NATIONAL EVIDENCE-BASED GUIDELINE ON
SECONDARY PREVENTION OF CARDIOVASCULAR DISEASE IN TYPE 2 DIABETES

Blood pressure lowering, lipid modification and anti-thrombotic therapy
Publication Approval

Australian Government
National Health and Medical Research Council

These guidelines (recommendations) on pages 2-5 were approved by the Chief Executive Officer of the National Health and Medical Research Council (NHMRC) on 9 December 2015 under section 14A of the National Health and Medical Research Council Act 1992. In approving the guidelines (recommendations), NHMRC considers that they meet the NHMRC standard for clinical practice guidelines. This approval is valid for a period of five years.

NHMRC is satisfied that the guidelines (recommendations) are systematically derived, based on the identification and synthesis of the best available scientific evidence, and developed for health professionals practising in an Australian health care setting.

This publication reflects the views of the authors and not necessarily the views of the Australian Government.
Short form Guideline for the
National Evidence Based Guideline on the
SECONDARY PREVENTION OF CARDIOVASCULAR DISEASE IN TYPE 2 DIABETES
Blood pressure lowering, lipid modification and anti-thrombotic therapy

| Summary |

The prevalence of type 2 diabetes is rapidly rising. This has major public health implications as type 2 diabetes is a major risk factor for the development of atherosclerosis of the major vessels. Most disability and premature mortality experienced by people with diabetes is related to cardiovascular disease. Indeed in 2010 in those aged 20-79 years around 5 million deaths globally were attributable to diabetes with 50% of these deaths attributable to cardiovascular disease.

This guideline addresses the management of adults with type 2 diabetes, in relation to the prevention of recurrence of cardiovascular events. The focus is on individuals already known to have symptomatic cardiovascular disease (e.g. prior myocardial infarction or stroke). This is a particularly high risk population, and therefore merits careful attention in clinical practice. The guideline is aimed mainly at primary care, and therefore does not provide advice on in-patient management (such as coronary artery stenting or surgery).

The major modifiable risk factors for the development of cardiovascular events are blood pressure, lipid levels and platelet function. This guideline addresses the main pharmacological approaches to controlling these risk factors. Lifestyle interventions are also important, but the levels of evidence for such interventions are generally lower, and they are comprehensively discussed elsewhere.

The guideline generally promotes an aggressive approach to management of risk factors, in recognition of the high risk of the target population. Nevertheless, it also advises caution in regard to contra-indications and adverse events, particularly in the elderly. It is important that management strategies are individualised to each patient, and the recommendations contained in this guideline are understood as just recommendations.
Summary of Evidence-Based Recommendations (EBR), Consensus Based Recommendations (CBR) and Practice Points (PP)

These recommendations for secondary prevention of cardiovascular disease apply to adults with type 2 diabetes who have had a previous cardiovascular event such as a myocardial infarction, coronary revascularisation (e.g. stent, surgery) or stroke. They provide guidance to assist practitioners in incorporating the latest evidence, but implementation for individual patients should take into account issues such as contra-indications, appropriate doses, environmental factors, age and the presence of co-morbidities such as renal disease.

NHMRC Grades of recommendation

A  Body of evidence can be trusted to guide practice

B  Body of evidence can be trusted to guide practice in most situations

C  Body of evidence provides some support for recommendation(s) but care should be taken in its application

D  Body of evidence is weak and recommendation must be applied with caution

Management – Blood Pressure

EBR 1  All adults with type 2 diabetes and known prior cardiovascular disease should receive blood pressure lowering therapy unless contra-indicated or clinically inappropriate. (Grade A)

PP1  Evidence of the effectiveness of BP lowering therapy for the prevention of cardiovascular events has been reported for people with a wide range of blood pressures including those in the normal range.

EBR 2  Initiate therapy with one of the following:
• Angiotensin converting enzyme (ACE) inhibitor (Grade A)
• Low dose thiazide or thiazide-like diuretic (Grade A)
• Calcium channel blocker (CCB) (Grade A)
• Angiotensin receptor blocker (ARB) (Grade B)

PP2  It should be noted that in the absence of a diagnosis of hypertension, only ACE inhibitors and the ARB telmisartan have licensed indications for cardiovascular protection.

CBR 1  For those with pre-treatment clinic blood pressure over 130/80 mmHg, blood pressure should be lowered to less than or equal to 130/80 mmHg if therapy is well tolerated. For those with pre-treatment clinic blood pressure less than or equal to 130/80 mmHg, no targets have been set but EBR 1 still applies.
EBR 3  If the blood pressure target (see CBR 1) is not achieved with monotherapy, add additional therapy from a different pharmacological class (Grade A). The preferred combinations are:
- ACE inhibitor plus CCB (Grade B)
- ACE inhibitor plus low dose thiazide or thiazide-like diuretic [indapamide or chlorthalidone] (Grade B)

EBR 4  For adults with type 2 diabetes and congestive heart failure, CCBs should be avoided. (Grade C)

EBR 5  All adults with type 2 diabetes, known prior cardiovascular disease and microalbuminuria, macroalbuminuria or proteinuria should preferentially receive treatment with an ACEI or an ARB but not the two together. (Grade A)

EBR 6  All adults with type 2 diabetes and prior acute myocardial infarction should receive long-term treatment with beta blockers. (Grade B)

EBR 7  All adults with type 2 diabetes and prior acute myocardial infarction should receive long-term treatment with ACE inhibitors. (Grade A)

**Management – Lipid Control**

EBR 8  All adults with type 2 diabetes and known prior cardiovascular disease (except haemorrhagic stroke) should receive the maximum tolerated dose of a statin, irrespective of their lipid levels. (Grade A)

Note: The maximum tolerated dose should not exceed the maximum available dose (e.g. 80 mg atorvastatin, 40 mg rosuvastatin).

CBR 2  Use caution with high dose statins as they are associated with increased adverse events, such as myalgia, and with drug interactions.

CBR 3  Only atorvastatin has good evidence for safety and efficacy at the maximum available dose.

CBR 4  Statins should not be routinely used in adults with haemorrhagic stroke, unless other indications exist.

EBR 9  Fibrates* should be commenced in addition to a statin or on their own (for those intolerant to statin) when fasting triglycerides are greater than or equal to 2.3mmol/l; or HDL is low**. (Grade B)
* Fenofibrate when used in combination with statins presents a lower risk of adverse events than other fibrates combined with statins.
** HDL<1.0 mmol/l (based on the cutoffs reported in the ACCORD and FIELD studies).
For adults with type 2 diabetes and known prior cardiovascular disease already on maximally tolerated statin dose or intolerant of statin therapy, if the fasting LDL cholesterol levels remain greater than or equal to 1.8 mmol/l consider commencing one of:

- Ezetimibe; or
- Bile acid binding resins; or
- Nicotinic acid.

Note 1: Side effect profiles of individual therapies should be considered when combining therapies.

Note 2: Use caution with bile acid binding resins and nicotinic acid as they can be poorly tolerated.

**Management – Antiplatelet Therapy**

**EBR 10** All adults with type 2 diabetes and known prior cardiovascular disease should receive long-term antiplatelet therapy unless there is a clear contra-indication\(^1\) (Grade A)

**EBR 11** All adults with type 2 diabetes and a history of ischaemic stroke or TIA should receive:
- Low-dose aspirin (Grade A) or
- Clopidogrel (Grade A) or
- Combination low dose aspirin and extended release dipyridamole (Grade B).

**EBR 12** All adults with type 2 diabetes and acute coronary syndrome and/or coronary stent should receive, for 12 months after the event or procedure:
- Combination low-dose aspirin and clopidogrel (Grade B) or
- Combination low-dose aspirin and prasugrel (Grade B) or
- Combination low-dose aspirin and ticagrelor (Grade C)

**EBR 13** All adults with type 2 diabetes and a history of coronary artery disease but no acute event in the last 12 months should receive:
- Long-term low-dose aspirin (Grade A) or
- Long-term clopidogrel if intolerant to aspirin (Grade B).

**PP 3**
In the presence of atrial fibrillation or other major risk factors for thromboembolism, there should be consideration of anticoagulant therapy according to other relevant guidelines.

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\(^{1}\) Clear contraindications to antiplatelet therapy include active bleeding disorders such as gastrointestinal or intracranial haemorrhage.
co-morbidities. These individuals are not well represented in most trials, often have a higher risk of adverse events, and their risk-benefit ratios for interventions may therefore differ from those reported in trials.

**PP 5**
Strategies to improve adherence should be considered, as there will frequently be a requirement to use multiple drugs.

**PP 6**
Strategies to promote a healthy lifestyle should be adopted, and should focus on smoking cessation, healthy nutrition, physical activity and avoidance of excess alcohol intake.

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**Glossary of Acronyms / Terms**

- **ACE** Angiotensin Converting Enzyme (inhibitor)
- **ARB** Angiotensin Receptor Blocker
- **BP** Blood Pressure
- **CBR** Consensus Based Recommendation
- **CCB** Calcium Channel Blocker
- **EBR** Evidenced-based recommendation
- **HDL** High-density Lipoprotein
- **LDL** Low-density Lipoprotein
- **MI** Myocardial Infarction
- **NHMRC** National Health and Medical Research Council
- **PP** Practice Point
Potential impact of recommendations on clinical practice and outcomes

These recommendations all lie within current clinical practice. Nevertheless, they advocate a high, though appropriate, level of control of cardiovascular risk factors, and need to be monitored carefully in each patient to ensure that adverse events do not occur. If applied appropriately, they should improve outcomes for people with type 2 diabetes.

**Flowchart for key evidence based recommendations for adults with type 2 diabetes and known cardiovascular disease**

- **Blood pressure**
  - In all patients, start one of:
    - ACEI (A)
    - Thiazide (A)
    - CCB (A)
    - ARB (B)
  - unless contra-indicated or clinically inappropriate
  - If BP remains >130/80, add an agent from another class. Preferred combinations are:
    - ACEI + CCB (B)
    - ACEI + Thiazide (B)
  - If patient has prior MI, include:
    - ACEI + beta blocker (B)
  - If patient has micro or macroalbuminuria, include:
    - ACEI or ARB (A)
  - If patient has heart failure:
    - avoid CCB (C)

- **Lipids**
  - Use a statin at the highest tolerated dose* (A)
  - Add a fibrate if TG >2.3 mmol/l or HDL <1.0 mmol/l (B)
  - Statins should not be routinely used in adults with haemorrhagic stroke, unless other indications exist.

- **Anti-platelet**
  - For 12 months after ACS, use combination of aspirin with clopidogrel (B), prasugrel (B) or ticagrelor (C)
  - Beyond 12 months after ACS, use one of aspirin (A) or clopidogrel (B)
  - For ischaemic stroke or TIA, start one of:
    - Low-dose aspirin (A)
    - Clopidogrel (A)
    - Combination low dose aspirin and extended release dipyridamole (B)

**Legend**
- BP blood pressure; ACEI angiotensin converting enzyme inhibitor; CCB calcium channel blocker; ARB angiotensin II receptor blocker; MI myocardial infarction; TG triglycerides; HDL high density lipoprotein cholesterol; ACS acute coronary syndrome; TIA transient ischaemic attack.
- (A) Grade A recommendation; (B) grade B recommendation; (C) grade C recommendation
- * Only atorvastatin has good evidence at the maximum available dose.

Caution should be exercised in implementing aggressive therapy in the elderly, and in those with multiple co-morbidities. These individuals are not well represented in most trials, often have a higher risk of side-effects, and their risk-benefit ratios for interventions may therefore differ from those reported in trials. Strategies to promote a healthy lifestyle should be adopted, and should focus on smoking cessation, healthy nutrition, physical activity and avoidance of excess alcohol intake.