



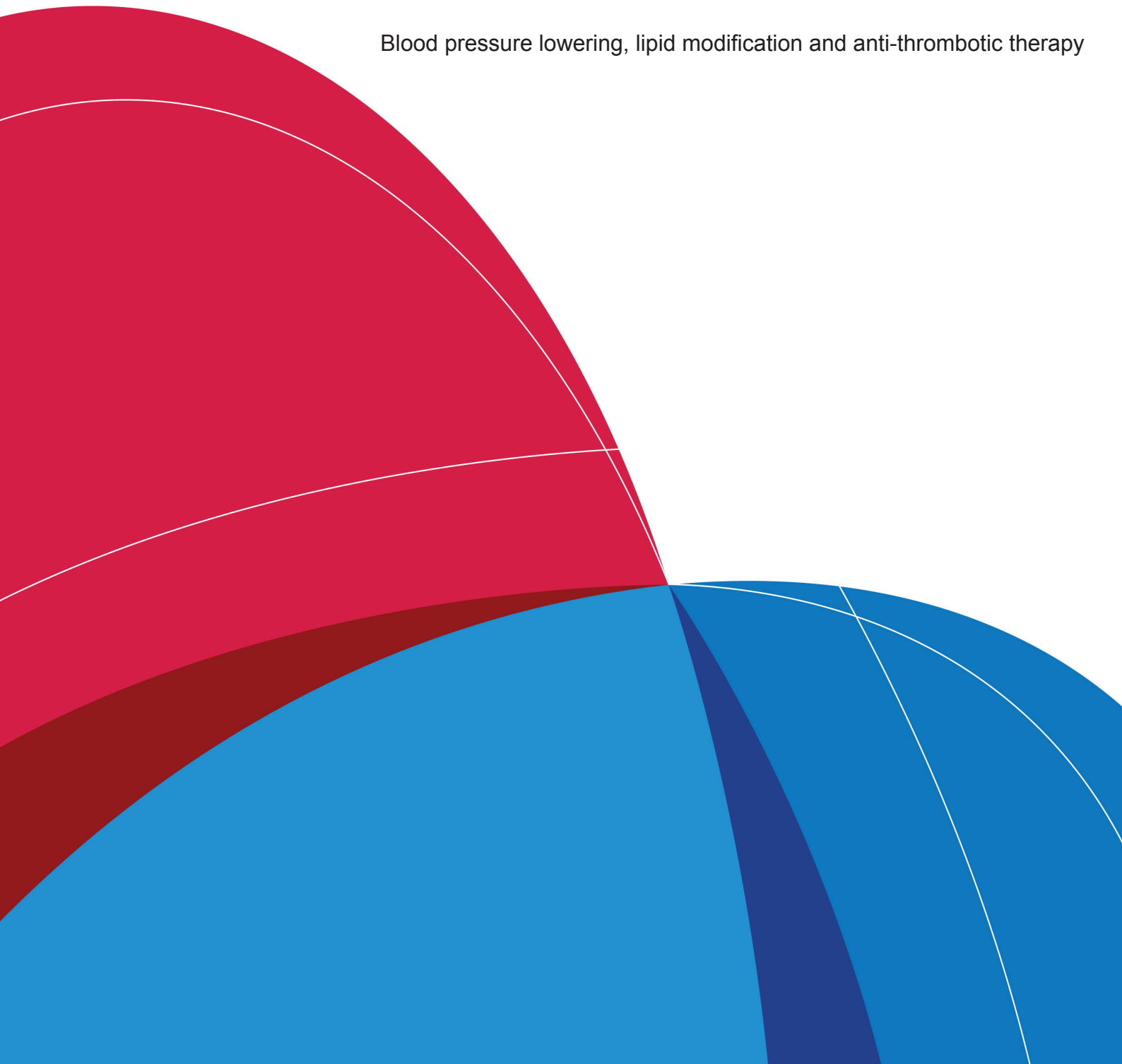
Baker IDI

HEART & DIABETES INSTITUTE

NATIONAL EVIDENCE-BASED GUIDELINE ON

SECONDARY PREVENTION OF CARDIOVASCULAR DISEASE IN TYPE 2 DIABETES

Blood pressure lowering, lipid modification and anti-thrombotic therapy



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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. Recommendations contained herein are based upon the best available evidence published from database inception up until **12 August 2014** for the last question searched. The relevance and appropriateness of the information and recommendations in this document depend on the individual circumstances. Moreover, the recommendations and guidelines are subject to change over time. Copies of the guideline and accompanying technical report and consumer and clinician summaries can be downloaded through the Baker IDI Heart & Diabetes website: www.bakeridi.edu.au or the Type 2 diabetes guideline website: <http://t2dgr.bakeridi.edu.au>

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Publication Approval



Australian Government

National Health and Medical Research Council

The guidelines (recommendations) on pages 2-5 of this document 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 and applies only to the guidelines (recommendations), not to any other supporting material published in this document.

NHMRC is satisfied that the guidelines (recommendations) on pages 2-5 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.

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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)[1, 2] Pg 18

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 [2].

EBR 2 Initiate therapy with one of the following: Pg 20

- Angiotensin converting enzyme (ACE) inhibitor (Grade A)[2-21]
- Low dose thiazide or thiazide-like diuretic (Grade A)[2, 3, 14-18, 22-34]
- Calcium channel blocker (CCB) (Grade A) [2, 3, 14-17, 23-34]
- Angiotensin receptor blocker (ARB) (Grade B)[2, 13, 14, 33-37]

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 130/80mmHg 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. Pg 29

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 Pg 27

preferred combinations are:

- ACE inhibitor plus CCB (Grade B) [2, 29, 38]
- ACE inhibitor plus low dose thiazide or thiazide-like diuretic [indapamide or chlorthalidone] (Grade B)[2, 39-43]

EBR 4	For adults with type 2 diabetes and congestive heart failure, CCBs should be avoided. (Grade C)[2, 17, 27, 28, 30]	Pg 26
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)[2-13, 19-21, 44]	Pg 20
EBR 6	All adults with type 2 diabetes and prior acute myocardial infarction should receive long-term treatment with beta blockers. (Grade B)[2, 3, 11, 45-47]	Pg 21
EBR 7	All adults with type 2 diabetes and prior acute myocardial infarction should receive long-term treatment with ACE inhibitors. (Grade A)[2-13, 19-21]	Pg 20

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)[48-73]	Pg 33
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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. Pg 34

CBR 3

Only atorvastatin has good evidence for safety and efficacy at the maximum available dose. Pg 34

CBR 4

Statins should not be routinely used in adults with haemorrhagic stroke, unless other indications exist. Pg 35

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)[74]	Pg 37
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* 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)

CBR 5

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 Pg 35

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-indication¹. (Grade A)[75] Pg 40

EBR 11 All adults with type 2 diabetes and a history of ischaemic stroke or TIA should receive:

- Low-dose aspirin (Grade A) [76-82] or
- Clopidogrel (Grade A) [80] or
- Combination low dose aspirin and extended release dipyridamole (Grade B). [83]

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) [84-89] or
- Combination low-dose aspirin and prasugrel (Grade B) [90-94] or
- Combination low-dose aspirin and ticagrelor (Grade C) [94-97]

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) [76-82] or
- Long-term clopidogrel if intolerant to aspirin (Grade B). [80, 98, 99]

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.

Management – general

PP 4

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 adverse events, and their risk-benefit ratios for interventions may therefore differ from those reported in trials.

¹ Clear contraindications to antiplatelet therapy include active bleeding disorders such as gastrointestinal or intracranial haemorrhage.

PP 5

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

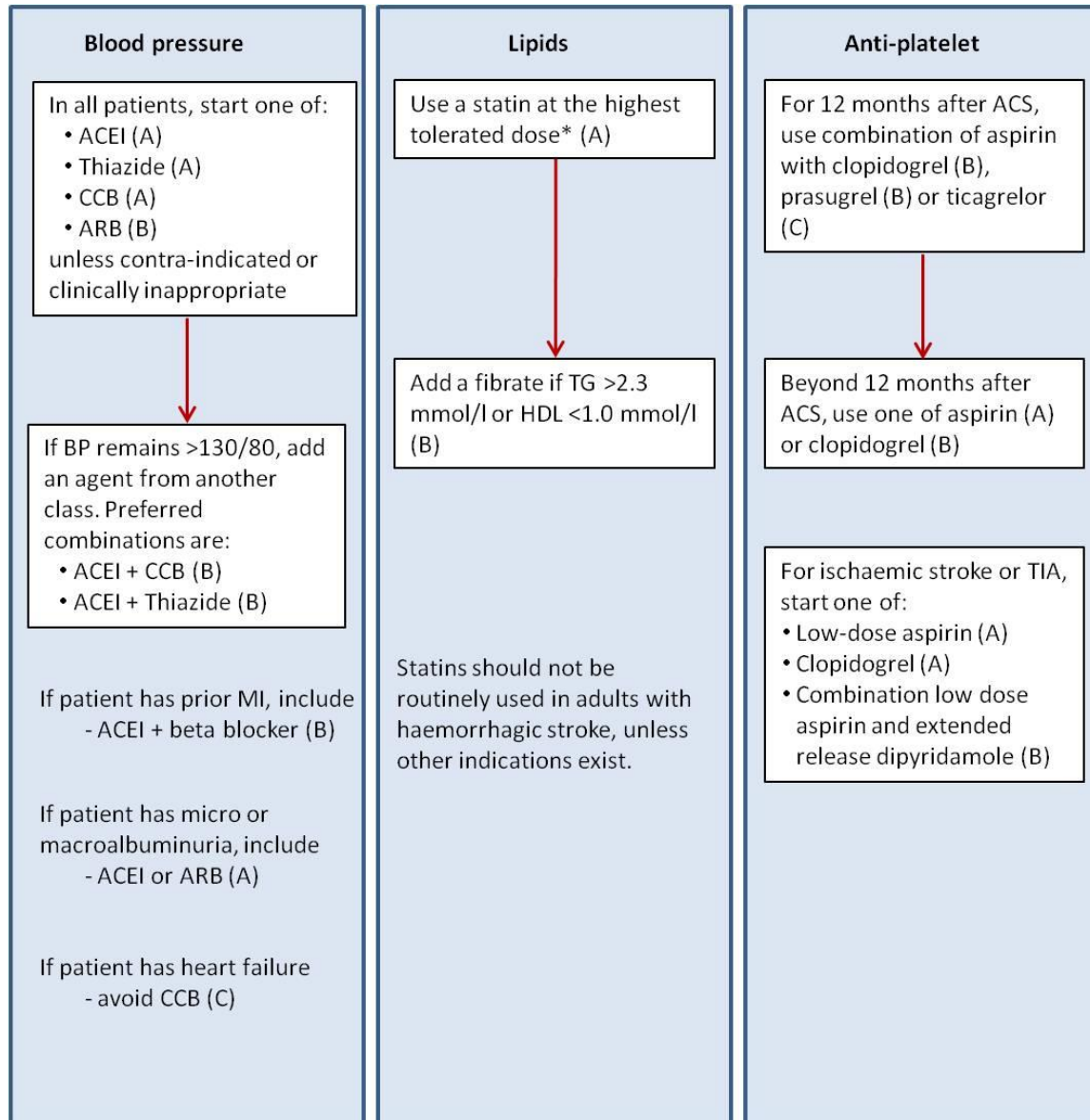
PP 6

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.

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



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.

Glossary of Acronyms / Terms

ACE	Angiotensin Converting Enzyme (inhibitor)
AIHW	Australian Institute of Health and Welfare
ARB	Angiotensin Receptor Blocker
AusDiab	Australian Diabetes, Obesity and Lifestyle Study
BP	Blood Pressure
CAD	Coronary Artery Disease
CBR	Consensus Based Recommendation
CCB	Calcium Channel Blocker
CVD	Cardiovascular Disease
EBR	Evidenced-based recommendation
GAC	Guidelines Advisory Committee
HDL	High-density Lipoprotein
HR	Hazards Ratio
IDF	International Diabetes Federation
LDL	Low-density Lipoprotein
MI	Myocardial Infarction
NHMRC	National Health and Medical Research Council
PAD	Peripheral Arterial Disease (also known as peripheral vascular disease- PVD)
PP	Practice Point
QALYs	Quality Adjusted Life Years
RCT	Randomised Controlled Trial
RR	Relative Risk
TG	Triglyceride

Project Outline

Scope and Purpose of the guideline

This guideline is part of an overall set of recommendations for the prevention, diagnosis and management of diabetes. The other components of the diabetes guidelines include:

- Primary Prevention
- Case Detection and Diagnosis
- Patient Education
- Blood Glucose Control
- Diagnosis, Prevention, and Management of Chronic Kidney Disease
- Management of Diabetic Retinopathy
- Prevention, Identification and Management of Foot Complications in Diabetes

This national evidence-based guideline addresses: **the secondary prevention of cardiovascular disease in type 2 diabetes**. Specifically, it focuses on blood pressure lowering, lipid modification and anti-thrombotic therapy, among adults with type 2 diabetes and a prior cardiovascular event. It does not provide recommendations on blood glucose lowering, as that is covered by another guideline ('Blood glucose control') in the suite of type 2 diabetes guidelines. Guidelines for the primary prevention of cardiovascular disease are available elsewhere (NVDPA 2012).

This guideline updates and replaces the secondary prevention components of three sections of the national evidence-based guidelines for the management of type 2 diabetes mellitus, namely:

Part 4 - Blood pressure control in type 2 diabetes (last updated 2004)

Part 5 - Prevention and detection of macrovascular disease in type 2 diabetes (last updated 2004)

Part 7 - Lipid control in type 2 diabetes (last updated 2004).

The purpose of this guideline is to inform a broad range of health professionals and health care workers of best practice in the ongoing management of people with type 2 diabetes who are known to have post-acute cardiovascular disease in both urban and rural/remote primary care and specialist settings.

No relevant cardiovascular outcome trials were identified that reported results for Aboriginal and Torres Strait Islander people. Nevertheless, the recommendations and consensus-based statements in this guideline apply equally to Aboriginal and Torres Strait Islander people and non-Indigenous Australians.

Structure of the guideline

Clinical questions² were developed by a panel of clinical and research experts (see Appendix 1) and used to structure the guideline into the following parts:

Part A gives a **general overview and describes the search strategy**.

Parts B, C, D and E summarise the **evidence for the secondary prevention of cardiovascular disease in type 2 diabetes**.

Part F discusses **future research and development**.

Part G discusses **implementation**.

Appendices provide additional information and details of the team that prepared the guideline.

² All clinical questions and methodological detail are provided in the accompanying Technical Report.

The findings from the reviewed studies are summarised in parts B to E. For studies conducted in mixed populations of people with and without diabetes, results are presented for the diabetic sub-group if they were reported in the study publication. Such results are explicitly indicated in the text as being from the diabetic population. If diabetes-specific results were not reported, only the overall study results are presented.

Guideline development process and life of the guideline

Baker IDI Heart and Diabetes Institute is the key organisation responsible for the development and publication of the Secondary Prevention of Cardiovascular Disease in Type 2 Diabetes Guideline. The development of this guideline commenced in 2009. Its aim was to update three of the 2004 national evidence-based guidelines for the management of type 2 diabetes: Part 4 *Blood Pressure Control in Type 2 Diabetes*, Part 5, *Prevention and Detection of Macrovascular Disease in Type 2 Diabetes* and Part 7 *Lipid Control in Type 2 Diabetes*. Significant work was undertaken including an extensive literature review, and we acknowledge the work of both the George Institute for Global Health (The George) and Adelaide Health Technology Assessment (AHTA) in their assistance in this initial part of the guideline development process. Matters relating to the failure of some members of the expert panel appointed in 2009 to declare conflicts of interest meant that recommendations derived from this work could not be used. However, the literature review, which was performed without the involvement of the expert panel by parties that were free of conflicts of interest, was retained in the current project. Baker IDI Heart and Diabetes Institute (Baker IDI) convened a new expert panel and a new guidelines advisory committee (GAC) in 2014 with a robust and transparent CoI process. Both the Expert Panel and the GAC determined that the previous literature review was free of conflicts and could be used as data to inform the deliberations of the Expert Panel.

The chair of the GAC was appointed by Baker IDI, on the basis of prior experience with guideline development, and with relevant NHMRC and government processes. Furthermore, the chair was selected so as not to be directly involved in the clinical management of type 2 diabetes. The membership of the GAC was determined by identifying organisations with professional, academic or consumer interests in the management of adults with type 2 diabetes. This was done by Baker IDI and the chair, and in consultation with representatives of the Commonwealth Department of Health. The membership of the EP was drawn from people with academic and/or clinical expertise in the management of adults with type 2 diabetes in primary or specialist care. It was important to identify individuals with adequate expertise, covering the major topics of the guideline (blood pressure, lipids, anti-thrombotic therapy, type 2 diabetes and indigenous health), and to be relatively free of conflicts. Furthermore, individuals needed to have adequate time to devote to the project. The invitation of members was undertaken by Baker IDI, and was reviewed and finalised by the GAC.

The process began with the development of clinical questions to address the key issues of clinical management. A protocol was developed to address these questions and outlined how the literature review would be conducted, according to gold standard, rigorous methodology for conducting systematic reviews and developing evidence-based guidelines [100]. Searches for evidence were conducted in relevant databases, bibliographies of identified relevant studies, guidelines and websites of relevant peak bodies (refer to technical report if this is where they are listed/documentated). The initial literature review performed by The George and AHTA covered literature published between 1966 and 2010. The search was subsequently updated and screened by the University of Sydney and Monash University to 12 August 2014. The Expert Panel and GAC met regularly throughout the period to review and approve the questions, protocol, findings from the systematic review and draft recommendations and approve the format of the guideline. Where evidence was of a high enough quality, the Expert Panel developed evidence based recommendations (EBR), but where evidence was not strong enough to support such a recommendation, consensus based recommendations (CBR) were made. For aspects of the guideline

that the Expert Panel felt were important for providing good clinical care, but about which no specific literature searches were undertaken, the advice was formulated as a practice point (PP). For each type of recommendation, the relevant evidence was discussed by the Expert Panel, and a recommendation, where appropriate, was proposed and then agreed on. As described in the Conflicts of Interest section (below), conflicts precluded some panel members from voting on some recommendations (though they may have been able to contribute to the discussion and drafting). This left five voting members for lipid recommendations, and four voting members for blood pressure and for anti-platelet therapy. In all cases, the EBRs, CBRs and PPs were supported by each of the available voting members of the Expert Panel.

Some areas were a particular focus of discussion and debate amongst both the Expert Panel and the Guidelines Advisory Committee. Most of this centred about how best to present and word the recommendations. There was debate about the extent to which harms and adverse events needed to be presented, as there was concern that under-treatment of the high-risk patients covered in this guideline was common, and that repeatedly emphasising treatment risks might exacerbate this problem. There was extensive discussion about how best to communicate the concept of using blood pressure lowering agents irrespective of the baseline blood pressure, and how to communicate that in a way that didn't put patients at undue risk of hypotension. The issue of the 130/80 mmHg blood pressure target (CBR 1) was extensively debated. Ultimately, it was supported by all but the GAC member representing the Heart Foundation, as it conflicts with the 140/90 mmHg target in a draft Heart Foundation guideline. There was also discussion about how the term 'elderly' (PP 4) should be defined. Whilst some felt it important to provide an age cut-off, most agreed that this was not possible, and it needed to be left to clinical judgement.

The draft guideline has undergone a 30-day public consultation period according to that set out by NHMRC [100]. Further detail about methodology can be found in the technical report.

A list of expert panel members, the project executive, and guideline advisory committee members is provided in Appendix 1, 2 and 3, respectively. Their declaration of competing interests can be found at <http://t2dgr.bakeridi.edu.au> under the conflict of interest quick links.

It is intended that this guideline will be reviewed within 5 years from date of release.

Grading Method

Each recommendation was formulated using evidence-based methods and graded using the NHMRC grades of recommendations.

Definition of NHMRC grades of recommendations

Grade of recommendation	Description
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

To develop grades for each recommendation, the body of evidence was assessed for amount, quality, consistency, generalisability, applicability and clinical impact, and was rated according to the criteria outlined in Table 1, using an Evidence Statement Form (ESF) This allows explicit and transparent formulation of the recommendation on the basis of the available evidence. The complete evidence grading tables can be found in Appendix B of the Technical Report.

The evidence-based recommendations are designed to be practical, clear and action-oriented in order to assist with clinical decision making. Evidence-based recommendations are identified in the text by the use of the acronym EBR.

A Consensus Based Recommendation (CBR) is a consensus statement formulated by the Expert Panel. These are provided to guide clinical practice where evidence is of poor quality and not considered reliable enough for an evidence-based recommendation to be formulated. Practice points (PP) were formulated by the expert panels to provide practical guidance and assist with the implementation of the evidence-based or consensus-based recommendations.

Table 1 Components of body of evidence considered when grading each recommendation [NHMRC]

Component	A	B	C	D
	Excellent	Good	Satisfactory	Poor
Evidence base^{1 2}	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias	One or two level II studies with a low risk of bias or a SR/several level III studies with a low risk of bias	One or two level III studies with a low risk of bias, or level I or II studies with a moderate risk of bias	Level IV studies, or level I to III studies/SRs with a high risk of bias
Consistency³	All studies consistent	Most studies consistent and inconsistency may be explained	Some inconsistency reflecting genuine uncertainty around clinical question	Evidence is inconsistent
Clinical impact	Very large	Moderate	Slight	Restricted
Generalisability	Population/s studied in body of evidence are the same as the target population for the guideline	Population/s studied in the body of evidence are similar to the target population for the guideline	Population/s studied in body of evidence differ to target population for guideline but it is clinically sensible to apply this evidence to target population ⁴	Population/s studied in body of evidence differ to target population and hard to judge whether it is sensible to generalise to target population
Applicability	Directly applicable to Australian healthcare context	Applicable to Australian healthcare context with few caveats	Probably applicable to Australian healthcare context with some caveats	Not applicable to Australian healthcare context

SR = systematic review; several = more than two studies

¹ Level of evidence determined from the NHMRC evidence hierarchy.

² Risk of bias was defined by the quality of the individual study. A rating of low, moderate or high risk of bias was assigned to studies of high, average and low quality, respectively.

³ If there is only one study, rank this component as 'not applicable'.

⁴For example, results in adults that are clinically sensible to apply to children OR psychosocial outcomes for one cancer that may be applicable to patients with another cancer.

Conflict of Interest Management

The identification and management of conflicts of interest is an issue of central importance in the preparation of Clinical Practice Guidelines, to ensure that there is no influence in decision making owing to a competing interest that could erode the integrity of decisions. The application of sound

policies for the identification, declaration and management of conflicts of interest is a necessary prerequisite to ensure public confidence.

Baker IDI as convenor for the Guideline Development Project nominated a Conflicts of Interest Officer (CIO) to provide expert administrative support for all matters pertaining to Conflicts of Interest (CoI). For the development of the Guidelines Project Plan, Baker IDI applied the Baker IDI CoI Policy for all personnel and activities that pertain to the Guidelines Development Project, since the principles and processes of the Baker IDI CoI Policy were consistent with the NHMRC guidance document for Guideline Development and Conflicts of Interest [101], but had not been specifically drafted for the purpose. Prior to recruitment of members to the Guidelines Advisory Committee and Expert Panels, Baker IDI developed and implemented a fit for purpose *Conflicts of Interest for Guideline Development Policy*. All CoI activities were then subject to this policy. According to the policy, it was required that the chair and the majority of the membership of the GAC and of the Expert Panel were to be free of relevant conflicts, and that individual members with relevant conflicts were excluded from various components of the decision-making process, according to their level of conflict. For the Expert Panel, the challenge of finding experts who were free of conflicts proved to be significant. For practical purposes, it was necessary to allow experts with significant conflicts of interest to participate in the Expert Panel. However, appropriate plans were put into place to minimise the influence of such conflicts (Appendix 7).

The Conflicts of Interest for Guideline Development policy and detailed procedures for identifying and managing Conflicts of Interest for members of the Guidelines Advisory Committee and Expert Panel can be found in Appendix 7.

For the purposes of consistency with NHMRC policy and to ensure that all CoI data were gathered in a uniform manner, Baker IDI developed a form based upon the NHMRC Disclosure of Interests form, for all individuals associated with the project, including the Project Executive, Guidelines Advisory Committee, Expert Panel, literature reviewers and the Implementation Committee. Additionally, at the commencement of each meeting of any guidelines committee, the relevant Chair reminded members of the Conflict of Interest Policy and asked for any new conflicts to be declared.

The declarations of conflicts of interest can be found at <http://t2dgr.bakeridi.edu.au> under the conflicts of interest quick links. The CoI review is led by GAC Chair, Professor Jeremy Oats, with administrative support by Guidelines Conflicts of Interest Officer, Dr Guy Krippner.

Technical Report

The full findings of the systematic literature review are available in the Technical Report at <http://t2dgr.bakeridi.edu.au/>

Administrative Report

The Administrative Report outlining the governance, stakeholder involvement, guideline recommendation development, and public consultation processes is at <http://t2dgr.bakeridi.edu.au/>

Part A Overview and Search Strategy

This part of the guideline gives a general overview of cardiovascular disease in type 2 diabetes based on recent review articles, international guidelines and information from Australian surveys and data collections.

Cardiovascular Disease in People with Diabetes

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 [102].

Macrovascular complications of diabetes include coronary artery disease, cerebrovascular disease and peripheral arterial disease. These conditions are grouped together as they share similar pathophysiological processes, risk factors and frequently occur together in the same person. The term macrovascular disease also serves to distinguish these diseases from involvement of the smaller blood vessels ("microvascular disease") found in diabetic nephropathy, retinopathy and neuropathy.

In formulating these guidelines, it was not possible to use a single definition of macrovascular disease to address the question of secondary prevention, simply because the different studies available do not have a uniform approach to the definition. Among the various trials, the most common definitions of macrovascular disease are myocardial infarction, coronary revascularisation, stroke and transient ischaemic attack. Thus, the guideline can be most easily applied to patients with these conditions. Less certainty may apply to people with other manifestations, such as angina and peripheral arterial disease. Conditions such as hypertension would not, on their own, be regarded as vascular disease for the purpose of the recommendations presented in this guideline.

Populations requiring Special Consideration

Aboriginal and Torres Strait Islander people

The prevalence of diabetes is much greater in Aboriginal and Torres Strait Islander people than in non-indigenous Australians [103]. Furthermore, Aboriginal and Torres Strait Islander people living in remote areas are more likely to have diabetes than those living in non-remote areas [103]. McDermott et al [104] reported the incidence of diabetes in remote community Aboriginal and Torres Strait Islander populations of far north Queensland to be nearly 4 times higher than the non-indigenous populations and 50% higher than the incidence reported 10 years earlier in Australian Aboriginals.

Search strategy

Based on the 2004 guidelines that were being updated, the primary focus of the search strategy was on interventions to reduce the risk of recurrent cardiovascular events by targeting blood pressure, lipid levels and blood clotting. Studies were only selected if they provided information on actual cardiovascular events; those reporting only changes in risk factor levels were not considered.

Healthy lifestyle strategies are of major importance in the prevention of cardiovascular disease. They were not part of the current literature review, as they have been extensively reviewed elsewhere.

The most appropriate and relevant advice can be found in the National Heart Foundation advice on the secondary prevention of CHD [105]. The summary of the lifestyle advice from the National Heart Foundation is shown in Table 2.

The Expert Panel developed a series of clinical questions, which formed the basis of the literature review, and of the recommendations. Since these questions were essentially a subset of those developed in 2009, the original search and data extraction, undertaken by Adelaide Health Technology Assessment Unit, who surveyed the literature from 1966 to April 2010, could be used. This search was then updated to 12th August 2014 by the University of Sydney and Monash University. The same PICO tables (Population Intervention Comparison Outcome) and search terms were used for the update as were used for the previous database search. However, some minor changes were incorporated and are listed below:

- 1 The inclusion criteria in the PICO tables for the current searches no longer include microvascular complications as a secondary outcome, or subgroup analysis for diabetic kidney disease. This reflects the change in clinical questions compared to the previous questions, which had previously included evaluation of the effects (of blood pressure lowering, lipid lowering, antithrombotic medications) on microvascular complications. No change was required in the search terms.
- 2 A clarification to the comparator was made in the PICO tables for questions about blood pressure treatment thresholds. This was to correct a typographical error in the PICO tables used for the 2010 search.

Table 2 Healthy lifestyle goals, based on the National Heart Foundation guide to secondary prevention of coronary heart disease ³

Smoking

Goals:

Patients with coronary heart disease completely stop smoking and avoid second-hand smoke.

Nutrition

Goals:

Patients with coronary heart disease establish and maintain healthy eating. This includes:

- *limiting saturated fatty acid (SFA) intake to < 7% and trans fatty acid (tFA) intake to < 1% of total energy intake **
- *consuming 1 g eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA) and > 2 g alpha linolenic acid (ALA) daily*
- *limiting salt intake to ≤4 g/day (1550 mg sodium).*

* National Heart Foundation of Australia. Position statement: Dietary fats and dietary sterols for cardiovascular health. Melbourne: National Heart Foundation of Australia, 2009.

Alcohol

Goal:

Patients with coronary heart disease consume a low-risk amount of alcohol.

Physical Activity

Goals:

Patients with coronary heart disease do at least 30 minutes of moderate-intensity[†] physical activity on most, if not all, days of the week (i.e. 150 minutes/week minimum). This amount can be accumulated in shorter bouts of 10 minutes' duration and can be built up over time.

For patients with advanced coronary heart disease, the goal amount of physical activity may need to be reduced.

Any progress towards reaching the recommended goal is beneficial.

[†]Moderate-intensity physical activity causes a moderate, noticeable increase in depth and rate of breathing, while still leaving you able to talk comfortably. Examples include brisk walking on level firm ground, swimming, water exercise and cycling for pleasure or transport.

³ *Reproduced with permission from Reducing risk in heart disease: an expert guide to clinical practice for secondary prevention of coronary heart disease. © 2012 National Heart Foundation of Australia.*

Clinical Questions

The systematic review of the literature addressed the following clinical questions:

Question Number	Question	Resulting EBR s and CBRs
Blood Pressure Lowering		
1	Does the use of pharmacological blood pressure lowering agents reduce the incidence of secondary cardiovascular disease events and all-cause mortality, compared to control?	EBR 1
2	Does any one class of pharmacological blood pressure lowering agents produce better protection from secondary cardiovascular disease events and all-cause mortality than any other class of pharmacological blood pressure lowering agents and what are the best classes?	EBR 2, EBR 4-7
3	What blood pressure thresholds identify those requiring treatment, and what are the targets for blood pressure lowering for producing the greatest reductions in the incidence of secondary cardiovascular disease events and all-cause mortality?	EBR 1, CBR 1
4	Do any combinations of pharmacological blood pressure lowering agents (either initiated together or sequentially) produce better protection from secondary cardiovascular disease events and all-cause mortality than other combinations or monotherapy? What are the best combinations?	EBR 3
Lipid Modification		
5	Does the use of pharmacological lipid modifying agents reduce the incidence of secondary cardiovascular disease events and all-cause mortality, compared to control?	EBR 8, EBR 9, CBR 2-5
6	What lipid thresholds identify those requiring treatment, and what are the targets for lipid modification for producing the greatest reductions in the incidence of secondary cardiovascular disease events and all-cause mortality?	EBR 8, EBR 9, CBR 5
7	Do any combinations of pharmacological lipid modifying agents produce better protection from secondary cardiovascular disease events and all-cause mortality than other combinations or monotherapy? What are the best combinations?	CBR 5
Antithrombotic Therapy		
8	Does the use of pharmacological antithrombotic agents reduce the incidence of secondary cardiovascular disease events and all-cause mortality, compared to control?	EBR 10
9	Does one pharmacological antithrombotic agent produce better protection from secondary cardiovascular disease events and all-cause mortality than other pharmacological antithrombotic agents, and which is the best agent?	EBR 11-13
10	Are combinations of anti-platelet agents more effective than single anti-platelet agents in reducing secondary CVD events, all-cause mortality and microvascular complications than other combinations, and what are the best combinations?	EBR 11-13

Part B Blood pressure management

This section provides a summary of current evidence on the management of blood pressure from the systematic literature review undertaken for the guideline.

Blood pressure is a particularly important determinant of cardiovascular risk in people with diabetes. Observational data showing a continuous association between blood pressure level and cardiovascular risk has suggested potential benefits of more intensive blood pressure lowering in those with diabetes. In those people with known cardiovascular disease, the value of blood pressure lowering is widely understood but the optimum blood pressure targets and relative benefits of particular therapeutic regimens continue to be debated.

Blood pressure lowering therapy

Blood Pressure lowering recommendations:

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) [1, 2]

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. [2]*

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.*

EBR 2

Initiate therapy with one of the following:

- *Angiotensin converting enzyme [ACE] inhibitor (Grade A) [2-21]*
- *Low dose thiazide or thiazide-like diuretic [indapamide or chlorthalidone] (Grade A) [2, 3, 14-18, 22-34]*
- *Calcium channel blocker [CCB] (Grade A) [2, 3, 14-17, 23-34]*
- *Angiotensin receptor blocker [ARB] (Grade B) [2, 13, 14, 33-37]*

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) [2, 29, 38]*
- *ACE inhibitor plus low dose thiazide or thiazide-like diuretic [indapamide or chlorthalidone] (Grade B)[2, 39-43].*

EBR 4

For adults with type 2 diabetes and congestive heart failure, CCBs should be avoided. (Grade C) [2, 17, 27, 28, 30]

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) [2-13, 19-21, 44]

EBR 6

All adults with type 2 diabetes and prior acute myocardial infarction should receive long-term treatment with beta blockers. (Grade B) [2, 3, 11, 45-47]

EBR 7

All adults with type 2 diabetes and prior acute myocardial infarction should receive long-term treatment with ACE inhibitors. (Grade A) [2-13, 19-21]

Findings of the systematic review

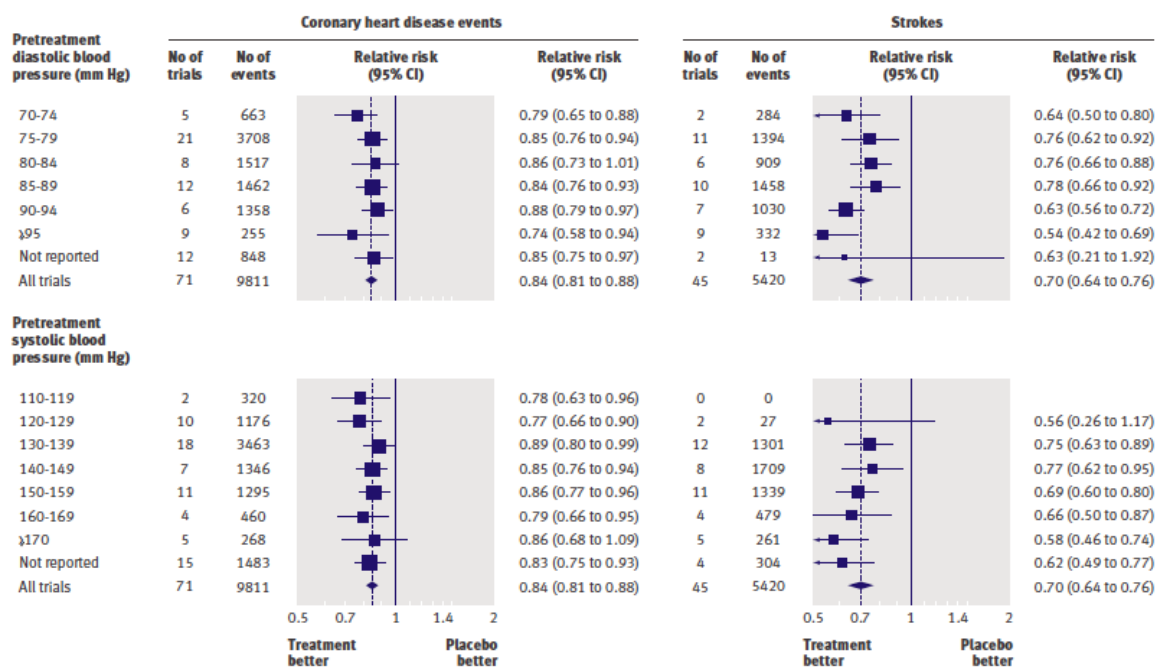
Two systematic reviews (one good quality and one average quality) examined the effects of all classes of blood pressure lowering therapy on the outcomes of coronary heart disease events, stroke, cardiovascular death and/or all-cause mortality [1, 2] The good quality review by Law et al 2009 [2] pooled data from 147 trials (n = 464,164) of which 74 trials included patients with known coronary heart disease or stroke. A significant reduction in the risk of coronary events and stroke with blood pressure lowering therapy was reported. Overall, blood pressure lowering resulted in a 16% reduction in risk of coronary events and a 30% reduction in risk of stroke. The proportional risk reduction provided by therapy was found to be similar regardless of blood pressure level (in the range of 11-26% for coronary events and 22-46% for stroke events, including benefits for patients with or without high blood pressure, see Box 2) and the presence or absence of existing cardiovascular disease at study entry. Benefits were observed for people with and without hypertension.

The average quality review by Lakhan et al 2009 [1] pooled data from 10 trials (n = 37,643) of patients with a history of stroke or TIA and reported a significant reduction in the risk of stroke and cardiovascular death, a trend to reduction in the risk of myocardial infarction and no significant effect on all-cause mortality.

Analyses of some trials have suggested that there is a J-shaped relationship between blood pressure achieved during a trial and subsequent outcomes. Thus, those achieving the lowest blood pressure levels have a worse outcome than those achieving higher levels. However, these are non-randomised analyses, which are affected by the same problems as all observational studies, and can only indicate associations. No such worsening of outcomes has been seen in trials which randomise people to more versus less aggressive blood pressure lowering.

Box 2 Relative risk estimates of heart and stroke events⁴

Relative risk estimates of coronary heart disease events and stroke in pooled blood pressure difference trials according to pre-treatment diastolic and systolic blood pressure levels [2].



One good quality systematic review [106] compared the effects of blood pressure lowering regimens in people with and without diabetes. Pooling data from 27 trials of 158,709 patients with and without diabetes (33,395 with diabetes, and 125,314 without diabetes), similar reductions in major cardiovascular events were reported for those with or without diabetes. When compared to higher blood pressure targets, lower blood pressure targets were also found to produce reductions in major cardiovascular events in both those with and without diabetes.

A number of studies examining the effects of specific blood pressure lowering drugs have also found the relative benefits of blood pressure lowering therapy to be similar in those with or without hypertension at study entry [107, 108]

Summary of Blood Pressure Management

The benefits of blood pressure lowering appear to be unrelated to the pre-treatment blood pressure level. Law et al [2] reported that the risk reductions were similar across all pre-treatment levels of blood pressure down to 110 mm Hg systolic and 70 mm Hg diastolic and in those with or without hypertension (Box 2). Furthermore, the ADVANCE trial [39] reported that in people with diabetes, and across a wide range of pre-treatment blood pressures (mean baseline blood pressure 145/81 mm Hg; standard deviation 22/11 mm Hg), the benefits of the addition of an ACE inhibitor and thiazide-like diuretic were not related to pre-treatment blood pressure.

Thus, there is clear evidence that blood pressure lowering therapy will reduce cardiovascular events in patients with diabetes known to have cardiovascular disease, regardless of blood pressure levels before treatment.

⁴ Reproduced with permission.

Therapies used for blood pressure lowering are generally safe and well tolerated. Overall, serious adverse events attributable to therapy occur in very small numbers of patients with less severe adverse events occurring more frequently. Nevertheless, it is recognised that some patients will need to discontinue therapy or switch to another therapy because of adverse events.

Although the absolute benefits of blood pressure lowering on risk of cardiovascular disease events are greater in the elderly, risks of adverse events are also greater. The definition of 'elderly' in this setting needs to be individualised, and to consider multiple factors, including chronological age, the presence of co-morbidities, degree of independence, life expectancy and patient expectations. In those considered to be elderly and in those with multiple co-morbidities, the following should be carefully considered:

- the benefits, contraindications and cautions associated with specific drugs,
- potential drug-drug interactions, and
- introducing blood pressure lowering therapy incrementally.

Evidence for specific classes of blood pressure lowering therapy versus placebo

One good quality systematic review and one additional good quality RCT (n=5665) examined the effects of thiazide diuretics or thiazide-like diuretics (indapamide or chlorthalidone) on recurrent cardiovascular events [2, 22]. Both reported significant reductions in recurrent coronary and stroke events with a thiazide diuretic (in most studies the dose was titrated as required to optimise blood pressure control) or thiazide-like diuretic (indapamide or chlorthalidone).

Seven good quality systematic reviews [2-7, 20] (n=5,416-464,164, DM=7%-39%) and three additional good quality RCTs [8-12] (n=116-12,218, DM=7%-12%) examined the effects of angiotensin converting enzyme (ACE) inhibitors on recurrent cardiovascular events. All reported significant reductions in recurrent coronary or stroke events and mortality with ACE inhibitor treatment. Significant reductions in recurrent coronary events and cardiovascular mortality were also separately reported for populations with diabetes. Two further studies [109, 110] considered the cost-effectiveness of ACE inhibitors against placebo. The results confirmed the cost-effectiveness of this treatment but this was dependent on the cost of the drug and of the events. Three good quality systematic reviews [2, 13, 14] examined the effects of angiotensin receptor blockers (ARBs) on recurrent cardiovascular outcomes. One review [2] reported no significant effect of ARBs on recurrent coronary events; however, the trials included in this review were relatively small, with the analysis also showing no differences between ARBs and other blood pressure lowering agents (see below). In contrast, the other review [14] (n=44,971) reported a modest but significant reduction in the risk of recurrent stroke. The effects in populations with diabetes (n=1,148) were not statistically significant in either review but neither was there evidence of significant heterogeneity of effects between groups with and without diabetes.

Two good quality systematic reviews [13, 44] (n=13,215, 12,564) examined the effects of ACE inhibitors, and ACE inhibitors or ARBs on renal outcomes. Both reported significant reductions in end stage renal disease. The review of ACE inhibitors also reported a significant reduction in progression from micro- to macro-albuminuria and significantly more regression from micro- to normo-albuminuria.

Two good quality RCTs [39, 108] examined the effects of combination therapy with an ACE inhibitor and thiazide-like diuretic on cardiovascular events and microvascular renal and eye outcomes. One trial [108] (n=6105, DM=12%) of patients with prior stroke reported significant reductions in major cardiovascular events and, particularly, stroke events. The other trial [39] (n=11,140, DM=100%) of

patients with diabetes at high risk of cardiovascular disease (prior cardiovascular disease or multiple risk factors) reported significant reductions in the composite outcomes of major cardiovascular and microvascular events as well as total coronary events, total renal events and all-cause and cardiovascular mortality. An average quality economic evaluation [111] of an ACE inhibitor-based regimen versus standard care in patients with a history of cerebrovascular events was conducted using effectiveness data obtained from the PROGRESS trial. Over a four-year analysis period, the length of the PROGRESS trial, the incremental cost-effectiveness ratio (ICER) was £6,927 per quality-adjusted life year (QALY) and greater (£10,133 per QALY) over a 20 year analysis period. The results were dependent on the costs of the ACE inhibitor, the stroke care unit and the length of hospital stay.

Five good quality systematic reviews [2, 3, 45-47], and one additional good quality RCT [11] (n=115, DM=7%) examined the effects of beta blockers (BBs) on recurrent cardiovascular events and death in patients presenting with acute myocardial infarction. The findings varied from no benefits of acute and short-term administration (2 days to 6 weeks) on short-term hospital outcomes (in hospital and 6 week mortality)[3, 11, 45] to significant benefits of ongoing administration on the long-term outcomes of recurrent cardiovascular events (coronary and stroke events)[2, 46].

Four systematic reviews (three good quality and one average quality) [2, 3, 31, 32] (n=17,759-464,164) examined the effects of calcium channel blockers (CCBs) on recurrent cardiovascular events and death. One review reported significant reductions in both recurrent coronary and stroke events. The second review reported significant reductions in stroke events, angina and heart failure but not mortality or acute myocardial infarction. The third review reporting on immediate or short term use of CCBs found no significant effects on mortality and the fourth review of older CCBs reported no significant effects on mortality or re-infarction rates. Thus CCBs clearly reduced stroke events but the effects on recurrent coronary events and death were less clear.

One good quality systematic review [3] (n=84,413) examined the effects of both immediate (2 days) and short-term (10 days) administration of nitrates within 24 hours of presentation with an acute cardiovascular event. Both immediate and short-term treatment significantly increased survival within the period of treatment. Significant long-term effects were not observed.

Table 3: Common side effects of blood pressure lowering agents, as reported in ACCORD [112]⁵

Variable	Intensive Therapy (N = 2362)	Standard Therapy (N = 2371)	P Value
Serious adverse events — no. (%)†			
Event attributed to blood-pressure medications	77 (3.3)	30 (1.27)	<0.001
Hypotension	17 (0.7)	1 (0.04)	<0.001
Syncope	12 (0.5)	5 (0.21)	0.10
Bradycardia or arrhythmia	12 (0.5)	3 (0.13)	0.02
Hyperkalaemia	9 (0.4)	1 (0.04)	0.01
Angioedema	6 (0.3)	4 (0.17)	0.55
Renal failure	5 (0.2)	1 (0.04)	0.12
End-stage renal disease or need for dialysis	59 (2.5)	58 (2.4)	0.93
Symptoms affecting quality of life — no./total no. (%)‡			
Hives or swelling	44/501 (8.8)	41/468 (8.8)	1.00
Dizziness when standing	217/501 (44.3)	188/467 (40.3)	0.36
Adverse laboratory measures — no. (%)			
Potassium <3.2 mmol/litre	49 (2.1)	27 (1.1)	0.01
Potassium >5.9 mmol/litre	73 (3.1)	72 (3.0)	0.93
Elevation in serum creatinine			
>133 micromoles per litre in men	304 (12.9)	199 (8.4)	<0.001
>115 micromoles per litre in women	257 (10.9)	168 (7.1)	<0.001
Estimated GFR <30 ml/min/1.73 m ²	99 (4.2)	52 (2.2)	<0.001

* Plus–minus values are means \pm SD. GFR denotes glomerular filtration rate.

† Serious adverse events are events that are life-threatening, cause permanent disability, or necessitate hospitalization.

‡ Symptoms were assessed at 12, 36, and 48 months after randomization in a random sample of 969 participants who were assessed for health-related quality of life.

Table 4: Potential adverse effects of blood pressure lowering medications [113]⁶

Common adverse effects	ACE inhibitors*	Angiotensin II receptor antagonists*†	Calcium channel blockers	Thiazide diuretics	Beta-blockers
Constipation	-	-	+ Especially verapamil	-	-
Cough, Angioedema	+	±	-	-	-
Dyspnoea	-	-	-	-	+
Gout	-	-	-	+	-
Headache	-	-	+	-	-
Hyperglycaemia flushing	-	-	-	+	-
Hyperkalaemia	+	+	-	-	-
Hypokalaemia	-	-	-	+	-
Hyponatraemia	+	-	-	+	-
Erectile Dysfunction	-	-	-	+	+
Lethargy	-	-	-	-	+
Oedema	-	-	+	-	-
Postural Hypotension	+	+	+	+	- [‡]

+predictable adverse effect; - clinically significant rates not reported; ±: rare reports

*An initial rise in serum creatinine is commonly observed after initiation of ACE inhibitors or angiotensin II receptor agonists. An increase of 30% or less is acceptable. If creatinine increases by more than 30% from baseline, consider possible contributory factors (e.g. hypovolaemia, renal artery stenosis, NSAIDs). If none present, consider ceasing treatment. Do not commence these agents if serum potassium is > 5.0 mmol/L.

ACE inhibitors and angiotensin II receptor antagonists are not nephrotoxic, but they reduce the kidney's ability to respond to an acute reduction in renal perfusion. Their use should be temporarily suspended during any episode which may lower renal perfusion (e.g. shock or sepsis).

†Caution should be exercised in introducing angiotensin II receptor antagonists in those who have experienced angioedema with ACE inhibitors.

‡Beta-blockers do not appear to induce or worsen postural hypotension.

⁶ Reproduced with permission from *Guide to management of hypertension 2008*. Updated December 2010. © 2008–2010 National Heart Foundation of Australia. This table is in the process of being substantially updated but the update is not available at this time.

ARBs versus other blood pressure lowering agents

Two average quality systematic reviews compared the effects of ARBs to ACE inhibitors on recurrent cardiovascular events and mortality [14, 35] (k=6, n=36,537). No statistically significant differences between ARBs and ACE inhibitors were observed for any of the outcomes studied including all-cause mortality, cardiovascular disease mortality, myocardial infarction, stroke and other cardiovascular disease events.

Two average quality systematic reviews [14, 34] and one RCT [33] (n=196) compared the effects of ARBs to CCBs on recurrent stroke and myocardial infarction in patients with a history of stroke, coronary heart disease, hypertension or type 2 diabetes. No significant difference in the risk of stroke was reported. However, a significant increase in the risk of myocardial infarction was reported for patients treated with ARBs compared to CCBs. The RCT found no difference in blood pressure reduction between patients receiving ARBs or CCBs.

One average quality RCT compared the effects of ARBs to BBs on cardiovascular events in hypertensive patients with ECG signs of left ventricular hypertrophy (25% with a history cardiovascular disease and 13% with diabetes) [36] (n=9,193, DM=13%). Significant reductions in the composite cardiovascular endpoint (cardiovascular mortality, stroke and myocardial infarction) and in the stroke endpoint were reported with ARBs compared with BBs.

Two systematic reviews, one good quality [2] and one average quality [34] (n=21,094, DM=40%), and one additional average quality RCT [37] (n=2,049, DM=38%) compared the effects of ARBs to all other blood pressure lowering drugs (diuretics, BBs, CCBs or ACE inhibitors) on coronary heart disease and stroke events in patients with hypertension, with or without prior cardiovascular disease and/or heart failure. No significant differences in the occurrence of coronary heart disease or stroke events were reported.

ACE inhibitors versus other blood pressure lowering agents

Three good quality systematic reviews compared the effects of ACE inhibitors to diuretics or BBs on cardiovascular events in patients with hypertension, or with high cardiovascular risk including previous cardiovascular events and type 2 diabetes [15-17] (n= 47,400, 46,553). No significant differences in mortality, coronary heart disease (a composite outcome of myocardial infarction and cardiovascular death), stroke or congestive heart failure events were reported.

One average quality RCT compared the effects of treatment with ACE inhibitors to nitrates on serious cardiovascular events in patients admitted to a coronary care unit within 24 hours of onset of acute myocardial infarction [114] (n=9,671). No significant differences in all-cause mortality or the primary composite cardiovascular endpoint at 6 weeks or 6 months were reported. Long-term effects were not examined.

One good quality systematic review compared the effects of treatment with ACE inhibitors to all other blood pressure lowering therapy (ARBs, CCBs, BBs and/or diuretics) on serious cardiovascular events in patients with hypertension, type 2 diabetes, coronary heart disease, acute myocardial infarction, stroke or heart failure [2]. No significant differences in the occurrence of coronary heart disease or stroke events were reported.

CCBs versus other blood pressure lowering agents

One average quality systematic review compared the effects of CCBs to ACE inhibitors on stroke and myocardial infarction in patients with hypertension (36% with cardiovascular disease and 36% with type 2 diabetes) or coronary artery disease [34]. A significant reduction in risk of stroke was reported for patients treated with CCBs compared to patients treated with ACE inhibitors. However, the risks of myocardial infarction did not significantly differ.

Three good quality systematic reviews compared the effects of CCBs to diuretics or BBs on recurrent cardiovascular events in patients with known prior cardiovascular disease or at high risk of cardiovascular disease [15-17]. No significant differences in the risk of coronary heart disease, all-cause mortality, cardiovascular mortality, or fatal and non-fatal myocardial infarction were reported. A significant reduction in risk of stroke was reported for patients treated with CCBs compared to diuretics or BBs. Additionally, a higher risk of congestive heart failure was reported for patients receiving CCBs compared to diuretics or BBs.

Six further RCTs (four good and two average quality) compared the effects of CCBs to diuretics or BBs on recurrent cardiovascular events or chronic kidney disease progression (defined by a doubling of serum creatinine concentration, estimated glomerular filtration rate <15mL/min/1.73m² or the need for dialysis) in patients with known prior cardiovascular disease or at high risk of cardiovascular disease.

One RCT [23, 25] (n=11,506, DM=60%) compared the effects of a CCB to diuretic on a background of ACE inhibitor therapy. No significant differences in the risk of all-cause mortality, fatal cardiovascular events, and fatal and non-fatal stroke were reported. However, significant reductions in the risks of fatal and non-fatal myocardial infarction and CKD progression were reported for patients receiving CCBs compared to diuretics.

One RCT [26] (n=1,882, DM=13%) compared the effects of CCB to diuretic therapy in patients aged at least 60 years, with isolated systolic hypertension (30% with prior cardiovascular disease and 13% with type 2 diabetes). At the end of the trial, 85% of patients in the CCB arm and 72% in the diuretic arm were still receiving monotherapy. Systolic blood pressure decreased markedly and similarly in both treatment groups. No significant difference in the risk of the primary composite endpoint of sudden death, fatal and non-fatal myocardial infarction, fatal and non-fatal stroke, fatal and non-fatal congestive heart failure, myocardial revascularisation, and carotid endarterectomy, was reported. Also no significant differences for the individual outcomes of sudden death, fatal and non-fatal myocardial infarction, fatal and non-fatal stroke, fatal and non-fatal heart failure, revascularisation and transient ischaemic attacks were reported. The number of adverse events was similar in both treatment groups.

One RCT compared the effects of primary CCB to primary BB therapy. No significant difference in the risk of the primary combined endpoint of non-fatal myocardial infarction (including silent) and fatal coronary heart disease was reported [24] (n=19,257, DM=27%). However, significant reductions in risks of all-cause mortality, cardiovascular mortality, total coronary events, total cardiovascular events and procedures, fatal and non-fatal stroke, unstable angina, peripheral arterial disease, and development of renal impairment were reported for patients receiving CCB compared to BB therapy. Significantly more patients receiving BB therapy discontinued treatment due to a serious adverse event than those receiving CCB therapy.

One RCT compared the effects of CCB to BB therapy in patients with documented stable coronary artery disease (including patients with heart failure classes I -III) [27] (n=22,576, DM=28%). At 24 months, only 15% of patients in both arms were still receiving monotherapy. The blood pressure reduction was similar in both groups. No significant difference in the risk of the primary composite endpoint of all-cause mortality, non-fatal myocardial infarction and non-fatal stroke was reported. Both drugs were generally well tolerated by the patients. However, patients in the CCB arm reported problems with cough and constipation significantly more frequently, and those in the BB arm reported significantly more dyspnoea, light-headedness, bradycardia and wheezing.

One RCT compared the effects of CCBs to BBs in patients presenting within one month of acute myocardial infarction [28] (n=1,090, DM=29%). No significant difference in the risks of the primary

composite outcome (cardiovascular death, non-fatal MI, uncontrolled unstable angina, or non-fatal stroke) and other outcomes of cardiovascular death, non-fatal reinfarction, unstable angina requiring hospitalisation and non-fatal stroke were reported. However, the risks of unstable angina due to coronary spasm and heart failure requiring hospitalisation were significantly reduced for patients receiving CCB compared to BB therapy.

One small RCT [30] (n=120, DM=30%) compared 25 to 50 mg of atenolol to 4–8 mg of benidipine in a population of 120 post-myocardial infarction patients over a median follow-up of 1,124 days. The primary endpoint was death from cardiovascular events or new onset of angina pectoris and silent myocardial ischemia which required PCI or the need for target lesion revascularization. No statistically significant difference was observed between use of atenolol and benidipine for the primary cardiovascular outcome in the sub-group of diabetic patients (n=36) or in the whole study population, although the study's low power limits the interpretation of the results.

One good quality systematic review compared the effects of treatment with CCBs to other blood pressure lowering therapy (ACE inhibitors, ARBs, BBs and/or diuretics) [2]. No significant difference in risk of coronary heart disease events was reported. However, a significant reduction in the risk of stroke and a significant increase in the risk of congestive heart failure were reported for patients receiving CCBs compared to other blood pressure lowering therapy.

An updated meta-analysis, conducted by AHTA, of trials comparing the effects of CCBs to diuretics or BBs indicated that for CCBs, there were significant reductions in the risks of all-cause mortality and stroke, no significant difference in the risk of cardiovascular events, non-fatal MI or cardiovascular mortality and a significant increase in the risk of congestive heart failure.

Diuretics or BBs versus other blood pressure lowering agents

Two good quality systematic reviews compared the effects of diuretics or BBs to other blood pressure lowering agents (ARBs, ACE inhibitors or CCBs) on cardiovascular morbidity and mortality in patients with hypertension, with or without prior cardiovascular disease and/or heart failure [2, 15]. Diuretics and BBs were slightly more effective at lowering systolic blood pressure but not diastolic blood pressure. No significant differences in the risks of coronary heart disease, all-cause mortality, cardiovascular mortality, cardiovascular events and myocardial infarction were reported. However, BBs were reported to significantly increase the risk of stroke and high dose thiazide diuretics were reported to significantly increase the risk of sudden cardiac death.

It should be noted that beta blockers can mask the symptoms of hypoglycaemia, and thus care should be taken when they are used in combination with sulphonylureas and insulin.

CCBs or ACE inhibitors versus diuretics or BBs

One average quality systematic [18] (k=4, n=4,223) review compared the effect of CCBs or ACE inhibitors to diuretics or BBs on the prevention of serious cardiovascular events in hypertensive patients with carotid atherosclerosis. No significant differences in the risk of all-cause mortality, cardiovascular mortality, fatal and non-fatal cardiovascular events, fatal and non-fatal stroke and fatal and non-fatal MI plus sudden death were reported.

Summary – Blood Pressure Lowering Agents

Not surprisingly, the large number of individual trials and meta-analyses do not produce completely consistent data. For example, placebo-controlled studies clearly demonstrate the benefits of ACE inhibitors but are much less convincing for ARBs. However, comparisons of ACE inhibitors to ARBs show no difference in outcomes between the two classes. Therefore, in developing recommendations, we considered the totality of trial evidence, along with the evidence that the

cardiovascular benefits of all classes of blood pressure lowering agents appear to be principally due to the reductions in blood pressure achieved with only small differences between classes attributable to blood pressure-independent effects of the agents.

As such, all the main classes of blood pressure lowering agents, low dose thiazide and thiazide-like diuretics (indapamide and chlorthalidone), ACE inhibitors, ARBs, CCBs and BBs, were considered effective in reducing the risk of recurrent cardiovascular events as long as effective blood pressure lowering is achieved. However, trials in specific populations and effects on selected outcomes such as acute myocardial infarction, stroke, heart failure and renal events have suggested some differences that may influence choice of therapy. For example, when compared to placebo, CCBs appeared to reduce the risk of congestive heart failure. However, when compared to other classes of blood pressure lowering therapy, CCBs performed less well. This indicates that CCBs are less effective at preventing new diagnoses of heart failure and preventing deterioration (hospital admission or death) than other drug classes. Ultimately, the majority of patients are likely to require combination therapy to achieve optimal blood pressure control so choice of first agent becomes a less important issue with the key decision likely to be which, and how many, other medications are to be added.

Combinations of blood pressure lowering agents

One good quality systematic review examined the effects of combination blood pressure lowering therapy on recurrent coronary events and stroke [2]. The combination therapies that were studied included thiazide diuretics plus ACE inhibitor (k = 1), thiazide diuretics plus beta-blockers (k = 2); thiazide diuretic plus methyl dopa (k = 1), thiazide diuretics plus rauwolfia (a plant extract) (k = 1) and thiazide diuretics plus rauwolfia plus hydralazine (k = 2). Of note, all secondary prevention studies were of patients with previous stroke. Irrespective of the type of treatment, combination blood pressure lowering therapy led to a significant reduction in both recurrent coronary events and stroke.

The good quality ACCOMPLISH [23, 25] (n=11,506, DM=60%) RCT involved patients aged 55 years and older who had hypertension and were at high risk of cardiovascular events; including those with prior myocardial infarction (23%), revascularisation (36%), stroke (13%), renal disease (6%), previous hospitalisation for unstable angina (11%), left ventricular hypertrophy (13%), and type 2 diabetes (60%). Patients were randomised to receive either a CCB or a diuretic. All patients also received an ACE inhibitor as background therapy. The authors reported a mean blood pressure difference between the two groups of 0.9 / 1.1 mmHg. Statistically there were significantly fewer fatal and non-fatal cardiovascular events in the group receiving the CCB. A sub-group analysis of the 2,842 diabetic patients with prior cardiovascular disease in the ACCOMPLISH trial [29](Weber, 2010) found similar results to the original trial (HR: 0.77, p=0.007).

The good quality ASCOT-BPLA [24] (n=19,257, DM=27%) RCT involved patients aged 40-79 years, with treated or untreated hypertension and at least three CVD risk factors (23% had prior CVD and 27% had type 2 diabetes). Patients were randomised to receive either a CCB ± an ACE inhibitor or a BB ± a diuretic. There were significantly fewer cardiovascular events in the group receiving the combination of CCB ± ACE inhibitor.

One good quality RCT (ADVANCE) (n=11,140, DM=100%) compared the effects of combination blood pressure lowering with an ACE inhibitor and thiazide-like diuretic to placebo among patients with diabetes at high risk of cardiovascular disease (prior cardiovascular disease or multiple risk factors) [39]. Significant reductions in the composite outcomes of major cardiovascular and microvascular events as well as in the individual outcomes of total coronary events, total renal

events and all-cause and cardiovascular mortality were reported for those receiving combination therapy compared with placebo.

Two good quality RCTs (ONTARGET n=17,078, DM=37%; VALIANT n=9,794, DM=23%) compared the effects on cardiovascular mortality and morbidity of combination blood pressure lowering with an ARB plus an ACE inhibitor (Telmisartan and Ramipril; Valsartan and Captopril) to an ACE inhibitor alone (Ramipril; Captopril)[115, 116]. No significant differences in the risks of the combined endpoints of cardiovascular death, MI, stroke or hospitalisation for heart failure, or cardiovascular death, MI, stroke, heart failure, or resuscitation after cardiac arrest were reported. A significantly greater proportion of patients receiving the combination ARB and ACE inhibitor therapy discontinued treatment as a result of adverse events.

One average quality RCT compared the short-term effects (within 3 months) of combination therapy with an ACE inhibitor and CCB (trandolapril and verapamil) to an ACE inhibitor alone (trandolapril) in patients with acute MI or patients receiving diuretics for congestive heart failure during MI [38] (n=100, DM=14%). A significant reduction in the risk of the primary composite endpoint of death, reinfarction, unstable angina pectoris or congestive heart failure was reported for patients receiving combination ACE inhibitor and CCB therapy compared to ACE inhibitor alone.

One small, average quality RCT compared the effects of combination therapy with an ACE inhibitor and BB (captopril and metoprolol) to either an ACE inhibitor or BB alone (captopril or metoprolol) on echocardiographically assessed left ventricular volume and function at 15 days, 3 and 6 months in patients with acute MI admitted to coronary care units within 24 hours of the onset of symptoms [117] (n=166, DM=4%). Cardiac outcomes were also assessed at 6 months. No significant differences in the risk of any spontaneous cardiac event (death, reinfarction, unstable angina and congestive heart failure) or requirement for percutaneous transluminal coronary angioplasty and coronary artery bypass grafting procedures were reported. However this study was not sufficiently powered to examine these clinical outcomes, so the validity of these findings remains uncertain given the strong evidence for the separate use of both BBs and ACE inhibitors in this patient group.

One average quality RCT compared the effects of combination therapy with an ACE inhibitor and transdermal glyceryl trinitrate (lisinopril and GTN) to either an ACE inhibitor or GTN alone (lisinopril or GTN) in patients with acute MI or angina within twenty-four hours of the onset of symptoms [118] (n=18,895, DM=16%). A significant reduction in the risk of the primary combined endpoint of all-cause mortality, late onset congestive heart failure or extensive left ventricular damage was reported at six weeks in the combination therapy group compared to the ACE-inhibitor or nitrate monotherapy groups. However, after six months these effects were diminished and no longer significantly different between the three groups. No significant difference in the risk of all-cause mortality was reported. A significantly larger proportion of patients receiving combination therapy experienced persistent hypotension and renal dysfunction compared to those taking nitrate monotherapy.

The following combinations should generally be avoided:

- Potassium-sparing diuretic plus either an ACEI or ARB
- Beta-blocker plus verapamil

Summary – Combinations of Blood Pressure Lowering Agents

Multi-drug combinations are likely to be required for many patients to achieve effective blood pressure control. On the basis of the current evidence, the preferred combinations of blood pressure lowering agents in people with diabetes and known cardiovascular disease are ACE inhibitor plus low dose thiazide or thiazide-like diuretic (indapamide and chlorthalidone) and ACE inhibitor plus CCB.

Lower blood pressure targets versus standard blood pressure targets

One good quality systematic review examined the effects of blood pressure control aiming for lower blood pressure targets ($\leq 135/85$ mmHg) compared to standard blood pressure targets ($\leq 140/90$ - 100 mmHg)[119] ($k=7$, $n=22,089$). RCTs comparing different systolic blood pressure (SBP) targets were not found for this systematic review, but seven RCTs comparing different diastolic blood pressure targets (DBP) were identified. The DBP target trials included hypertensive participants from the general population, including those with chronic renal disease or type 2 diabetes; most trials excluded participants with a recent cardiovascular event. A significantly lower SBP (pooled mean difference -6.81 [99% CI -12.26 , -1.36]; $p = 0.0013$) and DBP (pooled mean difference -5.46 [99% CI -8.22 , -2.69]; $p < 0.00001$) was reported for those assigned to the lower DBP targets than to standard DBP targets. However, no significant differences in the primary outcomes of total mortality, cardiovascular mortality, non-cardiovascular mortality, total serious adverse events, myocardial infarction, stroke, congestive heart failure, major cardiovascular events, and end stage renal disease were reported. Subgroup analyses of participants with diabetes ($k=3$, $n=2451$) or chronic kidney disease revealed a non-significant trend towards a benefit for total mortality and cardiovascular mortality for assignment to the lower DBP target compared to the standard DBP target. The power of these meta-analyses was limited by the size of the subgroups.

One good quality RCT [120] ($n=480$, $DM=100\%$) evaluated the effect of intensive blood pressure management compared to moderate blood pressure management with nisoldipine or enalapril in order to prevent cardiovascular events in patients with type 2 diabetes with or without previous cardiovascular events, including peripheral arterial disease. The results of the full trial were included in the meta-analysis conducted by Arguedas et al, described above. A post-hoc subgroup analysis of the ABCD trial [121] ($n=53$) reported on those who were normotensive and had a history of peripheral arterial disease at baseline. The trial compared the effect of intensive blood pressure control with a treatment goal of reducing DBP by 10mmHg from the mean baseline value to moderate blood pressure control with the aim of maintaining their baseline DBP. Significant reductions in risks of cardiovascular events were reported for diabetes patients with PAD receiving intensive blood pressure management compared to moderate blood pressure management, regardless of baseline ankle brachial pressure index. Considering the very small sample size and the post-hoc nature of this analysis, these results need to be confirmed by further research.

One good quality RCT (ACCORD) ($n=4,733$, $DM=100\%$) examined the effects of targeting SBP levels less than 120 mmHg (intensive therapy) compared with targeting SBP levels of less than 140 mmHg (standard therapy), among patients with type 2 diabetes who had cardiovascular disease or who were at high risk for cardiovascular events [112]. The SBP levels achieved with intensive therapy and standard therapy were 119.3 and 133.5 mmHg, respectively, with a between group difference of 14.2 [95% CI 13.7, 14.7] mmHg. The DBP levels achieved with intensive therapy and standard therapy were 64.4 [95% CI 64.1, 64.7] and 70.5 [95% CI 70.2, 70.8] mmHg respectively, with a between group of difference of 6.1 [95% CI 5.7, 6.5] mmHg. No significant differences in the risks of the primary composite cardiovascular outcome (cardiovascular death, non-fatal MI or stroke) or the secondary outcomes of non-fatal MI, total mortality or cardiovascular death were reported. The trial had only limited statistical power to detect plausible effects. A significant reduction in the risk of stroke (fatal or non-fatal) was reported for patients aiming for the lower SBP target compared to the standard blood pressure target (hazard ratio, 0.59; 95% CI, 0.39 to 0.89; $P=0.01$). When the effects were examined in those with and without prior cardiovascular disease, no differences were observed. Significantly more serious adverse events including hypotension, syncope, bradycardia or

arrhythmia, hyperkalaemia, angioedema and renal failure were attributed to the blood pressure lowering medications in the intensive therapy group than the standard therapy group (3.3% vs 1.3%). When considered separately, each of these serious adverse events were relatively uncommon, occurring in less than 1% of patients. Intensive therapy also led to more instances of hypokalaemia (2.1 vs 1.1%) and an estimated glomerular filtration rate of less than 30 ml/min/1.73m²(4.2 vs 2.2%) than standard therapy.

One good quality RCT (ADVANCE) (n=11,140, DM=100%) compared the effects of combination blood pressure lowering with an ACE inhibitor and thiazide-like diuretic to placebo among patients with diabetes at high risk of cardiovascular disease (prior cardiovascular disease or multiple risk factors) [39]. The mean entry blood pressure of all randomised patients was 145/81 mm Hg and 41% had a blood pressure less than 140 mm Hg systolic and 90 mm Hg diastolic. The mean SBP levels achieved with an ACE inhibitor and thiazide-like diuretic vs placebo were 135 and 140 mmHg respectively, with a mean difference of 5.6 mm Hg. The mean DBP levels achieved with an ACE inhibitor and thiazide-like diuretic vs placebo were 75 and 77 mmHg respectively, with a mean difference of 2.2 mm Hg. Significant reductions in the composite outcomes of major cardiovascular and microvascular events as well as total coronary events, total renal events and all-cause and cardiovascular mortality were reported for those receiving combination therapy compared with placebo. The benefits were observed irrespective of entry blood pressure level.

The SPS3 Group's 2013 trial [122] (n=3,020, DM=36%) compared a systolic BP target of 130–149 mmHg to a target <130 mmHg in a sub-group of 1,106 patients with diabetes who had recently had a lacunar stroke. Over a mean follow-up of 3.7 years the study found that there was no statistically significant difference between BP targets in prevention of recurrent stroke, with a non-significant risk reduction observed with the lower target (HR 0.85, 0.61–1.19).

Summary – Blood Pressure Targets

There is strong evidence that all patients with type 2 diabetes and cardiovascular disease should be on blood pressure lowering therapy irrespective of their baseline blood pressure level. Once blood pressure lowering therapy has been commenced, blood pressure targets need to be considered. Prior guidelines have advocated aiming for blood pressure levels below 130/80mmHg, and some more recent guidelines have changed this to 140/90 mmHg. There is insufficient definitive evidence to warrant a modification to the earlier approach in this patient group at this point in time. However, uncertainty remains in regard to this issue, which remains under active consideration by major guideline groups around the world.

Patients below the 130/80 mmHg target prior to starting therapy should still be commenced on therapy, unless there is concern about side-effects, as the evidence for lowering blood pressure irrespective of starting blood pressure is considerably stronger than is the evidence for any specific target. Furthermore, it has been standard advice for several years to commence therapy with ACEI in all those with prior CVD, and to commence a beta blocker in all those with prior MI. This advice has not been restricted by any blood pressure levels. More intensive blood pressure lowering substantially reduces the risk of stroke although the benefits for myocardial infarction are less clear. Intensification of therapy and polypharmacy are associated with greater risks of side effects, thus the balance of benefits and risks must be determined for each patient. Nonetheless, physicians should endeavour to achieve good blood pressure control in those who have diabetes and known cardiovascular disease as this group are at very high absolute risk of further events.

Part C Lipid management

This section provides a summary of current evidence on the management of blood lipids from the systematic literature review undertaken for the guideline.

High serum levels of total cholesterol and low-density lipoprotein cholesterol (LDL-C) are established risk factors for cardiovascular disease. Trials with clinical endpoints confirm that a reduction in LDL-C is a primary goal for the prevention of cardiovascular disease. Questions remain as to the target level of LDL-C to aim for to maximise the benefits of lipid lowering therapy for the secondary prevention of cardiovascular events.

High serum levels of triglycerides and low serum levels of high-density lipoprotein cholesterol (HDL-C) are also associated with an increased risk of cardiovascular disease. The specific role that modification of these lipid fractions plays for the secondary prevention of cardiovascular disease is less clear.

Lipid lowering therapy

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) [48-55] [56-73]

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

Statin 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 and HDL is low **. (Grade B) [74]*

** 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)*

CBR 5

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 1.8mmol/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.

Use of statins in lipid control

Eight good and one average quality systematic reviews and one additional good quality RCT investigated the effectiveness of LDL cholesterol reduction with statin therapy for the secondary prevention of serious cardiovascular events in patients with a history of coronary heart disease, stroke or transient ischaemic attack (TIA) [48-57, 123]. All showed similar reductions of about 20% in total combined vascular events including fatal and non-fatal myocardial infarction, total strokes. In the three larger trials (included in the systematic reviews) a reduction in total mortality with no increase in non-cardiovascular mortality were reported. These effects were similarly observed in men and women, younger or older patients, patients with and without diabetes and patients with or without hypertension. Reductions were also similar across all pre-treatment LDL levels, including baseline LDL cholesterol levels lower than 2 mmol/l. The magnitude of the protection afforded was directly related to the absolute reduction in LDL cholesterol achieved. Moreover, benefits were seen in the first year and increased in subsequent years.

Two small short-term studies [124, 125] (n=353, 1,016; DM=32%, 30%), which were not placebo-controlled, evaluated the effect of statins in comparison to standard treatment for the prevention of secondary cardiovascular events. The two studies supported the beneficial effect of statin on CVD outcomes but lacked evidence for hard clinical endpoints possibly due to the small samples and short time of follow up.

Overall, the meta-analyses report that statin therapy reduces the risk of myocardial infarction or coronary death by about 23-30%, coronary mortality by 19-28%, fatal or non-fatal strokes by 17-26% and total mortality by 12-16% (up to 26% in those aged over 65 years). These risk reductions broadly reflect the benefits of an approximately 1 mmol/l reduction in LDL cholesterol.

High versus moderate dose statin therapy

One good quality systematic review [58](Josan, 2008) and five additional RCTs, two of good quality [60, 62, 63, 66-68, 73] and two of average quality [59, 69](which were not included in the systematic review) evaluated the effects of lipid lowering using a high versus a moderate dose of statin on recurrent cardiovascular events in patients who had been hospitalised or had a documented history of acute myocardial infarction (MI) or coronary artery disease, and for whom statin therapy was not contraindicated.

The systematic review included seven trials and reported that intensive statin therapy significantly reduced the risk of acute coronary syndromes and coronary artery disease [58] (k=7, n=29,393, DM=12-24%). Moreover, while drug-related adverse events leading to drug discontinuation occurred more frequently in the more intensively-treated than in the less intensively-treated patients (7.8% vs 5.3%), this difference did not achieve statistical significance.

One average quality RCT (IDEAL) evaluated the effects of intensive atorvastatin therapy compared to less intensive simvastatin therapy on subsequent major cardiovascular events [59] (n=8,888, DM=12%). A significant reduction in the risk of a second, third or subsequent cardiovascular event was reported with intensive atorvastatin therapy compared with moderate simvastatin therapy. These benefits were particularly clear in patients older than 65 years.

One average quality RCT [69] (n=290, DM=71%) compared the effect of full-dose atorvastatin (80 mg/day) to conventional medical treatment (20 mg atorvastatin titrated to achieve LDL <2.5 mmol/l) on reducing ischaemic recurrences after non-ST-elevation acute myocardial infarction

(NSTE-AMI) in patients with severe and diffuse coronary artery disease (CAD) not amenable to any form of mechanical revascularisation. A significant reduction in the risk of the primary combined end point (cardiovascular death, non-fatal acute myocardial re-infarction (re-AMI) and disabling non-fatal stroke) was reported as compared with standard moderate statin therapy, and the reduction in the risk was mainly due to a reduced incidence of recurrent non-fatal AMI. About 70% of the study population had diabetes, though there was no analysis of the diabetes subgroup.

One large good quality RCT (TNT) (n=10,001, DM=15%) evaluated the effects of lipid modification to an LDL target of 1.9 mmol/l compared to a standard LDL target of 2.6mmol/l on recurrent cardiovascular events in patients with a documented history of coronary heart disease and LDL cholesterol levels of <3.4mmol/l [62-64, 73]. Patients were randomised to either atorvastatin 80 mg daily or to atorvastatin 10 mg daily. A significant reduction in risk of cardiovascular events primarily driven by a reduction in risk of non-fatal MI and fatal or non-fatal stroke was reported for those receiving atorvastatin 80mg compared with atorvastatin 10 mg.

One good quality RCT (PROVE IT-TIMI 22) (n=4,162, DM=18%) evaluated the effects of LDL-C lowering to a target of approximately 1.8mmol/l with atorvastatin 80 mg/day, compared to the target of approximately 2.6mmol/l using pravastatin 40 mg/day, on mortality and recurrent cardiovascular events in patients hospitalised for acute coronary syndromes [66-68]. A significantly lower risk of all-cause death or major cardiovascular event was reported for patients randomised to atorvastatin 80 mg. This clinical benefit became evident at 30 days and remained consistent over the follow-up period. Significant reductions in coronary revascularisation, hospitalisation for unstable angina and the composite outcome of MI, revascularisation or death from CHD were also reported. Event rates were higher in those with diabetes, but the benefits of the more intensive treatment were similar in those with and without diabetes.

One good quality RCT [126] (n=12,064, DM=11%) compared the effects of LDL-C lowering with simvastatin 80mg to simvastatin 20mg in over 12,000 patients with a history of myocardial infarction. Simvastatin 80 mg lowered LDL by an additional 0.35 mmol/l compared with simvastatin 20 mg. No significant difference in risk of major vascular events was reported. However, myopathy (defined as a creatine kinase over 5 times the normal level plus symptoms) was over 25 times more likely in the high dose simvastatin group as compared with lower dose simvastatin group.

Lipid lowering targets

One good quality RCT [127] (n=1,351, DM=9%) and two average quality RCTs [128, 129] (n=60-2,442; DM=8-23%) evaluated the thresholds and targets for lipid modification for producing the greatest reduction in secondary CVD events.

The good quality RCT compared the effect of targeting an LDL-C goal of 1.55-2.20 mmol/l (60-85 mg/dl) to targeting an LDL-C level of 3.36-3.62 mmol/l (130-140 mg/dl), for secondary prevention of cardiovascular events in dyslipidaemic patients with coronary heart disease. No treatment differences were reported in both arms for composite or individual outcomes.

Koren's 2004 (n=2,442, DM=22%) study evaluated the effectiveness of targeting an LDL-C goal of <2.07mmol/l (80 mg/dl) (atorvastatin up to 80 mg per day) compared to usual care of lipids with no pre-specified targets, for the secondary prevention of serious cardiovascular events in patients with coronary heart disease and hyperlipidaemia. Significant reduction of the occurrence of a recurrent cardiovascular event was reported in the intensive lipid therapy group as compared to the usual care group. This treatment effect for the primary endpoint was more pronounced in CKD and elderly patients.

Summary – Use of statins in lipid control

On the basis of the current evidence, statins significantly reduce the risk of cardiovascular events and do so in a wide range of patients including those with diabetes and known cardiovascular disease, and those whose pre-treatment LDL levels are at or below 2.0 mmol/l. The cardiovascular benefits are maximised by intensive lowering of LDL levels, with the strongest evidence for the benefits of a high dose of statin therapy from trials of atorvastatin 80 mg. Trials of simvastatin 80 mg reported no greater benefits than seen with lower doses of simvastatin but more adverse events. Very small numbers of patients with haemorrhagic strokes have been included in the statin trials. Since the pathophysiological processes of haemorrhagic stroke may be different to other forms of cardiovascular disease, the evidence cannot readily be extrapolated to this group.

The economic analyses performed on high dose statin use indicate that it is also likely to be cost-effective [130, 131].

Important other considerations in lipid lowering therapy

Secondary causes of dyslipidaemia need to be excluded and treated if present prior to commencement of statin treatment. These include kidney, liver and thyroid disease and excessive alcohol intake.

All lipid lowering therapies have side effects which increase as the dose of the drug increases and the number of drugs used increases. For secondary prevention it is generally accepted that the reduction in events from using the increased dose of the drug(s) usually outweighs the increased risk of side effects.

It is a requirement of the Pharmaceutical Benefits Scheme (PBS) that nutritional therapy be commenced simultaneously with commencement of statin therapy.

Note: Haemorrhagic stroke is not considered a cardiovascular disease event for the purpose of guiding decisions on requirement for statin therapy.

Other Lipid Lowering Agents (single or in combination with statin)

Nicotinic acid

One good quality systematic review [132] (n=5,137) pooling data from 7 RCTs evaluated the effects of lipid lowering with nicotinic acid compared with placebo on recurrent cardiovascular events in patients with coronary artery disease. Nicotinic acid was reported to significantly reduce the risk of non-fatal MI, stroke/TIA and coronary revascularisation. Despite these potential cardiovascular benefits, use of nicotinic acid remains limited by side effects such as severe flushing.

One good quality RCT [133] (n=3,414, DM=34%) evaluated whether extended-release niacin added to simvastatin to raise low levels of high-density lipoprotein (HDL) cholesterol was superior to simvastatin alone in reducing residual cardiovascular risk in patients with established cardiovascular disease. The trial showed no incremental clinical benefit from the addition of niacin to statin therapy during a 36-month follow-up period among patients with atherosclerotic cardiovascular disease and LDL cholesterol levels of less than 70 mg /dl (1.81 mmol/l), despite significant improvements in HDL cholesterol and triglyceride levels. The findings applied equally to those with and without diabetes.

Bile acid binding resins

The systematic review found no evidence that bile acid binding resins high doses reduce cardiovascular events. There are also no data describing the effects of the combination of bile acid binding resins and statins. However, bile acid binding resins are in use in Australia for lipid lowering and there is some indication that there may be a positive effect on cardiovascular outcomes [134, 135].

Plant sterols

There was no evidence found from the systematic review regarding the effect of plant sterols on reducing cardiovascular events despite their well-documented effects on lowering LDL levels.

Ezetimibe

The systematic review found no evidence of an effect of ezetimibe on cardiovascular events despite its well-documented effects on lowering LDL levels [136-138] (n=556-618, DM=25-54%). The IMPROVE-IT trial [139] was reported after the cut-off date for the literature review, and was therefore not included in the formal report from the literature. This study randomised over 18,000 patients with a recent acute coronary syndrome to simvastatin 40 mg plus ezetimibe 10 mg or to simvastatin 40 mg plus placebo. Over 6.4 years, there was a statistically significant 6.4% reduction in the primary composite outcome (cardiovascular death, non-fatal myocardial infarction, unstable angina, coronary revascularisation or non-fatal stroke) in the ezetimibe group. In a sub-group analysis, the benefit for the nearly 5,000 participants with diabetes was significantly greater than for those without diabetes, with a hazard ratio for the effects of ezetimibe of 0.86 (0.78-0.94) among those with diabetes.

Niacin extended release versus ezetimibe

One good quality RCT [140] (n=363, DM=40%) evaluated the effectiveness of lipid control with niacin compared to ezetimibe to prevent recurrence of major cardiovascular events in 363 patients with coronary artery disease on the background of long-term statin therapy. No statistically significant difference was observed for major cardiovascular events, though niacin significantly reduced total cholesterol and increased HDL cholesterol. Additionally, the use of niacin significantly increased the risk of adverse event compared to ezetimibe.

Fish Oils

The evidence for fish oils reducing the risk of recurrent cardiovascular events is somewhat inconsistent [141] (n=39,044). Further studies are required to clarify these effects.

Omega 3 fatty acids

A 2010 RCT [142] compared 1g omega-3 acid ethyl esters-90 (460 mg eicosapentaenoic acid, 380 mg docosahexaenoic acid) to placebo over 12 months in 3,818 post-MI patients, with the primary outcome of sudden cardiac death. The diabetic sub-group analysis (n=1,032) showed no difference between groups in the rate of events, however the study was underpowered.

A 2013 RCT [143] (n=12,513) compared the effects of 1g omega-3 fatty acids to placebo on the outcome of time to death from cardiovascular causes or hospital admission for cardiovascular causes over a median follow-up of 5 years. Patients had multiple cardiovascular risk factors or clinical evidence of atherosclerotic vascular disease. Among those with diabetes (n=7,491), no statistically significant difference between groups was observed for the primary cardiovascular outcome.

A good quality RCT [144] (n=4,837, DM=21%) examined the effect of the marine n-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and of the plant-derived alpha-linolenic acid (ALA) on the rate of cardiovascular events among patients who have had a myocardial

infarction. Neither EPA–DHA nor ALA reduced the primary end point (major cardiovascular events, which comprised fatal and nonfatal cardiovascular events and cardiac interventions). In a post hoc, exploratory analysis of data from patients with diabetes, the study showed reductions in arrhythmia-related events with EPA-DHA plus ALA as compared with placebo. Nevertheless, the results are based on a post hoc analysis and do not permit definitive conclusions to be drawn.

Novel agents- Secretary phospholipase A2 inhibitor

Nicholls et al.'s 2014 trial [145] compared varespladib 500 mg daily to placebo in 5,145 patients aged 40 years or older hospitalised with an acute coronary syndrome. In the diabetic sub-group analysis (n=1,604), no statistically significant difference was observed for the primary outcome of cardiovascular mortality, nonfatal MI, nonfatal stroke or unstable angina with evidence of ischemia requiring hospitalization (HR 1.29, 0.86-1.95). However, an increase in risk of MI with varespladib was observed (HR 2.38, 1.24-4.56).

Novel agents- CETP inhibitor

One good quality RCT [146] (n=15,871, DM=25%) evaluated the effects of dalcetrapib on cardiovascular events among patients with a recent acute coronary syndrome in addition to the best available care. In patients who had had a recent acute coronary syndrome, dalcetrapib increased HDL cholesterol levels but did not reduce the risk of recurrent cardiovascular events. Hypertension, diarrhoea and insomnia occurred more frequently in the dalcetrapib group.

Use of fibrates in lipid control

One good quality systematic review [74] (n=45,058) examined the effects of fibrates on cardiovascular events and other relevant outcomes. The meta-analysis included 18 trials and pooled data from trials of a variety of fibrates-clofibrate, bezafibrate, gemfibrozil, etofibrate and fenofibrate. Overall a significant 10% reduction in the risk of major cardiovascular events and a 13% reduction in the risk of coronary events, was reported with fibrate therapy. Generally, greater benefits were observed in trials of patients with higher baseline triglyceride levels (32% reduction in risk when the TG level was >2.0 mmol/l) and where large triglyceride reductions were achieved.

There was no clear effect on stroke or all-cause or cardiac mortality. Eleven of the trials studied people with known cardiovascular disease and six studied people with diabetes. In these patient groups the same benefits were observed as in the whole population.

Three of the trials reported on microalbuminuria in people with diabetes and found that fibrates reduced the risk of development of microalbuminuria by 14%.

One large good quality trial [147] (n=5,518, DM=100%) examined the effects of fenofibrate therapy added to background statin therapy on cardiovascular events. A significant reduction in the risk of cardiovascular events was not reported. However, the confidence intervals for this outcome did overlap with those of the fibrate meta-analysis. In the subgroup of patients with high triglyceride levels (top tertile i.e.>2.3 mmol/l) and low HDL cholesterol levels (bottom tertile i.e. <0.88 mmol/l), the benefits appeared to be greater (12.4% in the fenofibrate group, versus 17.3% in the placebo group) and were statistically significant. The effects for those with dyslipidaemia appeared similar to those in *post hoc* subgroup analyses performed by three of four other major fibrate trials, including the Helsinki Heart Study, the Bezafibrate Infarction Prevention trial and the FIELD trial.

It is well recognised that the combination of fenofibrate with statins is associated with a much lower rate of side-effects than the combination of other fibrates with statins [148]. Therefore, fenofibrate is the preferred fibrate for those patients already receiving statin therapy.

Although the Jun meta-analysis [74] (n=45,058) assessed the results on the basis of triglyceride (TG) levels >2.0 mmol/l, some of the trials within the meta-analysis actually used a higher TG cut-point for these subgroup analyses. The two fenofibrate trials showed the clearest benefits for a TG cut-point of 2.3 mmol/l, combined with low HDL (men HDL<1.03 mmol/l; women HDL<1.29 mmol/l) in the Australian-based trial [149] (n=9,795, DM=100%) HDL <0.9 mmol/l) and in the North American trial [147] (n=5,518, DM=100%).

It is a requirement of the Pharmaceutical Benefits Scheme (PBS) that nutritional therapy be commenced simultaneously with commencement of fibrate therapy.

An economic analysis based on the FIELD study outcomes suggests “potential cost advantages in the longer-term by applying fenofibrate in this type of patient cohort (quite possibly in combination with statin therapy) via a marked reduction in costly cardiac events and procedures” [150].

Cholesterol reducing therapies versus control

One poor quality systematic review [151] (k=62, n=216,606) reported that cholesterol reduction as a consequence of statin, fibrate or hormone replacement therapy might be beneficial to patients with and without coronary heart disease in terms of reducing all-cause mortality, and of reducing mortality and morbidity related to coronary heart disease.

Part D Antithrombotic management

This section outlines evidenced-based recommendations on pharmacological interventions and combined therapies using antithrombotic regimens for the treatment and secondary prevention of cardiovascular events in patients with diabetes.

For people with type 2 diabetes and cardiovascular disease the benefit of long-term antithrombotic therapy for reducing the risk of myocardial infarction, stroke and vascular death is well established. However, the emergence of new antithrombotic and antithrombotic agents has led to questions as to which regimen should be applied and how combinations should be used.

This section summarises the evidence for antithrombotic therapy from systematic reviews and meta-analyses considered for the secondary prevention of cardiovascular events in the post-acute setting.

Antithrombotic therapy

Antithrombotic therapy EBRs

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-indication⁷. (Grade A) [75]

EBR 11

All adults with type 2 diabetes and a history of ischaemic stroke or TIA should receive

- *Low-dose aspirin (Grade A) [76-82] or*
- *Clopidogrel (Grade A) [80] or*
- *Combination low dose aspirin and extended release dipyridamole (Grade B) [83]*

EBR 12

All adults with type 2 diabetes and recent 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) [84-89] or*
- *Combination low-dose aspirin and prasugrel (Grade B) [90-94] or*
- *Combination low-dose aspirin and ticagrelor (Grade C) [94-97]*

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) [76-82] or*
- *Long-term clopidogrel if intolerant to aspirin (Grade B). [80, 98, 99]*

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.

⁷ Clear contraindications to antiplatelet therapy include active bleeding disorders such as gastrointestinal or intracranial haemorrhage.

Findings of the systematic review

Sixteen systematic reviews and seventeen additional RCTs examined the effects of antithrombotic therapy on the risk of cardiovascular disease events and mortality.

Evidence for antithrombotic therapy

One good quality systematic review [75] examined the effects of antiplatelet therapy on recurrent cardiovascular disease events (non-fatal myocardial infarction, non-fatal stroke, and vascular deaths) and all-cause mortality. Data from 195 RCTs were pooled. Compared with placebo, antiplatelet therapy resulted in significant reductions in the risks of death, vascular death and non-fatal vascular events for patients with a previous myocardial infarction, an acute myocardial infarction, a previous stroke/TIA and an acute stroke. Significant increases in the risks of haemorrhagic stroke and extra-cranial bleeding events (e.g. gastrointestinal bleeds) were also reported for patients receiving antithrombotic therapy compared to placebo. Overall, for every 1,000 people with previous myocardial infarction or stroke, anti-platelet therapy prevented approximately 36 serious vascular events and caused approximately one major extracranial bleed per year.

Evidence for anticoagulant therapy (incl warfarin)

Two systematic reviews (one of good quality [152] and one of average quality [79]) examined the effects of anticoagulant agents (warfarin, dicoumarol, phenylindanedione, phenprocoumon, phenindione, acenocoumarin, and nicoumalone) on recurrent cardiovascular disease events. Two good quality systematic reviews [152, 153] and three additional RCTs compared the effects of oral anticoagulants to aspirin for the prevention of recurrent cardiovascular disease events in patients with previous coronary artery disease, transient ischaemic attack (TIA), stroke or heart failure.

The data from the RCTs in the systematic reviews were pooled with the data from the more recent RCTs. No significant differences in the risks of stroke or MI events were found. However, significant increases in the risks of major bleeding for those patients receiving oral anticoagulant therapy compared to those patients receiving aspirin were evident.

Clear indications for anticoagulation include atrial fibrillation and cardio-embolic stroke.

Evidence for specific antiplatelet agents

Aspirin

Seven (one good quality and six average quality) systematic reviews examined the effects of aspirin on recurrent cardiovascular disease events. The most recent of these reviews by Lievre and Cucherat (2009) [82] pooled data from 46 RCTs. Significant reductions in the risks of all-cause mortality, vascular events, non-fatal stroke and non-fatal myocardial infarction ($ORp = 0.86$ [95% CI 0.82, 0.90]; 0.79 [95% CI 0.76, 0.83]; 0.78 [95% CI 0.71, 0.85] and 0.60 [95% CI 0.53, 0.67], respectively), and significant increases in the risks of major bleeding events were reported for aspirin therapy compared to placebo (OR = 1.87 [95% CI 1.51, 2.32]). Similarly, significant reductions in the risks of all-cause mortality and vascular events, including myocardial infarction and stroke were reported by the other systematic reviews by Berger et al (2008) [76], Thijs et al (2008) [80], Weisman et al 2002 [81], He et al (1998) [77], Matchar et al (1994) [79] and Johnson et al (1999) [78]. Across a wide range of doses (50 – 1500 mg daily), there is no evidence of dose-related variation in the effects of aspirin in regard to benefit or to risks of haemorrhagic stroke [77, 78].

Dipyridamole

One good quality systematic review [83] (n=11,459) examined the effects of dipyridamole with or without aspirin on recurrent ischaemic stroke and other vascular events in patients with previous cerebrovascular disease. A meta-analysis of individual patient data from seven RCTs involving

11,459 patients was performed. Five trials were placebo-controlled and four had a randomised group that was treated with dipyridamole alone. An analysis of the effects of dipyridamole alone versus placebo was conducted. Significant reductions in the risks of fatal and non-fatal stroke but not of fatal and non-fatal MI, cardiovascular mortality, and cardiovascular events were reported for those patients receiving dipyridamole alone compared to those patients receiving placebo. In addition, patients taking dipyridamole were reported to experience significantly more headaches than patients taking placebo. No significant difference in the effects by age, gender, qualifying event or history of hypertension, was reported.

Dipyridamole vs aspirin

One good quality systematic review [154] (k=3, n=3,386) compared the effects of dipyridamole to aspirin for the prevention of recurrent cardiovascular disease events. No significant differences in the risks of vascular death or vascular events were reported for those patients receiving dipyridamole compared to those patients receiving aspirin.

Thienopyridines (incl clopidogrel) vs aspirin

Two systematic reviews (one good quality [99] (k=10, n=26,865) and one average quality [80] (k=24, n=42,688)), compared the effects of thienopyridines (clopidogrel or ticlopidine) to aspirin for the prevention of recurrent cardiovascular disease events. One review reported a small but significant reduction and the other no significant difference in the risk of serious cardiovascular disease events (stroke, myocardial infarction or vascular death) for patients receiving thienopyridines compared to those receiving aspirin.

One average quality RCT (n=1,047, DM=32%) not included in the systematic reviews, compared the effects of clopidogrel to aspirin in patients with heart failure [98]. No significant differences in the risks of cardiovascular disease events, mortality and major bleeding events were reported for those patients receiving clopidogrel compared to those receiving aspirin.

An economic analysis [155] suggests that clopidogrel may be cost-effective in patients with PAD or prior stroke however, not in patients with prior myocardial infarction.

Clopidogrel vs warfarin

One average quality RCT (n=1,064, DM=35%) compared the effects of warfarin with clopidogrel for the prevention of cardiovascular disease events in patients with heart failure [98]. Patients were randomised to warfarin (INR target 2.5-3.0) or clopidogrel 75 mg per day. A significant reduction in the risk of stroke was reported for those patients receiving warfarin compared to those patients receiving clopidogrel (RR = 0.24 [95% CI 0.07, 0.85]). The absolute number needed to treat for all strokes and non-fatal stroke was approximately 50. No significant differences in the risks of all-cause mortality, non-fatal MI, systemic embolism or a composite endpoint of all-cause mortality, non-fatal MI and non-fatal stroke were reported. An increase in the risk of major and minor bleeds was apparent in those patients receiving warfarin compared to those patients receiving clopidogrel (RR = 2.47 [95% CI 1.24, 4.90] and RR = 1.26 [95% CI 1.03, 1.55], respectively), with an absolute number needed to harm for major haemorrhage of approximately 30.

Prasugrel vs clopidogrel

One good quality RCT [90-92] (n =13,608) compared the effects of prasugrel to clopidogrel on a background of low dose aspirin in patients hospitalised with acute coronary syndrome, patients were randomised to prasugrel (60 mg loading dose and 10 mg maintenance dose) or clopidogrel (300 mg loading dose and 75 mg maintenance dose) [92].

A significant reduction in the risk of the composite endpoint of cardiovascular death, non-fatal MI and non-fatal stroke was reported for those patients receiving prasugrel compared to those patients receiving clopidogrel (9.9% vs. 12.1%, HR = 0.81 [95% CI 0.73, 0.90]). Similar results were reported for non-fatal myocardial infarction, urgent revascularisation, a composite of all-cause death, non-fatal MI or non-fatal stroke and a composite of cardiovascular death, non-fatal MI or urgent revascularisation. An increased risk of major and minor bleeding events was also reported with prasugrel compared to clopidogrel (5% vs. 3.8%, HR = 1.31 [95% CI 1.11, 1.56]).

A pre-specified subgroup analysis of patients with diabetes was reported from this trial (n = 3,146). In comparison to clopidogrel, prasugrel was more effective in reducing MI, a composite of MI and cardiovascular death, and a composite of MI, cardiovascular death and stroke (8.2% vs. 13.2%, HR = 0.60 [95% CI 0.48, 0.76]; 10.8% vs. 15.4%, HR = 0.68 [95% CI 0.56, 0.84] and 12.2% vs. 17.0%, HR = 0.70 [95% CI 0.58, 0.85], respectively). Similarly, the risk of stent thrombosis was significantly reduced with prasugrel treatment compared to clopidogrel (2.0% vs. 3.6%, HR = 0.52 [95% CI 0.33, 0.84]). No significant differences in the risks of major haemorrhage or major plus minor haemorrhage were reported for those patients with diabetes receiving prasugrel compared to clopidogrel although these subgroup analyses were likely under-powered.

A pre-specified subgroup analysis of patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction was also reported. In comparison to clopidogrel, prasugrel was more effective in reducing a composite outcome of cardiovascular death, non-fatal MI and non-fatal stroke (10% vs. 12.4%, HR = 0.79 [95% CI 0.61, 0.93]). Similar results were found for a composite outcome of cardiovascular death, non-fatal MI and urgent revascularisation as well as for a composite of cardiovascular death or MI and MI alone. A significant increase in the risk of major and 'major plus minor' bleeding events was also reported for patients with prior coronary artery bypass graft (CABG) who received prasugrel compared to clopidogrel (18.8% vs. 2.7%, OR = 8.19 [95% CI 1.76, 38.18] and 21.9% vs. 4.1%, OR = 6.53 [95% CI 1.78, 23.94], respectively).

Another good quality RCT [93] (n=7,243, DM=39%) evaluated up to 30 months of treatment with prasugrel versus clopidogrel among patients with unstable angina or myocardial infarction without ST-segment elevation, and not undergoing PCI. No significant difference in the risk of the primary end point (a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) was observed in those patients receiving prasugrel, as compared with clopidogrel, and similar risks of bleeding were observed between the two arms.

Ticagrelor vs clopidogrel

One good quality RCT (PLATO) [95] (n=18,642, DM=25%) compared the effects of ticagrelor to clopidogrel on a background of aspirin therapy in patients hospitalised for acute coronary syndrome with or without ST segment elevation or scheduled to undergo percutaneous coronary intervention (PCI). Patients were randomised to ticagrelor (180 mg loading dose followed by 90 mg twice a day) or clopidogrel (300-600 mg loading dose followed by 75 mg daily or a maintenance dose of 75 mg daily) and continued treatment for 6 to 12 months. All patients also received aspirin (75-325mg daily) unless intolerant.

A significant reduction in the risk of the primary composite endpoint of cardiovascular mortality, MI or stroke was reported for those patients receiving ticagrelor compared to those patients receiving clopidogrel (9.8% vs. 11.7%, HR = 0.84 [95% CI 0.77, 0.92], p < 0.001). With the exception of stroke, the risks of the individual components of the endpoint were significantly reduced for patients receiving ticagrelor. Although a secondary outcome, all-cause mortality was also reduced for patients receiving ticagrelor (4.5% vs. 5.9%, HR = 0.78 [95% CI 0.69, 0.89], p < 0.001). Pre-specified subgroup analyses did not detect any heterogeneity in the treatment effects in those with or without diabetes. With respect to safety, no significant differences in the rates of total major bleeding events

were reported, however, fatal intracranial bleeding and bleeding not related to cardiac bypass surgery was increased in those patients receiving ticagrelor compared to those patients receiving clopidogrel (0.3% vs. 0.2%, HR=1.87 [0.98, 3.58], $p = 0.06$ and 4.5% vs. 3.8%, HR=1.19 [1.02, 1.38], $p = 0.03$). Major bleeding rates were higher in those with diabetes compared to those without diabetes but were similar in those receiving ticagrelor or clopidogrel. Patients receiving ticagrelor were more likely to experience episodes of dyspnoea and ventricular pauses and increases in serum creatinine and uric acid than those receiving clopidogrel.

Analysis of reduction in first and recurrent cardiovascular events in the PLATO Study [96] showed that treatment with ticagrelor compared with clopidogrel resulted in a reduction in total events, including first and subsequent recurrent cardiovascular events. Additionally the time to second occurrence of the composite end point or all-cause death was also significantly reduced by ticagrelor, while recurrent PLATO major or TIMI major non-CABG bleeding events were infrequent and not different between the two therapies.

Clopidogrel vs ticlopidine

One average quality RCT [156] ($n=1,869$, DM=22%) compared the efficacy and safety of clopidogrel versus ticlopidine in Japanese patients with a history of stroke. No significant differences of the risks of cerebral infarction, MI or vascular death and total vascular events were observed between the two arms, but a significant effect on patient safety was observed for those patients receiving ticlopidine as compared with clopidogrel experiencing symptoms and/or laboratory changes in hepatic function.

Prasugrel vs ticagrelor

An average quality network meta-analysis [94] ($n=34,126$, DM=24%) compared two newer oral anti-platelet agents, prasugrel and ticagrelor, with clopidogrel, in reduction of ischemic events. Interpretation of data was hampered by differences between the text and the figures. This network meta-analysis suggested greater clinical efficacy of both prasugrel and ticagrelor compared with clopidogrel and an indirect comparison indicated that prasugrel may be more effective than ticagrelor for preventing stent thrombosis and recurrent ischemic events.

Aspirin plus clopidogrel vs aspirin alone

Six good quality RCTS and two average quality compared the effects of aspirin and clopidogrel to aspirin alone for the prevention of recurrent cardiovascular disease events. One good quality trial looked at a cost-effectiveness outcome.

One trial randomised patients with clinically evident cardiovascular disease (78%) or multiple cardiovascular risk factors to receive clopidogrel (75mg daily) plus aspirin (75-162 mg per day) or aspirin alone [84] ($n=14,603$, DM=45%). The primary outcome was a composite of MI, stroke, or death from cardiovascular causes, and median follow up was 2.3 years. Overall, no significant difference in the risk of the primary cardiovascular outcome was reported for those patients receiving clopidogrel plus aspirin compared to those patients receiving aspirin alone. However, a significant reduction in the risk of primary cardiovascular outcome was reported for the group with clinically evident cardiovascular disease (secondary prevention) (6.9% vs. 7.9%, RR=0.88 [95% CI 0.77, 0.998], $P=0.046$) but not for the group with cardiovascular disease risk factors (primary prevention). Those patients receiving clopidogrel plus aspirin were more likely to experience moderate bleeding (2.1% vs. 1.3%, RR = 1.62 [95% CI 1.27, 2.08], $p < 0.001$) but not severe bleeding than those patients receiving aspirin alone.

One trial (CLARITY-TIMI 38) [85] ($n=3,491$, DM=16%) randomised patients with acute MI (ischaemic discomfort and ST-segment elevation presenting within 12 hours of symptom onset) to

receive clopidogrel or placebo daily, plus aspirin and a fibrinolytic agent until the day they underwent coronary angiography or until day 8 of the hospitalisation or discharge. Angiography was scheduled for 2-8 days after commencement of study treatment. Patients were then followed for clinical end points for a period of up to 30 days. For those patients undergoing angiography, the primary outcome was a composite of occlusion of the infarct-related artery on angiography or recurrent myocardial MI or death prior to angiography.

A significant reduction in risk of the primary outcome was reported for patients receiving clopidogrel and aspirin compared to patients receiving aspirin alone. This was predominantly driven by a reduction in the risk of occlusion of the infarct-related artery at angiography. Significant reductions in the risks of the composite outcome of cardiovascular death, recurrent MI or recurrent ischemia leading to urgent revascularization and separate outcome recurrent MI were also reported with further follow up to 30 days. No significant differences in the risks of cardiovascular death or overall mortality were reported for any period of follow up. No significant differences were reported for subgroups defined by sex, age, and location of infarct. No significant differences in the risks of major or minor bleeding events were reported for those patients receiving clopidogrel and aspirin compared to those patients receiving aspirin alone.

The CREDO [157] (n=2,116, DM=26%) trial randomised patients (prior MI 34 %, prior stroke 7%, diabetes 26%) scheduled for routine PCI to receive clopidogrel (300mg loading dose followed by 75mg daily for 1 year) or placebo (placebo loading dose followed by clopidogrel 75 mg daily for 1 month followed by placebo for 1 year. All patients also received aspirin therapy (75-325mg daily) for 1 year. A significant reduction in the risk of death, MI and stroke was reported for those patients receiving clopidogrel plus aspirin for 12 months following PCI as compared to those patients receiving clopidogrel and aspirin for 4 weeks following PCI. No significant effect of the loading dose of clopidogrel was reported. No significant difference in the risk of major bleeding was reported.

The CURE trial [158] (n=12,562, DM=23%) randomised patients with symptoms of acute coronary syndrome without ST elevation (unstable angina or non-Q wave MI within 24 hours of onset of symptoms) to clopidogrel (300mg loading then 75mg daily) or placebo. All patients also received aspirin therapy (75-325mg daily) until the end of the follow-up (mean = 9 months, maximum = 12 months). The primary outcome was a composite of cardiovascular death, non-fatal MI or stroke. Clopidogrel plus aspirin led to a statistically significant reduction in risk for the primary outcome and also in the primary composite endpoint plus refractory ischaemia (9.3% vs. 11.4%, RR=0.80, 95%CI [0.72, 0.90], p < 0.001 and 16.5% vs. 18.8%, RR=0.86, 95%CI [0.79, 0.94], p < 0.001). This observed reduction in risk is likely to have been driven by the treatment effect seen on risk of myocardial infarction. Patients receiving clopidogrel plus aspirin experienced significantly more major bleeding events (3.7% vs. 2.7%, RR=1.38, 95%CI [1.13, 1.67], p = 0.001) but not more life-threatening bleeding events..Mehta et al [159] (n=2,658, DM=19%) reported on the CURE sub-group of patients with non-ST-elevation acute coronary syndrome undergoing PCI. PCI was performed after randomisation at the discretion of the investigator. Patients who underwent stent insertion also received open-label thienopyridine treatment for 2-4 weeks after the PCI. A significant reduction in the risk of the primary outcome was reported for those patients receiving clopidogrel plus aspirin compared to those patients receiving aspirin alone (4.5% vs. 6.4%, RR = 0.70 [95% CI 0.50, 0.97], p = 0.03). Significant reductions in the risks of in-hospital refractory or severe ischemia, heart failure, and revascularisation procedures were also reported.

In 2012 a good quality trial by the SPS3 group [86] (n=3020, DM=37%) compared 75mg clopidogrel daily added to aspirin, to placebo plus aspirin in patients with a recent lacunar stroke (diabetic sub-group N=1,106). Over a mean of 3.4 years, no statistically significant difference was found between

groups for the outcome of stroke recurrence (HR 0.93, 0.66–1.30). A post hoc analysis of 838 patients with ASA failure and recent lacunar stroke from the SPS3 cohort randomly [89] (n=838, DM=47%) reported that in patients with a recent lacunar stroke while taking ASA, the addition of clopidogrel did not result in reduction of vascular events vs continuing ASA only (HR=0.91 95%CI [0.61-1.37]), while the risk of gastrointestinal bleeding was increased (1.03% vs. 0.38%, HR=2.7 95%CI [1.1-6.9]).

An average quality study by Wang et al in 2013 [87] (n=5,170, DM=21%) also looked at the combination of clopidogrel and aspirin compared to placebo plus aspirin in patients with a history of stroke or TIA (diabetic subgroup N=1,093). No statistically significant difference was found between groups for the outcome of new stroke (HR 0.75, 0.52–1.07) over a short follow-up of 90 days.

Another average quality study [160] randomly assigned 224 aspirin-resistant patients (DM=38%) to receive clopidogrel 75 mg plus aspirin 300 mg (n=114) or aspirin-monotherapy 300 mg (n=110). The primary end point was a composite outcome of all-cause death, nonfatal myocardial infarction, stroke, or cardiovascular hospitalization assessed at 6 months postoperatively. The results indicated that the addition of clopidogrel in patients found to be aspirin resistant after coronary artery bypass grafting did not reduce the incidence of adverse events nor did it increase the number of recorded bleeding events. The results of the subgroup with diabetes were consistent with the whole study population.

A model-based economic evaluation of the treatment strategies, which included aspirin and clopidogrel for the secondary prevention of coronary heart disease, was conducted by Gaspoz et al in 2002 [161]. This analysis suggests that aspirin for the secondary prevention of coronary heart disease is a better option than clopidogrel from a cost-effectiveness perspective except in patients at high risk.

Chen et al's good quality 2011 [88] (n=12,513, DM=31%) trial compared the cost-effectiveness of the addition of 75mg daily clopidogrel to aspirin with placebo and aspirin in a sub-group of 3773 patients with diabetes and at high athero-thrombotic risk (cost per year of life gained). A cost of Canadian \$28,852 per life year gained was found. Other subgroups i.e. prior MI, prior stroke, peripheral vascular disease showed higher cost-effectiveness, with C/E ratios under \$19,000.

Clopidogrel plus aspirin vs clopidogrel alone

One good quality RCT (MATCH) [162] (n=7,599, DM=68%) compared the effects of clopidogrel plus aspirin therapy to clopidogrel alone in patients with a history of recent ischaemic stroke or TIA (in the previous three months) and an additional vascular risk factor of previous MI, angina pectoris, symptomatic peripheral arterial disease or diabetes. Patients were randomised to aspirin (75mg daily) or matching placebo. All patients also received clopidogrel 75mg daily for 18 months. The primary composite endpoint was ischaemic stroke, MI, vascular death or re-hospitalisation for an acute ischaemic event. No significant difference in the risk of the primary composite cardiovascular disease outcome or overall mortality was reported for those patients receiving aspirin and clopidogrel compared to those patients receiving clopidogrel alone. Those patients receiving combination therapy experienced more life threatening (3% vs. 1%, RD = 1.26% [95% CI 0.64%, 1.88%]), major (2% vs. 1%, RD = 1.36% [95% CI 0.86%, 1.86%]) and minor (3% vs. 1%, RD =2.16% [95% CI 1.51%, 2.81%]) bleeding events than those patients receiving clopidogrel alone. No significant difference in the risk of the primary cardiovascular disease outcome was reported for the subgroup with diabetes.

Aspirin plus dipyridamole vs aspirin alone

A good quality systematic review [163] (n=7,612, DM=16%) estimated the effect of dipyridamole plus aspirin versus aspirin therapy alone in patients with a history of transient ischaemic attack

(TIA) or minor stroke presumed to be of arterial origin. The results showed that the combination of dipyridamole and aspirin provided greater benefit in terms of reducing the risk of vascular death, non-fatal stroke or non-fatal myocardial infarction. Combination therapy also provided a reduced relative risk of recurrent stroke.

An average quality RCT [164] (n=1,294, DM=40%) investigated the efficacy and safety of extended-release dipyridamole (ER-DP) plus ASA versus 81 mg ASA over 1 year in the secondary prevention of stroke in Japan. No significant reduction of the risk of ischemic stroke was reported in patients receiving ER-DP as compared to ASA. The risks of major bleeding events and intracranial hemorrhage were found to be similar between the treatment arms. Possible reasons for this result include a small sample size, low event rates and too short a treatment duration (a minimum of 52 weeks, but not longer than 124 weeks).

Aspirin plus dipyridamole vs warfarin

A good quality systematic review [165] (n=279) compared the effects of aspirin plus dipyridamole to warfarin (phenprocoumon) for the prevention of re-occlusion in patients with symptomatic, chronic or acute peripheral arterial disease who had undergone endovascular treatment (femoropopliteal percutaneous transluminal angioplasty). Two RCTs were pooled in the review. The patients received 50 to 990 mg aspirin plus 225 to 400 mg dipyridamole daily (n = 155) or phenprocoumon (INR target unknown). No significant difference in the risk of re-occlusion was reported for those patients receiving aspirin plus dipyridamole compared to those receiving warfarin. Although the analysis was underpowered, the direction of the treatment effect suggested a beneficial trend for combination therapy.

Aspirin plus dipyridamole vs thienopyridines

One average quality systematic review [80] and one additional good quality RCT [166] compared the effects of aspirin plus dipyridamole to thienopyridines for the prevention of cardiovascular disease events (non-fatal stroke, non-fatal myocardial infarction or vascular death).

In a network meta-analysis [80] of 24 trials that randomised patients after TIA or stroke to a variety of antithrombotic agent combinations, an indirect comparison of the effects of aspirin plus dipyridamole compared to thienopyridines was reported. A significant reduction in the risk of recurrent cardiovascular disease events was reported for those patients receiving aspirin plus dipyridamole compared to those patients receiving thienopyridines.

One RCT [166] (n=20,332, DM=28%) compared the effects of aspirin plus extended-release dipyridamole to clopidogrel in patients with a recent history of ischaemic stroke. Patients were randomised to aspirin 25 mg plus extended-release dipyridamole 200 mg twice daily (n = 10,181) or clopidogrel 75 mg per day (n = 10,151). After a mean follow-up of 2.5 years, no significant difference in the risk of recurrent stroke was reported. Similar results for the other cardiovascular disease outcomes (stroke, MI, death or a composite of these three) were also reported. An increased risk of major bleeding events (4.1% vs. 3.6%, HR = 1.15 [95% CI 1.00, 1.32]) due mainly to an increase in non-fatal haemorrhagic stroke (0.6% vs. 0.3%, HR = 2.38 [95% CI 1.51, 3.76]) was reported in patients receiving combination therapy.

Aspirin plus dipyridamole versus pentoxifylline

One average quality RCT [167] (n=208, DM=16%) compared aspirin 75 mg per day plus dipyridamole 150 mg per day versus pentoxifylline (slow release) 1200 mg/day to determine any benefit in preventing transient ischaemic attack (TIA), stroke or death. No significant differences of the risks of the recurrence of a cerebral ischaemic event (TIA or stroke) and deaths of vascular origin were reported between two treatment arms.

Terutroban vs aspirin

Bousser et al's good quality 2011 trial [168] (n=19,100, DM=28%) compared 30 mg daily of terutroban to 100 mg daily aspirin in a sub-group of 5,299 diabetic patients with a recent ischaemic event. Over a mean follow-up of 28.3 months, no statistically significant difference between groups was found for the outcome of ischaemic stroke, myocardial infarction, or other vascular death (HR 1.03, 0.90–1.20).

Vorapaxar vs placebo

One good quality RCT [169] (n=26,469, DM=25%) compared vorapaxar 2.5mg daily with placebo in patients with a history of atherosclerosis (diabetic sub-group N= 6,724), on a background of aspirin and/or other anti-platelet therapy. Over the median follow-up of 30 months, a statistically significant difference between groups was found for the composite outcome of cardiovascular death, myocardial infarction and stroke (9.3% vs. 10.5%, HR=0.87, 95% CI [0.80-0.94]). Although the results for the diabetic sub-group were nominally non-significant, the interaction term for diabetes status was not significant, indicating that the overall study results should be applied to those with diabetes. There were significantly increased risks of GUSTO moderate to severe bleeding and intracranial haemorrhage (4.2% vs. 2.5%, HR=1.66, 95% CI [1.43, 1.93]).

In 2013, the same study group [170] (n=4,883, DM=29%) looked at a sub-population of patients who had had prior ischaemic stroke, again comparing vorapaxar 2.5mg daily to placebo, on a background of aspirin and/or other anti-platelet therapy (diabetic sub-group N=1,430). Over a shorter median follow-up of 24 months, no statistically significant difference between groups was found for the same outcome (16.6% vs. 16.6%, HR=1.03, 95% CI [0.76, 1.39]). Intracranial haemorrhage was increased in the vorapaxar group (2.5% vs. 1.0%, HR=2.52, 95% CI [1.46, 4.36]).

Another good quality RCT [171] (n=12,944, DM=31%) also compared vorapaxar to placebo, on a background of aspirin and/or other anti-platelet therapy, this time in patients with acute coronary syndromes. The primary end point was a composite of death from cardiovascular causes, myocardial infarction, stroke, recurrent ischemia with rehospitalisation, or urgent coronary revascularization. Follow-up in the trial was terminated early after a safety review. After a median follow-up of 502 days (interquartile range, 349 to 667), no statistically significant difference was found between groups for the primary end point, but there was a significantly increased risk of moderate and severe bleeding (7.2% vs. 5.2%, HR=1.35, 95%CI [1.16, 1.58], P<0.001), including intracranial haemorrhage in patients receiving vorapaxar, which led to early termination of the trial (1.1% vs. 0.2%, HR=3.39, 95% CI [1.78, 6.45], P<0.001). The results for the diabetic sub-group were consistent with the main study, and the interaction term for diabetes status was not significant.

The data from the above two RCTs were used for a meta-analysis on the effectiveness of vorapaxar therapy compared to placebo for the prevention of cardiovascular death, myocardial infarction, or stroke. The results showed there was a reduction of risk of cardiovascular disease in the vorapaxar group compared with placebo (RRp = 0.887 [95% CI 0.836, 0.941], p = 0.000). There was no significant heterogeneity between the two RCTs (P=0.591).

Cilostazol vs placebo

One good quality systematic review [172] (k=12, n=5,676, DM=12.1%-38.8%) and one good quality RCT[173] (n=1,095, DM=48%) evaluated the effectiveness of cilostazol compared to placebo in preventing secondary cardiovascular events. A significant reduction in cerebrovascular events was reported for those patients receiving the cilostazol. No significant difference in cardiac events was observed between the two arms.

A 2013 meta-analysis of average quality [174] (k=10, n=4,474) compared triple antiplatelet therapy (cilostazol + aspirin + clopidogrel) to dual antiplatelet therapy (aspirin + clopidogrel) in patients who recently underwent PCI. Among diabetic patients (N unspecified) there was a significantly decreased risk of major adverse cardiac events among those on triple antiplatelet therapy compared to dual (RR=0.41, 95% CI [0.28, 0.61]). There was no statistically significant difference in mortality outcomes (RR=0.62, 95% CI [0.23, 1.68]). The average length of follow-up was unspecified for each included study, and the method of allocation, blinding and intention to treat for at least 4 out of the 10 studies was unclear. Additionally there was significant publication bias according to Egger's test. Level of heterogeneity was not specified.

Cilostazol versus aspirin

Three good quality RCTs [175-177] (n=68-2,672, DM=9-29%) investigated the effectiveness of cilostazol versus aspirin for the prevention of cardiovascular events in patients with a previous ischaemic stroke. No significant differences in the risks of recurrent ischaemic stroke or other cardiovascular events were observed for those patients receiving cilostazol as compared to aspirin, but significantly fewer haemorrhagic events were reported for patients receiving cilostazol.

Picotamide versus placebo

Two RCTs [one of good quality [178, 179] (n=2,304, DM=19%) and one of average quality [180, 181] (n=50, DM=100%)] evaluated the use of picotamide versus placebo in the prevention of secondary cardiovascular disease. No significant reductions in the risk of cardiovascular events were reported for patients receiving picotamide as compared with aspirin, but a significant reduction in the risk of vascular events could be seen in diabetic patients taking picotamide in Milani's poc-host analysis [179].

Tiriflusal versus placebo

One systematic review of good quality [182] (K=2, n=403, DM=4%-21%) identified two RCTs that compared the effectiveness of triflusal and placebo in the secondary prevention of CVD. Significant increases in the risks of serious vascular events and non-fatal myocardial infarctions were reported for patients taking placebo, relative to triflusal, but not for vascular mortality and non-fatal ischaemic stroke. Although patients taking placebo were significantly less likely than patients taking triflusal to have any adverse event, there were no statistically significant differences between the two groups for any intracranial or major systemic haemorrhage, minor haemorrhage, or gastrointestinal adverse events.

Ketanserin versus placebo

One good quality RCT [183] (n=3,899, DM=14%) evaluated the effectiveness of ketanserin compared to placebo in preventing secondary cardiovascular events in patients with intermittent claudication. No significant differences of all-cause mortality, vascular mortality, and stroke were observed between the two groups.

Suloctidil versus placebo

One good quality RCT [184] (n=438, DM=19%) evaluated the effectiveness of suloctidil compared with placebo in 438 patients who had had a neurological deficit due to thromboembolic stroke associated with atherosclerosis no less than two weeks or more than four months prior to entry into the study. No statistically significant differences were detected for all-cause mortality, cardiovascular mortality, stroke or myocardial infarction for suloctidil compared to placebo. However, there was a statistically significant increase in the number of adverse events in the suloctidil group compared to the placebo group. In particular, patients taking suloctidil suffered

from vertigo/dizziness, constipation, personality changes and most disturbingly, suspected hepatitis more frequently than patients in the placebo group.

Sulfinpyrazone versus placebo

Five RCTs (four of good quality (The Anturane Reinfarction Trial Research Group, 1980[185] (n=1620, DM=9%); The Anturane Reinfarction Italian Study Group, 1982[186] (n=727, DM=10%); The Canadian Cooperative Study Group, 1978 [187] (n=295); Cairns, 1985[188] (n=279, DM=17%)) and one of poor quality [189] (n=39) investigated the use of sulfinpyrazone compared to placebo in the prevention of secondary cardiovascular disease in patients that have had a cardiac or cerebral vascular event. There was no statistically significant difference for all-cause mortality and fatal and non-fatal stroke outcomes between sulfinpyrazone and placebo but there was a statistically significant benefit for non-fatal myocardial infarctions, thromboembolic events, early cardiac mortality and gastrointestinal adverse events associated with sulfinpyrazone use.

Sulfinpyrazone versus aspirin

Two good quality RCTs [187, 188] (The Canadian Cooperative Study Group 1978: n=259; Cairns 1985: n=279, DM=15%) reported on the effectiveness of aspirin versus sulfinpyrazone for the prevention of death or stroke. The results indicated no statistically significant clinical effect of aspirin over sulfinpyrazone.

Aspirin versus triflusal

One good quality systematic review [182] (k=5, n=5,212, DM=22%) reported on the effectiveness of aspirin compared to triflusal for the prevention of secondary cardiovascular events in patients with a history of ischaemic stroke, transient ischaemic attack or myocardial infarction. The results indicated no significant differences were found between triflusal and aspirin for secondary prevention of serious vascular events in patients with stroke or TIA and AM. However, there was a statistically significant increase in the risk of fatal ischaemic stroke, a composite of fatal and non-fatal haemorrhagic stroke and haemorrhagic stroke alone for patients who received aspirin compared to triflusal (OR_{peto} = 2.71 [95% CI 1.12, 6.55], OR_{peto} = 2.15 [95% CI 1.15, 4.04] and OR_{peto} = 2.83 [95% CI 1.20, 6.68], respectively). Furthermore, the aspirin group had a higher proportion of haemorrhagic adverse events than the triflusal group (OR_{peto} = 1.73 [95% CI 1.44, 2.08]).

Picotamide versus aspirin

One good quality RCT [190] (n=1,209, DM=19%) evaluated the effectiveness of picotamide for the prevention of cardiovascular events in diabetes patients with peripheral arterial disease (PAD). Picotamide significantly reduced mortality compared to aspirin (RR 0.55 [95% CI 0.31, 0.98]). Given the width of the confidence interval and its proximity to unity, it would suggest that there is some uncertainty regarding the accuracy of this point estimate. Statistically significant differences were not observed for deaths with a cardiovascular cause, non-vascular deaths, fatal and non-fatal myocardial infarction, or stroke; rather the wide confidence intervals suggest a lack of statistical power to detect any differences. Bleeding events were reported in both treatment groups, but the difference was not statistically significant.

Summary – antithrombotic therapy

On the basis of the current evidence, all patients with diabetes and known ischaemic cardiovascular disease should receive antithrombotic therapy, unless contra-indications exist. Given the possibility of serious and fatal bleeding resulting from antithrombotic therapy, careful consideration of potential benefits and risks for each individual patient is important before commencing therapy. This should include consideration of factors such as age, comorbidities, and risk of falls.

Low dose aspirin or clopidogrel have both been demonstrated to reduce the risk of recurrent cardiovascular events. However, individual trials have also demonstrated reductions in stroke events with combination low dose aspirin and dipyridamole. Similarly, after acute coronary syndromes and coronary stent insertion, reductions in coronary events with combination low dose aspirin and clopidogrel therapy were observed. Thus the underlying vascular pathology and presentation of the patient will dictate the type of antithrombotic therapy or combination of antithrombotic therapy recommended as well as the length of treatment. The newer antithrombotic agents, such as prasugrel and ticagrelor, now have adequate evidence for them to be included in recommendations, and future trials will likely further refine how they are used.

Part E Management – general

Implementation of complex interventions involving both lifestyle and medication is challenging. Maximising success will need to actively involve the patient (and carer where necessary), as well as other agencies, such as pharmacists, and other relevant healthcare professionals. The specifics of these challenges fall outside the specific area of the literature review and of the clinical questions on which the review was based. However, in formulating the guideline, the developers recognised that some other issues that are important to general management of complex chronic diseases needed to be highlighted. Three main areas were identified.

First, it was noted that while many patients with type 2 diabetes and cardiovascular disease are elderly and have multiple co-morbidities, clinical trials often include very few participants in these categories. Furthermore, although absolute risk is higher, and therefore the potential for benefit is greater, their limited life expectancy, and greater risk of drug related adverse events raises the possibility that benefits and risks may be different in this group to those reported in clinical trials. Caution is therefore needed in incorporating the advice in this guideline into the care of such patients.

Second, the consequence of following the advice in this guideline will be that many patients are on multiple medications. Much evidence has shown that adherence to medication is a challenging problem, and that lack of adherence appears to increase with increasing numbers of medications prescribed. Thus, an awareness of this issue is important in attempting to reproduce the benefits reported in clinical trials, and strategies to improve adherence should be actively considered.

Finally, the guideline developers chose not to look for evidence relating to lifestyle interventions as there are many other sources of such advice. However, lifestyle advice remains a cornerstone of the management of diabetes, and is important for prevention of cardiovascular disease. Therefore, brief advice on the importance of lifestyle interventions is provided.

PP 4

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 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.

Particular areas for further research include:

- appropriate blood pressure and lipid targets
- trials of combination therapies within each of the three areas (blood pressure, lipids, anti-platelet)
- initiation with combination vs with monotherapy
- co-use of proton pump inhibitors and antithrombotics
- how to trade off risk and benefits
- lifestyle and other non-pharmacological approaches to management
- cardiac rehabilitation
- stroke rehabilitation

Introduction

An Implementation Committee has been established to specifically consider issues for implementation of the recommendations and advice contained in the guideline.

During the consultation period, the guideline developers will be invited a broad range of organisations, health professionals, other health workers and people with diabetes to explicitly comment on matters that were pertinent to the guideline's implementation. An on-line survey will ask individuals and organisations to provide views on whether evidence-based recommendations and expert opinions were current practice and what they saw as the possible barriers to implementation. Written submissions were also submitted. A total of fourteen submissions were received.

Deliberations by the Implementation Committee, the Expert Panel and the Guidelines Advisory Committee, will be combined with feedback from the public consultation process to identify implementation issues, priorities and ideas for consideration by policymakers, consumer and professional organisations. A robust Dissemination & Implementation Plan has been written.

An approach to implementation

In making suggestions for implementation of the secondary prevention of cardiovascular disease in type 2 diabetes guideline, what is increasingly understood is that one strategy on its own will not result in uptake of evidence-based guidelines. In an overview of systematic reviews on changing practitioner behaviour, Grimshaw et al [191] concluded that there were some promising results from strategies such as educational outreach (for prescribing) and reminders. However, they also concluded that multifaceted interventions targeting different barriers to change are more likely to be effective than single interventions. It is essential that the focus should not be entirely on practitioner behaviour and individual preferences or attitudes, but that system issues such as resourcing, organisational behaviour and institutional approaches need to be included in any strategy to change behaviour.

It is the strong view of the guideline developers that unless there is full integration of the guideline recommendations into the broad framework of current practice, then the guideline will fail to be implemented. The impact of producing written material disseminated in hard copy or electronically, is likely to be very limited. A co-ordinated, national, multifaceted, systems approach for implementation is considered essential.

Integration of the guideline into daily practice

The most effective method of implementation of evidence-based guidelines is via integration into everyday clinical practice. In most cases this means readily available prompts and tools at the clinical interface. For most medical practitioners, this means medical software that indicates the need for particular actions when a patient is in front of them, or that produces reminder notices for recalling the patient for monitoring, assessment or management activities.

Electronic decision support tools are available and in current use for some practitioners. They do, however, remain incomplete (diabetes is not yet one of the conditions included) and are not yet fully integrated into the current medical software programs that are in widespread use. The use of "sidebars", although highly effective when used, still relies on the practitioner choosing to load the

program in addition to their usual medical records and prescribing software. This currently represents a significant barrier to practicing evidence-based care.

Allied health professionals are currently less likely than general practitioners or medical specialists to use electronic records software in their clinical encounters. Therefore other means of delivering the recommendations on assessment and management of secondary prevention of cardiovascular disease in type 2 diabetes is imperative to explore with their professional representative bodies.

Aboriginal Community Controlled Health Services currently have access to electronic clinical medical record tools and can increasingly integrate guidelines into their activities through organisational policy and procedures. Encouragement to implement the recommendations of the secondary prevention of cardiovascular disease in type 2 diabetes guideline will be important. Awareness of the revised guideline amongst the network of Aboriginal Community Controlled Health Organisations would facilitate the uptake into practice.

A solution to the current impasse on integration of decision support tools into medical software is needed urgently. This could be driven by purchasing and funding policy of Government to ensure money is only provided for desktop systems that do integrate, update, and maintain relevant guidelines.

Awareness, education and training

There is limited evidence to show that education activities increase uptake of guidelines, especially when done in isolation from other systemic approaches. However there could be positive encouragement by professional bodies to make their members aware of the revised guideline via notices in journals and newsletters, on websites and via any other means possible such as conferences. Educational and skill development programs could be developed and conducted as widely as possible by professional bodies.

For people with diabetes, awareness of the self-care activities they could be undertaking as well as the expectations they should have of their health care providers and the health system generally would be useful in assisting with implementation of the guideline. A non-technical summary of the guideline will be prepared for this purpose. Vehicles such as the National Diabetes Services Scheme (NDSS) and Diabetes Australia (and its State counterparts) are obvious mechanisms for disseminating the information about evidence-based assessment and management of secondary prevention of cardiovascular disease in people with type 2 diabetes.

NPS MedicineWise have also agreed to support the implementation of this guideline within their educational visiting program.

We intend to approach the following organisations for endorsement: Australian Diabetes Educators Association (ADEA), Australian Diabetes Society (ADS), Cardiac Society of Australia and New Zealand (CSANZ), Consumers Health Forum, CRANAPlus, Diabetes Australia & NDSS, Dietitians Association of Australia (DAA), National Aboriginal Controlled Health Organisation (NACCHO), National Heart Foundation (NHF), National Stroke Foundation (NSF), Pharmaceutical Society of Australia (PSA) and the Royal Australian College of General Practitioners (RACGP).

Part H Related Australian and Overseas Guidelines and Resources

A number of Australian and international guidelines exist in this area that may assist clinicians in the management of cardiovascular disease complications from diabetes. This guideline is based upon more recent evidence and is tailored for the Australian health care system. The guideline developers are confident that the recommendations developed for this guideline are consistent with international guidelines or sensibly vary in instances where new evidence has become available.

Australian Dietary Guidelines (2013)

https://www.nhmrc.gov.au/files/nhmrc/publications/attachments/n55_australian_dietary_guidelines_130530.pdf

ASH_ISH Hypertension guidelines

<http://eurheartj.oxfordjournals.org/content/ehj/34/39/3035.full.pdf>

IAS guidelines for lipids

http://www.athero.org/download/IASPPGuidelines_FullReport_2.pdf

JNC 8 BP guidelines

<http://www.measureuppressuredown.com/HCPProf/Find/BPs/JNC8/specialCommunication.pdf>

National Vascular Disease Prevention Alliance (Australia)

The NVDPA has produced a guideline on primary prevention of vascular disease.

http://strokefoundation.com.au/site/media/AbsoluteCVD_GL_webready.pdf

National Stroke Guidelines (Australia)

The National Stroke Foundation has produced guidelines for stroke prevention and management.

http://strokefoundation.com.au/site/media/clinical_guidelines_stroke_managment_2010_interactive.pdf

National Evidence-Based Guidelines for Type 2 Diabetes (Australia)

Diabetes Australia and the University of Sydney produced guidelines on prevention and detection of diabetes, blood glucose control, and other aspects of type 2 diabetes management.

<http://www.nhmrc.gov.au/files/nhmrc/file/publications/synopses/di17-diabetes-detection-diagnosis.pdf>

National Heart Foundation Guidelines (Australia)

The National Heart Foundation has guidelines on various aspects of cardiovascular disease prevention and management.

<http://www.heartfoundation.org.au/SiteCollectionDocuments/Secondary-Prevention-of-cardiovascular-disease.pdf>

National Institute for Clinical Excellence (NICE) - UK

Type 2 Diabetes -National clinical guideline for management in primary and secondary care (2011)

<http://www.nice.org.uk/nicemedia/live/11983/40803/40803.pdf>

NACCHO Preventative Health Guideline (2012)

[http://www.naccho.org.au/download/aboriginal-health/1.National%20guide%20to%20a%20preventive%20health%20assessment%20for%20Aboriginal%20and%20Torres%20Strait%20Islander%20people%20\(2\).pdf](http://www.naccho.org.au/download/aboriginal-health/1.National%20guide%20to%20a%20preventive%20health%20assessment%20for%20Aboriginal%20and%20Torres%20Strait%20Islander%20people%20(2).pdf)

Scottish Intercollegiate Guideline Network – (Scotland)

Management of Diabetes - A national clinical guideline (March 2010)

<http://www.sign.ac.uk/pdf/sign116.pdf>

2013 ACC AHA Guidelines on the treatment of Blood Cholesterol

<https://circ.ahajournals.org/content/early/2013/11/11/01.cir.0000437738.63853.7a>

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Appendix 1: Expert Panel

The Expert Panel provided input on the scope and format of the current guideline and proposed the initial clinical questions to the Guidelines Advisory Committee (GAC) to be answered by the updated guideline. During the systematic review process, individual experts were called upon to provide advice or interpretation of the evidence as required. The Expert Panel developed the recommendations after reviewing the evidence. They subsequently responded to questions raised about the recommendations by the Guidelines Advisory Committee and by external reviewers.

<i>Member</i>	<i>Organisation</i>	<i>Expertise</i>
Professor Leon Piterman (Chair)	Monash University, Melbourne	Diabetes management in primary care
Dr Rob Grenfell	BUPA	Cardiovascular medicine; guideline development
Prof Peter Clifton	University of South Australia	Lipid disorders
Prof Karlheinz Peter	Baker IDI Heart and Diabetes Institute, Melbourne	Cardiovascular medicine
Prof Wah Cheung	University of Sydney	Diabetes care
Prof Chris Reid	Monash University, Melbourne	Trials in cardiovascular medicine
Assoc. Prof Louise Maple-Brown	Menzies School of Health Research, Darwin	Diabetes care, especially in indigenous populations

Systematic Reviewers, Adelaide Health Technology Assessment (AHTA) – synthesis of evidence up to May 2010

The technical report underpinning this guideline was completed by the team listed below:

- Elizabeth Buckley
- Judy Morona
- Vineet Juneja
- George Mnatzaganian
- Samuel Lehman
- Stynke Docter
- Edith Reddin
- David Tamblyn
- Benjamin Ellery
- Tracy Merlin

Systematic Review Update Team, University of Sydney & Baker IDI – synthesis of evidence from May 2010 - 12 August 2014

- Henry Ko
- Manoshayini Sooriyakumaran
- Lili Huo

Systematic Review Update Team, University of Sydney- search and screening from May 2010 - 12 August 2014

- Melina Willson

Systematic Review and Guideline Development Advisor, Monash Centre for Health Research and Implementation (MCHRI), Monash University

- Marie Misso

The Technical Report is available at: <http://t2dgr.bakeridi.edu.au> as is the declaration of competing interests of every team member.

Appendix 2: Project Executive

The Project Executive oversees quality, monitors timelines and ensures all deliverables are met. The Project Executive is not a decision making committee. Its primary role is to facilitate the guideline development process, ensure adherence to the Project Plan and provide support for the Guidelines Advisory Committee (GAC), the Expert Panel and the Implementation Committee.

All Reports and key deliverables will be signed-off by the Project Leader after consideration and input from the Project Executive. The Project Executive will also direct the Project Secretariat and its activities.

The Project Secretariat consists of the Project Manager and Project Co-ordinator, backed by administrative assistance from within Baker IDI, to cover all operational needs of the Project Executive, the Guidelines Advisory Committee, Expert Panel and the Implementation Committee.

Name	Organisation	Role
Associate Professor Jonathan Shaw	Baker IDI	Project Leader
Professor Bruce Neal	George Institute for Global Health	Deputy Project Leader
Professor Sophia Zoungas	Monash University	Senior Research Fellow
Ms Heidi Roache	Baker IDI	Project Manager
Dr Guy Krippner	Baker IDI	COI Officer
Ms Estella Ferenczy	Baker IDI	Project Co-ordinator

The competing interest of every team member can be found at: <http://t2dgr.bakeridi.edu.au>

Appendix 3: Guidelines Advisory Committee

The Guidelines Advisory Committee (GAC) oversees the review and updating of the guidelines. The GAC takes overall responsibility for ensuring that the guideline recommendations are appropriate and practical. The GAC reviewed the recommendations made by the Expert Panel, and sent comments back for reconsideration of the recommendations where necessary. The GAC provided final approval for the submitted documents. The committee is comprised of representatives from a broad range of stakeholder organisations relevant to diabetes and cardiovascular disease.

Name	Nominating Organisation	Perspective/Interests Represented
Professor Jeremy Oats	Baker IDI Heart and Diabetes Institute	Chairman GAC
Professor Greg Johnson	Diabetes Australia Ltd	People with diabetes
Professor Jeff Flack	Australian Diabetes Society	Specialist clinicians
A/Prof Marg McGill	Australian Diabetes Educators Association	Diabetes educators and nurses
A/Prof Margarite Vale	Dietitians Association of Australia	Dietitians and Nutritionists
Ms Helen Mikolaj Ms Julie Claessens	Consumers' Health Forum	People with diabetes and carers
Professor Mark Harris	Royal Australian College of General Practitioners	General practitioners Practice nurses
Mr Rod Jackson	An appropriate indigenous health organisation	Indigenous health
Dr Shane Jackson	Pharmaceutical Society of Australia	Community and hospital pharmacists
Ms Jinty Wilson	National Heart Foundation of Australia	Cardiovascular health
Mr Kelvin Hill	The Stroke Foundation & National Vascular Disease Prevention Alliance	Stroke care and cardiovascular absolute risk
Dr Bernie Towler (Observer)	Commonwealth Department of Health	Health policy

The competing interest of every team member can be found at: <http://t2dgr.bakeridi.edu.au>

Appendix 4: Implementation Committee

The Implementation Committee (IC), a sub group of the GAC, advises on putting the e guidelines. into practice and focuses on the practicalities of implementing the recommendation in the guideline.

Name	Organisation	Perspective/Interests Represented
Professor Jeremy Oats		Chairman GAC
Professor Jeff Flack	Australian Diabetes Society	Specialist clinicians
A/Prof Margarite Vale	Dietitians Association of Australia	Dietitians and Nutritionists
Ms Julie Claessens	Consumers' Health Forum	People with diabetes and carers
Professor Mark Harris	Royal Australian College of General Practitioners	General practitioners Practice nurses
Mr Rod Jackson	An appropriate indigenous health organisation	Indigenous health
Ms Jinty Wilson	National Heart Foundation of Australia	Cardiovascular health
Mr Kelvin Hill	The Stroke Foundation & National Vascular Disease Prevention Alliance	Stroke care and cardiovascular absolute risk

The competing interest of every team member can be found at: <http://t2dgr.bakeridi.edu.au>

Review of Col Data

Once the majority of prospective members had provided a complete statement of their interests, the information was reviewed by the GAC Chair, Professor Jeremy Oats with administrative support from the CIO. Conflicts were identified and managed in accordance with the Baker IDI Policy for Guideline Development.

The Baker IDI Conflict of Interest Policy for Guideline Development provides a stepwise process for assessing whether a particular interest represents a conflict with the interests of the Guideline being developed; for ranking the level of the conflict and for assigning a management plan that is appropriate. A stepwise summary of the process as applied to financial relationships, which have proven to be the most problematic conflict for this project, is provided in the Figure for clarity.

For the GAC, the first step was to confirm if the financial interest was with an affected company (a company marketing an intervention in the field of blood pressure lowering, lipid modification or anti-thrombotic therapy). If yes, the next step was to ascertain if the interest was specific to participation in a Scientific Advisory Board for a product that was potentially affected (defined above) by the Guidelines. If yes, the policy specifies a **high** level of conflict and requires that the GAC member be recused during discussion of Guidelines that are relevant to the product in question.

If the financial relationship with the affected company was below the threshold of \$5,000 per year, then the level of conflict was deemed **low** and the interest was managed by declaration. If the financial relationship with the affected company was above the threshold of \$5,000 per year, then the level of conflict was deemed **high** and requires that the GAC member be recused during discussion of Guidelines that are relevant to the affected company in question.

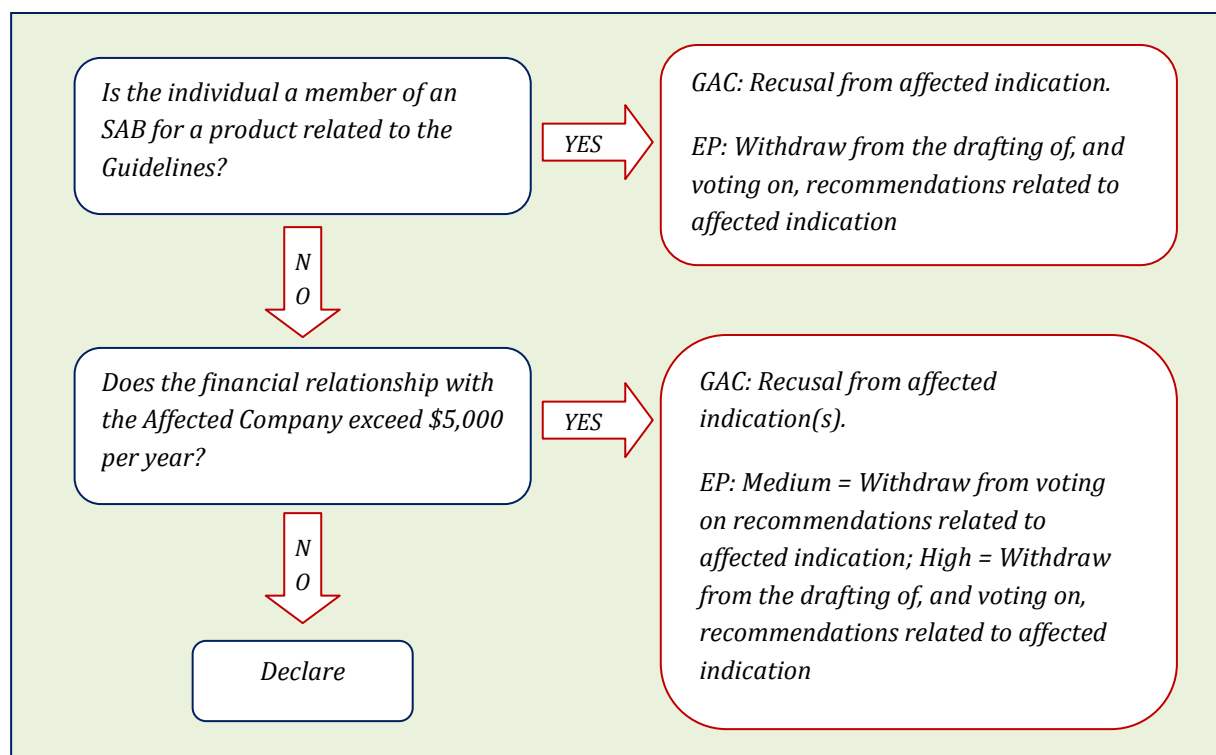


Figure. Decision process for determination of conflict of interest management plans for Guidelines

For the Expert Panel, the challenge of finding experts who are free of conflicts proved to be significant. For practical purposes, it was necessary to allow experts with significant conflicts of interest to participate in the Expert Panel, whilst taking care to put in place the appropriate management plans for all conflicts of interest.

It is the role of the Expert Panel to use their expert knowledge to understand a comprehensive review of the scientific literature, to refine this knowledge in a collective manner through panel discussion, as a group then to draft specific recommendations and then individually to confirm support of each drafted recommendation by voting. This process provides a management control by which panel members who have significant conflicts (**medium** or **high**, defined below) can make important contributions whilst minimising the impact of their conflicts. Thus, experts with significant conflicts are able to share their knowledge during the discussion phase, but are then required to withdraw from drafting and voting (if level of conflict is **high**) or withdraw from voting only (if level of conflict is **medium**).

Two mechanisms were in place to further protect the integrity of the panel. First, as per the policy, the Expert Panel must have a majority of participants that are free of significant conflicts. Second, all decisions made by the Expert Panel are reviewed by the GAC.

For Col review of the Expert Panel, the first step was to confirm if the financial interest was with an affected company. If yes, the next step was to ascertain if the interest was specific to participation in a Scientific Advisory Board for a product that was potentially affected in a commercial and/or regulatory manner by the Guidelines. If yes, the policy specifies a **high** level of conflict and requires that the Expert Panel member be recused during drafting/voting for recommendations that are relevant to the product in question.

If the financial relationship with the affected company was below the threshold of \$5,000 per year, then the level of conflict was deemed **low** and the interest was managed by declaration. If the financial relationship with the affected company was above the threshold of \$5,000 per year, it was deemed significant and then determination of the level of conflict as **medium** or **high** was adjudicated on by the collected Expert Panel in consultation with the GAC chair and CIO. Thus, a financial relationship within the range \$5,000 to \$30,000 in combination with either a non-leadership role (e.g. local investigator for a multi-site drug trial sponsored by an affected company) or peer reviewed research grant would constitute a **medium** level of conflict, whereas a leadership role or higher financial values were typically deemed **high**.

The constitution of each committee and the specific management plans for each member is provided in the following tables.

1. Col and the Guidelines Advisory Committee

The Summary Table below provides an overview of the conflicts of interest and the corresponding management plans for each of the GAC members, as determined through application of the Baker IDI Col Policy for Guideline Development.

Guideline Advisory Committee

Summary Table

GAC Panel member	No Conflict	Conflict	
		Declare	Recusal
<u>Blood pressure lowering</u>			
Jeremy Oats	✓		
Jeff Flack		✓	
Marg McGill		✓	✓
Margarite Vale	✓		
Helen Mikolaj	✓		
Julie Claessens	✓		
Mark Harris		✓	
Shane Jackson		✓	
Jinty Wilson		✓	
Kelvin Hill	✓		
Greg Johnson	✓		
Rod Jackson	✓		
Bernie Towler	✓		
<u>Lipid management</u>			
Jeremy Oats	✓		
Jeff Flack		✓	
Marg McGill		✓	✓
Margarite Vale	✓		
Helen Mikolaj	✓		
Julie Claessens	✓		
Mark Harris		✓	
Shane Jackson		✓	
Jinty Wilson		✓	
Kelvin Hill	✓		
Greg Johnson	✓		
Rod Jackson	✓		
Bernie Towler	✓		
<u>Anti-thrombosis</u>			
Jeremy Oats	✓		
Jeff Flack		✓	
Marg McGill		✓	✓
Margarite Vale	✓		
Helen Mikolaj	✓		
Julie Claessens	✓		
Mark Harris		✓	
Shane Jackson		✓	
Jinty Wilson		✓	
Kelvin Hill	✓		
Greg Johnson	✓		
Rod Jackson	✓		
Bernie Towler	✓		
<u>Diet and Lifestyle</u>			
Jeremy Oats	✓		

GAC Panel member	No Conflict	Conflict	
		Declare	Recusal
Jeff Flack	✓		
Marg McGill	✓		
Margarite Vale	✓		
Helen Mikolaj	✓		
Julie Claessens	✓		
Mark Harris		✓	
Shane Jackson	✓		
Jinty Wilson	✓		
Kelvin Hill	✓		
Greg Johnson	✓		
Rod Jackson	✓		
Bernie Towler	✓		

2. CoI and the Expert Panel

The summary table below provides an overview of the conflicts of interest and the corresponding management plans for each of the Expert Panel members, as determined through application of the Baker IDI CoI Policy for Guideline Development.

Expert Panel

Summary Table

EP Panel member	No conflict	Conflict		
		Declare	Abstain from voting	Not participate in drafting
<u>Blood pressure lowering</u>				
Leon Piterman	✓			
Peter Clifton		✓		
Karlheinz Peter	✓			
Chris Reid		✓	✓	
Wah Cheung		✓	✓	
Rob Grenfell	✓			
Louise Maple-Brown		✓	✓	✓
<u>Lipid management</u>				
Leon Piterman	✓			
Peter Clifton		✓		
Karlheinz Peter	✓			
Chris Reid				
Wah Cheung		✓	✓	
Rob Grenfell	✓			
Louise Maple-Brown		✓	✓	✓
<u>Anti-thrombosis</u>				
Leon Piterman	✓			
Peter Clifton		✓		

<i>EP Panel member</i>	<i>No conflict</i>	<i>Conflict</i>		
		<i>Declare</i>	<i>Abstain from voting</i>	<i>Not participate in drafting</i>
<i>Karlheinz Peter</i>	✓			
<i>Chris Reid</i>		✓	✓	✓
<i>Wah Cheung</i>		✓	✓	
<i>Rob Grenfell</i>	✓			
<i>Louise Maple-Brown</i>		✓	✓	✓
<u>Diet and Lifestyle</u>				
<i>Leon Piterman</i>	✓			
<i>Peter Clifton</i>		✓	✓	✓
<i>Karlheinz Peter</i>	✓			
<i>Chris Reid</i>	✓			
<i>Wah Cheung</i>	✓			
<i>Rob Grenfell</i>	✓			
<i>Louise Maple-Brown</i>		✓	✓	✓

3. Institutional Conflicts of Interest

Approximately 90% of institutions provided information in regard to their assessment of institutional interests that may be in conflict with the Guidelines project. The Menzies in Darwin (employer of Expert Panel member, Louise Maple Brown) was the only organisation to identify a significant conflict. None of the other organisations relevant to the guideline process identified any significant financial interests (in relation to their annual turnover) with affected companies.

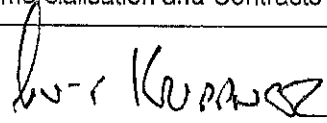
Summary Table

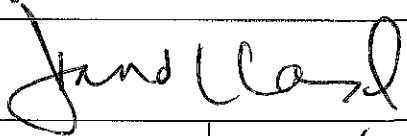
<i>Interest</i>	<i>Conflict</i>	<i>Management plan</i>
Hypertension	2013 Significant financial support to Menzies for clinical trial not involving Maple-Brown	Provide expertise but withdraw at guideline drafting/voting for Hypertension

CONFLICT OF INTEREST POLICY for GUIDELINE DEVELOPMENT

Policy – Conflict of Interest for Guideline Development	
<input checked="" type="checkbox"/>	New Policy
<input type="checkbox"/>	Revised Policy

Date of issue:	28 th February 2014
Version number:	1

Prepared by:	Guy Krippner	
	Exec GM Commercialisation and Contracts	
	SIGNATURE 	DATE 28 Feb 2014

Authorised by:	David Lloyd	
	Chief Operating Officer	
	SIGNATURE 	DATE 28 Feb 2014
Approved By IMC		Date 6 MARCH 2014

BAKER IDI:

1. Baker IDI's objectives are to reduce death and disability from cardiovascular disease, diabetes and other health disorders related to obesity, through research, clinical care, education and advocacy.
2. Baker IDI is a health promotion charity with stringent public accountability requirements, governments and donors who expect their donated funds to be used cautiously. Baker IDI recognises the need to protect its reputation by maintaining high ethical standards, fairness and integrity in all internal and external dealings. Accordingly, Baker IDI expects its staff to uphold these principles in all dealings.
3. One of the primary ways in which Baker IDI fulfils this responsibility is through the development of clinical practice guidelines, technology assessments, and clinical evidence reviews. Provider and public confidence in these guidelines depends on the cultivation of expert opinions based on the best available evidence and in a manner designed to minimize actual and perceived conflicts of interest.

PURPOSE:

Managing potential conflicts of interest (COI) is becoming increasingly important for all health research and applies equally to development of health advice in the form of clinical guidelines. Baker IDI aims to produce high quality clinical information. It is therefore important that there is a clear process to ensure that the guidelines are free from any real or perceived COI.

APPLICABLE TO:

This Policy applies to all individuals involved in guideline development for Baker IDI. This includes providing executive and administrative support to Guideline development, as well as drafting, reviewing, and approving guideline recommendations.

I. General Policy

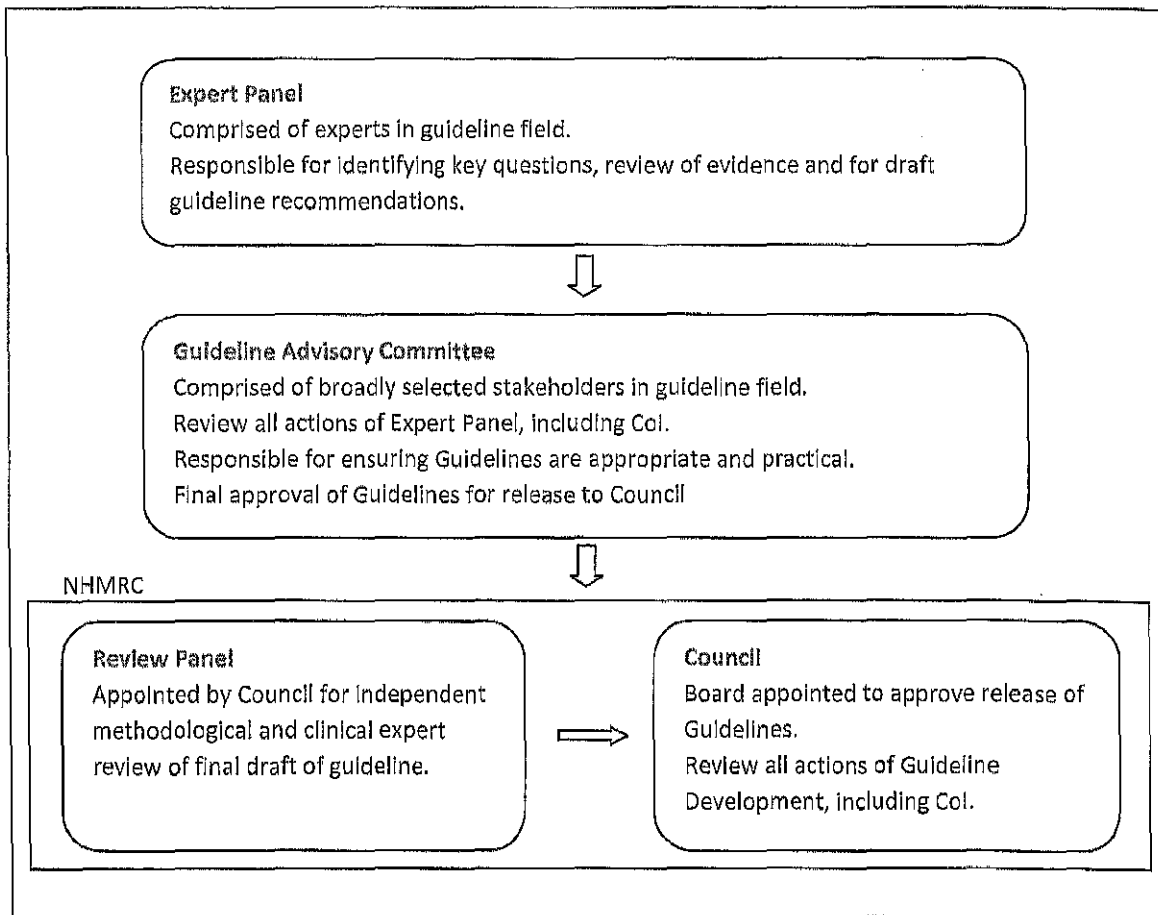
Baker IDI requires Conflict of Interest (COI) disclosure by individuals involved in drafting, reviewing, and approving guideline recommendations and sets limits on the financial relationships that participants in this process can have with Companies that could reasonably be affected by care delivered in accordance with guideline recommendations. Guidelines are typically developed by a series of committees or panels, which adopt a variety of roles. For those panels whose responsibility it is to develop and approve the guidelines (e.g. the Expert Panel and Guideline Advisory Committee (in general: Panels)), Baker IDI requires the majority (51%) of each, including the Panel chair, will be free of Direct Financial Relationships with affected Companies as described below. The remaining 49% of Panel members may be appointed to a Panel if they hold some relationships with affected Companies.

A Company is a for-profit entity that develops, produces, markets, or distributes drugs, devices, services or therapies used to diagnose, treat, monitor, manage, and alleviate health conditions.

A Direct Financial Relationship is a relationship held by an individual that results in wages, consulting fees, honoraria, or other compensation (in cash, in stock or stock options, or in kind), whether paid to the individual or to another entity at the direction of the individual, for the individual's services or expertise.

Baker IDI has a system of internal committee structures that reflect contemporary approaches to managing conflict of interest for Guideline development (see Figure). In particular, note that the evidence documents are reviewed and expert advice is provided by the Expert Panel, which is separate to and independent of the Guidelines Advisory Committee. Each successive layer of review will consider the COI matters of the prior panel. For NHMRC Clinical Guidelines, the NHMRC Council and NHMRC Review Panel will further consider the proposed guidelines, and will have their own COI policy for Guidelines.

An example of committee structures is shown in the box below.



II. Identifying Affected Companies

Companies with products affected by guidelines are considered “affected Companies” for purposes of determining whether a conflict of interest exists in the development of Baker IDI guidelines. A Company is an “affected Company” if there is a reasonable likelihood of *direct regulatory or commercial impact (positive or negative)* on the entity as a result of care delivered in accordance with guideline recommendations. Affected Companies will be identified at the time of development of the guideline protocol, prior to selection of Panel members, chairs or co-chairs.

Affected Companies will be identified by the Baker IDI COI Officer who will not serve as a Panel member. The list of affected Companies should remain consistent throughout guideline development and adoption. If changes in the marketplace or in the focus of the guideline make revisions necessary, a modified list may be developed or reviewed by the Baker IDI COI Officer. The list of Companies affected by a guideline will be made available to prospective Panel members.

III. Disclosure

Baker IDI’s policy is to promote the development of clinical practice guidelines in a manner that minimizes the risk of actual and perceived bias. Disclosure of relationships with Companies is the first step in Baker IDI’s process of evaluating and managing relationships that could result in actual or perceived bias.

a. General COI Disclosure

All prospective Panel members, including prospective Panel chairs and co-chairs, will disclose financial interests and other relationships with Companies in accordance with Baker IDI’s Principles for Interactions with Companies. All Panel members will be asked the same questions. Disclosure

categories include compensation received for employment, leadership positions, consulting activities, speaking engagements, and expert testimony; as well as ownership interests, research funding (to the individual or the institution), and licensing fees and royalties associated with intellectual property interests received by Panel members themselves and their immediate family members.

An individual's COI disclosures must be current in Baker IDI's COI Register prior to appointment to a panel. Panel members must keep their COI disclosures up to date.

b. Additional Disclosure

After reviewing the general disclosures and the list of affected Companies, the Guidelines Advisory Committee Chair or Baker IDI COI Officer may request more detailed information from an individual about the nature, value, or extent of his or her disclosed relationship with an affected Company in order to apply this Policy.

Occasionally, an individual may have a relevant indirect or non-financial interest or relationship that is not covered by Baker IDI's general COI disclosure, such as an intellectual property interest from which royalties or other payments have not yet been received; a strong professional or research opinion; or an outside affiliation. In these situations, the interest should be disclosed to the Guidelines Advisory Committee Chair or the Baker IDI COI Officer.

Disclosure reports identifying Expert Panel members' relationships with affected Companies will be available to the Expert Panel members throughout the guideline development process. Further to this, the Guideline Advisory Committee will have both the Expert Panel relationships, and the Guideline Advisory Committee relationships information available when considering guideline recommendations.

IV. Membership of Expert Panels and Guideline Advisory Committees

Baker IDI's goal is to assemble a diverse and well-qualified group of experts and stakeholders to develop and approve the guideline recommendations in a manner that minimizes the risk of actual and perceived bias.

a. Not Eligible to Serve on Panel

Having a relationship with a Company does not necessarily mean an individual is biased or has a conflict of interest. However, Baker IDI's policy is that certain financial relationships give rise to conflicts of interest that are not capable of being effectively managed and are, in fact, inconsistent with actual and perceived independence in the guideline development process. An individual is not eligible to serve on a clinical practice guideline Panel if he or she:

1. participates in a speakers' bureau (on any subject) on behalf of an affected Company;

"Speakers' bureau" means a compensated role as a presenter for which any of the following criteria are met: (a) a Company has a contractual right to dictate or control the content of the presentation or talk; (b) a Company creates the slides or presentation material or has final approval of the content and edits; or (c) the presenter is expected to act as a Company's agent or spokesperson for the primary;

2. is employed by an affected Company, or has been employed by an affected Company at any time during the year prior to appointment to the panel and to continue for one year after the publication of the guideline; or
3. holds a significant ownership interest (AU\$10,000) in an affected Company; or
4. holds a financial or other relationship whether with an affected Company or another interest that, in Baker IDI's discretion, presents a risk of actual or perceived bias that cannot be effectively managed or could undermine public confidence in the guideline.

b. Eligible to Serve as Panel Chair or Co-Chair

Generally, individuals who have disclosed financial interests in or relationships with affected Companies will not be appointed as Panel chairs or co-chairs. A Panel chair or co-chair must have been free of all interests and relationships for three years prior to appointment as chair and should commit to remain free of these interests and relationships throughout their tenure on the Panel.

However, the Guidelines Advisory Committee may appoint one Panel chair for the Expert Panel who receives research funding from an affected Company, if doing so would ultimately help the Expert Panel develop a better quality guideline. In this case, the Committee must appoint a co-chair who has no relationships with affected Companies, including research funding.

c. Eligible to Serve in the Panel Majority

A majority of Baker IDI guideline Panel members must be free of conflicts of interest relevant to the subject matter of the guideline. All relationships with Companies must be disclosed as described in Section IIIa. The Guidelines Advisory Committee Chair or Baker IDI COI Officer may ask for additional information about a relationship with an affected Company, as described in Section IIIb, to apply this Policy Implementation.

For the purpose of appointing at least 51% of guideline Panel members who are free of conflicts of interest, Baker IDI defines the following relationships as conflicts of interest:

1. Research funding from an affected Company, paid to the individual or his or her practice or institution if:
 - a. research payments are made directly from the affected Company to the individual;
 - b. the individual's salary is supported (in whole or part) through a research grant from an affected Company;
 - c. the individual is a national or overall principal investigator for a study funded by an affected Company;
 - d. the individual is a member of a steering committee of a study funded by an affected Company.
2. Compensation (including honoraria) from any one affected Company that equals, in aggregate, \$5,000 or more in a calendar year.
 - a. This includes fees and honoraria for leadership positions, consulting activities, speaking engagements, expert testimony, and patent or other licensing fees.
 - b. This excludes any compensation provided under any of the circumstances described in Section IVa.

Individuals with any of these relationships are not eligible to serve in the Panel majority, but may be eligible to serve in the Panel minority. A member of the Panel majority must remain free of these conflicts of interest from the time of his or her appointment to the Panel through to the end of the calendar year in which the guideline is published. If an individual's relationships change during that period such that he or she is no longer eligible to serve in the Panel majority, the Committee chair will shift the individual to the Panel minority. If that is not feasible given the Panel composition, the individual must resign from the Panel.

If an individual holds a patent in a technology that could be part of a guideline recommendation, the individual may be eligible to serve on the Panel minority as described in Section IVc with special requirements for COI management, or Baker IDI may find the individual ineligible to serve on the Panel under Section IVa.4 above.

If an individual holds stock options in an affected Company, as defined in Section II above, the individual may be eligible to serve on the Panel minority as described in Section IVc with special requirements for COI management, or Baker IDI may find the individual ineligible to serve on the Panel under Section IVa.4 above.

V. Voting in Expert Panel Meetings

At in-person meetings, Expert Panel recommendations must be adopted by a 75% majority of Panel members in attendance at a meeting where a simple majority of Panel members are present.

Because of the supermajority voting standard, Expert Panel members who have disclosed financial relationships with affected Companies do not need to recuse themselves from discussing and voting on guideline recommendations on these grounds.

V. Voting in Guideline Advisory Committee Meetings

a. Recusal

To underscore the independence and integrity of the Guideline Advisory Committee, guidelines will be recommended only by Committee members who do not have financial relationships with affected Companies or products. Therefore, disclosure of any financial relationship with an affected Company should be cause for recusal. Whether a relationship relates to the subject matter of the guideline is not a relevant consideration for purposes of determining recusal.

A Committee member recused from voting may take part in initial Committee discussion of the guideline manuscript, recognizing that there may be additional discussion by remaining Committee members after recusal and before the vote.

b. Voting in Guideline Advisory Committee Meetings

Generally, guidelines will be recommended by a vote of the Committee at a meeting where a quorum is present. However, if the quorum is lost by virtue of recusals as described in Section Va, the remaining Committee members in attendance will constitute a quorum as long as at least three voting members are present. Approval by majority vote of this group will be considered approval by the Committee.

VI. Publication and Peer Review

When Baker IDI publishes a guideline, all disclosures of Panel members will generally be published concurrently. This Policy Implementation is also posted publicly on Baker IDI's website.

VII. Joint Guidelines and Baker IDI-Endorsed Guidelines

From time to time, Baker IDI may join another organization to create a guideline or may endorse a relevant guideline produced by another organization. In these instances, the COI management procedures used for the development of the joint or endorsed guideline should be equivalent to the Baker IDI Conflicts of Interest for Guideline Development Policy.

VIII. Exceptions

Baker IDI's goal is to assemble a diverse and well-qualified group of experts and stakeholders to develop and approve guideline recommendations. If required to achieve this goal, these procedures may be adapted by the Baker IDI on a case-by case basis to the extent necessary.

IX. Decisions

Questions about the application of this Policy Implementation will be decided by Baker IDI. Baker IDI will consider recommendations from the panel chair and co-chair and the Committee Chair (unless the question concerns their roles). Baker IDI decisions can be made individually by the Chief Executive Officer or the Chief Operating Officer or General Counsel, with advice upon request from the Baker IDI COI Officer. Questions and decisions may concern, for instance, whether an individual is eligible to serve on a Panel, or as a Panel chair or co-chair, or in a Panel majority, or whether an individual should be recused from voting; or whether an exception is warranted.