, confirm that a reduction in LDL-C must be of primary concern in the prevention of CVD. This section summarises the evidence for lowering blood lipids from systematic reviews and meta-analyses considered for the primary prevention of cardiovascular events.

The preponderance of evidence suggests that, compared with placebo, statins reduce the risk of death or cardiovascular events in populations without a history of CVD, irrespective of age and gender and across a wide range of cholesterol levels (see Table 6). One meta-analysis of 14 trials found all-cause mortality was reduced by statins (RR 0.83, 95% CI 0.73–0.95) as were combined fatal and non-fatal CVD events (RR 0.70, 95% CI 0.61–0.79). Combined fatal and non-fatal stroke events were reduced (RR 0.78, 95% CI 0.65–0.94) as were combined fatal and non-fatal CHD events (RR 0.72, 95% CI 0.65–0.79). There was no clear evidence of any significant harm caused by statins or effects on patient quality of life.

Another meta-analysis of 26 trials (mixed primary and secondary prevention) focusing on the comparison of high and low doses of statins, reported a strong benefit of statin use, with a reduction in major vascular events in people without previous CVD (RR 0.75, 95% CI 0.69–0.82 per 1 mmol/L reduction in LDL-C) and a 0.4% lower risk difference per year in those taking statins. This result is similar to the approximately 20% reductions found in those with existing CVD (across all subgroups). The data confirmed an approximate linear relationship between LDL-C reduction and relative risk reduction of CVD events, independent of presenting levels, and that more intensive treatment can further lower the risks.

Similar benefits were observed in another meta-analysis of 10 trials, 94% of whom were in people without established CVD but with CVD risk factors. During a mean follow-up of 4.1 years, statin therapy significantly reduced the risk of all-cause mortality (OR 0.88, 95% CI 0.81–0.96), major coronary events (OR 0.70, 95% CI 0.61 to 0.81) and major stroke events (OR 0.81, 95% CI 0.71–0.93). There was no increased risk of cancer and the effects were similar in various clinical subgroups.

In contrast, two smaller meta-analyses showed trends towards decreased all-cause mortality that just failed to reach statistical significance. These include a recent meta-analysis of 11 trials specifically excluding those with pre-existing CVD (RR 0.93, 95% CI 0.86–1.00). No individual or composite CVD endpoints were considered as part of this review although there was a 1 mmol/L mean difference in LDL-C levels overall between the intervention and control groups after an average of 3.7 years of statin treatment (2.4 mmol/L on statin therapy vs. 3.5 mmol/L in control group; compared with 3.6 mmol/L at baseline). Finally, a slightly older meta-analysis based on only two trials found that statins were associated with a statistically significant reduction in the risk of non-fatal MI (RR 0.60, 95% CI 0.37 to 0.97) and of CHD death plus non-fatal MI (RR 0.66, 95% CI 0.46–0.96), but not all-cause mortality (RR 0.73, 95% CI 0.53–1.01) or CVD mortality (RR 0.67, 95% CI 0.40–1.10).

Three recent stroke specific primary prevention meta-analyses of those at high risk of CVD (all of which involved trials that included people with other CVD events at baseline) also confirm the risk reduction offered by statin therapy is in the order of 20% due primarily to the reduction in ischaemic stroke and other CVD events without any significant decrease or increase in haemorrhagic stroke.

Although similar overall, variations in results from the five most recent meta-analyses highlight the differences in the inclusion criteria (particularly the percentage of participants found to have existing CVD), review dates, outcomes chosen (individual versus composite endpoints), early termination of some included trials, and data analysis and reporting.

Collectively, the evidence confirms that there is a continuous, graded, strong relationship between serum cholesterol and risk for major cardiovascular events. Statin trials consistently found significant reductions in TC (net difference -0.99 mmol/L, 95% CI -1.60 to -0.38 mmol/L) and LDL-C (net difference -0.92 mmol/L, 95% CI -1.10 to -0.74 mmol/L). The effect of statin therapy appears to be related primarily to LDL-C reductions, which is confirmed in the recent meta-analysis of 26 trials that found a 25% relative reduction in CVD events for those
without CVD at baseline for each 1.0 mmol/L decrease in LDL-C.\textsuperscript{203}

The benefit of statin therapy is greatest for individuals at higher levels of risk.\textsuperscript{208} Of all the methods to modify lipids, the weight of evidence suggests that statins are the most effective agents and should be the first-line agent to reduce lipids.\textsuperscript{208, 209, 216-219}

Other than statins, lipid-lowering pharmacotherapy includes fibrates, bile acid binding resins), niacin (nicotinic acid) and selective cholesterol absorption inhibitors (e.g. ezetimibe).

Fibrates effectively lower triglycerides and increase HDL-C. However, they lower TC and LDL-C much less than statins.\textsuperscript{216, 219} A meta-analysis of 10 long-term, placebo controlled trials (two trials were exclusively primary prevention and two further trials were mixed) found on average fibrates reduced TC by 8% and plasma triglyceride levels by 30% and increased HDL-C levels by 9%. LDL-C was also reduced by 7% although most individual trials reported no statistically significant changes in LDL-C levels.\textsuperscript{220} There were no significant differences in the efficacy of the various fibrates in reducing triglyceride or increasing HDL-C levels. The use of fibrates significantly reduced the occurrence of non-fatal MI (OR 0.78, 95% CI 0.71–0.86) but had no significant effect on CVD or all-cause mortality, fatal MI or stroke – all of which have been found in other meta-analyses to be significantly reduced by statins.

Another recent meta-analysis of 18 trials (four primary prevention trials, three mixed primary and secondary trials, and 11 secondary prevention trials) found overall benefit of fibrates for the prevention of major CVD events (RR 0.90, 95% CI 0.82–1.00; p=0.048) primarily due to reduction in coronary disease (RR 0.87, 95% CI 0.81–0.93; p<0.0001) with no effect on stroke (RR 1.03, 95% CI 0.91–1.16), CVD mortality (RR 0.97, 95% CI 0.88–1.07) or all-cause mortality, fatal MI or stroke – all of which have been found in other meta-analyses to be significantly reduced by statins.

One trial of the bile acid resin cholestyramine monotherapy reported from the mid 1980s found a significant 19% reduction in risk of CHD death and/or nonfatal myocardial infarction, but an increase in side effects (mainly gastrointestinal irritation).\textsuperscript{223}

Ezetimibe is a relatively new agent that inhibits cholesterol absorption from the small intestine. Two meta-analyses (both with mixed primary and secondary prevention trials) were consistent in their findings that a combination of ezetimibe plus statin significantly reduced LDL-C and TC compared with statin alone.\textsuperscript{224} Patients on ezetimibe/statin relative to those on placebo/statin were more likely to reach the LDL-C treatment goal (RR 3.4, 95% CI 2.0–5.6; p<0.0001).\textsuperscript{224} Monotherapy with ezetimibe, for patients where a statin was not considered appropriate, also significantly reduced LDL-C levels compared with placebo (p<0.00001) but the reductions were smaller than that demonstrated for statins.\textsuperscript{225}

During the finalisation of this Guideline, the landmark SHARP trial reported that in a population of 9,270 with CKD (15% with history of vascular disease i.e. angina, stroke or peripheral vascular disease), a combination of ezetimibe 10 mg plus simvastatin 20 mg daily reduced LDL-C by an average of 0.85 mmol/L (SE 0.02; approximately 66% compliance, median follow-up of 4.9 years).\textsuperscript{226} There was a 17% reduction in major atherosclerotic events (non-fatal MI or coronary death, non-haemorrhagic stroke or any arterial revascularisation procedure) with combined therapy compared with placebo (RR 0.83, 95% CI 0.74–0.94) with no evidence of adverse effects.

Nicotinic acid, or niacin, has been found to reduce cholesterol. One meta-analysis of 30 trials (in mixed primary and secondary populations) found niacin significantly reduced TC (10%), increased net HDL-C (16%), reduced LDL-C (12%) and reduced triglycerides (20%).\textsuperscript{227} Similar results were found in another meta-analysis which included seven trials of niacin (all secondary prevention) which found a 17% reduction in non HDL-C and a 17% reduction in CHD risk, over 6.2 years although there was significant heterogeneity among the mostly small trials and most used combination therapy (mainly with statins).\textsuperscript{218} Only one main outcome trial in those with existing MI reported significant reduction in events by 14% with no change in mortality although the eight-year follow up of this trial found significantly reduced mortality with niacin monotherapy.\textsuperscript{228} No outcome trials for niacin were found in those without existing CVD.

Omega 3 fatty acid (fish based rather than plant based) has been found to significantly reduce levels of triglycerides and increase levels of HDL-C but has not been found
to reduce TC or LDL-C. While observational data suggest a reduction in CVD events with n-3 fatty acids (refer to section 2.1.1) only one major outcomes trial has been published. The JELIS trial involved 18,645 Japanese with TC >6.5mmol/L (26% of participants had a prior history of MI, angina or revascularisation therapy). Fish oil supplementation (1,800 mg/day) was given in addition to regular statin therapy. After a mean follow-up of 4.6 years there was a significant reduction in major coronary events (OR 0.81, 95% CI 0.69–0.95), but this benefit was not statistically significant in the primary prevention subgroup (OR 0.82, 95% CI 0.63–1.06).

An important result of the studies reported here is that the benefits of lipid-lowering therapy depend on initial levels of risk: the absolute reductions in risk were highest in people at the highest baseline risk irrespective of initial lipid levels. The decision to treat people at moderate levels of risk with lipid-lowering pharmacotherapy is more complex and can be determined by responsiveness to lifestyle interventions, taking into consideration other risk factors not included in the FRE.

### Other considerations

In clinical practice, it is important to consider and exclude treatable causes for dyslipidaemia before starting treatment, since often the treatment of underlying disease improves dyslipidaemia and no other lipid-lowering therapy is necessary. Causes of dyslipidaemia may include diet and alcohol influences, hypothyroidism, diabetes, liver disease, nephrotic syndrome and steroid treatment.

A family history of premature CVD and/or central adiposity should also be considered as both these factors increase overall risk, independently of traditional risk factors.

A family history of premature CVD refers to an event that occurs in relatives including parents, grandparents, uncles and/or aunts before the age of 55 years.

### Table 6: Effect of lipid-lowering on CVD outcomes: summary of key evidence

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study details</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allerman et al (2006)</td>
<td>Good quality SR (8 RCTs). 12,249 participants with type 2 diabetes +/- CVD (78% were primary prevention)</td>
<td>Fibrates vs placebo</td>
<td>↓CHD events (RR 0.84, 95% CI 0.74–0.96). No effect on death due to CHD, MI or stroke. No difference between primary and secondary prevention trials.</td>
</tr>
<tr>
<td>Amarenco et al (2009)</td>
<td>Good quality SR (n=26 RCTs). 165,792 participants. Mix of primary and secondary prevention.</td>
<td>Statins vs placebo</td>
<td>Each 1.0 mmol/L decrease in LDL-C equates to a reduction in relative risk for stroke of 21.1% (96% CI 6.3–33.5, p=0.009).</td>
</tr>
<tr>
<td>Ara et al (2008)</td>
<td>Good quality SR (n=13 RCTs). No clinical outcome studies of &gt;12 weeks found so included studies using surrogate outcomes.</td>
<td>Ezetimibe alone or + statin vs statin alone, placebo or other</td>
<td>Ezetimibe monotherapy significantly ↓ LDL-C levels compared with placebo (p &lt; 0.00001). Ezetimibe and statin significant ↓LDL-C and TC compared with statin alone (p &lt; 0.00001).</td>
</tr>
<tr>
<td>Brugts et al (2009)</td>
<td>Good quality SR (n=10 RCTs). 70,388 participants. Inclusion of trials if &gt;80% without CVD or reported primary prevention data separately. Mean follow-up at least 1 yr.</td>
<td>Statins vs placebo control or usual care</td>
<td>↓all-cause mortality (OR 0.88, 95% CI 0.81–0.96), ↓major coronary events (OR 0.70, 95% CI 0.61–0.81), ↓major strokes (OR 0.81, 95% CI 0.71–0.93).</td>
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<tr>
<td>Cholesterol Treatment Trialists' Collaboration; Baigent et al (2010)</td>
<td>Moderate quality SR (n=21 RCTs of statins vs control). 129,526 subjects; 54% (70,025) without prior CVD.</td>
<td>Statins vs placebo</td>
<td>25% ↓in major vascular events in those without CVD at baseline per 1.0 mmol/L reduction in LDL cholesterol (1.4% vs 1.8% per year; RR 0.75, 95% CI 0.69–0.82).</td>
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<tr>
<td>Reference</td>
<td>Study details</td>
<td>Intervention</td>
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<tr>
<td>Corvol et al (2003)</td>
<td>Moderate quality SR (n=38 RCTs). 10 primary, 28 secondary prevention studies. 83,161 subjects, mean follow-up of 4.7 years</td>
<td>All lipid-lowering therapies</td>
<td>Lipid-lowering therapies ↓ overall stroke by approx. 17%, with the most convincing effects from statins (RRR 26%). ↓ 22% of MI. NNT overall stroke = 735, MI = 93. No difference between primary and secondary trials.</td>
</tr>
<tr>
<td>Delahoy et al (2009)</td>
<td>Good quality SR (n=25 RCTs; 8 identified as primary prevention and 2 mixed primary/secondary prevention). Total 155,613 subjects. Mean follow-up of at least 1 year.</td>
<td>Statins vs placebo</td>
<td>Meta regression analysis for every 25 mg/dL (0.65-mmol/L) reduction in LDL-C: ↓ vascular mortality (RR 0.89, 95% CI 0.87-0.92); ↓ major CV events (RR 0.86, 95% CI 0.84-0.88); ↓ major coronary events (RR 0.84, 95% CI 0.82-0.86); and ↓ stroke (RR 0.90, 95% CI 0.86-0.94). No difference between primary and secondary trials reported (no data given)</td>
</tr>
<tr>
<td>Henyan et al (2007)</td>
<td>Good quality SR (n=37 RCTs). Mixture of primary and secondary CVD prevention (focus on prevention of stroke). 100,560 participants, mostly white males with a history of hyperlipidemia.</td>
<td>Statins vs placebo</td>
<td>CV events (RR 0.83, 95% CI 0.76-0.91), ↓ ischaemic stroke (RR 0.79, 95% CI 0.63-0.99), no effect on haemorrhagic stroke (RR 1.11, 95% CI 0.77-1.60)</td>
</tr>
<tr>
<td>Jun et al (2010)</td>
<td>Good quality SR (n=18 RCTs) Primary (n=4), secondary (n=11) studies and 3 were mixed. 45,058 participants mean age 46–68 years, mean follow-up 2.7–8.8 yrs.</td>
<td>Fibrates vs placebo</td>
<td>Primary prevention only: coronary events (RR 0.75, 95% CI 0.58–0.97). Combined data: major CVD events (RR 0.90, 95% CI 0.82–1.00; p=0.048), ↓ CHD (RR 0.87, 95% CI 0.81–0.93), stroke (RR 1.03, 95% CI 0.91–1.16), CVD mortality (RR 0.97, 95% CI 0.88–1.07) or all-cause mortality (RR 1.00, 95% CI 0.93–1.08).</td>
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<tr>
<td>Mikhailidis et al</td>
<td>Good quality SR (n=5 RCTs). 5,039 adults with hypercholesterolaemia who have failed to reach goals on statin alone. Minimum treatment duration of 6 weeks. 3/5 trials included those with CHD.</td>
<td>Ezetimibe + statin vs placebo + statin +/- a fibrate</td>
<td>Ezetimibe co-administered with ongoing statin therapy provides significant additional lipid-lowering in patients not at LDL-C target on statin therapy alone, allowing more patients to reach their LDL-C target (RR 3.4, 95% CI 2.0-5.6; p &lt; 0.0001). Consistent results in those with and without CHD.</td>
</tr>
<tr>
<td>Navaneethan et al</td>
<td>Good quality SR (n=26 RCT and quasi RCTs). 25,017 CKD patients not requiring dialysis but +/- CVD.</td>
<td>Statins vs placebo</td>
<td>↓ all-cause mortality (RR 0.81, 95% CI 0.74-0.89) and CV mortality (RR 0.80, 95% CI 0.70-0.90). Statins decreased 24-hour urinary protein excretion but didn’t seem to change renal function (creatinine clearance). No difference in adverse effects.</td>
</tr>
<tr>
<td>O’Regan et al (2008)</td>
<td>Good quality SR (n=42 RCTs; 14 RCTs with no prior stroke or &lt;10% CHD); 24 RCTs with either all stroke or CHD. Others mixed populations. 121,000 participants.</td>
<td>Statins vs placebo or usual care</td>
<td>↓ all-cause mortality (RR 0.88, 95% CI 0.83–0.93), ↓ combined stroke (RR 0.84, 95% CI 0.79–0.91) – due to ↓ in ischaemic stroke without difference in haemorrhagic stroke or fatal stroke. ↓ CVD mortality (RR 0.81, 95% CI 0.74-0.90)</td>
</tr>
<tr>
<td>Ray et al (2010)</td>
<td>Good quality SR (n=11 RCTs) 65,229 participants without CVD. Mean follow-up ranged from 2.2-4.9 years</td>
<td>Statins vs placebo</td>
<td>Non-significant ↓ all-cause mortality (RR 0.91; 95% CI 0.83–1.01).</td>
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<tr>
<td>Reference</td>
<td>Study details</td>
<td>Intervention</td>
<td>Results</td>
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<tr>
<td>Robinson et al (2009)²¹⁸</td>
<td>Moderate quality SR (n=23 RCTs); 132,021 participants. Mixed primary and secondary prevention. 14 statin trials, 7 fibrate trials, 6 niacin trials, and 1 trial each of bile acid sequestrant, diet, and ileal bypass surgery.</td>
<td>All lipid-lowering therapies</td>
<td>The relationship between non-HDL-C lowering and CHD risk reduction is similar for statins and fibrates (only one fibrate trial). Most lipid-modifying drugs used as monotherapy appear to have an approx. 1:1 relationship between percent non–HDL-C lowering and CHD reduction.</td>
</tr>
<tr>
<td>Saha et al (2007)²²⁰</td>
<td>Good quality SR (n=10 RCTs) 36,489 participants; 2 trials completely primary prevention, and 2 others partly. Mean duration of follow-up ≥1 year</td>
<td>Fibrates vs placebo</td>
<td>No significant benefit on mortality, fatal MI, or stroke. ↓non-fatal MI (OR 0.78, 95% CI 0.71–0.86) in patients with non-LDL dyslipidaemia to a comparable extent with that seen with statins in patients with high LDL-C levels.</td>
</tr>
<tr>
<td>Studer et al (2005)²¹⁹</td>
<td>Good quality SR (n=97 RCTs) Follow-up of at least 6 months. For primary prevention only (&lt;10% CHD at baseline): 9 statin RCTs; 3 fibrate RCTs; 1 resin RCT; no niacin RCT; 1 small RCT of n-3 fatty acid; 5 diet RCTs.</td>
<td>All lipid-lowering therapies</td>
<td>Statins: ↓all cause mortality (RR 0.86, 95% CI 0.76-0.99) Fibrates: ↑all cause mortality (RR 1.25, 95% CI 1.05-1.48) Resins: no difference in all cause mortality n-3 fatty acids: no difference in all cause mortality Diet: no difference in all cause mortality</td>
</tr>
<tr>
<td>Taylor et al (2011)²³⁸</td>
<td>Good quality SR (n=14 RCTs), 34,272 participants. Trials of minimum duration of one year, &gt;6 months follow-up, &lt;10% pre-existing CVD.</td>
<td>Statins vs placebo</td>
<td>↓all-cause mortality (RR 0.83, 95% CI 0.73–0.95), ↓CVD events (RR 0.70, 95% CI 0.61–0.79), ↓combined fatal and non-fatal stroke (RR 0.78, 95% CI 0.65–0.94), ↓combined fatal and non-fatal CVD events (RR 0.72, 95% CI 0.65–0.79). No difference in harms.</td>
</tr>
<tr>
<td>Thavendiranathan et al (2006)²¹⁰</td>
<td>Good quality SR (n=7 RCTs), 42,848 participants; 90% had no history of CVD (inclusion of &gt;80% without CVD); Mean follow-up 4.3 years.</td>
<td>Statins vs placebo, active control, or usual care</td>
<td>↓major coronary (RR 0.71; 95% CI 0.60–0.83) and cerebrovascular events (RR 0.86; 95% CI 0.75–0.97), but not CHD disease mortality (RR 0.77; 95% CI 0.56–1.08) or overall mortality (RR 0.92; 95% CI 0.84–1.01).</td>
</tr>
<tr>
<td>Ward et al (2007)²¹¹</td>
<td>Good quality SR (n=31 RCTs) Adults with, or at risk of, CHD (2 RCTs specifically without CVD, multiple trials with or without CVD)</td>
<td>Statins vs placebo</td>
<td>Overall: ↓all-cause mortality (RR 0.84; 95% CI 0.78–0.90), ↓CHD mortality (RR 0.77; 95% CI 0.72–0.83) and ↓fatal MI (RR 0.55; 95% CI 0.45–0.67). Two exclusively primary prevention studies: ↓non-fatal MI (RR 0.60, 95% CI 0.37- 0.97) and ↓CHD death plus non-fatal MI (RR 0.66, 95% CI 0.46–0.96), but not all-cause mortality (RR 0.73, 95% CI 0.53–1.01) or CVD mortality (RR 0.67, 95% CI 0.40–1.10).</td>
</tr>
<tr>
<td>Zhou et al (2006)²³⁶</td>
<td>Good quality SR (n=8 RCTs; 4 pravastatin trials (25,572 participants), 2 simvastatin trials (24,980 participants), and 2 atorvastatin trials (13,143 participants), % of those with existing CVD not specified. Minimum follow-up of 1 year.</td>
<td>Statins vs placebo</td>
<td>Pravastatin, simvastatin, and atorvastatin, when used at their standard dosages, show no statistically significant difference in their effect on long-term cardiovascular prevention.</td>
</tr>
</tbody>
</table>

CHD: coronary heart disease; CI: confidence interval; LDL-C: low density lipoprotein cholesterol; MI: myocardial infarction; NA: not available; OR: odds ratio; RCTs: randomised control trials; RR: relative risk; RRR: relative risk reduction; SR: systematic review; TC: total cholesterol.
2.2.3 Antiplatelet therapy

Aspirin is of limited benefit when risks/benefits are considered

For people with established CVD the benefit to risk profile of long-term aspirin for reducing the risk of MI, stroke and vascular death is well established. However, the role of aspirin in primary prevention is less clear. This section summarises the evidence for antiplatelet agents from systematic reviews and individual trials considered for the primary prevention of cardiovascular events and does not consider other reported effects for aspirin such as cancer.

Evidence from three meta-analyses indicates that aspirin does not affect all-cause or CVD-related mortality, but does have a small benefit for the reduction of non-fatal vascular events (e.g., MI or stroke) – a benefit driven largely by a reduction in non-fatal MI among men. In the most recent meta-analysis by the Antiplatelet Trialists’ Collaboration, based on six primary prevention trials, aspirin (at doses of 75–100 g/day) reduced the relative risk of serious vascular events by approximately 12% (ARR 0.51% aspirin vs. 0.57% control per year, p=0.0001); a result driven largely by a 23% relative reduction in non-fatal MI (0.18% vs. 0.23% per year, p=0.0001). All-cause mortality and stroke incidence were not shown to be affected, and the reduction in non-fatal MI was statistically significant in men, but not in women. Conversely, for ischaemic stroke, the proportional risk reduction was greater in women than in men, although that result was not statistically significant. Aspirin increased the relative risk for gastrointestinal and extracranial bleeds by 54% (AR 0.10% vs 0.07% per year, p<0.0001).

These results concur with another good-quality meta-analysis where a review of the same six primary prevention trials involving 51,342 women and 44,114 men, showed that low-dose aspirin (50–500 mg daily) was associated with a 12% and 14% reduction in the relative risk of cardiovascular events (non-fatal MI, non-fatal stroke and cardiovascular mortality) in men and women, respectively, but with an approximate 70% increase in the risk of major bleeding events. For women, there was a significant reduction in the likelihood of stroke (mainly ischaemic stroke) whereas in men, no significant effect was observed on all strokes; however, a significant 32% reduction in the relative risk of MI was observed.

Based on the absolute benefits and risks observed in this analysis (absolute benefit: 0.30% and 0.37%; AR 0.25% and 0.33%, for women and men, respectively), aspirin therapy for an average of 6.4 years prevents approximately three cardiovascular events per 1,000 women and results in 2.5 major bleeding events. In 1,000 men treated for the same period, aspirin prevents four cardiovascular events and results in three major bleeding events. There was no evidence that higher doses of aspirin are more effective in reducing the risk of cardiovascular events. It is questionable whether the additional resources required to treat such a large number of people to prevent a small number of events is justified. In addition, any effect of aspirin on cardiovascular events needs to be balanced against the potential for harm.

In one subsequent study, the benefits of once-daily aspirin (100 mg) or placebo in 3,350 patients without clinical CVD, identified with a low ankle brachial index (ABI, ≤0.95) were assessed. After a mean follow-up of 8.2 ± 1.6 years, no statistically significant difference was found between groups for the primary endpoint of a composite of fatal or non-fatal coronary events or stroke or revascularisation (13.7 events per 1,000 person-years in the aspirin group vs 13.3 in the placebo group; hazard ratio, 1.03; 95% CI 0.84–1.27). Furthermore, the combined secondary endpoint (composite of the primary endpoint or angina, intermittent claudication or TIA) also failed to show statistical significance (22.8 events per 1,000 person-years in the aspirin group vs 22.9 in the placebo group; hazard ratio, 1.00; 95% CI 0.85–1.17). Although the study was underpowered to identify a potentially small beneficial effect of aspirin, given the large NNT to benefit as identified in the analysis above, questions remain of the usefulness of routine aspirin for preventing CVD.

Studies modelling the potential benefits and harms of aspirin on 5- and 10-year risk of CVD are conflicting. In the Antiplatelet Trialists’ Collaboration review, the proportional reduction did not differ significantly between individuals with predicted 5-year risk of CHD less than 2.5%, 2.5–5%, 5–10%, or 10% or more; although statistical analysis in the highest risk group was limited by small participant numbers. In that meta-analysis, the majority of people were not taking statin therapy. When the risk was assumed to be halved by other drugs first (e.g. statin and BP lowering), then the further absolute benefit of adding aspirin was found to be only half as large as was suggested by the trials, but the main bleeding hazards would remain. In that case, the benefits and hazards of adding long-term aspirin in people without pre-existing disease were found to be approximately equivalent.

Other modelling based on older meta-analysis data, found that a risk of CHD of ≥15% over 10 years was the point where benefit was greater than harm for people without existing CVD. Recently, another study modelling by risk category and age group found benefits were greater than harms in those with cardiovascular risk >15% up to the age
of 80 years; however, for men 70–79 years, consideration of lipid and blood pressure-lowering therapies was suggested first before reassessment of whether aspirin added additional net benefit. It is important to consider that there is significant overlap between the major risk factors for CVD events which might be prevented with aspirin and risk factors for bleeding with treatment. Given the various assumptions in all models and small absolute benefits but increased risk of harm with aspirin, a conservative approach to aspirin is suggested for prevention of CVD.

### Table 7: Effect of aspirin on CVD outcomes: summary of key evidence

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study details</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithrombotic Trialists’ (ATT) Collaboration; Baigent et al (2009)</td>
<td>Good quality SR (n=22 RCTs). Included six primary prevention trials, 95,456 participants.</td>
<td>Aspirin vs placebo</td>
<td>12% ↓CV events (0.51% aspirin vs. 0.57% control per year, p=0.0001), ↓non-fatal MI (0.18% vs. 0.23% per year, p&lt;0.0001), no effect on vascular mortality (0.19% vs 0.19% per year, p=0.7). Risk of CV events in those with diabetes (RR 0.88, 95% CI 0.67–1.15). ↑major GI and extracranial bleeds (0.10% vs. 0.07% per year, p&lt;0.0001). No difference in those at low, moderate and high risk.</td>
</tr>
<tr>
<td>Berger et al (2006)</td>
<td>Good quality SR (n=6 RCTs –same as above). 51,342 women and 44,114 men.</td>
<td>Aspirin vs placebo</td>
<td>CV events (OR 0.88, 95% CI, 0.79 to 0.99). No effect on MI or CV mortality. In men, 32% ↓MI (OR 0.68, 95% CI 0.54–0.86). In women, 24% ↓ischaemic stroke (OR 0.76; 95% CI 0.63–0.93). Aspirin ↑risk of bleeding in both men and women.</td>
</tr>
<tr>
<td>Calvin et al (2009)</td>
<td>Good quality SR (n=8 RCTs). 89,392 participants without CVD; 11,634 with diabetes.</td>
<td>Aspirin vs placebo</td>
<td>Overall mortality (OR 0.93, 95% CI 0.85–1.03), MI (OR 0.79, 95% CI 0.66–0.95), and ischaemic stroke (OR 0.73, 95% CI 0.43–1.22). For those with diabetes: MI (RR 0.86, 95% CI 0.67–1.11), ischaemic stroke (RR 0.62, 95% CI 0.31–1.24).</td>
</tr>
<tr>
<td>De Berardis et al (2009)</td>
<td>Good quality SR (n=6 RCTs). 10,117 diabetic participants without CVD.</td>
<td>Aspirin vs placebo</td>
<td>Major CV events (RR 0.90, 95% CI 0.81–1.00), CV mortality (RR 0.94, 95% CI 0.72–1.23), all-cause mortality (RR 0.93, 95% CI 0.82–1.05), MI (RR 0.86, 95% CI 0.61–1.21), stroke (RR 0.83, 95% CI 0.60–1.14). ↓risk of MI in men (RR 0.57, 95% CI 0.34–0.94). No effect for ↓stroke for men or women.</td>
</tr>
<tr>
<td>Pignone et al (2010)</td>
<td>Moderate quality SR (n=9 RCTs). 11,787 diabetic participants without CVD.</td>
<td>Aspirin vs placebo</td>
<td>CHD events (RR 0.91, 95% CI 0.79 –1.05), Strokes (RR 0.85, 95% CI 0.66 –1.11).</td>
</tr>
<tr>
<td>Zhang et al (2010)</td>
<td>Moderate quality SR (n=7 RCTs). 11,618 diabetic participants without CVD.</td>
<td>Aspirin vs placebo</td>
<td>Major CV events (RR 0.92, 95% CI 0.83–1.02), all-cause mortality (RR 0.95, 95% CI 0.85–1.06), CV mortality (RR 0.95, 95% CI 0.71–1.27), stroke (RR 0.83, 95% CI 0.63–1.10), MI (RR 0.85, 95% CI 0.65–1.11). Trend to ↑major bleeding risk (RR 2.46, 95% CI 0.70–8.61).</td>
</tr>
</tbody>
</table>

CI: confidence interval; CV: cardiovascular; CVD: cardiovascular disease; GI: gastrointestinal; MI: myocardial infarction; OR: odds ratio; RCTs: randomised controlled trials; RR: relative risk; SR: systematic review.
People with diabetes

Four systematic reviews and one clinical guideline were identified with data on aspirin for primary prevention of CVD among diabetic individuals. These reviews consistently report that aspirin therapy is associated with a statistically non-significant 8–12% reduction in risk of major cardiovascular events in people with diabetes. When individual endpoints are considered in people with diabetes, sex-specific trends have also been reported: that is, reduced risk of MI in men and reduced risk of stroke in women. As the effects in people with diabetes are smaller than those for the general population, a conservative approach to use of aspirin therapy is suggested for prevention of CVD.

People with atrial fibrillation

The increased risk of stroke in people with non-valvular AF is well recognised and scoring systems (e.g. CHADS2) are recommended to determine risk levels and need for pharmacotherapy. Three robust systematic reviews and three notable randomised controlled trials have investigated the benefits of antplatelet or anticoagulant therapy in primary prevention populations. Two separate reviews report consistent reductions in the combination of stroke, MI or vascular death (OR 0.71, 95% CI 0.51–0.97) with aspirin (75–125 mg daily or 125 mg every second day) and clear benefits of warfarin for preventing stroke (OR 0.39, 95% CI 0.26–0.59), all cause mortality (OR 0.69, 95% CI 0.50–0.94) and the combined endpoint of all stroke, MI or vascular death (OR 0.56, 95% CI 0.42–0.76). A third systematic review assessed the relative effect of long-term oral anticoagulant treatment compared with antplatelet therapy on major vascular events in eight trials involving 9,598 individuals. Overall, warfarin and related oral anticoagulants reduced stroke, disabling stroke and other major vascular events by about one-third and are clearly recommended compared with antplatelet therapy.

However, anticoagulation therapy may be unsuitable for a small percentage of individuals with AF. In a trial, 7,554 patients with AF in whom warfarin therapy was unsuitable were assigned clopidogrel (75 mg/day) plus aspirin (75–100 mg/day) or aspirin alone. The primary outcome was the composite of stroke, MI, non-central nervous system systemic embolism or death from vascular causes. At a median of 3.6 years of follow-up, the incidence of major vascular events was 6.8% and 7.6% per year for clopidogrel plus aspirin and aspirin alone, respectively (RR 0.89, 95% CI 0.81 - 0.98; p=0.01). The difference was primarily due to a reduction in the rate of stroke with clopidogrel. However, the benefits were offset by an increased incidence of major bleeding (2.0% per year for people receiving dual antplatelet therapy and 1.3% per year for individuals receiving aspirin alone, RR 1.57, 95% CI 1.29–1.92; p=0.001). It is unclear from this study what percentage were individuals without established CVD. Another recent trial randomised 5,599 patients with AF, in whom warfarin therapy was deemed unsuitable, to receive apixaban, a novel factor Xa inhibitor (at a dose of 5 mg twice daily) or aspirin (81–324 mg/day). The trial was terminated early for safety concerns with apixaban found to significantly reduce the risk of stroke or systemic embolism (HR 0.45, 95% CI 0.32–0.62; P<0.001) and non-significantly reduce mortality per year (HR 0.79, 95% CI 0.62–1.02; P=0.07). No difference in adverse events was found.

Readers are referred to an Australian evidence summary and international guidelines for a discussion of the general evidence related to AF management.

Dual antplatelet therapy is not appropriate for primary prevention

Only one high-quality randomised controlled trial has examined the efficacy and safety of dual antplatelet therapy with clopidogrel and aspirin vs aspirin alone in a primary prevention population. In the Clopidogrel for High Atherothrombotic Risk and Ischaemic Stabilization, Management, and Avoidance (CHARISMA) trial, approximately 2,289 of the 15,603 participants were free of existing CVD at baseline. Individuals were randomly assigned to receive clopidogrel (75 mg/day) plus low-dose aspirin (75–162 mg/day) or placebo plus low-dose aspirin and followed for a median of 28 months. The primary efficacy endpoint was a composite of MI, stroke or death from cardiovascular causes. In the primary prevention cohort, the rate of cardiovascular death for single vs dual-antplatelet therapy was 1.8% and 3.0%, respectively (p=0.07). Furthermore, multivariate analysis of the primary prevention group showed a trend towards excess cardiovascular death (HR 1.72, 95% CI 0.99–2.97; p=0.054) with dual-antplatelet therapy. Results from the CHARISMA trial suggest that a dual antplatelet strategy with clopidogrel and aspirin should not be used for primary prevention.
2.2.4 Pharmacological approaches to simultaneously lower blood pressure and lipids

There is robust evidence to support the efficacy of using medication to reduce both BP and cholesterol to reduce CVD risk. Several studies have evaluated the co-administration of amlodipine and atorvastatin, and found the same or improved effectiveness from simultaneously administering both drugs, compared with a single drug regimen. In the AVALON trial, co-administration of amlodipine and atorvastatin was compared with single drug therapy, and placebo in 847 patients. At week 8, 45% of the people receiving amlodipine 5 mg once daily and atorvastatin 10 mg once daily reached both their BP and LDL-C targets, compared with 8.3% with amlodipine (p<0.001), 28.6% with atorvastatin (p<0.001) and 3.5% with placebo. At 28 weeks, 67.1% of people co-administered amlodipine and atorvastatin (mean doses, 7.6 mg and 28.4 mg, respectively) achieved both targets. Furthermore, the Framingham estimated 10-year risk of CHD in that group declined from baseline levels of 15.1% to 6.9% at week 28.

Similar results were observed in the ASCOT-LLA and the RESPOND study. In the ASCOTT-LLA study, people with baseline hypertension and TC ≥6.5 mmol/L, received atorvastatin (10 mg once daily) in addition to their antihypertensive routine for a mean duration of 3.3 years. This combined treatment led to a 36% reduction in the relative risk of non-fatal MI and fatal CHD, compared with the group receiving placebo plus antihypertensive therapy. In the RESPOND study, the use of amlodipine and atorvastatin together did not differ from the efficacy achieved with each medication alone. However, the estimated 10-year Framingham risk with combination therapy declined from baseline values of 15.8–18.0% to 7.3–10.7%.

Comparative and non-comparative studies investigating the efficacy of single pill combination therapy with amlodipine and atorvastatin in people with elevated BP and lipids at baseline have, in general, demonstrated similar results. The proportion of people achieving both improved BP and LDL-C levels in those trials ranged from 48.3% to 57.7% and 10-year Framingham risk scores were reduced by up to 52%.

2.3 Initiation and maintenance of pharmacotherapy

2.3.1 Blood pressure-lowering therapy

Blood pressure-lowering therapy should be determined by individual needs and aimed towards optimal blood pressure levels.

The relationship between BP and CVD risk is continuous, and guidelines have recommended reduced BP targets over recent years as evidence of benefit and safety have accumulated. While there has been general consensus that the most important clinical implication is to achieve the correct total dosage to achieve appropriate BP control, new data from several systematic reviews has reopened the issue as to whether lowering BP as far as possible – a ‘lower the pressure the better’ approach – is of any greater value than lowering it to below standard BP targets (i.e. 140/90 mmHg). The Blood Pressure-lowering Treatment Trialists’ Collaboration found that BP lowering reduced major cardiovascular events. The magnitude of this effect could be attributed to the degree of BP lowering. More recently, a Cochrane review was conducted to determine if lower BP targets (≤135/85 mmHg) are associated with a reduction in mortality and morbidity as compared with standard BP targets (≤140–160/90–100 mmHg). No trials comparing different SBP targets were found; however, seven trials comparing different DBPs were identified involving 22,089 adults. Despite a -4/-3 mmHg greater achieved reduction in SBP/DBP (p<0.001), attempting to achieve ‘lower targets’ instead of ‘standard targets’ had no significant effect on total mortality (RR 0.92, 95% CI 0.86–1.15), MI (RR 0.90, 95% CI 0.74–1.09), stroke (RR 0.99, 95% CI 0.79–1.25), congestive heart failure (RR 0.88, 95% CI 0.59-1.32), major cardiovascular events (RR 0.94, 95% CI 0.83–1.07) or end-stage renal disease (RR 1.01, 95% CI 0.81–1.27).

These results coincide with other systematic reviews that have confirmed a proportional relationship between BP levels and cardiovascular events. A meta-analysis of 30 trials and more than 149,000 people demonstrated that the relationship between the odds ratio for fatal and non-fatal cardiovascular outcomes and the corresponding within-trial differences in SBP is curvilinear, and when these outcomes were combined, there was no further benefit if the within-trial differences in SBP exceeded ~15 mmHg. In another systematic review, the incidence of major cardiovascular events in BP-lowering trials was...
calculated after classifying each trial into four categories according to people's baseline cardiovascular risk: low risk, elderly, diabetic and high risk. Of note, low rates of major cardiovascular events (3–6% in five years) were only achieved in trials enrolling low risk people. In contrast, the incidence of major cardiovascular events in trials enrolling elderly hypertensive people, hypertensive people with diabetes or people with previous CVD or events was rarely reduced to below 12–14% in five years. People enrolled in these trials remained at high risk despite aggressive BP reduction and extensive use of concomitant medications, suggesting that pre-existing high risk sets a ceiling effect to the benefits of treatment.

Current evidence indicates that more intensive BP lowering produces greater reductions in cardiovascular events and all-cause mortality. Although treatment targets are generally recognised and can be used to monitor treatment effects, the extra effort required to achieve lower levels of BP should be assessed against the benefits and risks to the individual patient.

<table>
<thead>
<tr>
<th>Evidence-based recommendation</th>
<th>Grade</th>
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<tbody>
<tr>
<td><strong>Pharmacotherapy</strong></td>
<td></td>
</tr>
<tr>
<td><strong>EBR 9:</strong> Aspirin or other antiplatelet therapy is not routinely recommended for primary prevention of CVD.</td>
<td>B234, 237, 238, 242, 243</td>
</tr>
<tr>
<td><strong>For adults at high risk of CVD</strong></td>
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<tr>
<td><strong>EBR 10:</strong> Adults at high absolute risk of CVD should be simultaneously treated with lipid and blood pressure-lowering pharmacotherapy in addition to lifestyle advice unless contraindicated or clinically inappropriate.</td>
<td>B192, 195, 204, 206, 207</td>
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<thead>
<tr>
<th>Consensus-based recommendations</th>
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<tr>
<td><strong>For adults at moderate risk of CVD</strong></td>
<td></td>
</tr>
<tr>
<td><strong>CBR 3:</strong> Adults at moderate absolute risk of CVD should have their risk factors initially managed by lifestyle interventions. Pharmacotherapy for blood pressure and/or lipid lowering is not routinely recommended but may be considered if 3–6 months of lifestyle intervention does not reduce the individual's risk factors.</td>
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<tr>
<td><strong>CBR 4:</strong> Adults at moderate absolute risk of CVD may be treated with pharmacotherapy for blood pressure and/or lipid lowering in addition to lifestyle intervention if one or more of the following applies:</td>
<td></td>
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<tr>
<td>• Persistent blood pressure ≥160/100 mmHg</td>
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<tr>
<td>• Family history of premature CVD</td>
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<tr>
<td>• Aboriginal and Torres Strait Islander peoples</td>
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<tr>
<td>• Other populations where FRE is known to underestimate risk (South Asians, Maori and Pacific Islanders, people from the Middle East).</td>
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<th><strong>For adults at low risk of CVD</strong></th>
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<tbody>
<tr>
<td><strong>CBR 5:</strong> Pharmacotherapy for blood pressure and lipid lowering is not routinely recommended for adults at low absolute risk of CVD.</td>
<td></td>
</tr>
<tr>
<td><strong>CBR 6:</strong> Adults at low absolute risk of CVD who have persistent blood pressure ≥160/100 mmHg may be treated with blood pressure-lowering pharmacotherapy in addition to lifestyle intervention.</td>
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</table>
People with diabetes

BP lowering reduces cardiovascular events and all-cause mortality in people with type 2 diabetes to a similar or even greater extent than for the general population. However, the target levels for BP therapy have been based on little direct evidence.

Two major recent randomised controlled trials are of particular interest in informing target BP levels for those with diabetes. The ADVANCE trial randomised 11,140 participants with type 2 diabetes to either perindopril-indapamide versus placebo (double-blind comparison) and intensive glucose control with a glitazone MR-based regimen (target A1C ≤6.5%) versus standard glucose control (open comparison). During an average follow-up period of 4.3 years, the risks of major macrovascular and microvascular events were considered jointly and separately, in addition to renal events and death. Those treated to lower SBP (achieved mean updated SBP during the study 134.7 mmHg) were found to have reduced all-cause and CVD mortality (OR 0.86, 95% CI 0.75–0.98; and OR 0.81, 95% CI 0.68–0.98, respectively) but surprisingly had no effect on stroke (OR 0.99, 95% CI 0.81–1.19). Compared with neither intervention, combination treatment with BP lowering and intensive glucose control reduced the risk of all-cause mortality by 18% (95% CI 1–32%, p=0.04), reduced new or worsening nephropathy by 33% (95% CI 12–50%, p=0.005), reduced new onset of microalbuminuria by 54% (95% CI 35–68%, p<0.0001) and reduced new onset of microalbuminuria by 26% (95% CI 17–34%).

The ACCORD investigators tested the effect of a target SBP <120 mmHg on a composite outcome of non-fatal MI, non-fatal stroke or death from cardiovascular causes. In that trial, 4,733 participants were randomly assigned to lower their BP by receiving either intensive therapy (SBP target <120 mmHg) or standard therapy (SBP target <140 mmHg). The mean follow-up period was 4.7 years and 34% of participants had existing CVD. After one year, the mean SBP was 119.3 mmHg and 133.5 mmHg in the intensive therapy and standard therapy groups, respectively and this difference was maintained throughout the study. The annual rate of the primary outcome was similar between groups: 1.87% in the intensive-therapy group and 2.09% in the standard-therapy group (HR 0.88, 95% CI 0.73–1.06; p=0.20). However, the incidence of serious adverse events, including deterioration in renal function, was significantly higher in participants randomised to the intensive-therapy group (3.3% vs 1.3%, p<0.001). Of interest, however, was the annual incidence of stroke, a pre-specified secondary outcome: 0.32% and 0.53% in the intensive therapy and standard therapy groups, respectively (HR 0.59, 95% CI 0.39–0.89; p=0.01).

During finalisation of these guidelines, two meta-analyses were published that updated previous meta-analyses with important trials such as those discussed above. One meta-analysis included 13 trials (mixed primary and secondary prevention) and found that intensive BP control (achieving SBP ≤135 mmHg) was associated with a reduction in all-cause mortality (OR 0.90, 95% CI 0.83–0.98 and a reduction in stroke (OR 0.83, 95% CI 0.83–0.98), but with an increase in serious adverse effects (OR 1.2, 95% CI 1.08–1.32). There were similar outcomes for other macrovascular and microvascular (cardiac, renal and retinal) events compared with standard BP control (SBP ≤140 mmHg). More intensive BP control (SBP ≤130 mmHg) was associated with further reduction in stroke only and there was a 40% increase in serious adverse events compared to standard BP control (95% CI 1.19–1.64; P=0.01), but significant heterogeneity was noted.

The other meta-analysis included 31 trials (mixed primary and secondary prevention) and reported intensive therapy (mean SBP 129 mmHg vs SBP 139 mmHg) significantly reduced the risk of stroke (RR 0.61, 95% CI 0.48–0.79; based on five trials) but not MI (OR 0.87, 95% CI 0.74–1.02; based on six trials). The effects were found to occur with reductions in SBP or DBP with meta-regression analysis noting the risk of stroke decreased by 13% (95% CI 5–20%) for each 5 mmHg reduction in SBP and by 11.5% (95% CI 5–17%) for each 2 mmHg reduction in DBP.

In general, people with diabetes appear to benefit from modestly more aggressive thresholds for treatment than the general population with targets towards SBP 130 mmHg and DBP 80 mmHg. However, based on the ACCORD and ADVANCE study results and the newer meta-analyses, this target is currently being reconsidered by a number of organisations world-wide and the SBP may be adjusted upwards. Until such deliberations are complete, the general international BP target for people with diabetes remains ≤130/80 mmHg.

People with CKD

Recent evidence considered during the finalisation of these guidelines suggests that treating people with CKD to lower BP targets than the general population does not improve clinical outcomes. New targets are currently being considered internationally and may be adjusted upwards. The EWG, after detailed consultation locally and internationally, has adjusted the recommended targets for Australia based on the recent evidence. Target BP for
people with CKD is now ≤140/90 mmHg and for people with micro or macroalbuminuria (UACR >2.5 mg/mmol in men and >3.5 mg/mmol in women) the target is now 130/80 mmHg. Available evidence suggests that treatment using agents that lower BP reduces CVD morbidity and mortality for people on maintenance dialysis; however, specialist advice and management of BP is usually required for people on dialysis.

**Initiation of blood pressure-lowering treatment**

There is now a large body of evidence on BP-lowering therapies, both those comparing active treatment versus placebo and those comparing different treatment regimens. Results from nine systematic reviews of BP-lowering drugs in the prevention of cardiovascular events confirm that:

a) The main benefits of BP-lowering therapies are due to the reduction of BP and are largely independent of the drugs employed;

b) Thiazide diuretics, calcium channel blockers (CCB), angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs) have similar BP-lowering outcomes and significantly reduce cardiovascular morbidity and mortality;

c) There is no interaction between age and effect of treatment on cardiovascular events for any BP-lowering treatment compared with control.

Apart from beta-blockers, in primary prevention, no one class of agent appears to offer a major advantage over another. However, there are exceptions in certain situations. In terms of medication adherence and/or persistence, two systematic reviews assessed the results of trials involving ARBs, ACE inhibitors, CCBs, beta-blockers and diuretics. In one meta-analysis of eight trials, ARBs provided a non-significant BP reduction compared with ACE inhibitors (net difference 1.8/1.0 mmHg). However, compliance at 12 months with ARBs was consistently higher (42–64%) than that observed for other therapeutic classes. This is similar to the other systematic review of 17 trials, which found adherence lowest for diuretics and beta-blockers, and highest in ARBs and then ACE inhibitors.

With regard to individual endpoints (e.g. stroke, MI, heart failure) the literature does suggest differences between various BP-lowering therapies. Beta-blockers have been found to be less effective in reducing the risk of stroke, while CCBs may have a slightly superior effect on stroke prevention. In contrast, the benefit of CCBs does not appear to extend equally to the prevention of heart failure. In one large meta-analysis, therapies other than CCBs (with the exception of non-cardioselective beta-blockers) reduced the incidence of heart failure by 24% (19–28%). CCBs reduced the incidence of heart failure by 19% (6–31%).

The first class of drugs to use for management of elevated BP has always been a matter of debate. Low-dose thiazide diuretics have been recommended based on results obtained in a systematic review of 24 trials and more than 58,000 participants. In that review, the reduction in morbidity and mortality was similar between low-dose thiazides, ACE inhibitors and CCBs; however, the authors note that the data for thiazide diuretics is more robust than that available for the latter therapeutic classes. In contrast, first-line therapy with high-dose thiazide diuretics or beta-blockers is inferior to first-line therapy with low-dose thiazides and, in some reports, the use of high-dose (four times standard) thiazides has increased the risk of sudden cardiac death.

The extent of BP reductions is similar at standard doses for the five therapeutic categories of blood pressure-lowering agents: average reduction was 9.1 mmHg systolic and 5 mmHg diastolic. However, in practice, more than one drug is often required to lower BP to optimal levels and, in these situations, the effect of combinations of two or more drugs on BP is additive. Furthermore, the adverse effect profiles of drugs can be minimised by using half-standard or standard doses, rather than titrating any given drug to higher doses. The exceptions are ACE inhibitors and ARBs, where the adverse effects are either present or absent. In a large meta-analysis, one drug at standard dose reduced the incidence of CHD by about 24% and stroke by 35% in 60–69 year olds with a DBP of 90 mmHg. Three drugs at half standard doses approximately doubled this effect, reducing CHD by 45% and stroke by 60%. At higher BPs (e.g. 180/105 mmHg) and lower BPs (e.g. 120/75 mmHg), the effect of one drug at standard dose is about 7% and 9% greater and smaller, respectively. Three drugs at half standard dose is about 12% and 14% greater and smaller.

In summary, thiazide diuretics, CCBs, ACE inhibitors and ARBs are all suitable for initiation of BP-lowering therapy. In addition, they can all be used for maintenance of BP-lowering therapy, either as monotherapy or in combination. Beta-blockers appear to offer less clinical efficacy in terms of CVD prevention.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study details</th>
<th>Intervention</th>
<th>Results</th>
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<tbody>
<tr>
<td>Arguedas et al (2009)[270]</td>
<td>Good quality SR (n=7 RCTs). 22,089 subjects comparing different DBP targets.</td>
<td>All BP-lowering medications with lower or vs standard BP targets.</td>
<td>No difference between standard targets (≤140/90) and lower targets (≤135/85). Mortality (RR 0.92, 95% CI 0.86-1.15), MI (RR 0.90, 95% CI 0.74-1.09), stroke (RR 0.99, 95% CI 0.79-1.25), CHF (RR 0.88, 95% CI 0.59-1.32), major CV events (RR 0.94, 95% CI 0.83-1.07), or end-stage renal disease (RR 1.01, 95% CI 0.81-1.27). No difference for diabetes and CKD.</td>
</tr>
<tr>
<td>Bangalore et al (2011)[275]</td>
<td>Good quality SR (n=13 RCTs) 37,736 participants with type 2 diabetes or pre diabetes.</td>
<td>All BP-lowering medications vs placebo or less intensive control.</td>
<td>Intensive BP control had 10% ↓ all-cause mortality, 17% ↓ stroke, and a 20% ↑ in serious adverse effects with similar outcomes for other macrovascular and microvascular events. For targets &lt;130 mm Hg SBP, 40% ↑ in serious adverse events (heterogeneity noted) without other benefits. Meta-regression analysis found only ↓ stroke with ↓ BP.</td>
</tr>
<tr>
<td>BP Lowering Treatment Trialists’ Collaboration; Turnbull et al (2003)[272]</td>
<td>Good quality SR (n=29 RCTs). 162,341 participants. Most trials selected people on basis of existing CVD or risk factors.</td>
<td>All BP-lowering medications vs placebo or less intensive control.</td>
<td>Regimens targeting lower BP goals ↓ stroke and CV events without any convincing evidence of j-curve relationship.</td>
</tr>
<tr>
<td>Law et al (2009)[192]</td>
<td>Good quality SR (n=147 RCTs; 464,000 participants). 26 RCTs specifically with no history of CVD.</td>
<td>All BP lowering medications vs placebo or other class of drug.</td>
<td>For a reduction of 10mmHg SBP or 5mmHg DBP: ↓CHD events (RR 0.79, 95% CI 0.72-0.86), ↓ stroke (RR 0.54, 95% CI 0.45-0.65). No significant trend in proportional disease reduction with lower pre-treatment blood pressure, indicating a constant proportional effect (although too few data &lt;110/70 mmHg).</td>
</tr>
<tr>
<td>Reboldi et al (2011)[276]</td>
<td>Good quality SR (n=31 RCTs). 73,913 participants with diabetes.</td>
<td>All BP-lowering medications with lower or vs standard BP targets.</td>
<td>Overall, treatment ↓ stroke by 9% (P=0.0059), and MI by 11% (P=0.0015). Allocation to more-tight, compared with less tight, BP control ↓ stroke by 31% (RR 0.61, 95% CI 0.48-0.79) but not risk of MI (OR 0.87, 95% CI 0.74-1.02). Meta-regression found clear link between ↓BP and stroke but not MI.</td>
</tr>
<tr>
<td>Upadhyay et al (2011)[277]</td>
<td>Good quality SR (n=3 RCTs). 2,272 adults with non-dialysis-dependent CKD but excluded type 1 diabetes and had few with type 2 diabetes.</td>
<td>All BP-lowering medications with lower or vs standard BP targets.</td>
<td>Included trials failed to demonstrate improved outcomes for lower BP targets. Lower-quality evidence suggests that a low target may be beneficial in subgroups with proteinuria greater than 300 to 1000 mg/d. Participants with lower targets required more BP medications and had a slightly higher rate of adverse events.</td>
</tr>
</tbody>
</table>

BP: blood pressure; CI: confidence interval; CHF: chronic heart failure; CKDL: chronic kidney disease; CV: cardiovascular; CVD: cardiovascular disease; DBP: diastolic blood pressure; MI: myocardial infarction; RCTs: randomised controlled trials; RR: relative risk; SBP: systolic blood pressure; SR: systematic review.
## Table 9: Blood pressure-lowering therapy: summary of key evidence

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study details</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP Lowering Treatment Trialists’ Collaboration; Turnbull et al (2008)</td>
<td>Good quality SR (n=31 RCTs; 190,606 participants). Compared age groups &lt;65 and above 65. Mixed primary and secondary prevention.</td>
<td>All BP-lowering medications vs placebo or less intensive control.</td>
<td>No difference in reductions in major CV events between age groups for any comparison. No difference between the effects of any class of drug on risk of CV events.</td>
</tr>
<tr>
<td>Bramlage et al (2009)</td>
<td>Fair quality SR (n=8 cohort studies) Mixed primary and secondary prevention</td>
<td>All BP lowering medications.</td>
<td>Persistence was higher with ARBs than any other therapeutic class.</td>
</tr>
<tr>
<td>Kronish et al (2011)</td>
<td>Good quality SR (n=17 cohort studies). Mixed primary and secondary prevention.</td>
<td>All BP lowering medications.</td>
<td>ARBs had the highest adherence followed by ACEi, CCBs, diuretics and BBs. After consideration of publication bias there was no difference between ARBs and ACEi (HR 1.10, 95% CI 0.94-1.30) or diuretics and BBs (HR 1.13, 95% CI 0.89-1.44). The pooled mean adherence ranged from 28% for BBs to 65% for ARBs.</td>
</tr>
<tr>
<td>Law et al (2009)</td>
<td>Good quality SR (n=147 RCTs; 464,000 participants). 26 RCTs specifically with no history of CVD.</td>
<td>All BP lowering medications vs placebo or no treatment.</td>
<td>Effect is similar for all classes of blood pressure-lowering drugs for CHD although CCBs were slightly more effective for stroke prevention and BBs slightly less effective. CCBs ↓HF by 19% whereas for other classes ↓24%. One drug at standard dose reduces CHD and stroke by approximately 24% and 35%, respectively in 60–69 year olds with SBP of 90 mmHg. Three drugs modelled at half standard doses approximately double this effect.</td>
</tr>
<tr>
<td>Musini et al (2009)</td>
<td>Good quality SR (n=9 RCTs). 460 patients with primary hypertension defined as BP &gt;140/90 mmHg at baseline.</td>
<td>Loop diuretics vs placebo.</td>
<td>The BP-lowering effects of loop diuretics is modest (approx. 8/4 mmHg) and whether the effects are greater or lower than other classes of BP-lowering agents is difficult to say.</td>
</tr>
<tr>
<td>Webb et al (2010)</td>
<td>Good quality SR (n=389 RCTs). Mixed primary and secondary prevention.</td>
<td>All BP lowering medications vs placebo or no treatment.</td>
<td>Compared with other drug classes, CCBs and non-loop diuretic drugs reduced interindividual variation in SBP whereas ACEi, ARBs, and BBs increased it. CCB was most effective vs placebo. Interindividual variation in SBP accounted for the effects on risk of stroke independently of differences in mean SBP.</td>
</tr>
<tr>
<td>Wright et al (2009)</td>
<td>Good quality SR (n=24 RCTs; 28 arms). 58,040 people, 42,196 (72.7%) were primary prevention. Included trials had &gt;70% of people with BP &gt;140/90 mmHg at baseline and were for &gt; 1 year duration.</td>
<td>All BP lowering medications vs placebo or other class of drug.</td>
<td>Low-dose thiazides ↓mortality (RR 0.89, 95% CI 0.83-0.96) and ↓CV events (RR 0.70, 95% CI 0.64-0.76). BBs ↓CV events (RR 0.89, 95% CI 0.80-0.98) but not CHD or mortality. ACEi ↓mortality (RR 0.83, 95% CI 0.72-0.95) and CV events (RR 0.76, 95% CI 0.67-0.85). CCBs ↓CV events (RR 0.71, 95% CI 0.57 to 0.87) but not CHD or mortality. Overall there are more trials of low-dose thiazides but CCBs and ACEi have similar effect and BBs are less effective.</td>
</tr>
</tbody>
</table>

## Evidence-based recommendations

### Blood pressure-lowering therapy

**EBR 11:** Treatment should begin with any one of the following agents:

- ACE inhibitor
- Angiotensin receptor blocker
- Calcium channel blocker
- Low-dose thiazide or thiazide-like diuretic

**EBR 12:** If monotherapy does not sufficiently reduce blood pressure add a second agent from a different pharmacological class.

<table>
<thead>
<tr>
<th>Grade</th>
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<tr>
<td>A&lt;sup&gt;102, 109&lt;/sup&gt;</td>
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</table>

## Practice points

### Blood pressure-lowering therapy

**PP 13:** If blood pressure is not responding to pharmacotherapy, reassess for:

- non-adherence
- undiagnosed secondary causes of raised blood pressure
- hypertensive effects of other drugs
- treatment resistance due to sleep apnoea
- undisclosed use of alcohol or recreational drugs
- unrecognized high salt intake (particularly in patients taking ACE inhibitors or angiotensin receptor blockers)
- ‘white coat’ raised blood pressure
- technical factors affecting measurement
- volume overload, especially with CKD

**PP 14:** If dual therapy at higher doses does not sufficiently reduce blood pressure, add an additional agent.

**PP 15:** If combination therapy does not sufficiently reduce blood pressure, consider specialist advice.

**PP 16:** Treatable secondary causes for raised blood pressure should be considered before commencing blood pressure drug therapy.

**PP 17:** The following combinations should generally be avoided:

- potassium-sparing diuretic plus either ACE inhibitor or angiotensin receptor blocker
- beta-blocker plus verapamil
2.3.2 Lipid-lowering therapy

Lipid-lowering therapy should be determined by individual needs and should aim towards optimal lipid levels

Evidence from several systematic reviews and meta-analyses suggests that more intensive lipid modification produces greater reductions in cardiovascular events. In a meta-analysis of 26 randomised trials (mixed populations) of statins, each 1.0 mmol/L decrease in LDL-C equated to a 25% reduction in major vascular events in people without previous CVD (RR 0.75, 95% CI 0.69–0.82) and a 0.4% lower risk difference per year. However, there are no clinical trials that have evaluated the relative and absolute benefits of cholesterol lowering to different TC and LDL-C targets in relation to clinical events. Establishing a cholesterol target for therapy is therefore an extrapolation from the apparent benefits indicated by major trials of lipid lowering, while maintaining appropriate margins for safety, given that there are still no long-term follow up studies of statin therapy.

The recommendations in these guidelines also refer to levels of non-HDL-C and triglycerides. Non-HDL-C refers to the cholesterol in LDL, intermediate density lipoprotein and very low-density lipoproteins and is calculated by subtracting HDL-C from TC. Unlike LDL-C, the calculation of non-HDL-C does not require triglycerides to be less than 4.5 mmol/L. This makes it particularly useful for people with high triglycerides. Triglyceride levels are also important. Hypertriglyceridaemia is associated with the development of early onset CVD and significantly increases the risk of acute pancreatitis.

The evidence for fixed-dose or individual titration of statin therapy is limited. One large meta-analysis performed a pre-determined assessment on the effects of statin dose based on secondary prevention studies. Intuitively, one would expect that as the dose of a drug is increased, a greater amount of benefit is attained. However, with statin therapy, this was not the case above a certain dose. Over the range of doses reported, all statins, with the exception of pravastatin, showed some evidence of a dose response for reduction in TC and/or LDL-C with fixed dosing, but not with dose titration. Overall, there appeared to be no major difference between dose titration regimens or use of a fixed dose in studies of longer duration.

In summary, lipid lowering reduces cardiovascular events irrespective of initial lipid levels. Targets for lipid-lowering therapy have been developed by extrapolation from the apparent benefits indicated by major trials of lipid lowering, therefore treatment for lipid lowering should aim towards these targets rather than consider them definitive.

Order of lipid-lowering treatment

Lipid-lowering pharmaconotherapy includes statins, fibrates, bile acid binding resins, niacin (nicotinic acid) and selective cholesterol absorption inhibitors (e.g. ezetimibe). The effectiveness of each of these agents is covered in section 2.2.2 Lipid-lowering therapy. Of all the methods to modify lipids, the weight of evidence suggests that statins are the most effective and should be the first-line agent. For the reduction of cardiovascular events, meta-analyses suggest that although the point estimates of their effect sizes vary, the confidence intervals overlap in each case except for non-fatal MI where simvastatin can just be differentiated from pravastatin (RR 0.62, 95% CI 0.56–0.69 and 0.78, 95% CI 0.70–0.87, respectively). Another meta-analysis of 164 short-term primary and secondary trials found rosuvastatin 5 mg/day, atorvastatin 10 mg/day and lovastatin or simvastatin 40 mg/day reduced LDL-C by about 35%, but fluvastatin and pravastatin produced smaller reductions. Rosuvastatin 10 mg/day, atorvastatin 20 mg/day and lovastatin or simvastatin 80 mg/day reduced LDL-C by about 45% and rosuvastatin 80 mg/day by about 60%. In clinical practice, the choice of statin is more likely to be related to the dosage required for lowering TC and LDL-C. Combination therapies (e.g., statins and ezetimibe) may also be considered when target LDL-C levels are not achievable with statins alone.

Systematic reviews have confirmed that statins, as first-line therapy, are safe and easy to use. Liver dysfunction is occasional and reversible. Rhabdomyolysis is very rare and severe muscle pain may require immediate cessation of therapy. Because statins are prescribed on a long-term basis, possible interactions with drugs that are metabolised by the cytochrome P450 pathway (e.g. cyclosporin, macrolides, azole antifungals, calcium antagonists, protease inhibitors, sildenafil, warfarin, digoxin, nicotinic acid, fibrates, etc.) also deserves particular attention. In cases where there is potential for interaction via this pathway, pravastatin is an acceptable alternative to atorvastatin or simvastatin. All patients started on a statin should be advised to report unexplained muscle pains or other adverse effects promptly, especially if associated with fever or malaise. If such effects are mild, a different statin may be tried and/or the statin dose reduced after discussing the risks involved with the patient. If severe side effects are experienced, statin therapy should be discontinued.
Due to the weight of evidence in favour of statins, fibrate monotherapy cannot be recommended as first-line treatment for raised lipid levels, but may be considered in those whose triglyceride levels remain elevated despite treatment with the maximally tolerated dose of statins and who have persistently low HDL-C levels. Triglyceride levels greater than 10mmol/L pose a risk of pancreatitis and should be treated with fenofibrate, nicotinic acid or fish oil as first-line therapy.

Nicotinic acids and ezetimibe may be considered in addition to statin therapy where insufficient lipid control has been achieved. Bile acid sequestrants using cholestyramine may be considered as monotherapy where statins are not tolerated or are contraindicated. They may also be considered in addition to statin therapy. Overall, there is limited evidence for various lipid lowering agents either in combination with statins or alone.

**People with diabetes**

Several systematic reviews have looked exclusively at responses to lipid modification of people with type 2 diabetes. The results from these reviews are consistent and suggest that people with diabetes gain similar benefits from statin therapy as people without. Perhaps the best evidence for people with diabetes comes from the Collaborative Atorvastatin Diabetes Study (CARDS), a large study conducted entirely in people with diabetes who did not have either raised cholesterol levels or a clinical history of CVD, even though many were hypertensive. In that study, the AR reduction attributable to statin therapy was 1.70% (95% CI 0.11—3.29) for all-cause mortality and 1.35% (95% CI 0.30—2.40) for total stroke. The NNT for four years to prevent one death was 59 (95% CI 30.4—88.5).

The evidence for fibrates in people with type 2 diabetes is less clear. One systematic review of 11 trials (78% of population were deemed primary prevention) reported a significant reduction in non-fatal coronary events (RR 0.84, 95% CI 0.74—0.96) but no effect on stroke or mortality outcomes. In the largest study included in the review, the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, fenofibrate therapy did not significantly reduce the risk of coronary events. However, it did reduce total cardiovascular events, mainly due to fewer non-fatal MIs and revascularisations. Furthermore, in people with dyslipidaemia (defined as low HDL-C with high triglycerides), the benefit of fenofibrate appeared to be more pronounced. In that group, CVD events occurred in 16.3% of people randomised to placebo and 14.0% in people receiving fenofibrate (p=0.06).

A more recent trial (ACCORD) found that the combination of fenofibrate and simvastatin did not reduce the rate of fatal CVD events, non-fatal MI or non-fatal stroke, compared with simvastatin alone. Of interest, however, was a possible benefit according to lipid subgroups. People with dyslipidaemia displayed a more pronounced benefit (p=0.057 for interaction), similar to the result reported in the FIELD study. However, in contrast to the FIELD study, a gender difference was observed, with the primary outcome rate increasing by 38% for women and decreasing by 18% for men.

Collectively, these findings do not support the routine use of combination therapy with fenofibrate and statins to reduce CVD risk in people with type 2 diabetes, except in those with dyslipidaemia. Clinicians should note that in primary prevention, the treatment threshold is determined by the level of AR while the treatment target for triglycerides is <2.0mmol/L. In contrast, in secondary prevention of CVD for people with type 2 diabetes, the treatment threshold is a triglyceride level above 2.3 mmol/L in combination with HDL levels below 1.0 mmol/L (refer to the National Evidence-based Guideline on Secondary Prevention of Vascular Disease in type 2 diabetes).

**People with CKD**

The benefits provided by statin therapy for people with CKD are similar to those observed in the general population. Statin therapy decreased all-cause mortality (RR 0.81, 95% CI 0.74—0.89) and cardiovascular mortality (RR 0.80, 95% CI 0.70—0.90) among people with non-dialysis dependent CKD to an extent similar to that found in the general population. The same authors reported that statins reduced fatal cardiovascular events (RR 0.81, 95% CI 0.73—0.90) and non-fatal cardiovascular events (RR 0.78, 95% CI 0.73—0.84), for all stages of CKD but had no significant effect on all-cause mortality (RR 0.92, 95% CI 0.82—1.03). Importantly there were no significant differences in adverse events reported (including rhabdomyolysis and elevated liver enzymes). However, trials usually included people with pre-existing CVD. Meta-regression analysis found that treatment effects did not vary significantly with stage of CKD. This is consistent with a subgroup analysis in another meta-analysis, which found no difference in the effect of statins with varying levels of GFR.

The Study of Heart and Renal Protection (SHARP) represents the largest trial of lipid modification in people with CKD performed to date. In that study, 9,438 participants with advanced CKD and no known history of CHD were randomised to one of three treatment arms: ezetimibe 10 mg plus simvastatin 20 mg daily, matching placebo or simvastatin 20 mg daily. In the latter arm, participants were re-randomised at one year to either ezetimibe 10 mg plus simvastatin 20 mg daily, or to placebo. The primary
endpoint was a composite of MI, coronary death, ischaemic stroke or any revascularisation procedure. Compared with placebo, randomisation to ezetimibe 10 mg plus simvastatin 20 mg daily yielded average LDL-C differences of 1.10 mmol/L at one year and 0.85 mmol/L at 2.5 years. Recent evidence from the SHARP trial, published during the finalisation of these guidelines, showed similar reductions in LDL-C (0.86 mmol/L) at a median follow up of 4.9 years. This data reported a 17% proportional reduction in major atherosclerotic events compared with placebo (RR 0.83, 95% CI 0.74-0.94) with no evidence of adverse effects. While this evidence did not result in a regrading of recommendation EBR14, the outcome data further support the use of ezetimibe in combination with a statin if LDL-C levels are not sufficiently reduced on a statin alone.

A secondary analysis from the Justification for the Use of Statins in Prevention – an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial reported positive effects from statin therapy on cardiovascular and mortality outcomes among people with moderate CKD (eGFR <60 ml/min/1.73 m²) at study entry (n=3,267), compared with those with baseline eGFR ≥60 ml/min/1.73 m² (n=14,528). Over a median follow-up period of 1.9 years, a higher rate of vascular events was observed in the group with moderate CKD (HR 1.54, 95% CI 1.23–1.92, p=0.0002). In the same group, rosuvastatin was associated with a 45% reduction in risk of the combined primary endpoint – MI, stroke, hospital stay for unstable angina, arterial revascularisation or confirmed cardiovascular death (HR 0.55, 95% CI 0.38–0.82, p=0.002) and a 44% reduction in all-cause mortality (HR 0.56, 95% CI 0.37–0.85, p=0.005). An almost identical effect of rosuvastatin on the primary endpoint was observed among those with more preserved renal function (HR 0.57, 95% CI 0.45–0.72, p<0.001).

### Evidence-based recommendations

#### Lipid-lowering therapy

**EBR 13:** Statins should be used as first-line therapy

**EBR 14:** If LDL-C levels are not sufficiently reduced on maximally tolerated doses of statin, one or more of the following may be added:
- ezetimibe
- bile acid binding resin
- nicotinic acid.

**EBR 15:** Where statins cannot be tolerated at all, one or more of the following can be used:
- ezetimibe
- bile acid binding resin
- nicotinic acid.

**EBR 16:** If triglyceride levels remain elevated, treatment with one of the following may be considered:
- fenofibrate (especially if HDL is below target)
- nicotinic acid
- fish oil.

### Practice point

**PP 18:** Treatable secondary causes of dyslipidaemia should be considered before commencing lipid lowering pharmacotherapy.
2.3.3 Principles of pharmacological therapy

A number of issues should be considered when making treatment decisions for the management of CVD risk.

Balancing the benefits and risks of treatment

For all individuals, a clinical judgment should be made to assess the balance between the benefits and risks of pharmacological treatment. Clear benefits in preventing cardiovascular events and reducing premature mortality have been demonstrated for BP and lipid-lowering therapy in many clinical trials. However not all clinical situations in which their use may be considered have been covered by clinical trials, e.g. in the elderly.

Use of these therapies are associated with risks and other negative effects which should be taken into consideration when deciding the appropriateness of implementing the treatment recommendations contained in these guidelines. These therapies may be contraindicated in some situations and their use may result in troublesome side effects. In addition, polypharmacy may be unaffordable to some, may increase the risk of side effects and may impact on quality of life.

The appropriateness of general treatment targets to the individual should also be considered. CVD risk associated with lipid and BP levels is continuous and specific targets are somewhat arbitrary and should be used as a guide to treatment and not as a requirement, especially if they cannot be easily achieved without causing unwanted effects. The risks associated with the effort required to reach a particular target as opposed to achieving a near-target value may outweigh any small absolute benefit. Any reduction in a risk factor will be associated with some benefit.

Prescribing pharmacological treatment

Benefits and risk should be carefully considered before initiating or changing pharmacological treatment. The primary consideration is clinical need and clinical appropriateness of a particular therapy. The choice of agent should be guided by clinical effectiveness but once the decision on the class of drug has been made, further consideration should be given to the cost to both the individual and government. The use of cheaper alternatives such as generic medications instead of more expensive options achieves similar health gains while increasing consumer and societal affordability.

2.4 Populations requiring special consideration

2.4.1 People with diabetes

CVD is the major cause of death in people with diabetes with nearly 11,900 Australian deaths in 2005 of which CVD was involved in more than 50%: CHD (48%), stroke (16%) and PVD in 6%. Diabetes approximately doubles the risk for a range of cardiovascular diseases independently of traditional risk factors. While diabetes is a clear risk factor for CVD the role of improved control of blood glucose for preventing CVD morbidity and mortality in people with type 2 diabetes is unclear although it has been found to prevent or reduce microvascular complications (retinopathy, renal disease and neuropathy).

Lifestyle

Lifestyle modification and support (particularly diet, weight control and physical activity) is critically important in diabetes care. The lifestyle recommendations in these guidelines for CVD prevention in the general population apply equally for people with diabetes.

Pharmacotherapy

BP lowering reduces cardiovascular events and all-cause mortality in people with type 2 diabetes in the same manner as for the general population. While no difference is noted between different classes of BP-lowering therapy for CVD outcomes, there is clear evidence that in people with type 2 diabetes, antihypertensive therapy with an ARB or ACE inhibitor decreases the rate of progression of albuminuria, promotes regression to normoalbuminuria and may reduce the risk of decline in renal function. The benefit in terms of renal protection was also found in the recent ROADMAP study which included 4,447 people with type 2 diabetes and normoalbuminuria but additional risk factors (33.4% had pre-existing CVD). While overall baseline BP was already low (mean 136/81 mm Hg) treatment to low BP targets (<130/80 mmHg) was achieved by more people in the intervention arm using an ARB vs other agents (80% vs 71%). Treatment with ARB prevented (8.2% v 9.8%) and delayed the onset of microalbuminuria (23% delay to onset; p=0.01). An increase in CVD mortality was noted although numbers are low (15 v 3) and the difference greater in those with CHD (2.0% mortality with ARB v 0.2% mortality with other agents, p=0.02). A post hoc analysis found a reduction in combined cardiac morbidity (acute coronary syndrome, silent MI, coronary
revascularization and hospitalization because of congestive heart failure) (1.1% v 2.3%; p<0.01).

Given the importance of preventing and managing renal complications in people with diabetes, these classes of drugs (ACE inhibitor or ARB) should be preferred as first-line therapy. However, more than one agent is often needed to reduce BP. In a pre-specified subgroup analysis from the ACCOMPLISH trial, those with diabetes (n=6,946; 15% had previous MI and 8% had previous stroke) significantly reduced the risk of CVD events with a combination of a CCB plus an ACE inhibitor compared with those treated with a combination of a thiazide diuretic plus an ACE inhibitor (HR 0.79, 95% CI 0.68–0.92, p=0.003) even though mean blood pressure was similar in both groups (~132/73 mmHg). In the pre-specified subgroup analysis of the ASCOT trial for those with diabetes (n=5,137, at least 38% had pre-existing CVD), the CCB based combination (mostly with an ACE inhibitor) compared to the Beta Blocker combination (mostly with a thiazide diuretic) reduced the risk of combined CVD events and procedures (HR 0.86, 95% CI 0.76–0.98, p=0.026). There was a greater reduction of in-trial BP with the CCB combination (mean difference on CCB combination was 3.0 mmHg SBP and 1.9 mmHg DBP lower), however, there was no difference by the end of the study (~135/75 mmHg in each group).

In the ADVANCE trial (n=11,140, 32% had major macrovascular disease) treatment with a fixed dose ACE inhibitor plus a diuretic reduced the risk of combined macro and micro disease (HR 0.91, 95% CI 0.83–1.00, p=0.04) compared to placebo. Evidence for BP targets for those with diabetes has also been recently updated (refer to section 2.3.1 Blood pressure-lowering therapy).

Several systematic reviews have looked exclusively at responses to lipid modification of people with type 2 diabetes. The results from these reviews are consistent and suggest that people with diabetes gain similar benefits from statin therapy as people without. In the CARDS study, the AR reduction attributable to statin therapy was 1.70% (95% CI 0.11–3.29) for all-cause mortality and 1.35% (95% CI 0.30–2.40) for total stroke. The NNT for four years to prevent one death was 59 (95% CI 30.4–88.5).

Evidence for the benefit of lipid lowering with fibrates in people with type 2 diabetes is less clear. In the trials performed to date, fenofibrate therapy alone did not significantly reduce the risk of coronary events or stroke in people with type 2 diabetes, nor did the combination of fenofibrate and simvastatin. However, two of those trials (ACCORD and FIELD studies), demonstrated beneficial effects with fenofibrate therapy on lowering microvascular complications.

The role of aspirin for the primary prevention of cardiovascular events in people with type 2 diabetes has been assessed in four systematic reviews. These reviews consistently report that aspirin therapy is associated with a modest non-significant reduction in risk of major cardiovascular events in people with diabetes. Given that these effects are less than those for the general population the recommendations to not routinely treat with aspirin are consistent for people with or without diabetes (refer to section 2.2.3 Antiplatelet therapy).

Readers are referred to other guidelines for information on pharmacotherapy specific to diabetes care (blood glucose management). Recommendations for the secondary prevention of CVD in those with diabetes is covered in the National Evidence-Based Guideline on Secondary Prevention of Vascular Disease in type 2 diabetes (2011). While recommendations are consistent in primary and secondary populations some of the grading of individual recommendations differs slightly, due to the underlying evidence for the different populations.
2.4.2 People with CKD

People with CKD are at significantly increased risk of cardiovascular events. In a pooled analysis of four large community-based, longitudinal studies, CKD (eGFR 15–60 ml/min/1.73 m²) was associated with a 20% increased risk of cardiovascular events and death. This is consistent with a recent meta-analysis, which found CKD and albuminuria are independent predictors of all-cause mortality and cardiovascular mortality in the general population. For this reason, individuals with CKD should be identified early so that appropriate preventative measures can be taken. This section provides a summary of the evidence for CKD, as it pertains to absolute CVD risk reduction. The reader is directed to the main text for more detailed information.

Lifestyle

Limited evidence exists on the effects of lifestyle modification (i.e. smoking, physical activity and alcohol) on CVD outcomes in patients with CKD. Dietary recommendations outlined for the prevention of CVD apply equally to those with CKD. Furthermore, all adults should be encouraged to participate in at least 30 minutes of moderate activity on most or preferably every day of the week and all smokers should be advised to stop.

Pharmacotherapy

High BP is common in CKD and represents a major target for intervention to prevent disease progression. In general, the clinical evidence suggests that people with CKD receive the same or similar benefits from BP-lowering therapy as the general population, irrespective of the level of kidney function. A recent systematic review considered during finalisation of these guidelines, included three trials which compared different BP targets in adults with CKD and showed no difference in outcomes for people treated to lower BP targets (<125/75 to 130/80 mmHg) versus higher targets (<140/90 mmHg). More BP-lowering pharmacotherapy was needed to achieve the lower BP targets, and this group had a slightly higher rate of adverse events. Much less evidence is available for people on maintenance dialysis. However, the available evidence suggests that treatment using agents that lower BP reduces cardiovascular morbidity and mortality for this group. While more studies are required, the possible risks and benefits of BP lowering should be considered for all people receiving dialysis.

Two meta-analyses provide evidence that ACE inhibitors and ARBs are the preferred agents for BP lowering in people with CKD because of their renoprotective effects more than their impact on mortality outcomes. In the first meta-analysis, ACE inhibitors compared with placebo significantly reduced the risk of developing microalbuminuria in normoalbuminuric people with diabetes (RR 0.60, 95% CI 0.43–0.84). No subgroup analysis was conducted for those with and without existing CVD. No effect was seen for doubling of creatinine (RR 0.81, 95% CI 0.24–2.71) or all-cause mortality (RR 0.81, 95% CI 0.64–1.03). When compared with CCBs, ACE inhibitors significantly reduced progression to microalbuminuria (RR 0.58, 95% CI 0.40–0.84). The effect of ACE inhibitors was independent of baseline BP, renal function and type of diabetes; however, there was insufficient data to be certain that these factors are not important effect modifiers.

The second meta-analysis compared the survival effects of ACE inhibitors and ARBs in 49 trials with mixed populations of primary and secondary CVD. No significant difference was found in the risk of all-cause mortality for ACE inhibitors compared with placebo (RR 0.91, 95% CI 0.71–1.17) and ARBs compared with placebo (RR 0.99, 95% CI 0.85–1.17). However, ACE inhibitors showed a significant reduction in the risk of all-cause mortality when given at maximally tolerated dose compared with half or less than half the maximally tolerated dose (RR 0.78, 95% CI 0.61–0.98). ACE inhibitors and ARBs had similar beneficial effects on renal outcomes.

The benefits provided by statin therapy are similar in people with CKD to those observed in the general population. In a Cochrane review, statin therapy decreased all-cause mortality and cardiovascular mortality among people with non-dialysis dependent CKD to an extent similar to that found in the general population. The same authors reported in an expanded meta-analysis that statins significantly reduced lipid levels in those with CKD, irrespective of stage of disease, but showed no benefit on all-cause mortality. A secondary analysis from the JUPITER trial in people with moderate CKD (eGFR < 60 ml/min/1.73 m²) at study entry (n=3,267), compared with those with baseline eGFR ≥ 60 ml/min/1.73 m² (n=14,528) and found rosuvastatin was associated with a 45% reduction in risk of the combined primary endpoint – MI, stroke, hospital stay for unstable angina, arterial revascularisation or confirmed cardiovascular death (HR 0.55, 95% CI 0.38–0.82; p=0.002) and a 44% reduction in all-cause mortality (HR 0.56, 95% CI 0.37–0.85, p=0.005). Recently, the landmark SHARP trial reported a combination of ezetimibe 10 mg plus simvastatin 20 mg daily reduced LDL-C by an average of 0.85 mmol/L and reduced major CVD events
by 17% (RR 0.83, 95% CI 0.74–0.94) compared to statin therapy alone, without evidence of adverse events.\textsuperscript{226}

In summary, the evidence suggests that, apart from choice of agent for initiation of BP-lowering treatment, people with CKD should be managed for CVD risk in the same way as the general population.

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<tr>
<th>Evidence-based recommendation</th>
<th>Grade</th>
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<td><strong>Populations requiring special consideration: people with CKD</strong></td>
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</tr>
<tr>
<td><strong>EBR 19</strong>: Blood pressure-lowering therapy in people with CKD should begin with an ACE inhibitor or angiotensin receptor blocker.</td>
<td>A\textsuperscript{202, 303}</td>
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</tbody>
</table>
Chapter 3: Monitoring of Pharmacotherapy

The goal for management of absolute CVD risk is to reduce the person’s level of AR. This is achieved by treatment of multiple individual risk factors such as blood pressure and lipid levels which have been shown to have a continuous association with the risk of CVD events.

Moderate reductions in several risk factors is considered more effective in reducing overall CVD risk than a major reduction in one factor. Decisions regarding management of risk are therefore made according to the person’s AR level, while response to treatment is monitored by measurement of individual risk factors.

In people with moderate to high CVD risk, having an effective strategy for monitoring treatment response is essential for achieving long-term CVD prevention. There is some evidence to support the use of monitoring, particularly to measure response to treatment of individual risk factors and for adherence. In general, the literature to support medication monitoring and/or adherence is consistent and reports either improvement in individual risk factors or, in some instances, a reduction in overall CVD risk.

3.1 Maximising the benefits of pharmacotherapy

The literature reports several methods for monitoring adherence to pharmacological interventions in terms of effect (e.g., BP or lipid levels). These methods include self-monitoring, tele-monitoring, case management and individualised provision of information. These studies consistently report that regular monitoring of individual risk factors is associated with improvement in CVD risk factor outcomes. Furthermore, several studies report that lack of monitoring contributes to poor adherence to statin therapy and therefore worse outcomes.

Although targets for BP and lipid levels have been generally agreed, based on extrapolations of what has been achieved in clinical trials, the relationship between BP levels, lipid levels and CVD risk is known to be continuous. Therefore, targets should be considered indicative and should be used for monitoring treatment effects and adherence to medication while considering the individual person’s risk/benefit profile. After commencement of BP lowering therapy and until treatment is stable or targets achieved, BP levels should be reviewed at intervals of six weeks unless there are concerns or indications for more frequent monitoring. Similarly, after commencement of lipid therapy, lipid levels should be reviewed at 12 weekly intervals.

Monitoring of patient response to treatment may lead to reconsideration of appropriate management. In some patients who make significant and sustained lifestyle changes such as smoking cessation or loss of 10–20% of body weight, there will be a consequent significant reduction of individual risk factors. Reduction or withdrawal of pharmacotherapy may be considered in these cases; however, monitoring should continue for at least 12 months to ensure a sustainable impact on the risk factors.
Consensus-based recommendations

Maximising the benefits of pharmacotherapy

CBR 7: Pharmacotherapy for blood pressure-lowering should aim towards the following targets while balancing the risks/benefits:

- ≤140/90 mmHg for adults without CVD (including those with CKD)
- ≤130/80 mmHg for adults with micro or macro albuminuria (UACR >2.5 mg/mmol in males and >3.5 mg/mmol in females)
- ≤130/80 mmHg for all adults with diabetes

CBR 8: Pharmacotherapy for lipid lowering should aim towards the following targets while balancing the risks/benefits:

- TC <4.0 mmol/L
- HDL-C ≥1.0 mmol/L
- LDL-C <2.0 mmol/L
- Non HDL-C <2.5 mmol/L
- TG <2.0 mmol/L

Practice point

Maximising the benefits of pharmacotherapy

PP 19: Adults who commence pharmacotherapy should have their medication adjusted as required and response assessed regularly (approximately 6-12 weekly) until sufficient improvement has been achieved or maximum tolerated dose has been reached.

PP 20: Reduction or withdrawal of pharmacotherapy may be considered in adults who make sustained lifestyle changes which significantly reduce their risk. (e.g. smoking cessation, significant weight loss).

3.2 Patient adherence

Failure to take prescribed medication is a major barrier to optimal prevention of CVD, however the literature concerning interventions to improve adherence to medications remains surprisingly weak. One Cochrane review involving 78 trials found only modest effects for interventions to improve adherence to medications across a range of populations and settings. Conflicting evidence for short-term interventions on compliance was found and very few studies reported changes in patient outcomes. Almost all of the interventions that were effective for long-term compliance were complex, including combinations of more convenient care, information, reminders, self-monitoring, reinforcement, counselling, family therapy, psychological therapy, crisis intervention, telephone follow-up and supportive care.

One recent Cochrane review (72 trials) assessed different interventions to improve BP control in hypertensive adults in a primary care, outpatient or community setting. Organisational interventions (nine trials) to enable regular review in tandem with a rigorous stepped-care approach to antihypertensive drug treatment were found to be the most effective, but this finding was dominated by findings from a single large trial – the Hypertension Detection and Follow-Up study. Self-monitoring (18 trials) was associated with a reduction in SBP (2.5 mmHg) and DBP (1.8 mmHg) and may be a useful adjunct strategy. Other interventions assessed in this systematic review did not produce clear results. Educational interventions directed at physicians (10 trials) did not change BP control, but education for patients (20 trials) may have a modest effect although heterogeneity was noted. Use of health care professionals such as nurses and pharmacists (12 trials) demonstrated generally favourable but heterogeneous results. Lastly, reminders (postal, computer or telephone) improved follow-up and control of patients, but produced heterogeneous results in terms of BP reduction.

Another Cochrane review (38 trials) specific to BP-lowering therapy in an ambulatory setting suggested that simplifying dosing regimens was the most consistently effective intervention (seven out of nine studies). Motivational strategies (e.g. financial incentives or reminder packages/aids) and complex interventions involving
more than one technique were less consistent. Effects were generally modest and patient education alone was largely ineffective.315 Further, in a systematic review of 11 trials investigating the effects of home BP monitoring on medication adherence, six of the 11 trials reported a statistically significant improvement in medication adherence; 84% of these were complex interventions using home BP monitoring in combination with other adherence-enhancing strategies such as patient counselling by nurses, pharmacists or telephone-linked systems, patient education and the use of timed medication reminders.316 Two moderate quality reviews of simplifying doses by using fixed-dose combinations to improve adherence for raised BP reported improved compliance with combination treatment (24% decrease risk of non-compliance in one review).317, 318

Another systematic review (11 trials) found strategies for patient re-enforcement and reminding (e.g. telephone reminders or pharmacist review) to have the most consistent benefits in improving adherence for lipid-lowering therapy (four of six trials were positive with absolute improvement in adherence of 6–24%).319 Other strategies found to increase adherence, included simplification of the drug regimen (11% improvement) and patient information and education (13% improvement), although results were inconsistent and the quality of some studies was low. One high-quality systematic review (21 trials) in people with type 2 diabetes failed to find clear benefits for various strategies including nurse-led interventions, home aids, diabetes education, pharmacy led interventions, adaptation of dosing and frequency of medication taking.320 The evidence is difficult to interpret due to heterogeneity; however overall there seems to be a modest improvement in adherence from the more complex interventions.
Appendix 1: 
Guidelines development groups and terms of reference

The guidelines development process was coordinated by the National Stroke Foundation on behalf of the National Vascular Disease Prevention Alliance (NVDPA) with partner agencies represented on the advisory and/or expert working group committees as appropriate. The guidelines have been developed according to the processes outlined in the document *NHMRC Standards and Procedures for Externally Developed Guidelines (2007).*

**Project Committees**

Three groups were established in the development of the guidelines.

**Advisory Committee**

The Advisory Committee had 17 representatives from a wide range of backgrounds including diabetes, nephrology, stroke, cardiology, Indigenous health, general practice, economics, a consumer and the Pharmaceutical Benefits Advisory Committee (PBAC). The Committee was responsible for:

- overseeing operational aspects of the guidelines development
- determining the topics and questions to be addressed in the guidelines
- advising on a plan for communication, dissemination and implementation
- assisting the EWG as needed (particularly in regard to responding to consultation where significant difference in opinion exists)
- developing recommendations for periodically updating the guidelines
- regular reporting to the full committee of the NVDPA.

Members of the Advisory Committee included:

- Dr Erin Lalor (Chair)
  - Chief Executive Officer, National Stroke Foundation
  - Chair of NVDPA
- Dr Andrew Boyd (until February 2011)
  - National Director-Clinical Issues, National Heart Foundation
- Dr Dominique Cadilhac
  - Head, Public Health Division, National Stroke Research Institute
- Professor Stephen Colagiuri
  - Diabetologist, Boden Institute of Obesity, Nutrition, Exercise and Eating Disorders, The University of Sydney
- Professor Jennifer Doust (PBAC representative until August 2010)
  - Epidemiology and Public Health, Bond University
- Ms Dianne Fraser
  - Assistant Director, Chronic Disease Branch, Department of Health and Ageing
- Professor Mark Harris (RACGP representative)
  - General Practitioner, Centre for Primary Health Care and Equity, The University of New South Wales
- Dr Nancy Huang (until March 2010)
  - National Manager Clinical Programs, National Heart Foundation

Appendix 1:
Guidelines development groups and terms of reference
Expert Working Group

The EWG had 12 members including endocrinologists, cardiologists, nephrologists, general practitioners, geriatricians, a consumer and a PBAC representative. The EWG was responsible for:

- assisting as required with the appraisal and grading of identified research
- using the evidence base to develop the guidelines recommendations
- assisting with the drafting of the guidelines document
- linking with members of the corresponding group where relevant
- assisting with the consultation process
- assisting with the response to feedback gained during the consultation process.

The NVDPA is grateful to the members of the EWG who provided their time and expertise to develop these guidelines.

Members of the EWG included:

Professor Stephen Colagiuri (Chair)
Diabetologist,
Boden Institute of Obesity, Nutrition, Exercise and Eating Disorders,
The University of Sydney

Professor Andrew Tonkin
Cardiologist, Cardiovascular Research Unit,
Monash University

Professor Leonard Arnolda
Cardiologist,
Canberra Hospital and Australian National University

Professor Alex Brown
Indigenous Health,
Executive Director and Margaret Ross Chair of Indigenous Health,
Baker IDI Central Australia

Professor Terry Campbell, AM
Cardiologist (PBAC representative),
University of New South Wales

Professor Derek Chew
Cardiologist,
Flinders University

Professor David Johnson
Nephrologist,
Princess Alexandra Hospital and University of Queensland

Professor Greg Johnson (from November 2010)
Chief Executive Officer,
Diabetes Australia – Victoria

Dr Nadia Lusis (NACCHO representative)
Public Health Medical Officer,
Victorian Aboriginal Community Controlled Health Organisation (VACCHO)

Associate Professor Timothy Mathew
National Medical Director,
Kidney Health Australia

Mr Noel Muller (Consumer Health Forum representative)
Consumer

Dr Rashmi Sharma (PBAC representative from December 2010)
General Practitioner,
Isabella Plains Medical Centre, ACT

Associate Professor Jonathan Shaw (Baker IDI guideline development group representative)
Associate Director,
Baker IDI Heart and Diabetes Institute

Dr Ian White (until December 2010)
National Policy Manager,
Diabetes Australia

Ms Jinty Wilson (from March 2011)
National Manager Clinical Programs,
National Heart Foundation
Corresponding Group

The Corresponding Group had 22 members with wide representation across all of the previously identified groups and also broad representation across the lifestyle issues such as smoking, physical activity, nutrition, depression and alcohol. This group was responsible for:

- assisting as required with the appraisal and grading of identified research
- assisting with the drafting of the guidelines document (including recommendations)
- linking with members of the EWG where relevant
- assisting with the consultation process
- assisting with the response to feedback gained during the consultation process.

The NVDPA wishes to thank the members of the Corresponding Group for their input to the development of the guidelines.

Members of the Corresponding Group included:

- Professor Philip Barter
  Lipid management,
  University of Sydney
- Professor Adrian Bauman
  Behavioural Epidemiology and Health Promotion,
  University of Sydney
- Dr Dominique Cadilhac
  Head, Public Health Division,
  National Stroke Research Institute
- Professor David Clarke
  Psychology,
  Beyondblue,
  Monash University
- Professor Peter Clifton
  Nutrition,
  Australian Atherosclerosis Society
- Dr Emil Djakic
  General Practitioner,
  Australian General Practice Network
- Dr Martin Gallagher
  Nephrologist,
  Caring for Australians with Renal Impairment
- Dr Melina Gattellari
  Public Health,
  Stroke Society of Australasia
- Associate Professor Timothy Gill
  Public health nutrition,
  National Heart Foundation
- Professor Leonard Kritharides
  Cardiologist,
  Concord Hospital and
  The University of Sydney
- Dr Alasdair MacDonald
  General practitioner,
  Internal Medicine Society of Australia and New Zealand
- Associate Professor Arduino Mangoni
  Cardiologist,
  Flinders University
Professor Manny Noakes
Nutrition,
CSIRO

Professor Caryl Nowson
Nutrition,
Deakin University

Associate Professor Anushka Patel
Cardiologist,
The George Institute for Global Health

Ms Adriana Platona
The Australian Government,
Department of Health and Ageing

Professor Vlado Perkovic
Nephrologist,
The George Institute for Global Health

Professor Prasuna Reddy
Psychologist,
Deakin University

Professor Jo Salmon
Nutrition,
Deakin University

Associate Professor Markus Schlaich
Renal Physician,
High Blood Pressure Research Council of Australia

Dr Lynn Weekes
Pharmaceutical,
National Prescribing Service

Associate Professor Margarite Vale
Nutrition,
Cardiac Society of Australia and New Zealand

Editorial Independence
The EWG was responsible for the content of the guidelines with independence from the funding source. A DOHA representative formed part of the Advisory Committee to oversee the process of the guidelines development.

Conflict of Interest
A policy regarding disclosure and management of potential conflicts of interest (COI) was implemented. All Advisory Committee and EWG members completed COI forms and a COI register was maintained and updated regularly.

COI were managed in the following manner:
- Open disclosure of all COI to all members of the committee and public declaration of all COI in guidelines
- If the COI is deemed significant, individuals may be restricted from involvement in discussions and decisions on related topics. This is determined by the chair of the relevant committee and has occurred once
- If the COI is considered exclusionary, the individual will be excluded from membership of the relevant committee or from employment in the guidelines team. This will be determined by the chair of the relevant committee and the CEO of the NSF, the lead agency for this project. This level of COI has been experienced and the relevant member resigned from the committee.

A copy of the Conflict of Interest Policy can be supplied on request.

National Stroke Foundation Guidelines
Project Team
Ms Ruth Friedman
Senior Project Manager, CVD Guidelines,
National Stroke Foundation

Mr Kelvin Hill
Manager, Guidelines Program,
National Stroke Foundation

Ms Diana Reddan
Senior Administration Assistant,
National Stroke Foundation

External Consultants
medScript
Mr Brad Dalton
Medical writer
Appendix 2:
Guidelines development process report

1. Methodology

These guidelines were developed according the standards outlined in the NHMRC Standards and Procedures forExternally Developed Guidelines (2007).

2. Clinical questions

The clinical questions were initially framed by building on the work undertaken in the development of the Guidelines for the Assessment of Absolute Cardiovascular Disease Risk. Further refinement was undertaken after consultation with international guidelines groups in Scotland and New Zealand. Questions were then grouped under topics and circulated to experts for comment. Some experts were consulted individually for further detailed comments. In response to the comments from experts, the questions were modified for further discussion and final approval at a face-to-face meeting of the Advisory Committee held on 26 November 2009.

The clinical questions are outlined below:

Absolute risk assessment

1. Which AR assessment method is most predictive of future CVD events in a mixed adult (aged >18) population not known to have CVD or diabetes?

2. Which AR assessment method is most predictive of future CVD events in a mixed adult (aged >18) population not known to have CVD and who have diabetes?

3. Which AR assessment method is most predictive of future CVD events in a mixed adult (aged >18) population not known to have CVD and who are overweight (defined as BMI within the range 25.0–29.9 kg/m²) or obese (BMI ≥30kg/m²)?

4. Which AR assessment method is most predictive of future CVD events in adult (aged >18) Aboriginal and Torres Strait Islander peoples not known to have CVD?

5. Which AR assessment method is most predictive of future CVD events in adult (aged >18) people with chronic kidney disease (eGFR <45ml/min1.73 m²) not known to have CVD?

Aims of treatment, monitoring and follow-up

6. Is there evidence that multiple risk intervention is more effective in reducing CVD events and all cause mortality than intervention on single risk factors? NOTE: evidence was systematically identified but used in narrative review (rather than comprehensive critical appraisal and summary process) to form important part of main body of guidelines.

7. What evidence exists to support the benefit of monitoring treatment effects? Report evidence for secondary outcomes defined as AR levels; individual risk factor levels; side effects; compliance with treatment.

8. Do strategies to promote concordance with medication reduce the risk of CVD? NOTE: as for Q6 evidence was systematically identified but used in narrative review to form important part of main body of guidelines.

Blood pressure

9. Does pharmacological blood pressure-lowering reduce CVD events and all cause mortality compared to ‘control’?
10. What is the evidence for one blood pressure-lowering drug class or any combination of drug classes being more effective than any other blood pressure-lowering drug class or combination for reducing CVD events and all cause mortality? Report evidence for secondary outcome defined as: Reduction of BP.

11. Should blood pressure therapy be initiated with a single drug or with a combination?

12. Should antihypertensive therapy employ drugs at fixed doses or should individuals always be titrated to target blood pressure levels?

13. Does more intensive blood pressure-lowering produce greater reductions in CVD events and all cause mortality?

Lipids

14. Does pharmacological lipid modification compared to control reduce CVD events and all cause mortality?

15. What is the evidence for one lipid modifying drug class or any combination of drug classes being more effective than any other lipid-modifying drug class or combination for the reduction of CVD events and all cause mortality? Report evidence for secondary outcome defined as: Reduction of blood lipids.

16. Should lipid lowering therapy employ drugs at fixed doses or should individuals always be titrated to target lipid levels?

17. Does more intensive lipid modification treatment produce greater reductions in CVD events and all cause mortality?

Antiplatelets


19. What is the evidence for one antiplatelet therapy or dose or any combination of therapy/doses being more effective than any other antiplatelet therapy/dose or combination for the reduction of CVD events and all cause mortality? Report evidence for secondary outcome: Bleeding complications.

Diet and nutrition

21. Is there evidence that following dietary advice reduces CVD events and all cause mortality? Report evidence for outcomes: BP; Lipid parameters; Diabetes.

Physical activity

22. Is there evidence that physical activity reduces CVD events and all cause mortality?

23. What is the evidence for physical activity type and dose or any combination of type/doses being more effective than any other physical activity type and dose or combination for the reduction of CVD events and all cause mortality? Report evidence for secondary outcomes: BP; Lipid parameters.

Alcohol

24. What is the evidence that the patterns and levels of alcohol consumption alter CVD events and all cause mortality? Report evidence for secondary outcomes: BP; Lipid parameters.

Smoking

25. Does smoking cessation reduce CVD events and all cause mortality?

Depression

26. Does treatment (pharmacological and non pharmacological) of depression reduce CVD events and all cause mortality?

3. Literature review

The systematic literature review was undertaken according to the process outlined in the NHMRC Standards and Procedures for Externally Developed Guidelines (2007) by an external group from the Centre for Allied Health Evidence (iCAHE), University of South Australia, led by Dr Susan Hillier and Professor Karen Grimmer-Somers.

Searches were conducted in relevant databases using an agreed search protocol which lists details of search terms, inclusion/exclusion criteria, and data extraction and appraisal methodology. Additional hand searching was conducted by the NSF project team in several key journals to identify any major trials or meta-analyses published after the systematic literature review.
3.1 Criteria for considering studies for the review

Search dates

The search dates were 2006 to June 2010 for the first five questions relating to assessment of CVD risk which updated the search conducted for the Clinical Guidelines for the Assessment of Absolute Cardiovascular Disease Risk (which used no limits on the date of publication). The search dates were 2002 to June 2010 for the remaining questions relating to management of absolute CVD risk. Hand searching was conducted between June 2010 and May 2011.

Types of studies

Existing guidelines, systematic reviews (Level 1 evidence, based on the NHMRC Levels of Evidence and Grades for Recommendations for Developers of Guidelines (2009), randomised controlled trials (Level II evidence) were considered for inclusion, crossing intervention and diagnostic domains. Where there was a scarcity of Level I or Level II evidence, it was planned to expand the review to consider lower levels of evidence. Studies were limited to English language only.

Types of participants

The review included research conducted in adults without pre-existing CVD or in those with and without CVD but where those without CVD were reported separately.

Types of outcomes

In principle, the primary outcome for each question was cardiovascular events (definition for CVD as for the Guidelines for the Assessment of Absolute Cardiovascular Disease Risk).

The secondary outcome of interest was AR reduction, followed by surrogate outcomes such as individual risk factor reduction as specified in the questions (e.g. BP control).

3.2 Search strategy for identification of studies

A broad search strategy using the following databases and sources was used to identify potential studies:

- Medline
- Embase
- Cinahl
- PsychINFO
- Cochrane Library, including CENTRAL Cochrane Controlled Trial Register (CCTR) and DARE for some topics.

In addition, the following websites were searched including Australian Centre for Clinical Effectiveness, National Institute for Health and Clinical Excellence, National Library for Health, Swedish Council on Technology Assessment in Healthcare, US Agency for Healthcare Research and Quality, and the US National Guidelines Clearing House. The EWG were sent interim search reports and asked to identify any additional studies.

Hand searching undertaken after the online database searching included the following journals: British Medical Journal, New England Journal of Medicine, LANCET, Circulation, Journal of the American Medical Association, Archives of Internal Medicine, Medical Journal of Australia and Diabetes Care.

The Cochrane library was also reviewed to incorporate new or updated reviews. Hand searching was undertaken to identify major meta-analyses or landmark trials to maximise the currency of the text. In one situation, literature identified after the comprehensive literature review period was deemed by the EWG to be sufficiently important to result in a change to the recommendations (i.e. BP targets for those with CKD). This decision took into consideration the quality of evidence (all high-quality meta-analyses), the need to provide clinicians with the most useful recommendation, alignment to draft international CKD guidelines, and the likely scenario that the current guidelines could be out of date before they were published.
In addition to the initial searches, economic literature was searched via EBSCOhost database (Econlit & CINAHL), Ovid database (EMBASE, Medline), BioMed central and Cochrane library database (Health Technology Assessment, NHS Economic Evaluation). A broad search strategy of Australian and international literature (developed countries including European, North American and Canadian) for the years 2002–2010 was used. The cut-off dates build on the SIGN guidelines used during the systematic review phase.

**Search terms**

Search terms were used for each group of clinical questions/topics. Search terms were based on those reported in the Supplementary Guidelines Material (SIGN) where the first series of strings are disease/population identifiers and the additional strings relate to the specific question, i.e. intervention (e.g. alcohol and euphemisms). Search strategies used in other databases were adjusted for different databases, but were substantially the same. Searches were combined with guidelines, systematic review, and trial filters as appropriate.

### 3.3 Study selection

One reviewer assessed the titles and available abstracts of all studies identified by the initial broad searches (based on population and intervention) and excluded any clearly irrelevant studies. Two reviewers then independently assessed papers identified as potentially eligible studies using the inclusion criteria and resolved disagreements on inclusion by consensus, with reference to a third reviewer if necessary. This second phase thus focused on selection of studies based on the outcomes, treatment comparisons and any population subgroups (e.g. diabetes, CKD) which may have different effects of an intervention.

Hand searching identified 44 potential new trials or meta-analyses of which 9 were included in the final guidelines. During finalising of the guidelines two further meta-analyses on BP treatment in those with diabetes were identified and included.

Search terms used in the economic literature review were essentially the same for each database. A broad population identifier (CVD or cardiovascular disease OR coronary disease OR heart attack OR stroke) was used followed by the following terms: Exp “cost and cost analysis”; Costs. ti/ab; Cost effective$.ti/ab; Cost benefit analys$.ti/ab; Exp health care costs/; (economic adj2 evaluat$).ti/ab; and finally primary prevention. Additional snowballing searches were undertaken. The total number of hits was 204 of which 28 were considered in more detail by one member of the project team. Reviewing staff at Deakin University scrutinised the 16 abstracts for omissions and 9 additional appropriate papers were retrieved and reviewed.

The following criteria were used to select economic studies:

- overseas evidence in developed countries of Europe, UK, North America, Canada
- AR of cardiovascular disease criteria
- primary prevention population included has no previous history of CVD
- BP-lowering diuretics, beta blockers, CCBs, ACE inhibitors
- cholesterol-lowering medications statins
- antiplatelets (aspirin)
- adults 35–84
- health outcome measured in Disability Adjusted Life Years (DALYs) or QALYs.
### Questions 1-5: Absolute risk assessment

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**Sources:**
- Medline; Embase; Cinahl; PsychINFO; Cochrane Library, including CENTRAL Cochrane Controlled Trial Register (CCTR)
- Other sources: See protocol for details of guidelines and internet sites; pearling; EWG.

**Search terms:** as per Assessment guidelines then adapted
- CVD or cardiovascular disease OR coronary disease OR heart attack OR stroke; AR assessment OR Global risk assessment OR Multivariate risk assessment OR Framingham OR PROCAM

**Outcomes:**
- Measures of predictive accuracy; odds ratios, relative risk and risk of observed CVD events (including CVD mortality, MI, CHD, stroke, and peripheral vascular disease).

### Questions 6–8: Aims of treatment, monitoring and follow-up

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<td>31</td>
<td>(Q6) 18 (Q7 and 8) 13</td>
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**Sources a/a**

**Search Terms:**
- Multiple intervention, single intervention/treatment, monitor, cardiovascular, primary prevention, risk factors, compliance, adherence, AR, side effects.

**Outcomes:**
- Primary: CVD events (including CVD mortality, MI, CHD, stroke, and peripheral vascular disease), all case mortality
- Secondary (Q7 only): AR levels, Individual risk factor levels, Side effects, Compliance with treatment.

### Questions 9-13: Blood pressure

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**Sources a/a**

**Search Terms:**
- Blood Pressure; Antihypertensive Agents; Adrenergic beta-antagonists; DIURETICS; Angiotensin-Converting Enzyme Inhibitors Receptors, Angiotensin; Angiotensin II Type 1 Receptor Blockers, Calcium Channel Blockers; lower$ adj2 blood pressure$; centrally acting agents; alpha blockers.

**Outcomes:**
- Primary: CVD events (including CVD mortality, MI, CHD, stroke, and peripheral vascular disease), all case mortality
- Secondary (Q10 only): BP changes, microvascular complications (particularly for those with diabetes and/or CKD)

### Questions 14-17: Lipids

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**Sources a/a**
### Search Terms:

antilipemic agent; hypocholesterolemic agent$; lipid$ adj2 (low$ or depress$) lipid modifying drugs; Dislipidaemia; Statins; HMGCoA inhibitors; familial hypercholesterolemia
Added: HMGCoA Reductase; Inhibitors, Simvastatin, Clofibrate, Procetafen, Bezaftibrate, Niacin, Azetidienes, Colesevelam, Fibrate, Fenofibrate, Nicotinic Acid, Ezetimibe, Anticholesterolemic agent, Omega-3 fatty acids, Bioacids

### Outcomes:

Primary: CVD events (including CVD mortality, MI, CHD, stroke, and peripheral vascular disease), all case mortality
Secondary (Q15 only): lipid changes

### Q18-19: Antiplatelets

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#### Search Terms:

Aspirin; Platelet Aggregation Inhibitors; Clopidogrel; dipyriramole; acetyl salicylic acid; antiplatelet; Warfarin; Antithrombotic agents; Thrombin inhibitors; Thrombin receptor antagonists; Heparinoids

#### Outcomes:

Primary: CVD events (including CVD mortality, MI, CHD, stroke, and peripheral vascular disease), all case mortality
Secondary: Bleeding complications

### Q20: Obesity

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#### Search Terms:

Weight loss; weight reduction; reducing weight; Bariatric surgery; antiobesity medications; behavioural therapy

#### Outcomes:

Primary: CVD events (including CVD mortality, MI, CHD, stroke, and peripheral vascular disease), all case mortality
Secondary: Bleeding complications

### Q21: Diet and Nutrition

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#### Search Terms:

Diet; Intervention; Advice; Lifestyle; Sodium chloride/salt; Saturated fats; Antioxidants; Omega-3 fatty acids; Soy protein; Glycaemic index or load; Vegetables; Phytosterols, sterols, stanols; Nuts; Low carbohydrate; Low fat; High protein; Weight loss/ energy restriction; Fibre pectin; soluble fibre; Trans fats

#### Outcomes:

Primary: CVD events (including CVD mortality, MI, CHD, stroke, and peripheral vascular disease), all case mortality
Secondary: Blood pressure, Lipid parameters, Diabetes

### Q22-23: Physical Activity

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</tr>
</thead>
<tbody>
<tr>
<td>2002-2010</td>
<td>1211</td>
<td>103+2</td>
<td>17</td>
</tr>
</tbody>
</table>

#### Search Terms:

Exercise; sports; physical education and training; exertion; physical$ adj2 Fit; physical$ adj2 fitness; physical adj2 train$; physical adj2 activit$; train$ adj2 strength$; train$ adj2 aerobic$; aerobic$ adj2 exercise$; exercise$ adj2 train$; Added FITNESS adj (Train$ or program$); Resistance training.
### Outcomes:

**Primary:** CVD events (including CVD mortality, MI, CHD, stroke, and peripheral vascular disease), all case mortality  
**Secondary (Q23):** Blood pressure, Lipid parameters

### Q24: Alcohol

<table>
<thead>
<tr>
<th>Dates</th>
<th>Total hits</th>
<th>Retrieval list</th>
<th>Included</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002-2010</td>
<td>139</td>
<td>76</td>
<td>13</td>
</tr>
</tbody>
</table>

**Search Terms:** Alcohol Drinking; Alcohol drinking quantity; Alcohol drinking pattern; ALCOHOLIC BEVERAGES; BEER; WINE; alcohol; spirits

**Outcomes:** Primary: CVD events (including CVD mortality, MI, CHD, stroke, and peripheral vascular disease), all case mortality  
**Secondary:** Blood pressure, Lipid parameters

### Q25: Smoking

<table>
<thead>
<tr>
<th>Dates</th>
<th>Total hits</th>
<th>Retrieval list</th>
<th>Included</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002-2010</td>
<td>417</td>
<td>79</td>
<td>1</td>
</tr>
</tbody>
</table>

**Search Terms:** Smoking Cessation; “TOBACCO USE DISORDER”; TOBACCO; NICOTINE; Tobacco, Smokeless; SMOKING; (quit$ or stop$ or ceas$ or giv$) adj2 smoking; TOBACCO; SMOKE POLLUTION; Second hand smoking; Passive smoking

**Outcomes:** Primary: CVD events (including CVD mortality, MI, CHD, stroke, and peripheral vascular disease), all case mortality

### Q26 – Depression

<table>
<thead>
<tr>
<th>Dates</th>
<th>Total hits</th>
<th>Retrieval list</th>
<th>Included</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002-2010</td>
<td>1178</td>
<td>22</td>
<td>0</td>
</tr>
</tbody>
</table>

**Search Terms:** Depressive disorder; Dysthymic disorder; depression/ depression, involutional/ depression, postpartum/; Seasonal affective disorder; Major depressive disorder; Treatment pharmacological or other; Screening for depression

**Outcomes:** Primary: CVD events (including CVD mortality, MI, CHD, stroke, and peripheral vascular disease), all case mortality

### 4. Evidence tables

Data from included studies was abstracted along with a methodological appraisal (see below). This included information including citation, study type, evidence level (as per NHMRC Levels of Evidence and Grades for Recommendations for Developers of Guidelines (2009)) patient number and characteristics, intervention/s, comparison, length of follow-up, outcome measure, effect size and funding source (as appropriate).

### Methodological quality assessment

Two reviewers independently assessed the methodological quality of each included trial and resolved disagreements by consensus, with reference to a third reviewer if necessary. Methodological quality of existing guidelines was assessed using the Appraisal of Guidelines Research and Evaluation Collaboration (AGREE) Agree instrument. Methodological quality of included systematic reviews and controlled trials was assessed using a modified checklist based on the Scottish Intercollegiate Guidelines Network (SIGN) Methodology checklist for systematic reviews and meta-analyses and the Guidelines International Network draft.
evidence tables. These checklists were developed and used previously by the NSF. Methodological quality of included cohort studies was assessed using the SIGN Methodology checklist for cohort studies. For diagnostic studies identified, the SIGN Methodological checklist for diagnostic studies was used.

5. Formulation of recommendations

To assist in the formulation of recommendations, where a body of evidence exists for each question, the NHMRC Grades process has been applied. This has resulted in an Evidence Statement for each question. The project team including the chair of the EWG, along with input of individual members of the EWG or corresponding group, used these statements and the underlying evidence to draft recommendations. The draft recommendations along with the summary matrices were initially discussed by the EWG at a face-to-face meeting of the working group on 7 September 2010. In addition to the summary matrices, economic modelling on the cost benefit of various drug therapies was commissioned and used to inform the development of the recommendations. Subsequent meetings via teleconferences were undertaken followed by a modified Delphi process (over two rounds) to achieve consensus (defined as >75% of responses from EWG) of the final wording of the recommendations. The recommended grading matrix was used to guide the strength of the recommendation.

5.1 Link between research and recommendations following an absolute risk approach

These guidelines take an AR approach to the management of CVD risk which has posed some challenges in formulation of the recommendations. This is because although there is robust and compelling evidence in the published literature which clearly shows that pharmacotherapy reduces the levels of individual risk factors (blood pressure and lipids) with consequent reduction in CVD mortality or CVD events, this evidence is based on a single risk factor/relative risk approach. Therefore the expert panel carefully considered the literature before making and grading the recommendations in an AR paradigm. When examining the evidence, consideration was given to any heterogeneity found between subgroups and the generalisability of the findings. The final grading of these recommendations was downgraded to account for the uncertainty of applying evidence from a relative risk approach to an AR paradigm.

Reporting of study results

Study results have been reported in the text of these guidelines in the same form as reported in the research i.e. where relative risk reduction has been the measure used in the study, the results are reported using this term and have not been converted to AR reduction.

5.2 NHMRC grade of recommendation matrix: evidence-based recommendations

<table>
<thead>
<tr>
<th>Grade of recommendation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Body of evidence can be trusted to guide practice</td>
</tr>
<tr>
<td>B</td>
<td>Body of evidence can be trusted to guide practice in most situations</td>
</tr>
<tr>
<td>C</td>
<td>Body of evidence provides some support for recommendation but care should be taken in its application</td>
</tr>
<tr>
<td>D</td>
<td>Body of evidence is weak and recommendation must be applied with caution</td>
</tr>
</tbody>
</table>

Matrix reproduced from NHMRC Levels of Evidence and Grades for Recommendations for Developers of Guidelines (2009)
Additional guidance

Where no robust evidence was found for the search questions, the EWG followed the consensus process to develop consensus-based recommendations. Practice points were provided to give practical guidance to facilitate the implementation of the guidelines.

| CBR | Consensus-based recommendations: developed by the guidelines expert working group when a systematic review of the evidence found either an absence of direct evidence which answered the clinical question or poor quality evidence, which was deemed not to be strong enough to formulate an evidence-based recommendation. |
| PP | Practice points: developed by the guidelines expert working group where a systematic review had not been conducted but there was a need to provide practical guidance to support the implementation of the evidence-based and/or consensus-based recommendations. |

6. Consultation

6.1 Correlation with the National Evidence-Based Guideline on Secondary Prevention of Vascular Disease in type 2 diabetes

These guidelines were developed at the same time as the National Evidence-Based Guideline on Secondary Prevention of Vascular Disease in type 2 diabetes (currently being drafted). The two groups consulted extensively to ensure that the two guidelines provided a consistent continuum of care for patients (including cross representation on each advisory committee). As far as possible, given the evidence available for the different populations, the guidelines are consistent. Where there are differences in the grading of recommendations, this is due to the difference in evidence for the two populations.

5.3 Guidelines text

The body of the text was drafted by a consultant medical writer (medScript) based on an agreed framework. Early drafts were circulated for input from the EWG and finalised by the project team for public consultation.

6.2 Public Consultation

In line with the requirement under Section 14A of the National Health and Medical Research Council Act 1992, the public consultation process invited feedback during a month-long period in April 2011 and included an advertisement in the press inviting public comment. In addition, a notice of the opportunity for comment was posted on the websites of NVDPA member organisations and copies of the guidelines were distributed to a broad group of identified stakeholders and networks. Consumer organisations were also contacted for comment. Finally, the draft document was circulated via the networks of the various experts supporting the project. Five prompted questions, modified from key questions included in the Guidelines Implementability Tool, were also included in the consultation feedback form to provide general feedback.

Overall there were 388 individual comments received from 24 individuals and 19 organisations (including key organisations such as the Royal Australian College of General Practitioners, Stroke Society of Australasia, state health departments, Australian General Practice Network and the Cardiac Society of Australia and New Zealand). Public consultation resulted in many detailed responses, including many positive comments.

The major contentious issues and changes made in response to the public consultation are outlined below:
6.3 Contentious issues and responses

<table>
<thead>
<tr>
<th>Issue</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BP treatment thresholds</strong>&lt;br&gt;Concerns were raised by a number of individuals and organisations regarding the lack of a BP treatment for the low AR group. Suggestions were made to use the 160/100 mmHg threshold as had been recommended for the moderate-risk group.</td>
<td>The EWG agreed that pharmacotherapy for low risk adults is generally not appropriate taking an AR approach. However, it was agreed that a BP ≥160/100 mmHg should be treated with pharmacotherapy, both for the CVD risk and to prevent non-CVD complications such as heart failure and renal failure, therefore, a recommendation has been included to treat adults at low CVD risk who have persistent BP ≥160/100 mmHg with BP-lowering pharmacotherapy in addition to lifestyle intervention.</td>
</tr>
<tr>
<td><strong>Assessment for under 45s and over 75s</strong>&lt;br&gt;Concerns were raised about imputing age 30 and using FRE as this will overestimate risk. Similarly concern that imputing 74 will underestimate risk in the over 74 age group.</td>
<td>The EWG balanced the lack of strong evidence supporting CVD risk assessment for people aged under 45 with the need to provide some guidance for General Practitioners. The EWG therefore agreed that recommendations would not be made for CVD risk assessment of the under 45 year old age group (35 for A&amp;TSI peoples). The text has been modified to remove the recommendations for risk assessment of younger people and to include some broad guidance on ensuring that people in this age group who have a strong family history of CVD or single, isolated, elevated risk factors are appropriately managed. The text was modified for the older age group to clarify that FRE is used to ensure that age is not the only consideration when assessing risk in this age group.</td>
</tr>
<tr>
<td><strong>Moderate risk treatment</strong>&lt;br&gt;Lack of clarity about this recommendation.</td>
<td>Recommendation has been divided into two recommendations to clarify the meaning.</td>
</tr>
<tr>
<td><strong>Lipids</strong>&lt;br&gt;Queries arose regarding interpretation of the evidence especially for low-risk populations.</td>
<td>References have been reviewed and text modified to ensure that primary and secondary prevention evidence is appropriately identified. Evidence was also updated with recent meta-analyses.</td>
</tr>
<tr>
<td><strong>Monitoring</strong>&lt;br&gt;Lack of clarity about whether AR is used to monitor progress of treatment or whether treatment is monitored by individual risk factors.</td>
<td>Text inserted to explain that AR is the entry point for treatment and treatment decisions are made on the basis of risk level, but treatment response is monitored by measurement of multiple individual risk factors.</td>
</tr>
</tbody>
</table>

7. Strategy for updating the guidelines

The guidelines will need to be updated no later than five years after being published (i.e. by 2016/7). However, given the current national reform activity around guidelines and standards no decision has been made regarding the strategy to review the currency of the guidelines and any method of updating the guidelines. These decisions will be made by the NVDPA in consultation with the NHMRC and other bodies (e.g. The Australian Commission on Safety and Quality in Health Care).
8. Implementation considerations

8.1 Background

The NVDPA’s new Guidelines for the Management of Absolute Cardiovascular Disease Risk is an important step along the path to improved prevention of CVD in Australia. Of greater importance is the dissemination and application in practice. Like the guidelines themselves, implementation strategies should use an evidence-based approach based on an underlying framework for CVD prevention. In addition to the various NVDPA guideline development groups, establishment of this plan was enhanced by obtaining structured feedback at a meeting of key stakeholders (46 government, non-government, consumer and professional organisation representatives) on 3 March 2011. This meeting was called to specifically address implementation considerations from a broad range of perspectives.

8.2 Strategic framework

These guidelines are one important part of a coordinated strategic framework for improving CVD prevention in Australia. This framework includes activities at an individual and population level to raise awareness of CVD risk, assess risk and manage risk to prevent CVD as outlined in diagram 8.2. These guidelines focus only on comprehensive risk assessment and management aimed at primary prevention of CVD. Therefore, the guidelines and implementation strategies should not be considered as a standalone process but need to be linked to other important strategies both at an individual and population level to maximise their impact.

8.3 Levels to consider when implementing guidelines

Local factors operate over several different levels; all need to be considered to maximise the effect of guidelines. These levels are broadly described into four main categories: professional, organisational, consumers and regulatory/financial. Strategies to address barriers identified at each of these levels need to be developed. Strategies that enhance enabling factors should also be created. These are briefly described below:

1. Professional level: strategies supporting health professionals to adopt recommendations in the guidelines. Strategies include:

   - Risk awareness raising: help individuals identify that they may be at risk
     - General Practice: Proactive and opportunistic
     - Community settings and workplaces: Proactive

   - Comprehensive risk assessment in primary care: degree of risk determined for CVD, diabetes, CKD
     - Questions (eg. Family history)
     - Measurements (eg. Blood pressure)
     - Blood tests (eg. Cholesterol check)

   - Management and follow up in primary care: risk factors modified through lifestyle changes and/or medication
     - Low Risk
     - Moderate Risk
     - High Risk
     - Established Disease

Adapted from “Putting prevention first,” Department of Health (England) 2008
a. dissemination/distribution of the guidelines
b. education and training
c. audit and feedback, reminders or decision support tools
d. use of local consensus processes.

2. Organisational level: strategies supporting organisational change to facilitate adoption of the guidelines. Such strategies may include quality improvement systems, accreditation processes, adoption of policies and protocols.


4. Regulatory or financial level: strategies targeting regulatory systems to support change at all levels. This may include change in reimbursement items for GPs, incentives, approval and cost of medicines.

8.4 Evidence-based implementation of clinical guidelines

Several systematic reviews of evidence for guidelines implementation have been undertaken.321-329 While most strategies have been found to lead to small to moderate improvement (e.g. 5–10%) there is no simple or single strategy that will apply in all settings.326 However methodological weaknesses and poor reporting of the study setting and uncertainty about the generalisability of the results limit the strength of the conclusions.326

It is suggested that strategies to implement the guidelines will be most effective where a concrete plan is developed that tailors specific strategies based on an analysis of local factors necessary for clinical behaviour change.321 Such factors include assessment of both the barriers and enablers to achieving the recommendations in the clinical guidelines.321 More than one approach is often needed to overcome barriers because these occur at different operational levels within the health system. These levels are discussed above.

Evidence (generally focused on changes at the professional level) from recent systematic reviews indicates:

- educational meetings alone are not likely to be effective for changing complex behaviours but can be effective if used with other interventions324
- inter-professional collaboration (collaboration between professionals within and across locations) may have a positive effect in patient outcomes329
- interventions tailored to identified barriers (for example, through interactive group work) are more likely to improve professional practice than no intervention or dissemination of guidelines alone321
- printed education materials may have some benefits compared with no material but the effect is unclear compared with other interventions323
- local opinion leaders can successfully reduce non-compliance with evidence-based practice322
- quality improvement collaboratives may have some benefit, but the evidence for this, although positive, was limited.328 However, this approach has been successfully utilised by the Australian Primary Care Collaboratives (APCC) to improve best-practice care for diabetes and chronic heart disease in general practice.330

8.5 Recommended implementation activities

Considering the evidence for guideline implementation, strategies to implement the Guidelines for the Management of Absolute Cardiovascular Disease Risk will need to be chosen based on the target audience and level of focus (e.g. professional, organisational, consumer or regulatory/financial level). Each strategy will need to consider potential barriers (or enablers) and be tailored to address identified factors. Some initial examples are provided below.

Consultation with stakeholders and a review of the evidence has led to potential examples of barriers, enablers and possible solutions for each level to be considered when implementing the guidelines.
Professional level

Potential barriers

- Recommendations between different guidelines may be inconsistent, as well as guidelines presented as discrete publications
- Guidelines need to be adopted by multiple stakeholders, all of whom may have different roles to play in their implementation
- Change in clinical practice requires adopting new principles and beliefs about risk assessment and management (e.g., not treating individuals at low AR, moving away from treatment based on single risk factor targets, use of the Framingham Risk Equation, etc.)
- Education on a relative risk approach may continue for some time through other agencies
- Different descriptions/definitions of risk
- Evidence base for interventions taking an AR approach
- Health professionals (particularly GPs) have little time and heavy workloads
- Workforce shortage of allied health professionals may create issues for appropriate referral
- Training (at post graduate and undergraduate level); different curricula for different health professionals, messages from curriculum and supervisors may be inconsistent
- Relevant CVD risk data not currently integrated into medical software used in primary care
- Concept of lifestyle prescription still vague amongst health professionals and consumers
- Limited evaluation of ‘Lifescrpts’ program

Potential enablers

- APCC network and systems
- IT platforms used in most primary care settings
- Health reform including Medicare Locals, performance reporting and role of the Australian Commission on Safety and Quality in Health Care in implementation of guidelines and setting national clinical standards
- Pressure of colleagues and system
- Local champions, e.g., proposed lead clinicians groups
- Clinical and professional association networks
- Proposed expansion of practice nurse/allied health professionals roles in management of patients
**Dissemination:** Ensure broad access to information regarding new guidelines

**Target audience**
- GPs
- Practice nurses
- Health care professionals
- Medical specialists
- Clinical networks
- Primary health care organisations (PHCOs)
- Medicare Locals
- Aboriginal Health Workers and similar Health Professional Associations
- Emergency departments (especially rural)

- Publication in a variety of sources/formats:
  - summaries in medical journals
  - summaries drawing various, related guidelines together
  - use websites and NHMRC Clinical Practice Guidelines Portal
  - develop and distribute concise and/or integrated summaries
  - distribute via endorsing organisations, clinical networks and other existing networks
  - promote heavily on launch via media and PR
  - electronic dissemination and inclusion in medical software (see below)

- Presentations and educational activities (see below)
- Ensure alignment and inclusion in other guidelines, e.g. Red Book, CARPA Manual
- Use of existing industry representatives where appropriate

**Education: individuals, groups:** Move practice from relative risk to AR approach

**Target audience**
- GPs
- Practice Nurses
- Health care professionals
- Specialists
- Emergency departments
- Undergraduate and post graduate course coordinators for all health professionals

- Education resources developed and promoted e.g. algorithms (important to develop separate resources and education for indigenous population)
- Professional development. Use of key opinion leaders in educational activities:
  - workshops (face to face)
  - online educational activities
  - conference presentations
  - education outreach to individual practices
- Use existing programs, e.g. National Prescribing Service (NPS) education program, RACGP
- Link to CPD points for all relevant activities and disciplines
- Pathways (e.g. Practice protocols for GP clinics/Indigenous health providers/emergency departments to develop roles for each health professional, i.e. practice nurses, allied health in addition to GP)
- Up-skill other people, e.g. practice nurses
- Regular reminders about available programs to referring practitioners for management
- Work with undergraduate and post-graduate education providers (all relevant disciplines) to include in curriculum and communicate out to supervisors
- Use of existing industry representatives where appropriate
### Reminders or Clinical Decision Support Tools (CDST): Support practice of AR

**Target audience**

**Primary**
Medical software industry (e.g. PEN), RACGP

**Secondary**
GP, Practice nurses, specialists

- Integrate recommendations into current systems (including automatic calculation of risk)
- Integrate guidelines with other guidelines in CDST and with clinical history
- Link with audit and feedback tools
- Ensure inclusion of mechanisms to prompt management action and recall so practice IT systems can be used to send reminder letters to patients for assessment
- Resources developed and promoted, e.g. algorithms
- Consolidation of referral databases to lifestyle management programmes

### Audit and Feedback: Highlight current practice and actions for improvement

**Target audience**

GP
Practice Nurses
Practice Managers
Health care professionals
Specialists

- Build on current work to establish systems to audit clinical data to determine adherence to recommendations (including benchmarking)
- Build capacity for easily developed reports on performance at practice and individual level.
- Involvement in primary care collaborative and QI activities
- Link feedback with other strategies for education such as key opinion leaders
- Publications, conference presentations.

### Local Consensus Processes: Inclusion of participating providers in discussion to ensure that they agree that the chosen clinical problem is important and the approach to managing the problem is appropriate

**Target audience**

GP
Practice nurses
Specialists
Primary health care organisations (PHCOs)
Health care professionals

- Involvement in primary care collaborative and QI activities
- Supported discussions at local level to develop consensus
- Solutions to improve systems for QI (see organisational level solutions)
- Use existing programs and clinical and association networks.
Consumer level

Potential barriers

- Concept of risk (particularly AR) is complex and difficult to explain
- Behaviour change recommended in guidelines often difficult to maintain (particularly lifestyle and maintaining medications over time)
- Consumers often at GP for reasons other than a risk assessment
- Consumers may receive too much information and material that is too complex
- Concept of lifestyle prescription still vague amongst health professionals and consumers
- Social, geographical and cultural barriers to access to services (particularly A&TSI communities and those in remote settings)

Potential enablers

- Health reform establishing new agencies that may support implementation (e.g. National Prevention Agency and its social marketing activities)
- Other agencies developing information for consumers that may send common messages (e.g. RACGP Red Book, CARPA Manual, NPS fact sheets)
- Community networks e.g. NACCHO and its state organisations

Potential activities at consumer level

Education or systems to involve consumers: Improves awareness, engagement and adherence to management

Target audience
General population >45 years old (> 35 years if A&TSI population)
Consumer Health Forum, relevant peak and professional bodies who are involved in producing information for consumers

- Develop online and printed educational materials for consumers including simple explanations of risk
- Support inclusion of common consumer messages in communication channels of other agencies and websites (e.g. Consumers Health Forum, NACCHO, Better Health channel, RACGP Red Book, NPS, etc.)
- Campaigns educating people of CVD risk, and need for risk assessments
- Include consumers in development of material and develop in line with standard health literacy levels and also consider Indigenous and Culturally and Linguistically Diverse (CALD) backgrounds
- Develop online consumer tools aimed at prompting discussion with GP
- Develop evidence-based tools health professionals can use to demonstrate risk and how it will change over time and through modification of risk factors.
Potential activities at organisational level

**Organisational level**

**Potential barriers**

- Data for quality improvement, and to support decision making is not integrated into clinical software
- Uncertainty around data integrity and validity
- Time required to record and analyse data and plan quality improvement activities
- Geographical barriers in rural and remote services (limited access to adequate staffing and equipment)
- Other agencies may promote data based on relative risk approach

**Potential enablers**

- Practices already undertaking QI activities
- RACGP developing primary care audit activities
- Health reform including Medicare Locals, performance reporting and role of the Australian Commission on Safety and Quality in Health Care in implementation of guidelines and setting national clinical standards
- Existing ‘Lifescripts’ program and diabetes lifestyle programs
- Electronic health records activity

**Systems to focus on quality improvement:** Improves access to quality improvement systems

**Partners**

- RACGP
- Australian College of Rural and Remote Medicine (ACRRM)
- APCC

- Develop nationally agreed performance indicators related to CVD risk reduction
- Improve data collection systems and develop mechanisms to interrogate data and feedback areas for improvement to practices (and other areas such as CVD and related disease admissions)
- Integrate tools and data into medical software
- Continue to promote practice support programs focusing on IT and data collection
- Consider more intense QI programs which offer practice visits to analyse data broadly, provide feedback and identify gaps that can drive quality improvement
- Information targeted especially to users: GP vs. practice nurse vs. Aboriginal health workers
- Link other strategies at professional level (e.g. feedback and education)
- Advertise/encourage practices to become involved in APCC around CVD prevention
- Reallocate roles or add workforce to focus on implementing guidelines
- Introduction of technology, e.g. electronic transmission of ECG and echocardiography from regional to metropolitan centres
- Change organisational structure and processes designed to improve implementation (e.g. new GP super clinic, or Medicare Locals)
- Make sure strong input from key opinion leaders (including proposed Lead Clinicians Groups and other existing clinical governance bodies)
### Regulatory/financial level

#### Potential barriers
- Concerns about the potential costs of guideline recommendations
- Potential disconnect between current reimbursement for PBS items and new recommendations
- Current Medicare Benefits Schedule (MBS) policy does not support practice recommended in guidelines
- Limitations of other government policies e.g. Enhanced Primary Care limit of five annual visits prevents people from receiving a range of specialist care

#### Potential enablers
- Home medicines review program
- New preventative health agenda
- Current additional supports in MBS and Pharmaceutical Benefits Scheme (PBS) for Indigenous and Torres Strait Islander peoples
- Current MBS review
- Electronic health records activity
- Development of Medicare Locals
- Accreditation activities

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### Potential activities at regulatory/financial level

**Policy change:** System change to support practice of AR

**Partners**
- Australian Government Department of Health and Ageing (MBS, PBS, Preventive Health Agency)
- APCC
- NHMRC/NICS, Commission on Safety and Quality
- NPS

- Undertake economic modelling around guideline implementation to provide evidence for policy decision making
- Explore the Practice Incentives Program to identify opportunities to support system and practice change
- Review of PBS criteria for medications recommended in the guidelines to ensure consistency
- Policy change to support programs identifying people in the community who may require risk assessment and management
- Review Enhanced Primary Care program to broaden scope and provide incentives for private allied health practices
- Link and integrate policy and programs for related diseases (e.g. vascular, diabetes and kidney)
Appendix 3:
Economic Considerations

This report was prepared by: Anne Magnus, Deakin Health Economics, Strategic Research Centre- Population Health.

Economic evaluation of NVDPA Guidelines for the Management of Absolute Cardiovascular Disease Risk

1.0 Introduction

Cardiovascular disease is the most expensive disease group in Australia in terms of annual direct health care costs which have been recently estimated to be more than $5.2 billion in 2004–05. Therefore, providing cost-effective cardiovascular disease prevention, management and treatment is important to avoid unnecessary costs to society. This report presents a review of the cost-effectiveness literature on evidence-based CVD prevention with pharmacotherapy. A systematic review was conducted as part of the guidelines process (see Appendix 2, Guidelines development process report for search strategy). As the breadth of pharmaceuticals under study was wide (incorporating BP-lowering, cholesterol-lowering agents, aspirin and combinations of the same) and the methods used quite disparate, a narrative review was deemed the most appropriate way to summarise the cost-effectiveness evidence. The literature was firstly assessed for internal validity of each paper and secondly assessed for its generalisability to the Australian context.

The need to review the cost-effectiveness literature occurs because, although a newly proposed strategy may be more clinically effective than the comparator, it may also cost more to achieve additional health benefits. Or the reverse situation can occur, where the proposed strategy is less clinically effective but costs less to achieve its benefits. In an ideal setting, the proposed strategy would yield both more benefits and cost less than the current strategy, i.e. it would dominate current practice by saving more health and saving dollars. The most efficient strategy is the one with the lowest incremental cost-effectiveness ratio (ICER). The strategy with the lowest ICER is not necessarily the one with the most total health benefits or the one with the least total expenditure. What constitutes a cost-effective intervention is a value judgment and is not the only policy objective used in the evaluation of proposed changes in the health sector, as more expensive treatments may be considered necessary on the basis of value judgements. In previous Australian policy decisions, $30,000–50,000 per QALY saved has been considered to represent value-for-money from the perspective of the health sector.

2.0 Aim of the guidelines

The aim of the Guidelines for Management of Absolute CVD Risk project is to develop high-quality clinical guidelines and resources for management of CVD risk using an absolute risk approach in adults aged over 45 years (35 for Aboriginal and Torres Strait Islander peoples) with no previous history of CVD. The Guidelines for Management of Absolute CVD Risk make recommendations that relate to the use of medications listed on the PBS. The development process has included an economic assessment of the cost-effectiveness of initiation and on-going use of CVD preventive drug therapy (including BP-lowering medications, cholesterol-lowering medications and potentially antiplatelets) by AR criteria and a comparison of this approach with the impact and costs currently incurred by the health system around the use of these medications. Current practice in Australia is not easy to describe in detail, but is informed by the previously existing individual risk factor management guidelines, such as those for management of hypertension and lipid levels. Limited survey data of current prescribing patterns in Australia reflect departures from the perfect adoption of the existing individual risk factor management guidelines.
2.1 Economic question within the proposed guidelines

Is the AR approach to prevention of CVD in adults aged over 45 years (35 for Aboriginal and Torres Strait Islander peoples) with no history of CVD, more cost-effective than current practice from a health sector perspective, considering lifetime costs and benefits of pharmacotherapy which includes BP-lowering medications, cholesterol lowering statins and antiplatelets?

2.2 The economic framework of the literature review

The objective of this review was to answer the economic research question by reference to the available literature. This required estimating the additional direct health sector cost per additional unit of effect gained, measured in life years adjusted for quality, using a robust, consistent and standard method.

3.0 Steps in the economic evaluation

The internal validity of the studies for each class of drug was undertaken for each drug separately and in combinations, since this more closely approximated the recommendations of the guidelines. Studies which examined the drugs in comparison to placebo were excluded as the objective was not to assess the cost-effectiveness of these drugs compared to doing nothing, but rather to compare to current practice or some other consideration of patient risk profile.

3.1 Evaluation of internal validity

Using a well-respected strategy proposed by Drummond, the following items were used to critically appraise the economic literature for internal validity:

- Was the study question well defined?
- Were appropriate health care options chosen and clearly described?
- Was the effectiveness of the health care options established?
- Were all the relevant costs and consequences identified for each health care option?
- Were costs and consequences measured accurately?
- Were costs and consequences valued credibly?
- Was differential timing considered?
- Was incremental analysis performed?
- Was a sensitivity analysis performed?
- Were all issues of concern presented with results?

3.2 Evaluation of external validity and generalisability to the Australian situation

Once the evidence from the literature was gathered, each of the major components of an economic evaluation (i.e. clinical, economic, epidemiological, health care patterns, treatment comparators) was verified versus Australian conditions before a study’s results were deemed potentially transferable. To this end the patient group, the health system, the prevention strategy options, the incremental costs and benefits, and other factors relating to these particular guidelines were considered.

4 Internal Validity

4.1 Single use of drugs

a) Aspirin

Selection of studies

Five studies examined the cost-effectiveness of aspirin for single use in the prevention of CVD. Since it is an inexpensive drug, even the small health benefits reported in various meta-analyses noted within these guidelines would yield a favourable cost-effectiveness ratio. However, the absolute benefit of aspirin in addition to other effective pharmacotherapy (to lower BP or lipids) is unclear, while underpowered recent evidence raises questions of the health benefits at the risk of important side effects, therefore its use for primary prevention has not been recommended in these guidelines. For this reason no further evaluation of the cost effectiveness of aspirin has been included.

b) Lipid-lowering pharmacotherapy

Selection of studies

Five studies examined the cost-effectiveness of statins for single use in the prevention of CVD. Gumbs et al was a systematic review of older cost-effectiveness literature and Pilote et al a cost outcome study with subgroup analysis, so was of limited relevance to this review. The remaining four studies were all evaluations using Markov models (two set in the US and two in the UK), comparing single use of a statin with either current practice or no statin use (an ambiguous comparator situation that may include the use of other drugs). The schARR models relating to the UK health system were the best examples of model
design and economic evaluation, giving consideration to all important elements of model design, validation and cost-effectiveness assessment that others have excluded, e.g. much sensitivity analysis and consideration of comparators, discount rates and compliance issues therefore were included in the analysis.

**Statins**

Ward et al estimated the discounted cost per QALY for primary prevention using statins (as a drug class) at the age of 45 ranged between £9,500 and £30,500 for men and women as annual CHD risk levels ranged from 3% to 0.5%. By the age of 85 years the corresponding values were £36,800 and £110,600. In the UK setting the value for money threshold is usually considered to be between £20,000 to £30,000 per QALY, making these drugs cost effective for the younger age groups. Ward et al particularly highlight greater uncertainty in the results for young persons, which arose in the modelling due to the requirement to extrapolate benefits well beyond the timeframes of the trials, and particularly so in the case of young people.

The US studies extrapolated trial based efficacy data over a timeframe of 5–25 years rather than lifetime. Ramsay et al reported a drug company-funded study and concluded that when prescribing atorvastatin compared to no statins, there was a need to give the expensive drug for a long time before it became cost effective. At five years the ICER for atorvastatin was US$137,000/QALY (i.e. not cost effective) whereas after 25 years the intervention was dominant (i.e. both cost and health saving). While Ramsey et al was one of the more relevant studies it used a shorter timeframe for analysis and was silent concerning the impact of compliance with therapy. Pletcher et al assessed the cost-utility of ATPIII guidelines compared to current practice and concluded that the guidelines would be cost-effective when statin prices were moderate. However Pletcher et al included the costs of unrelated future health care events within their analysis, excluded consideration of strokes, and used a shorter time horizon for evaluation of benefits and costs.

**Ezetimibe**

The other scHARR model developed by Ara et al evaluated the use of ezetimibe as monotherapy and concluded there was enormous uncertainty around its cost-effectiveness credentials due to the short-term trial periods for establishment of efficacy. There was a wide range of results depending on the treatment strategies compared. When comparing ezetimibe monotherapy with no treatment in individuals with baseline LDL-C values of 3.0–4.0 mmol/L, the results ranged from £21,000 to £50,000 per QALY (i.e. some treatments were cost effective). Results for individuals with baseline LDL-C values over 5.0 mmol/L were below £30,000 per QALY (i.e. all treatments were cost effective).

c) Blood pressure-lowering pharmacotherapy

**Selection of studies**

Four studies were found and examined. Lundkvist et al was eliminated because it evaluated placebo as the comparator to BP-lowering treatment. One study related to the US, one to the UK and the remaining study presented ICERs for four European countries. A number of weaknesses appeared in the European study comparison including reliance on efficacy results from a small trial (n=59), adoption of the Framingham risk prediction equations developed in the US without calibration to local population events, adoption of the same utility weights for vastly different clinical conditions (MI and angina: stroke and TIA), and non translation of local country costs to a comparable unit. The results of this study, while relevant, were considered of limited use here.

**ACE Inhibitors**

The US study examined the cost effectiveness of ACE inhibitor therapy as first-line BP-lowering therapy compared to conventional BP-lowering therapy with beta blockers or diuretics and presented the ICERs over a lifetime in 40-year-old males only, concluding that the ICERs were unattractively high.

d) Combination pharmacotherapy

**Selection of studies**

Eleven studies were identified that evaluated various combinations of the drugs of interest to this review. Studies were selected that included aspirin as an element of the intervention or comparator even though it was not evaluated as monotherapy. These combination therapy evaluations were expected to provide more insight into the potential cost-effectiveness of the proposed guidelines, however, issues of internal validity were found, that limited their usefulness. Two were eliminated as they pertained to developing countries and Argentina, and were outside the scope of this evaluation. Three were eliminated as they were cost-effectiveness studies which measured cost per reduction in BP or cardiac event prevented or coronary event free life years. It was necessary to have a common
unit of benefit measurement, which made these studies of limited value without translation into QALYs. No cost offsets were incorporated for cardiac events prevented by the intervention in two studies.\textsuperscript{350,352} This meant that the costs of all the relevant alternatives had not been included in the analysis. The comparator was either not clearly stated or referred to as ‘no intervention’ in four studies.\textsuperscript{350-354} As no drug regime was stipulated clearly as comparator, the cost-effectiveness ratios presented in these studies was of limited value. The remaining two studies (Newman \textit{et al} and Ara \textit{et al}) were stronger economic evaluations having none of these aforementioned limitations but they were somewhat limited in scope to either males only\textsuperscript{355} or the drug ezetimibe,\textsuperscript{225} prescribed in addition to statins in patients not achieving adequate lipid control on statins. Newman \textit{et al} did not clearly state the perspective of the analysis, or the timeframe for measurement of costs and benefits which limited interpretation of the results. Ara \textit{et al} considered all the relevant issues for a sound cost-effectiveness study but were limited in their modelling by the paucity of clinical information. Ara \textit{et al} concluded that comparing the costs and benefits of adding ezetimibe to ongoing statin treatment with maintaining statin treatment at the current dose, the lifetime ICERs range from £25,000 to £66,000 per QALY for the primary cohorts.

Another issue of concern was the use of US-based Framingham risk equations to predict CVD events in UK or Europe without calibration to relevant country CVD risk profiles and events. It was also uncommon to find Markov models that have been validated against other source data. There was little discussion of adherence/compliance assumptions stated in the modelling when this can have an impact on both costs and consequences.\textsuperscript{356} Negative side effects of therapy were not always included in analyses and therefore the impact of these remains unclear.

5.0 External validity

5.1 Patient group

Cardiovascular risk factor profile

In assessing the role of any strategy for primary CVD prevention in Australia it is important to know the number of CVD events that would be prevented in actual practice as that is the number that generates the economic impact. The baseline population risk of an event is determined by the presence of CVD risk factors which include age, elevated BP, cholesterol, BMI, smoking, family history of CHD and diabetes. It is this baseline risk that will be reduced by the relative risk reduction reported in trials conducted either in Australia or elsewhere. In order to produce meaningful comparisons, the Australian population CVD risk factor profile should be the same as the population profile in cost-effectiveness studies and modelling conducted in other countries. This analysis examined age, BP, cholesterol and BMI as CVD risk factors to assess the usefulness of the international cost-effectiveness findings.

Increasing age is a CVD risk factor. There is a higher proportion in the over 65 years category (16.6% and 18.3%) in both the European and UK 2010 populations respectively, than in Australia and the US (13.6% and 14.0% respectively). On this CVD risk factor Australia has a similar risk profile to the US, without giving consideration to gender distribution.
## Population age structure, International comparison(a) – at 30 June

<table>
<thead>
<tr>
<th>Selected countries</th>
<th>2010</th>
<th>2015(b)</th>
<th>2010-2015</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aged 0–14 years</td>
<td>Aged 15–64 years</td>
<td>Aged 65 years and over</td>
</tr>
<tr>
<td>Australia</td>
<td>18.9</td>
<td>67.5</td>
<td>13.6</td>
</tr>
<tr>
<td>Canada</td>
<td>16.3</td>
<td>69.6</td>
<td>14.1</td>
</tr>
<tr>
<td>China (excl. SARs and Taiwan)</td>
<td>19.9</td>
<td>71.9</td>
<td>8.2</td>
</tr>
<tr>
<td>Hong Kong (SARs of China)</td>
<td>11.5</td>
<td>75.6</td>
<td>12.9</td>
</tr>
<tr>
<td>France</td>
<td>18.4</td>
<td>64.6</td>
<td>17.0</td>
</tr>
<tr>
<td>Greece</td>
<td>14.2</td>
<td>67.5</td>
<td>18.3</td>
</tr>
<tr>
<td>India</td>
<td>30.8</td>
<td>64.3</td>
<td>4.9</td>
</tr>
<tr>
<td>Indonesia</td>
<td>26.7</td>
<td>67.2</td>
<td>6.1</td>
</tr>
<tr>
<td>Italy</td>
<td>14.2</td>
<td>65.4</td>
<td>20.4</td>
</tr>
<tr>
<td>Japan</td>
<td>13.2</td>
<td>64.2</td>
<td>22.6</td>
</tr>
<tr>
<td>Republic of Korea</td>
<td>16.2</td>
<td>72.8</td>
<td>11.0</td>
</tr>
<tr>
<td>Malaysia</td>
<td>29.1</td>
<td>66.1</td>
<td>4.8</td>
</tr>
<tr>
<td>New Zealand</td>
<td>20.2</td>
<td>66.8</td>
<td>13.0</td>
</tr>
<tr>
<td>Papua New Guinea</td>
<td>39.5</td>
<td>58.1</td>
<td>2.5</td>
</tr>
<tr>
<td>Philippines</td>
<td>33.5</td>
<td>62.2</td>
<td>4.3</td>
</tr>
<tr>
<td>Singapore</td>
<td>15.6</td>
<td>74.2</td>
<td>10.2</td>
</tr>
<tr>
<td>South Africa</td>
<td>30.3</td>
<td>65.1</td>
<td>4.6</td>
</tr>
<tr>
<td>Sweden</td>
<td>16.5</td>
<td>65.2</td>
<td>18.3</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>17.4</td>
<td>66.0</td>
<td>16.6</td>
</tr>
<tr>
<td>United States of America</td>
<td>20.2</td>
<td>66.8</td>
<td>13.0</td>
</tr>
<tr>
<td>Vietnam</td>
<td>25.1</td>
<td>68.6</td>
<td>6.3</td>
</tr>
<tr>
<td><strong>World</strong></td>
<td><strong>26.9</strong></td>
<td><strong>65.5</strong></td>
<td><strong>7.6</strong></td>
</tr>
</tbody>
</table>

(a) Selected countries included major OECD countries, the world's most populous countries, Australia's closest neighbours and trading partners.

(b) International data are United Nations medium variant projections. Australian data are ABS medium series (Series B) projections.

(c) Births per woman. United Nations are medium variant projections for the period 2010–2015.

(d) Life expectancy at birth. United nations are medium variant projections for the period 2010–2015, for males and females combined.

Source: All international data and Australian total fertility rate and life expectancy figures have been sourced from World Population Prospects, 2008 Revision. Australian 2010 estimates from this publication are from ABS, Australian Demographic Statistics (cat. no. 3101.0) and Australian 2015 population projections are from ABS, Population Projections, Australia 2006 to 2101 (cat. no. 3222.0).
5.2 Framingham prediction equations

Any application of Framingham CVD prediction equations (developed in the US population), in international studies should be first validated or recalibrated to local population data. This is rarely done and makes the health benefits reported in UK and European studies subject to bias (overestimation or underestimation depending on the risk factor prevalence). When Framingham based predictions are applied in models to US data, the length of time elapsed since the estimation of the equations is also important to consider, since CVD rates have fallen in the US beyond what could be attributed to shifts in risk factors alone.

5.3 Gender-based data

There is limited data from clinical studies in women so greater uncertainty surrounds estimates of cost-effectiveness of any drug therapy in this group.

5.4 Health system setting

Exactly what constitutes service delivery in UK, US Europe and Australia requires consideration of access to services and service offerings. There will be variability in the rates of conducting procedures, the types of staff working/treating in and out of hospital settings. What is considered a health sector cost or health funder cost within these different country settings differs due to system funding structures (i.e. the relative mix of public/private/out of pocket costs). What constitutes ‘usual care’ or current conventional care will differ between countries and has not necessarily been enumerated in the studies covered in this review. Results taken from any other country require consideration of all these factors before further consideration of translation of local currency into a common currency and year for comparison purposes.

5.5 Health care option

For effective comparison, the comparators should be relevant to the policy question within the proposed guidelines. Thus this review has not considered placebo as a valid comparator, but rather current practice since the aim was to evaluate alternative mixes of existing drugs rather than the addition of a new adjunctive therapy. In considering the proposed health care options, caution was taken since the reviewed modelling over the lifetime of the population far exceeded the timeframe of trials that contributed benefits of drug therapy. Trial-based assessments of costs can be quite different from routine practice in that additional monitoring may have been required, thus the trial based costings were not readily generalisable without adjustment to a routine setting.
5.6 Resource costs

Prices of drugs vary over time as patents expire and prescribing patterns may or may not shift to more generic drugs. This can contribute to different results in cross-country comparisons and drug price has often been identified in sensitivity analysis as the most important factor influencing the cost-effectiveness outcomes. This was particularly relevant to the evaluation of expensive statin therapy and should be factored in to any future modelling in the Australian setting. US costs are higher than other countries and have been quite often valued on the basis of cost-to-charge ratios since data was more readily available on charges in administrative databases. This made the resulting estimates further questionable in comparison with Australia.

Compliance with therapy has been previously highlighted as an issue that has an effect on the generalisability of a cost-effectiveness study. Compliance affects costs in an unknown direction since scripts can be filled but not taken (keeping costs high but without benefit) or scripts may not be filled (reducing overall costs and benefits). Irregular drug use, affecting costs and unknown impact on benefits has not been accounted for in any of the models considered here. Compliance can be measured in trials in several ways, but it is not well studied in the long term past 3–5 years. The real impact of compliance is unknown and assumptions need to be made in each study and the impact on the results compared in sensitivity analysis.

5.7 Marginal versus average cost

Studies that presented average costs of preventive therapy were not considered. Studies estimating the incremental cost effectiveness of therapy were included, since this evidence informs the research question.

5.8 Other specific issues relating to the guidelines

For resource allocation policy impact, consideration of final health outcomes such as mortality and morbidity should be made in preference to intermediate health outcomes such as reduction in cholesterol or BP. To this end all studies not presenting results in the desired format have been excluded.

6.0 Conclusion

It is difficult to extrapolate cost-effectiveness results from international studies to the Australian context given differences in health services provision and funding, pharmaceutical pricing policies and practices, and the potential variations in CVD risk in target populations. Overall the evidence from overseas studies was particularly limited, not only by the number of suitable studies found which were relevant to the issues addressed in the Guidelines for Management of Absolute CVD Risk, but also by several questions relating to internal validity and by some considerable issues with external validity which prevented the direct application of overseas cost-effectiveness conclusions to the Australian situation. However, despite the limitations, one consistent conclusion recurring in most analyses wherever conducted was the sensitivity of cost-effectiveness results to statin prices.

7.0 Further work

As the review of international cost-effectiveness literature did not yield useful evidence with which to compare the new guidelines, specific cost modelling of the recommendations using Australian data has also been undertaken by external consultants as part of the guidelines development process. This process included cost effectiveness modelling for various drugs, which was used to inform the development of the recommendations. Further modelling was done after completion of the recommendations, to determine the total costs and the cost effectiveness of the finalised recommendations.
Table 1. Analysis of studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Publication year</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Study setting</th>
<th>Type of evaluation</th>
<th>Gender</th>
<th>Age</th>
<th>Risk factor/ co-morbidity</th>
<th>Analytic horizon</th>
<th>Discounting</th>
<th>Perspective</th>
<th>Compliance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annemans et al</td>
<td>2006</td>
<td>Low-dose aspirin with omeprazole</td>
<td>Placebo</td>
<td>UK Germany Spain and Italy</td>
<td>Cost utility</td>
<td>Both</td>
<td>50, 55, 60</td>
<td>Patient groups at 2%, 3%, 4%, 5% risk of a fatal coronary heart disease event in 10 years using SCORE algorithm</td>
<td>10 yrs</td>
<td>Country- specific rates for both costs and benefits applied. The rates vary from 3% to 6%</td>
<td>Health care payer</td>
<td>No statement</td>
</tr>
<tr>
<td>A'ra et al</td>
<td>2008</td>
<td>Ezetimibe in combination with statins</td>
<td>Statin monotherapy</td>
<td>UK</td>
<td>Cost utility</td>
<td>Both</td>
<td>60</td>
<td>Individuals who have not achieved cholesterol control with statins</td>
<td>Lifetime</td>
<td>3.5%</td>
<td>National Health Service</td>
<td>Discussed</td>
</tr>
<tr>
<td>Earnshaw et al</td>
<td>2011</td>
<td>Low dose aspirin with omeprazole 20 mg/d</td>
<td>Low dose aspirin alone,</td>
<td>US</td>
<td>Cost utility</td>
<td>Men</td>
<td>45, 55, 65</td>
<td>A range of underlying 10 year CHD risk (2.5%, 5%, 7.5%, 10%, 15%, 25%)</td>
<td>Lifetime</td>
<td>3%</td>
<td>Third-party payer</td>
<td>100% assumed</td>
</tr>
<tr>
<td>Franco et al</td>
<td>2007</td>
<td>Smoking cessation to smokers, aspirin</td>
<td>No intervention</td>
<td>Netherlands</td>
<td>Cost effectiveness</td>
<td>Men</td>
<td>45-55 &amp; 55-65</td>
<td>Framingham study participants meeting age and risk thresholds (low moderate and high)</td>
<td>10 years</td>
<td>4%</td>
<td>Third-party payer</td>
<td>No statement</td>
</tr>
<tr>
<td>Gaziano et al</td>
<td>2006</td>
<td>Aspirin, CCB, ace inhibitor and statins for primary prevention</td>
<td>No treatment</td>
<td>Developing country regions (WHO)</td>
<td>Cost utility</td>
<td>Both</td>
<td>35-74</td>
<td>Multiple levels of 10-year risk for CHD</td>
<td>Lifetime</td>
<td>3%</td>
<td>Societal</td>
<td>Sensitivity analysis</td>
</tr>
<tr>
<td>Greving et al</td>
<td>2008</td>
<td>Low-dose aspirin, no quantity listed</td>
<td>No aspirin</td>
<td>Netherlands</td>
<td>Cost utility</td>
<td>Both</td>
<td>45, 55, 65</td>
<td>At various levels of 10 year cardiovascular disease risk based on number of risk factors</td>
<td>10 yrs</td>
<td>4% for costs &amp; 1.5% for benefits</td>
<td>Health care payer</td>
<td>No statement</td>
</tr>
<tr>
<td>Grover et al</td>
<td>2008</td>
<td>Lipid treatment or hypertension management</td>
<td>Not stated</td>
<td>Canada</td>
<td>Cost effectiveness (averages)</td>
<td>Both</td>
<td>40–74</td>
<td>2,121 participants surveyed from the Canadian heart health survey without CVD who qualify for lipid treatment or hypertension management</td>
<td>Lifetime</td>
<td>3%</td>
<td>Health care system</td>
<td>No statement</td>
</tr>
<tr>
<td>Jonsson et al</td>
<td>2003</td>
<td>Anti hypertensive treatment with felodipine</td>
<td>The lowest change in BP</td>
<td>26 countries</td>
<td>Cost effectiveness</td>
<td>Both</td>
<td>60–80</td>
<td>18,790 trial patients with hypertension</td>
<td>Trial length of 3.8 yrs</td>
<td>None</td>
<td>Societal</td>
<td>No statement</td>
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<tr>
<td>Lamotte et al</td>
<td>2006</td>
<td>Low-dose aspirin</td>
<td>No aspirin</td>
<td>Europe, 4 countries</td>
<td>Cost utility</td>
<td>Both</td>
<td>Not specified</td>
<td>1.5% 10-year risk of a coronary heart disease event</td>
<td>10 yrs</td>
<td>Country specific</td>
<td>Public healthcare payer</td>
<td>No statement</td>
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<tr>
<td>Lungqvist et al</td>
<td>2005</td>
<td>Candesartan anti hypertensive treatment</td>
<td>Placebo</td>
<td>Europe</td>
<td>Cost utility</td>
<td>Both</td>
<td>70–89</td>
<td>Elderly patients with mild to moderate hypertension</td>
<td>Lifetime</td>
<td>3%</td>
<td>Societal</td>
<td>No statement</td>
</tr>
<tr>
<td>Marshall et al</td>
<td>2006</td>
<td>Treatment with aspirin or up to 4 BP-lowering drugs and statins</td>
<td>Do nothing</td>
<td>UK</td>
<td>Cost effectiveness</td>
<td>Both</td>
<td>Not specified</td>
<td>Taken from the Health Survey for England of 1998 using eligibility criteria for treatments with Joint British recommendations</td>
<td>10 yrs</td>
<td>3%</td>
<td>Health services</td>
<td>100% assumed</td>
</tr>
<tr>
<td>Montgomery et al</td>
<td>2003</td>
<td>Hypertensive medication not specified clearly</td>
<td>No treatment not further specified</td>
<td>UK</td>
<td>Cost utility</td>
<td>Both</td>
<td>30-70</td>
<td>Low- and high-risk groups defined with smoking, BP, diabetes, etc</td>
<td>Lifetime</td>
<td>6% for costs &amp; 1.5% for benefits</td>
<td>Health services</td>
<td>Discussed</td>
</tr>
</tbody>
</table>

Table 1. Target Population
<table>
<thead>
<tr>
<th>Author</th>
<th>Publication year</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Study setting</th>
<th>Type of evaluation</th>
<th>Gender</th>
<th>Age</th>
<th>Risk factor/ co-morbidity</th>
<th>Analytic horizon</th>
<th>Discounting</th>
<th>Perspective</th>
<th>Compliance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murray et al</td>
<td>2003</td>
<td>Statin, diuretic, BP-lowering drug and aspirin</td>
<td>No intervention</td>
<td>3 World regions</td>
<td>Cost utility</td>
<td>Both</td>
<td>30-100</td>
<td>People with an estimated combined risk of 10 years of heart disease over the next decade above a given threshold. Thresholds reported as 35%, 25%, 15%, 5%</td>
<td>100 yrs</td>
<td>3%</td>
<td>Decision makers not further specified</td>
<td>Discussed</td>
</tr>
<tr>
<td>Newman et al</td>
<td>2008</td>
<td>Polypill combination therapy of simvastatin, captopril, hydrochlorothiazide and amlodipine</td>
<td>Current standard care</td>
<td>US</td>
<td>Cost utility</td>
<td>Men</td>
<td>&gt;65 yrs</td>
<td>Regardless of baseline risk factors</td>
<td>Not stated</td>
<td>3%</td>
<td>Not stated</td>
<td>100%</td>
</tr>
<tr>
<td>Neyt et al</td>
<td>2009</td>
<td>Low dose pravastatin</td>
<td>Smoking cessation, or aspirin interventions</td>
<td>Belgium</td>
<td>Cost effectiveness</td>
<td>Men</td>
<td>50 &amp; 60 yrs</td>
<td>Moderate and high risk of coronary heart disease</td>
<td>10 yrs</td>
<td>3% for costs &amp; 1.5% for benefits</td>
<td>Belgian decision makers</td>
<td>Discussed</td>
</tr>
<tr>
<td>Nordman et al</td>
<td>2003</td>
<td>ACE inhibitors to all</td>
<td>Conventional therapy</td>
<td>US</td>
<td>Cost utility</td>
<td>Men</td>
<td>40 yrs</td>
<td>Requiring antihypertensives but no other comorbidity</td>
<td>Lifetime</td>
<td>5%</td>
<td>Third-party payer</td>
<td>Sensitivity analysis</td>
</tr>
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<td>Pignone et al</td>
<td>2006</td>
<td>Low-dose aspirin, a statin, both drugs as a combination</td>
<td>No therapy</td>
<td>US</td>
<td>Cost utility</td>
<td>Men</td>
<td>65 yrs old</td>
<td>Various levels of 10-year risk for CHD</td>
<td>Lifetime</td>
<td>3%</td>
<td>Third-party payer</td>
<td>100% assumed</td>
</tr>
<tr>
<td>Pignone et al</td>
<td>2007</td>
<td>Aspirin</td>
<td>No therapy</td>
<td>US</td>
<td>Cost utility</td>
<td>Women</td>
<td>65 yrs</td>
<td>7.5% 10-year risk of a coronary heart disease event</td>
<td>Lifetime</td>
<td>3%</td>
<td>Third-party payer</td>
<td>100% assumed</td>
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<tr>
<td>Piotte et al</td>
<td>2005</td>
<td>Lipids to people w/o CVD</td>
<td>Lipids to people with CVD</td>
<td>Canada</td>
<td>Cost outcome with subgroup analysis</td>
<td>Both</td>
<td>30-74</td>
<td>Population survey with Canadian Heart Health Survey</td>
<td>Lifetime</td>
<td>5%</td>
<td>Societal</td>
<td>No statement</td>
</tr>
<tr>
<td>Fletcher et al</td>
<td>2009</td>
<td>ATP III guidelines and a number of risk based and age-based strategies</td>
<td>Current practice</td>
<td>US</td>
<td>Cost utility</td>
<td>Both</td>
<td>35-65</td>
<td>10-year CHD risk varying from &gt; 0 to &gt;15%</td>
<td>30 years</td>
<td>3%</td>
<td>Healthcare system</td>
<td>100% assumed</td>
</tr>
<tr>
<td>Ramsay et al</td>
<td>2008</td>
<td>10mg/day atorvastatin</td>
<td>No HMG-CoA reductase inhibitor (statin) therapy</td>
<td>US</td>
<td>Cost utility</td>
<td>Both</td>
<td>&gt;20 yrs</td>
<td>People with type 2 diabetes, and one additional risk factor (retinopathy, albuminuria, current smoking or hypertension), but no CVD history</td>
<td>6,10,25 years</td>
<td>3%</td>
<td>US payer</td>
<td>No statement</td>
</tr>
<tr>
<td>Schwander et al</td>
<td>2009</td>
<td>eprosartan</td>
<td>enalapril</td>
<td>6 countries within Europe</td>
<td>Cost utility</td>
<td>Both</td>
<td>Adult</td>
<td>Populations of 6 European countries</td>
<td>Lifetime</td>
<td>Country-specific rates for both costs and benefits applied. The rates vary from 3% to 5%</td>
<td>European health care-payer perspective</td>
<td>Compliance entered to the model</td>
</tr>
<tr>
<td>Ward et al</td>
<td>2007</td>
<td>Statins for primary and secondary prevention of CHD or CVD</td>
<td>Non use of statins</td>
<td>UK</td>
<td>Cost utility</td>
<td>Both</td>
<td>45-85</td>
<td>Multiple levels of risk for CHD in next 10 years</td>
<td>Lifetime</td>
<td>6% for costs &amp; 1.5% for benefits</td>
<td>National Health Service</td>
<td>Accounts for increasing non-compliance for 5 years and holds constant from then on</td>
</tr>
<tr>
<td>Study</td>
<td>Base year/ currency</td>
<td>Cost-effectiveness results</td>
<td>Relevance/quality/ comments</td>
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</table>
| Annemans et al 2006 | 2003 Euros         | Low-dose aspirin is dominant in all countries at all levels of risk except for Italy due to the higher cost of a gastrointestinal bleed there.                                                                        | Not relevant  
Aspirin not relevant to the guidelines  
Compared to placebo  
Sponsorship from Bayer                                                                 |
| Ara et al 2008      | 2006 British pounds | The lifetime results for treatment Scenario 1 (ezetimibe 10 mg plus current weighted statin versus current weighted statin titrated by one dose) range from £24,000 per QALY for males aged 45 years with a baseline LDL-C of 3.5mmol/L and no history of CVD to £62,000 per QALY for females aged 75 years with a baseline LDL-C of 2.5 mmol/L and no history of CVD. | Relevant study  
Well-designed cost-utility study that acknowledges limitations in the source data  
National Institute for Health Research HTA Programme sponsored                                                                 |
| Earnshaw et al 2011 | 2009 US$           | Treatment with aspirin for CHD prevention is less costly and more effective than no treatment in men > 45 years with > 10-year, 10% CHD risks.                                                                 | Not relevant  
Aspirin not relevant to the guidelines  
Sponsorship from Bayer                                                                 |
| Franco et al 2007   | 2003 Euros         | The most cost-effective treatment is smoking cessation therapy, representing savings in all situations. Statin therapy is the least cost-effective treatment (ranging from €73,971 to €19,027 per YLS). Aspirin was the second most cost-effective intervention (ranging from €2,263 to €16,949 per YLS) followed by antihypertensive treatment (ranging from Euros 28,187 to Euros 79,843 per YLS). These rankings were maintained for all age group/risk group categories analysed. A cut-off value for the ICER of Euros 20,000 per YLS was chosen | Limited relevance  
Some quality considerations including: Not a cost-utility study, limited to males, initial comparator is no intervention, 10-year time horizon, adverse events not included  
Sponsorship from the Netherlands Heart Foundation                                                                 |
Conducted for developing countries  
Sponsorship from Fogarty International Centre, National Institutes of Health                                                                 |
| Greving et al 2008  | 2005 Euros         | Aspirin treatment for primary prevention is cost-effective for men with a 10-year CVD risk of >10% and for women with a risk of >15%. This occurs much later in life for women than men.                                           | Not relevant  
Aspirin not relevant to the guidelines  
Sponsorship from Netherlands Organization for Health Research and Development                                                                 |
| Grover et al 2008   | 2002 Canadian $    | The average cost-effectiveness of lipid therapy would be approximately CA$16,700 per YOLS while hypertension therapy would be approximately CA$37,100 per YOLS                                                                 | Limited relevance  
Not a cost-utility study  
Incremental results not presented  
Sponsorship from Astra Zeneca                                                                 |
<table>
<thead>
<tr>
<th>Study</th>
<th>Base year/ currency</th>
<th>Cost-effectiveness results</th>
<th>Relevance/quality/comments</th>
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</thead>
<tbody>
<tr>
<td>Gumbs et al 2007</td>
<td>Review</td>
<td>Policymakers who want to use economic evaluations should use those that employed appropriate methodology and produced valid results. In that regard it seems that policymakers are better informed using recent publications, as the quality of considered studies appears to have increased over time. However policymakers should remain critical regarding the methodology employed as the overall quality of the policy context economic evaluations is disappointing. This review focused on the methodology employed by the studies but policymakers should also consider whether the results are applicable to their own setting.</td>
<td>Focussed on quality of the economic evaluations&lt;br&gt;Not included in Table 1&lt;br&gt;Sponsorship not stated</td>
</tr>
<tr>
<td>Jonsson et al 2003</td>
<td>1995 Swedish Krona</td>
<td>The CV-related health care cost per patient during 3.8 years of follow-up was SEK32, 000 and SEK35,000 for the target groups 90 and 80 DBP, respectively.</td>
<td>Not relevant.  Cost-effectiveness study of cost per reductions in BP&lt;br&gt;Some quality considerations including:- no discussion of compliance issues&lt;br&gt;Sponsorship from Astra Zeneca</td>
</tr>
<tr>
<td>Lamotte et al 2006</td>
<td>2003 Euros</td>
<td>In patients at low risk of CHD and low risk of gastrointestinal bleed, low-dose aspirin is cost-effective. For patients with an annual risk of CHD of 1.5%, the model resulted in 10-year savings with low-dose aspirin of on average €201, 281, 797, and 427 per patient in UK, Germany, Spain and Italy respectively.</td>
<td>Not relevant  &lt;br&gt;Aspirin not relevant to the guidelines&lt;br&gt;Compared to placebo&lt;br&gt;Sponsorship from Bayer</td>
</tr>
<tr>
<td>Lundkuist et al 2005</td>
<td>2001 Euros</td>
<td>Candesavtan-based antihypertensive treatment was associated with 0.0289 additional QALY per patient and an incremental cost per QALY gained of approximately €13,000.</td>
<td>Not relevant&lt;br&gt;Compared to placebo&lt;br&gt;Sponsorship not stated</td>
</tr>
</tbody>
</table>
| Marshall 2006         | 1996 British Pounds | Cost per cardiovascular event prevented is strongly determined by cardiovascular risk. For any treatment it is over £45 000 in an individual at under 10%, 10-year CVD risk and under £30 000 for any treatment in a patient at over 45%, 10-year CVD risk. | Not relevant<br>Cost-effectiveness evaluation per change in risk category<br>Some quality considerations including:- the costs of coronary events is not included in the comparisons of health states, age not specified, short 10-year time horizon, comparator is do nothing.  
Sponsored by UK Medical Research Council Training fellowship and UK NHS Primary Career Scientist Award |
| Montgomery et al 2003 | 2002 British Pounds | In terms of cost-effectiveness, treatment was more effective, but also cost more than non-treatment for all age, sex, and risk strata except the oldest high-risk men and women. Incremental cost per QALY among low-risk groups ranged from £1030 to £3304. Cost-effectiveness results for low-risk individuals were sensitive to the utility of receiving antihypertensive treatment. Treatment of high-risk individuals was highly cost effective, such that it was the dominant strategy in the oldest age group, and resulted in incremental costs per QALY ranging from £34 to £265 in younger age groups. | Relevant study<br>Some quality considerations including: differential discount rates applied to costs and benefits, no adverse events were included, the treatment intervention was not described in detail, only strokes and myocardial infarctions considered, Framingham equations applied without calibration to the population under study  
Sponsored by UK Medical Research Council Training fellowship and UK NHS Primary Career Scientist Award |
<table>
<thead>
<tr>
<th>Study</th>
<th>Base year/currency</th>
<th>Cost-effectiveness results</th>
<th>Relevance/quality/comments</th>
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<tbody>
<tr>
<td>Murray et al 2003</td>
<td>2000 International dollars using purchasing power parity exchange rates</td>
<td>Combination treatment for people whose risk of a cardiovascular event over the next 10 years is above 35% is cost effective leading to substantial additional health benefits by averting an additional 63 million DALYs per year worldwide. The absolute-risk approach at a threshold of 35% is always more cost effective than treatment based on either the measured systolic BP or the measured cholesterol concentration. From the perspective of how best to achieve the best population health for the available resources, the optimum overall strategy is a combination of the population-wide and individual-based interventions.</td>
<td>Relevant study. Some quality considerations including: Comparator was no intervention, no cost offsets were included for cardiac events prevented. Sponsorship not stated.</td>
</tr>
<tr>
<td>Newman et al 2008</td>
<td>2003/04 US$</td>
<td>Under baseline assumptions, combination polypharmacy was less expensive and more effective than the current standard, namely, no treatment. Thus, the use of combination polypharmacy was a dominant strategy.</td>
<td>Relevant study. Some quality considerations including: limited to males ≥55 years, the analytic time horizon and perspective not stated. Sponsorship not stated.</td>
</tr>
<tr>
<td>Neyt et al 2009</td>
<td>2007 Euros</td>
<td>The results showed that smoking cessation is an intervention that should be encouraged. Low-dose aspirin was more cost-effective ranging from €3.854/LYG to €29.509/LYG compared to smoking cessation for smokers and ranging from €401/LYG to €13,451/LYG compared to no-treatment for non-smokers. The results for statin treatment are less cost effective. Only for the high risk group aged 60, the cost-effectiveness was about €30,000/LYG under the assumption that the cheapest alternative statin would be prescribed. For other subgroups the ICER for statin treatment was about €50,000/LYG.</td>
<td>Limited relevance. Some quality considerations including: limited to males, aged 50 and 60, the analytic time horizon was only 10 years, differential discounting applied to costs and benefits, the comparator interventions are less relevant than current practice. Sponsorship stated as ‘no external funding’.</td>
</tr>
<tr>
<td>Nordmann et al 2003</td>
<td>1999 US$</td>
<td>The cost-effectiveness ratios are unattractively high: US$200,000 per QALY gained for the echocardiology strategy (compared with ECG), and US$700,000 for the ‘ACE inhibitor for all’ strategy (compared with ECG). The incremental cost effectiveness of prescribing ACE inhibitor therapy to everybody was never less than US$100,000/QALY in the sensitivity analysis.</td>
<td>Relevant study. Some quality considerations including: 40-year-old males only. Sponsorship not stated.</td>
</tr>
<tr>
<td>Pignone et al 2006</td>
<td>2003 US$</td>
<td>For 45-year-old men who do not smoke, are not hypertensive and have a 10-year risk for CHD of 7.5%, aspirin was more effective and less costly than no treatment. The addition of a statin to aspirin therapy produced an incremental cost-utility ratio of US$56,200 per quality-adjusted life-year gained compared with aspirin alone. The addition of a statin is more cost-effective as risk increases.</td>
<td>Relevant study. Some quality considerations including: limited analysis of 45 year old males, the comparator is aspirin and no therapy. Sponsorship from Bayer.</td>
</tr>
<tr>
<td>Pignone et al 2007</td>
<td>2005 US$</td>
<td>Aspirin use cost US$13,300 per additional QALY gained in the base case. Results were sensitive to age, CVD risk, relative risk reductions with aspirin for ischaemic strokes and MI, excess risk of haemorrhagic stroke and gastrointestinal bleeding, and the disutility of taking medication. Probabilistic sensitivity analysis for 65-year-old women at moderate CVD risk found a 27% chance that aspirin produces fewer QALYs than no treatment, a 35% chance that the cost-utility ratio was less than US$50,000 per QALY gained, and a 37% probability that it was greater than US$50,000 per QALY gained.</td>
<td>Not relevant. Aspirin not relevant to the guidelines. Sponsorship from Bayer.</td>
</tr>
<tr>
<td>Study</td>
<td>Base year/currency</td>
<td>Cost-effectiveness results</td>
<td>Relevance/quality/comments</td>
</tr>
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<tr>
<td>Pilote et al 2005</td>
<td>1996 Canadian$</td>
<td>Among the surveyed individuals with a TC level higher than 6.2mmol/L the proportions of individuals for which lipid-lowering therapy was cost-effective (at a threshold level of CA$50,000/year of life saved) were 85.6% of men and 28.7% of women for primary prevention.</td>
<td>Limited relevance. Average cost effectiveness only. Not a cost-utility study. Sponsorship provided by a grant from the Fonds de la Recherche en Santé de Québec.</td>
</tr>
<tr>
<td>Pletcher et al 2009</td>
<td>2006 US$</td>
<td>Full adherence to ATP III primary prevention guidelines would require starting (9.7 million) or intensifying (1.4 million) statin therapy for 11.1 million adults and would prevent 20,000 myocardial infarctions and 10,000 CHD deaths per year at an annual net cost of US$3.6 billion (US$42,000/QALY) if low-intensity statins cost US$2.11 per pill. The ATP III guidelines would be preferred over alternative strategies if society is willing to pay US$50,000/QALY and statins cost US$1.54 to US$2.21 per pill. At higher statin costs, ATP III is not cost-effective; at lower costs, more liberal statin-prescribing strategies would be preferred; and at costs less than US$0.10 per pill, treating all persons with low-density lipoprotein cholesterol levels greater than 3.4 mmol/L (130 mg/dl) would yield net cost savings.</td>
<td>Relevant study Some quality considerations including: Study included unrelated health care costs. Shorter than lifetime horizon analysed Sponsorship from Flight Attendants Medical Research Institute and Swanson Family Fund</td>
</tr>
<tr>
<td>Ramsey et al 2008</td>
<td>2005 US$</td>
<td>Within the time horizon of the trial (5 years), the cost effectiveness of atorvastatin was US$137,276 per QALY. At 10 years, the incremental cost per QALY improved to US$3,640 per QALY. At 25 years, the overall costs were lower and QALYs higher in the atorvastatin arm. Costs of managing CV events were lower after five years for patients treated with atorvastatin. For patients with type 2 diabetes and one additional risk factor for CV disease, normal LDL-cholesterol and no history of a CV event, primary prevention with atorvastatin appears to be cost saving and improve outcomes over 25 years although it is costly from a short-term US-payer perspective.</td>
<td>Relevant study Some quality considerations including: Cost of adverse events not included No statement on compliance Sponsored by Pfizer</td>
</tr>
<tr>
<td>Schwander et al 2009</td>
<td>2007 Euros</td>
<td>Comparing eprosartan to enalapril in a primary prevention setting the mean costs per quality adjusted life year (QALY) gained were highest in Germany (€24,036) followed by Belgium (€17,863), the UK (€16,364), Norway (€13,834), Sweden (€11,691) and Spain (€7,918).</td>
<td>Relevant study Some quality considerations including: no adverse events included, utility weights applied may not be appropriate, Framingham equations applied without calibration to the population under study, effectiveness data taken from one small trial (n=59) Sponsored by Solvay Pharmaceuticals</td>
</tr>
<tr>
<td>Ward et al 2007</td>
<td>2004 British Pounds</td>
<td>The cost-effectiveness of statins depends on the CHD risk in the population treated and the age and gender of the population under consideration. In primary prevention the discounted cost per QALY estimates for primary prevention at the age of 45 range between £9,500 and £30,500 for men and women as annual CHD risk levels fall from 3% to 0.5%. By the age of 85 years the corresponding values are £36,800 and £110,600</td>
<td>Relevant study High-quality study except for differential discount rates applied to costs and benefits National Institute for Health Research HTA Programme sponsored</td>
</tr>
</tbody>
</table>
Appendix 4: Assessment and Management summary

Risk Assessment and Management Algorithm: Adults aged 45 years and over without known history of CVD

**Already known to be at increased risk?**

Adults with any of the following conditions do not require absolute CVD risk assessment using the Framingham Risk Equation because they are already known to be at clinically determined high risk of CVD: *(EBR: Grade D)*

- Diabetes and age >60 years
- Diabetes with microalbuminuria (>20 mcg/min or urinary albumin:creatinine ratio >2.5 mg/mmol for males, >3.5 mg/mmol for females)
- Moderate or severe CKD (persistent proteinuria or estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m²)
- A previous diagnosis of familial hypercholesterolaemia
- Systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg
- Serum total cholesterol >7.5 mmol/L

---

**Calculate risk level using Framingham Risk Equation (EBR: Grade B):**

- Australian cardiovascular risk charts
- Web calculator (www.cvdcheck.org.au)
- Enter age 74 for adults aged 74+ *(CBR)*

**Is one of the following present?**

- BP persistently ≥160/100 mmHg
- Family history of premature CVD
- South Asian, Middle Eastern, Maori or Pacific Islander peoples

**Moderate:** 10-15% risk of CVD within the next 5 years *(PP)*

- Provide lifestyle advice and support *(CBR)*

**Is one of the following present?**

- BP persistently ≥160/100 mmHg
- Family history of premature CVD
- South Asian, Middle Eastern, Maori or Pacific Islander peoples

---

**High:** greater than 15% risk of CVD within the next 5 years (includes clinically determined high risk) *(PP)*

- Provide frequent and sustained lifestyle advice, support and follow-up *(CBR)*
- Commence BP + lipid-lowering therapy unless contraindicated or clinically inappropriate *(EBR: Grade B)*

---

**Monitor response *(PP)*

- Review absolute risk according to clinical context *(PP)*

---

**Review absolute risk in 6-12 months *(PP)*

---

**Review absolute risk in 2 years *(PP)*

---

**Has risk improved?**

- Review absolute risk in 6-12 months *(PP)*

---

**Review absolute risk in 6-12 months *(PP)*

---

**Review absolute risk in 2 years *(PP)*

---

**EBR: Evidence-based recommendation (Graded A-D) CBR: Consensus-based recommendation PP: Practice point**
Risk Assessment and Management Algorithm:
Aboriginal and Torres Straight Islander adults aged 35 and over without known history of CVD

**Already known to be at increased risk?**

Adults with any of the following conditions do not require absolute CVD risk assessment using the Framingham Risk Equation because they are already known to be at clinically determined high risk of CVD:  
**EBR: Grade D**

- Diabetes and age >60 years
- Diabetes with microalbuminuria (>20 mcg/min or urinary albumin:creatinine ratio >2.5 mg/mmol for males, >3.5 mg/mmol for females)
- Moderate or severe CKD (persistent proteinuria or estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m²)
- A previous diagnosis of familial hypercholesterolaemia
- Systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg
- Serum total cholesterol >7.5 mmol/L
- Aboriginal and Torres Strait Islander adults aged over 74  

**Conduct formal absolute risk assessment**

Calculate risk level using Framingham Risk Equation  
**EBR: Grade B:**

- Australian cardiovascular risk charts
- Web calculator www.cvdcheck.org.au

**High:** greater than 15% risk of CVD within the next 5 years (includes clinically determined high risk)  

- Provide frequent and sustained lifestyle advice, support and follow-up  
- Commence BP + lipid lowering therapy unless contraindicated or clinically inappropriate  

**Moderate:** 10-15% risk of CVD within the next 5 years  

- Identify all other risk factors
- Continue with lifestyle intervention
- Treat for BP and/or lipid-lowering

**Low:** less than 10% risk of CVD within the next 5 years

- Provide lifestyle advice

**Is BP persistently ≥160/100mmHg?**

**YES**

- Treat BP
- Continue with lifestyle advice

**NO**

- Monitor response

**Review absolute risk in 2 years**  

**Review absolute risk according to clinical context**  

**Review absolute risk in 6-12 months**  

**Monitor individual risk factor response to treatment**

**EBR: Evidence-based recommendation (Graded A-D), CBR: Consensus-based recommendation, PP: Practice Point**
<table>
<thead>
<tr>
<th>CVD risk</th>
<th>Lifestyle</th>
<th>Pharmacotherapy</th>
<th>Targets</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High risk</strong></td>
<td>Frequent and sustained specific advice and support regarding diet and physical activity.</td>
<td>Treat simultaneously with lipid lowering unless contraindicated or clinically inappropriate.</td>
<td>Not routinely recommended BP: ≤140/90 mmHg in general or people with CKD; ≤130/80 mmHg in all people with diabetes; ≤130/80 mmHg if micro or macro albuminuria (UACR &gt; 2.5 mg/mmol in men and &gt;3.5 mg/mmol in women</td>
<td>BP and lipids monitored at approx 6 weekly intervals until sufficient improvement achieved or maximum tolerated dose reached.</td>
</tr>
<tr>
<td>Clinically determined</td>
<td>Appropriate advice, support and pharmacotherapy for smoking cessation.</td>
<td>Consider other treatable causes for raised BP before starting therapy.</td>
<td>Adjust medication as required.</td>
<td>Review of AR according to clinical context.</td>
</tr>
<tr>
<td>Diabetes and age &gt;60 years</td>
<td>Advice given simultaneously with blood pressure and lipid lowering pharmacotherapy</td>
<td>Commence with ACE inhibitor OR angiotensin receptor blocker OR CCB OR Low dose thiazide or thiazide-like diuretic.</td>
<td>Lipids: TC &lt; 4.0 mmol/L; HDL-C ≥ 1.0 mmol/L; LDL-C &lt;2.0 mmol/L; Non HDL-C &lt;2.5 mmol/L; TG &lt; 2.0 mmol/L.</td>
<td></td>
</tr>
<tr>
<td>Diabetes with microalbuminuria</td>
<td>For diabetes or CKD commence with ACE inhibitor or angiotensin receptor blocker.</td>
<td>Add second or third agent from different class as needed towards target.</td>
<td>Lifestyle: Smoking cessation (if smoker); consume diet rich in vegetables and fruit, low in salt and saturated and trans fats; at least 30 mins physical activity on most or preferably every day of the week; limit alcohol intake.</td>
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<tr>
<td>(&gt;20 mcg/min or UACR &gt;2.5 mg/ mmol for males, &gt;3.5 mg/mmol for females)</td>
<td>Add fenofibrate, nicotinic acid or fish oil to statin if TG levels not sufficiently reduced.</td>
<td>Consider withdrawal of therapy for people who make profound lifestyle changes.</td>
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<tr>
<td>Moderate or severe CKD</td>
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<tr>
<td>(persistent proteinuria or eGFR &lt;45 mL/min/1.73 m²)</td>
<td>Add ezetimibe, bile acid binding resin or nicotinic acid if LDL-C levels not sufficiently reduced or required dose of statin not tolerated. Use these agents as monotherapy if statins not tolerated at all.</td>
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<tr>
<td>A previous diagnosis of FH</td>
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<td>SBP ≥180 mmHg or DBP ≥110 mmHg</td>
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<tr>
<td>Serum TC &gt;7.5 mmol/L</td>
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<tr>
<td>A&amp;TSI adults aged &gt;74 years or calculated using FRE as &gt;15% AR of CVD events over 5 years</td>
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</table>
## Risk Management Summary - Moderate Risk

<table>
<thead>
<tr>
<th>CVD risk</th>
<th>Lifestyle</th>
<th>Pharmacotherapy</th>
<th>Targets</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Moderate risk</strong>&lt;br&gt;Calculated using FRE as 10–15% AR of CVD events over 5 years</td>
<td>Appropriate, specific advice and support regarding diet and physical activity.</td>
<td>Not routinely recommended&lt;br&gt;Consider BP lowering if 3–6 months of lifestyle does not reduce risk.&lt;br&gt;Consider BP-lowering therapy in addition to lifestyle advice if:&lt;br&gt;• BP persistently ≥160/100 mmHg&lt;br&gt;• Family history of premature CVD&lt;br&gt;• Specific population where the FRE underestimates risk e.g. A&amp;TSI peoples, South Asian, Maori and Pacific Islander, Middle Eastern.&lt;br&gt;Consider other treatable causes for raised BP before starting therapy.&lt;br&gt;Commence any agent as for high risk. Add second or third agent from different class as needed to reach target. Consider withdrawal of therapy for people who make profound lifestyle changes.</td>
<td>Not routinely recommended&lt;br&gt;Consider lipid lowering if 3–6 months of lifestyle does not reduce risk.&lt;br&gt;Consider lipid-lowering therapy in addition to lifestyle advice if:&lt;br&gt;• Family history of premature CVD&lt;br&gt;• Specific population where the FRE underestimates risk e.g. A&amp;TSI peoples, South Asian, Maori and Pacific Islander, Middle Eastern.&lt;br&gt;Consider other treatable causes for dyslipidaemia before starting therapy.</td>
<td>BP: ≤140/90 mmHg in general or people with CKD; ≤130/80 mmHg in all people with diabetes; ≤130/80 mmHg if micro or macro albuminuria (UACR &gt; 2.5 mg/mmol in men and &gt;3.5 mg/mmol in women)</td>
</tr>
</tbody>
</table>

### BP: ≤140/90 mmHg in general or people with CKD; ≤130/80 mmHg in all people with diabetes; ≤130/80 mmHg if micro or macro albuminuria (UACR > 2.5 mg/mmol in men and >3.5 mg/mmol in women)
- Lipids: TC <4.0 mmol/L; HDL-C ≥1.0 mmol/L; LDL-C <2.0 mmol/L; Non HDL-C <2.5 mmol/L; TG <2.0 mmol/L
- Lifestyle: Smoking cessation (if smoker); consume diet rich in vegetables and fruit, low in salt and saturated and trans fats; at least 30 mins physical activity on most or preferably every day of the week; limit alcohol intake.

### BP and lipids monitored at approx 6 weekly intervals until sufficient improvement achieved or maximum tolerated dose reached.

### Adjust medication as required.

### Review of AR every 6–12 months
## Risk Management Summary - Low Risk

<table>
<thead>
<tr>
<th>CVD risk</th>
<th>Lifestyle</th>
<th>Pharmacotherapy</th>
<th>Targets</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>Brief, general lifestyle advice regarding diet and physical activity.</td>
<td>BP lowering Not routinely recommended.</td>
<td>BP: ≤140/90 mmHg in general or people with CKD; ≤130/80 mmHg in all people with diabetes; ≤130/80 mmHg if micro or macro albuminuria (UACR &gt;2.5 mg/mmol in men and &gt;3.5 mg/mmol in women</td>
<td>BP monitored at approx 6 weekly intervals until sufficient improvement achieved or maximum tolerated dose reached. Adjust medication as required. Review AR every 2 years. Blood test results within 5 years can be used.</td>
</tr>
<tr>
<td></td>
<td>Appropriate advice, support and pharmacotherapy for smoking cessation</td>
<td>Lipid lowering Not routinely recommended</td>
<td>Lipids: TC &lt;4.0 mmol/L; HDL-C ≥1.0 mmol/L; LDL-C &lt;2.0 mmol/L; Non HDL-C &lt;2.5 mmol/L; TG &lt; 2.0 mmol/L</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Antiplatelet Not routinely recommended</td>
<td>Lifestyle: Smoking cessation (if smoker); consume diet rich in vegetables and fruit, low in salt and saturated and trans fats; at least 30 mins physical activity on most or preferably every day of the week; limit alcohol intake.</td>
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</tbody>
</table>

**A&TSI**: Aboriginal and Torres Strait Islander peoples; **BP**: Blood Pressure; **CKD**: Chronic Kidney Disease; **DBP**: Diastolic Blood Pressure; **FH**: Familial Hypercholesterolaemia; **FRE**: Framingham Risk Equation; **HDL-C**: High Density Lipoprotein Cholesterol; **LDL-C**: Low Density Lipoprotein Cholesterol; **SBP**: Systolic Blood Pressure; **TC**: Total Cholesterol; **TG**: Triglycerides.
Appendix 5:
Recommendations for future research

The recommendations in these guidelines have been developed from the current evidence base, using methodology from NHMRC Levels of Evidence and Grades for Recommendations for Developers of Guidelines (2009) to appraise and evaluate the quality of the evidence. However, these guidelines are based on an AR approach rather than assessing individual risk factors. Almost all of the research reviewed during the development process selected study participants based on one or more factors (but not on a formal comprehensive risk assessment considering a number of factors together). This has meant a larger number of practice points are provided compared with previous guidelines which have used a single risk factor approach. This difference in single verses AR highlights major gaps in evidence for this approach. Hence a list of future research priorities has been included here. Research priorities should be based on consideration of the burden of disease, the potential to conduct high quality research in the area and the potential impact on health outcomes.

Assessment tools

- Validation of the FRE or other tools in populations including the aged and adults aged 18-30 years and determination of the optimum age for risk assessment.
- Investigation of the extra predictive value of significant risk factors that are not currently included in the FRE such as obesity, physical inactivity, family history of CVD, socioeconomic status and psychosocial factors.
- Comparison of the predictive value of emerging biomarkers with current risk assessment tools.
- Development of a risk assessment equation for people already on pharmacotherapy for blood pressure or lipid lowering.

Absolute risk prediction in specific subpopulations

- Investigation of new or modified tools for absolute CVD risk assessment based on risk equations specific to the Australian population, especially the indigenous population.
- Determination of the best predictive tool for people with diabetes and/or CKD.

Treatment

- Clinical trials for pharmacotherapy to lower blood pressure or lipids to be conducted and analysed using AR selection criteria.
- Clinical trials of the value of including aspirin for management of CVD risk using an AR approach in combination with blood pressure and/or lipid lowering therapy.
- New combination therapies such as various versions of the Polypill to be investigated for effect on population AR reduction.
• Studies of lifestyle measures to be conducted with more methodological rigour, such as statistically significant sample sizes, exclusion of people with CVD at baseline, and appropriate time for follow-up.

Cost effectiveness of absolute risk

• Detailed local study of the cost effectiveness of various AR assessment tools compared to current practice to determine whether AR improves outcomes and reduces health care costs;

• Study of the cost effectiveness of various health system models for identification and management of chronic diseases.

Patient adherence

• High quality study comparing different interventions for improvement of patient adherence to medication.

• Communication of risk information to consumers

• Development of an effective method for communication to consumers of AR status and the potential impact of management strategies.
Glossary of terms

Abdominal obesity
Excess body fat predominantly around the waist.

Absolute risk (global risk, total risk)
The numerical probability of an event occurring within a specified period, usually expressed as a percentage. (e.g. 5-year AR of 15% means there is a 15% probability that the individual will experience a cardiovascular event within five years).

Absolute risk reduction
The arithmetic difference between event rates in two groups (e.g. the rates of CVD in a lipid-lowering treatment group subtracted from the rate in the untreated group). For any given relative risk reduction, the AR reduction decreases when event rates are low in the given population.

Albuminuria
The presence of excessive amounts of a protein called albumin in the urine.

Anti-platelet agents
Medicines that reduce the risk of abnormal blood clotting (e.g. aspirin, clopidogrel).

Atrial fibrillation (AF)
Rapid, irregular beating of the heart which can mean that the heart is not pumping efficiently.

Blood pressure (BP)
The pressure of the blood against the inner walls of the arteries as it is pumped around the body by the heart. Blood pressure varies from moment to moment and is affected by factors such as body position, breathing, emotional state, physical activity and sleep.

Body mass index (BMI)
A calculated number used to identify and measure underweight, overweight or obesity, calculated from a person’s height and weight. BMI = weight (in kg) divided by height (in m) squared.

Cardiovascular disease (CVD)
Group term for all medical conditions affecting the heart or blood vessels (e.g. coronary heart disease, stroke, peripheral arterial disease, some types of kidney disease).

Cardiovascular events
Group of outcomes which may vary between trials but normally includes myocardial infarction, stroke, death from a vascular cause (including coronary, pulmonary embolism, haemorrhage) or any arterial revascularisation procedure.

Cholesterol
See lipids.

Chronic heart failure (CHF)
A condition in which the heart does not pump blood effectively, typically resulting in breathlessness and fatigue.

Chronic kidney disease (CKD)
Long-term inability of the kidney/s to function normally, most commonly caused by diabetes, inflammation of the kidneys or high blood pressure.

Cochrane review
A comprehensive systematic review and meta-analysis (where possible).

Cohort studies
A type of medical research in which a selected group of people is studied over time, often over a period of several years.
Coronary heart disease (CHD)
A disease in which arteries that surround the heart and supply blood to the heart muscle become partly blocked.

Diabetes mellitus (diabetes)
A long-term disease that affects the way body cells take up and use glucose (sugar) from the blood, resulting in abnormally high levels of glucose in the blood.

Dyslipidaemia
An abnormal amount of lipids (e.g. cholesterol or triglycerides) in the blood, usually abnormally high levels.

Family history of CVD
A family history of premature cardiovascular disease refers to an event that occurs in relatives including parents, grandparents, uncles and/or aunts before the age of 55 years.

Familial hypercholesterolaemia
An inherited condition in which removal of cholesterol from the blood is reduced, causing high blood cholesterol levels and early heart disease in some families.

Framingham Risk Equation
A statistical method of predicting an individual's likelihood of developing CVD within the next five or 10 years, based on risk factors such as age, sex and blood pressure.

Hypertension
Raised blood pressure.

Lipids
Fatty substances naturally occurring in the blood (cholesterol and triglycerides).

Macroalbuminuria
A raised level of albumin in the urine (more than 300mg of albumin in the urine per day).

Microalbuminuria
A slightly raised level of albumin in the urine (between 30 mg and 300 mg per day).

Myocardial infarction (heart attack)
Temporary loss of blood supply to the heart muscle, typically caused by a blood clot that suddenly blocks a narrowed artery. This can result in heart muscle damage.

Non HDL-C: The cholesterol in low density lipoprotein, intermediate density lipoprotein and very low density lipoprotein.

Peripheral arterial disease (PAD)
Disease affecting the arteries other than those of the heart or brain.

Proteinuria
The presence of excessive amounts of protein (>150 mg per day) in the urine. These proteins are typically albumin, but also consist of low molecular weight immunoglobulin, lysozyme, insulin and beta-2 microglobulin.

Relative risk (RR)
The ratio of the rate of events (e.g. CVD) in the population exposed to a risk factor to the rate among the unexposed population (e.g. the risk of someone developing a CVD event who has a given set of risk factors, compared with the risk in someone of the same age and sex who does not have those risk factors).

Relative risk reduction (RRR)
The difference in event rates between two groups (e.g. treatment group versus control group), expressed as a proportion of the event rate in the untreated group. Often remains constant whether event rates are high or low within the population.

Renovascular disease
Cardiovascular disease affecting the blood vessels supplying the kidney.

Risk factor
A characteristic of a person (or people) that is positively associated with a particular disease or condition.

Stroke
Sudden loss of blood supply to the brain (e.g. due to blockage of an artery by a blood clot, or because the artery breaks or bursts).

TC: HDL ratio
Total cholesterol divided by high density lipoprotein. Used in the Framingham Risk Equation.

Triglycerides
See Lipids.
**Abbreviations**

ACE: Angiotensin-converting enzyme  
AF: Atrial fibrillation  
APCC: Australian Primary Care Collaboratives  
AR: Absolute risk  
ARB: Angiotensin receptor blocker  
A&TSI: Aboriginal and Torres Strait Islander Peoples  
AUC: Area Under the ROC curve  
BP: Blood pressure  
BMI: Body mass index  
CAD: Coronary artery disease  
CCB: Calcium channel blocker  
CHD: Coronary heart disease  
CKD: Chronic kidney disease  
CI: Confidence interval  
CVD: Cardiovascular disease  
DALY: Disability adjusted life years  
DBP: Diastolic blood pressure  
DoHA: Department of Health and Ageing  
ECG: Electrocardiography  
EGFR: Estimated glomerular filtration rate  
EWG: Expert working group  
FRE: Framingham Risk Equation  
GFR: Glomerular filtration rate  
GP: General practitioner  
HDL: High-density lipoprotein cholesterol (also HDL-C)  
HMG-CoA: 3-hydroxy-3-methylglutaryl-coenzyme A (statin)  
ICER: Incremental cost-effectiveness ratio  
LDL: Low-density lipoprotein cholesterol (also LDL-C)  
LVH: Left ventricular hypertrophy  
MBS: Medicare Benefits Schedule  
MI: Myocardial infarction  
NHMRC: National Health and Medical Research Council  
NNT: Numbers needed to treat  
NVDPA: National Vascular Disease Prevention Alliance  
OGTT: Oral Glucose Tolerance Test  
OR: Odds ratio  
PBAC: Pharmaceutical Benefits Advisory Committee  
PBS: Pharmaceutical Benefits Scheme  
QALY: Quality adjusted life year  
RACGP: Royal Australian College of General Practitioners  
RCT: Randomised controlled trial  
RR: Relative risk  
RRR: Relative risk reduction  
SBP: Systolic blood pressure  
SCORE: Systematic Coronary Risk Evaluation project  
SR: Systematic review  
TC: Total cholesterol  
TG: Triglyceride  
TIA: Transient ischaemic attack  
UACR: Urinary albumin:creatinine ratio  
UKPDS: United Kingdom Prospective Diabetes Study
Bibliography


An initiative of the National Vascular Disease Prevention Alliance