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

_Blood pressure lowering, lipid modification and anti-thrombotic therapy_

Administrative Report
September 2015

Prepared for

NHMRC
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GOVERNANCE AND STAKEHOLDER INVOLVEMENT

1. Organisation/s responsible for developing and publishing 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. In undertaking this project, Baker IDI has also involved a broad range of stakeholders, drawn from academia, health professional and consumer organisations.

2. Sources of funding for guideline development, publication and dissemination

This project has been solely funded by the Commonwealth Department of Health.

3. A multidisciplinary group that includes end-users, relevant disciplines and clinical experts is convened to develop the purposes, scope and content of the guideline, and the process and criteria for selecting members

There are a number of committees within the Guideline Project:

**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. The panel then reviewed the evidence and formulated the recommendations. The Expert Panel was comprised of clinicians and clinical researchers with expertise in diabetes, cardiovascular disease or general practice. Appointments of suitable individuals followed a review of any potential conflicts *(please refer Point 6 Conflicts of Interest)* and was formally approved by the GAC.

The Expert Panel was comprised as follows:

<table>
<thead>
<tr>
<th>Organisation</th>
<th>Name</th>
<th>Perspective / Interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monash University</td>
<td>Prof Leon Piterman (Chairman)</td>
<td>General Practice</td>
</tr>
<tr>
<td>University of SA</td>
<td>Prof Peter Clifton</td>
<td>Lipids</td>
</tr>
<tr>
<td>Baker IDI</td>
<td>Prof Karlheinz Peter</td>
<td>Cardiology</td>
</tr>
<tr>
<td>Monash University</td>
<td>Prof Chris Reid</td>
<td>Cardiovascular trials</td>
</tr>
<tr>
<td>University of Sydney</td>
<td>Prof Wah Cheung</td>
<td>Diabetes</td>
</tr>
<tr>
<td>BUPA (&amp; formally Heart Foundation)</td>
<td>Dr Robert Grenfell</td>
<td>Cardiology</td>
</tr>
<tr>
<td>Menzies School of Health Research</td>
<td>Dr Louise Maple-Brown</td>
<td>Diabetes, incl. indigenous</td>
</tr>
</tbody>
</table>
Guidelines Advisory Committee (GAC)

The GAC took overall responsibility for ensuring that the project was appropriately managed, and that the guideline recommendations were appropriate and practical. The committee comprised representatives from a broad range of stakeholder organisations relevant to diabetes and cardiovascular disease. Appointments of suitable individuals followed a review of any potential conflicts (*please refer Point 6 Conflicts of Interest*).

The GAC was comprised as follows:

<table>
<thead>
<tr>
<th>Organisation</th>
<th>Name</th>
<th>Perspective Represented</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of Melbourne</td>
<td>Prof Jeremy Oats</td>
<td>Chairman GAC</td>
</tr>
<tr>
<td>Australian Diabetes Society</td>
<td>Prof Jeff Flack</td>
<td>Specialist clinicians</td>
</tr>
<tr>
<td>Australian Diabetes Educators Association</td>
<td>A/Prof Marg McGill</td>
<td>Diabetes educators</td>
</tr>
<tr>
<td>Consumers Health Forum</td>
<td>Ms Helen Mikolaj</td>
<td>People with diabetes &amp; their carers</td>
</tr>
<tr>
<td>Consumers Health Forum</td>
<td>Ms Julie Claessens</td>
<td>People with diabetes &amp; their carers</td>
</tr>
<tr>
<td>Department of Health</td>
<td>Dr Bernie Towler</td>
<td>Health policy [observer]</td>
</tr>
<tr>
<td>Diabetes Australia Ltd</td>
<td>Prof Greg Johnson</td>
<td>People with diabetes</td>
</tr>
<tr>
<td>Dietitians Association of Australia</td>
<td>A/Prof Margarite Vale</td>
<td>Dietitians and Nutritionists</td>
</tr>
<tr>
<td>Pharmaceutical Society of Australia</td>
<td>Dr Shane Jackson</td>
<td>Community and hospital pharmacists</td>
</tr>
<tr>
<td>National Heart Foundation of Australia</td>
<td>Ms Jinty Wilson</td>
<td>Cardiovascular health</td>
</tr>
<tr>
<td>National Vascular Disease Prevention Alliance / Stroke Foundation</td>
<td>Mr Kelvin Hill</td>
<td>Cardiovascular health</td>
</tr>
<tr>
<td>Royal Australian College of General Practitioners</td>
<td>Prof Mark Harris</td>
<td>General practice</td>
</tr>
<tr>
<td>Wathuroung Cooperative</td>
<td>Rod Jackson</td>
<td>Indigenous health</td>
</tr>
</tbody>
</table>
Implementation Committee

The Implementation Committee, a sub-committee of the GAC, focussed on the practicalities of implementing the recommendations in the guideline, considered what barriers might apply to putting each recommendation into practice, and advised on methods of dissemination of the guideline. Appointments of suitable individuals followed a review of any potential conflicts (please refer Point 6 Conflicts of Interest). The Implementation Committee was selected by GAC Chair, Professor Jeremy Oats.

The Implementation Committee was comprised as follows:

<table>
<thead>
<tr>
<th>Organisation</th>
<th>Name</th>
<th>Perspective Represented</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australian Diabetes Society</td>
<td>Prof Jeff Flack</td>
<td>Specialist clinicians in diabetes</td>
</tr>
<tr>
<td>Consumers Health Forum</td>
<td>Ms Julie Claessens</td>
<td>People with diabetes &amp; their carers</td>
</tr>
<tr>
<td>Dietitians Association of Australia</td>
<td>A/Prof Margarite Vale</td>
<td>Dietitians and Nutritionists</td>
</tr>
<tr>
<td>NVDPA / Stroke Foundation</td>
<td>Mr Kelvin Hill</td>
<td>Cardiovascular absolute risk</td>
</tr>
<tr>
<td>National Heart Foundation of Australia</td>
<td>Ms Jinty Wilson</td>
<td>Cardiovascular health</td>
</tr>
<tr>
<td>RACGP</td>
<td>Prof Mark Harris</td>
<td>General practice</td>
</tr>
<tr>
<td>Wathuroung Cooperative</td>
<td>Rod Jackson</td>
<td>Indigenous health</td>
</tr>
</tbody>
</table>

Project Executive Committee

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 GAC, the Expert Panel and the Implementation Committee. The Project Executive was selected by Baker IDI.

The Project Executive was comprised as follows:

<table>
<thead>
<tr>
<th>Name</th>
<th>Organisation</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/Prof Jonathan Shaw</td>
<td>Baker IDI</td>
<td>Project Leader</td>
</tr>
<tr>
<td>Prof Bruce Neal</td>
<td>George Institute</td>
<td>Deputy Project Leader</td>
</tr>
<tr>
<td>A/Prof Sophia Zoungas</td>
<td>George Institute</td>
<td>Executive Member</td>
</tr>
<tr>
<td>Ms Heidi Roache</td>
<td>Baker IDI</td>
<td>Project Manager</td>
</tr>
<tr>
<td>Ms Estella Ferenczy</td>
<td>Baker IDI</td>
<td>Project Coordinator</td>
</tr>
<tr>
<td>Dr Guy Krippner</td>
<td>Baker IDI</td>
<td>Conflict of Interest Officer</td>
</tr>
</tbody>
</table>
4 Participation of, and processes employed to recruit, involve and support consumer participants

Two active representatives on the GAC represented the consumer voice: Julie Claessens and Helen Mikolaj, with many years experience between them. The GAC also contained Prof Greg Johnson, who represents Diabetes Australia, a consumer focussed organisation with a strong membership and advocacy base. These members, like other members of the GAC, provided input throughout the guideline process. This included the appointment of committee members, the development of the clinical questions and of the recommendations, and strategies to disseminate the guideline. Thus, consumer input was encouraged and sought throughout the whole process. Where necessary, the Project Executive, and other members of the GAC, provided support for the consumer representatives in relation to technical and clinical matters. We also carried out a consumer / public consultation period for eight weeks when the draft guideline became available. The consultation process was consistent with the "Procedures and requirements for meeting the 2011 NHMRC standard for clinical practice guidelines" (May 2011).

5 Complete listing of people involved in the guideline development process

Expert Panel Committee
- Prof Leon Piterman (Chairman), Monash University
- Prof Peter Clifton, Baker IDI
- Prof Karlheinz Peter, Baker IDI
- Prof Chris Reid, Monash University
- Prof Wah Cheung, University of Sydney
- Dr Robert Grenfell, BUPA
- Dr Louise Maple-Brown, Menzies

Guidelines Advisory Committee
- Prof Jeremy Oats (Chairman), University of Melbourne
- Prof Greg Johnson, Diabetes Australia Ltd
- Prof Jeff Flack, Australian Diabetes Society
- A/Prof Margaret McGill, Australian Diabetes Educators Association
- A/Prof Margarite Vale, Dieticians Assoc. of Australia
- Ms Helen Mikolaj, Consumers Health Forum
- Mr Rod Jackson, Wahroong Cooperative
- Ms Julie Claessens, Consumers Health Forum
- Prof Mark Harris, RACGP
- Dr Shane Jackson, Pharmaceutical Society of Australia
- Ms Jinty Wilson, National Heart Foundation
- Mr Kelvin Hill, NVDPA (Stroke Foundation)
- Dr Bernie Towler (Observer), Department of Health
6. **Conflict of Interest management**

The identification and management of conflicts of interest (CoI) is an issue of central importance in the preparation of clinical practice guidelines to ensure that there was 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 in the integrity of guidelines. Conflicts were identified and managed in accordance with Baker IDI’s *Conflict of Interest Policy for Guideline Development* (refer Appendix 1).
The Declarations of Conflicts of Interest are listed in Appendix 5 of Administrative Report, which can also be found at http://t2dgr.bakeridi.edu.au. The CoI review is led by GAC Chair, Professor Jeremy Oats, with administrative support by Guidelines Conflicts of Interest Officer, Dr Guy Krippner.

The members of the Expert Panel and GAC were asked to provide information about their, and their employer’s, potential conflicts at the start of the project, and were asked to provide any updates before each meeting. Where conflicts existed, a conflicts management plan was put in place that ranged from simply notifying other committee members of the conflict to withdrawal from some or all of the components of discussing evidence, and drafting and voting on recommendations. At the start of each meeting, the available conflicts were tabled, so that all committee members were aware of them before discussions about the recommendations began. Each meeting was attended by the Conflicts of Interest Officer (or nominee) to ensure that all potential conflicts were appropriately handled.

7 List of organisations formally endorsing the guideline

Some of these organisations will be targeted for endorsement:

- Australian Diabetes Educators Association (ADEA)
- Australian Diabetes Society (ADS)
- Cardiac Society of Australia and New Zealand (CSANZ)
- Consumers’ Health Forum (CHF)
- CRANAplus
- Diabetes Australia Ltd (DA) and NDSS
- Dietitians Association of Australia (DAA)
- Kidney Health Australia (KHA)
- National Aboriginal Community Controlled Health Organisation (NACCHO)
- National Heart Foundation (NHF)
- National Stroke Foundation (NSF)
- Pharmaceutical Society of Australia (PSA)
- Royal Australian College of General Practitioners (RACGP)

8 Total funding received from each source

The Department of Health was the sole funding body and has provided $1,366,582.80 for this project.
Participation of, and processes employed to recruit, involve and support Aboriginal and Torres Strait Islander peoples

One of the members of the Expert Panel, A/Prof Louise Maple-Brown is an endocrinologist working mainly in Indigenous health. There is also an Indigenous member of the GAC, Mr Rod Jackson, who is currently the CEO of the Wathaurong Cooperative.

**GUIDELINE RECOMMENDATIONS**

10  **Method used for evidence based recommendations, consensus based recommendations and practice points**

By way of background, the evidence review team searched and summarised the relevant published literature. Critical appraisal of the included systematic reviews, randomised and non-randomised studies used the NHMRC quality criteria. Data extraction used forms and tables that met the NHMRC Minimum Requirements for extracting data. Summary statements of the evidence were developed for each clinical question.

Where evidence was sufficiently strong, an evidence based recommendation (EBR) was formulated, using the information in evidence tables and summary statements. These recommendations were each assigned a grade based on the body of evidence, using the NHMRC additional levels of evidence and grades for recommendations approach. The grades were determined from the formal evidence summaries, with all of the relevant information being presented in the Technical Report to provide transparency. The evidence review team ensured that the EBRs were consistent with the literature.

Where there was insufficient evidence to support an EBR (e.g. no appropriate clinical trials), the Expert Panel formulated a consensus based recommendation if they felt the issue was important enough. For some aspects of the guideline, it became apparent that clinical advice was required, but it was in an area that was not covered by the literature review. In these instances, a practice point was formulated by the Expert Panel.

Formulation of each of these types of recommendation followed a presentation of the data from the literature review. The Expert Panel (with relevant exclusions relating to conflicts of interest) discussed the evidence and developed draft recommendations. In cases where there was not a uniform consensus on the wording of a recommendation, there was the facility to vote, but this was not required for any of the recommendations.
11 **External review of Guideline and recommendations (using the AGREE II instrument)**

Baker IDI commissioned two AGREE II Appraisals one through Monash University and the other through AHTA.

The first review by Monash, before public consultation, concluded that it was a ‘high quality guideline, with particularly strong methods of development and clarity of presentation’. It provided an overall score of 6/7, and recommended the guideline for use, with modifications.

The second review by AHTA, after public consultation, similarly concluded it was a high quality guideline, and recommended its use with modifications. Those relevant changes, including some minor regrading in evidence tables, were then made.

**PUBLIC CONSULTATION**

12 **Public consultation process**

Wide consultation on the draft guideline has taken place.

An advertisement inviting comment was placed in The Australian on 6 June 2015 regarding the draft guideline. The advertisement met the requirements of the NHMRC.

A broad mail-out to key stakeholders was also undertaken (these key stakeholders represented our target audience and included organisations focusing on policy, advocacy, professional practice, standard setting, and research). The mail-out alerted organisations to the commencement of the consultation and ensured they were appropriately directed to the website to download the draft Guideline to access the on-line feedback tool or make a written submission.

Please refer to Appendix 2 for complete stakeholder list.

13 **During the public consultation period, the developer has undertaken and documented consultation with: the Director-General, Chief Executive or Secretary of each state, territory and Commonwealth health department**

Baker IDI contacted all Heads of State and Commonwealth government health departments during public consultation, please refer Appendix 2.
Documented public consultation with relevant authorities when a guideline makes any recommendations specifying interventions not available or restricted in Australia

No recommendations were made for interventions that are unavailable in Australia. Since there are restrictions on Medicare funding of some of the drugs that were recommended, Medicare was consulted, via the Pharmaceutical Benefits Scheme.

Key professional organisations and consumer organisations involved in, or affected by, the implementation of the guideline

- Australian Diabetes Society
- Australian Diabetes Educators Association
- Consumers Health Forum
- Department of Health
- Diabetes Australia
- Dieticians Association of Australia
- NACCHO
- Pharmaceutical Society of Australia
- Royal Australian College of General Practitioners (RACGP)

Public consultation submissions summary

Please refer to Public Consultation Summary in Appendix 3.
Appendix 1

Baker IDI Conflict of Interest Policy for Guideline Development
# CONFLICT OF INTEREST POLICY for GUIDELINE DEVELOPMENT

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<th>Policy – Conflict of Interest for Guideline Development</th>
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<tr>
<td>☑  New Policy</td>
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<tr>
<td>☐  Revised Policy</td>
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<table>
<thead>
<tr>
<th>Date of issue:</th>
<th>28th February 2014</th>
</tr>
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<tbody>
<tr>
<td>Version number:</td>
<td>1</td>
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</table>

<table>
<thead>
<tr>
<th>Prepared by:</th>
<th>Guy Krippner</th>
</tr>
</thead>
<tbody>
<tr>
<td>Executive GM Commercialisation and Contracts</td>
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</table>

<table>
<thead>
<tr>
<th>Signature</th>
<th>Date</th>
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<tbody>
<tr>
<td></td>
<td>28 Feb 2014</td>
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</table>

<table>
<thead>
<tr>
<th>Authorised by:</th>
<th>David Lloyd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chief Operating Officer</td>
<td></td>
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<th>Signature</th>
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<td></td>
<td>28 Feb 2014</td>
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<tr>
<th>Approved By IMC</th>
<th>Date</th>
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<tr>
<td></td>
<td>6 March 2014</td>
</tr>
</tbody>
</table>
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 Guidelines 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 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.
Appendix 2

Public consultation stakeholder list
<table>
<thead>
<tr>
<th>ORGANISATION</th>
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<tbody>
<tr>
<td>Australian Association of Consultant Pharmacy (AACP)</td>
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<tr>
<td>Australasian Podiatry Council</td>
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<tr>
<td>Australian College of Rural &amp; Remote Medicine</td>
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<tr>
<td>Australian Diabetes Educators Association</td>
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<tr>
<td>Australian Diabetes Society</td>
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<tr>
<td>Australian General Practice Network (AGPN)</td>
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<tr>
<td>Australian Indigenous Doctors Association (AIDA)</td>
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<tr>
<td>Australian Medical Association (AMA)</td>
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<tr>
<td>Australian Practice Nurses Association</td>
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<tr>
<td>Cardiac Society of Australia and New Zealand</td>
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<tr>
<td>Central Australian Rural Practitioners Association</td>
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<tr>
<td>Congress of Aboriginal Torres Strait Islander Nurses and Midwives (CATSINaM)</td>
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<tr>
<td>Consumers' Health Forum of Australia</td>
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<tr>
<td>Council Remote Area Nurses Australia</td>
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<tr>
<td>Department of Health</td>
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<tr>
<td>Department of Health &amp; Human Services [VIC]</td>
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<td>Department of Health [NT]</td>
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<tr>
<td>Department of Health [TAS]</td>
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<tr>
<td>Diabetes Australia Limited</td>
</tr>
<tr>
<td>Dietitians Association of Australia</td>
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<tr>
<td>Kidney Health Australia</td>
</tr>
</tbody>
</table>
Public consultation submissions summary
## Public consultation feedback on the Type 2 Diabetes Guidelines Recommendations

<table>
<thead>
<tr>
<th>Ref</th>
<th>Submission Name &amp; Date rcvd</th>
<th>General Comments</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Org 1</td>
<td>Congress of Aboriginal and Torres Strait Islander Nurses &amp; Midwives rcvd 11/06/2015</td>
<td>In addition to my email below, we looked at the guidelines excluding the clinical/technical details, from a population health perspective and found that the reference to Aboriginal and Torres Strait Islander peoples was rather light on as it only suggested special consideration is required, but why and what type of consideration is missing. At our conference this year, we are having one of our nurse practitioners conduct a CPD workshop around diabetes and kidney disease to specifically up skill new and experienced nurses around working with Aboriginal and Torres Strait Islander peoples who have these chronic disease conditions, as communication is a key barrier to good health outcomes as well as lack of understanding of context. The guidelines don’t provide this level of supportive information which we think is a gap, especially as the guidelines are for those that don’t necessarily work in Aboriginal health.</td>
<td>The issue of use in Aboriginal and Torres Straits Islanders was carefully considered. No evidence from CV outcomes trials was available on this population. However, the guideline clearly states that all recommendation apply equally to Aboriginal and Torres Straits Islanders, and to the general population. Implementation of the guideline will attempt to deal with communication issues in a range of settings, but this will also be a responsibility of the various health provision and health support agencies.</td>
</tr>
<tr>
<td>Org 2</td>
<td>TGA rcvd 12/06/2015</td>
<td>I am writing to advise that we have conducted a preliminary review and noted that there are only minor differences between our respective guidelines.</td>
<td></td>
</tr>
<tr>
<td>Org 3</td>
<td>The George Institute rcvd 15/06/2015</td>
<td>Well presented and clear. One of main (known) barriers to implementation is multiple guidelines. While this can be overcome by high quality decision support systems, a single cardiovascular disease prevention guideline (primary, secondary, major patient subgroups)</td>
<td>This is an important issue, but is beyond the scope of the current guideline project to deal with, other than in relation to implementation.</td>
</tr>
</tbody>
</table>
including diabetes and CKD, we will always make implementation of guidelines that much more challenging.

Not clear why blood glucose control not included (even if the recommendation is at best modest effect - CONTROL systematic review). Not specifically mentioning people with a symptomatic PVD misses out one of the highest risk and most under-treated groups.

Barriers to implementing EBR1 = Having an arbitrary clinical condition called "hypertension".

Barriers to implementing EBR3 = PBS restrictions on use of combination therapies. Old paradigms of slow up-titration of BP lowering treatment still being advocated.

Barriers to implementing EBR4 = Uncertain evidence base, especially among individuals with preserved left ventricular systolic function.

This is outside the scope of this particular guideline update and will need to be considered by the Glucose management guideline developers.

We agree that even though the guideline does not refer to the clinical condition of hypertension, this is likely to be a barrier.

Agree on slow up-titration. Not clear what PBS restrictions exist.

The expert panel is confident in the evidence underpinning the recommendation. Meta analysis by Verdecchia et al (2009) including 11 RCTs reported a higher risk of CHF for people receiving CCBs compared to diuretics or BBs in patients with hypertension with or without previous cardiovascular disease and/or type 2 diabetes, and with no overt heart failure, and an updated meta-analysis (including ACCOMPLISH), conducted by AHTA showed similar results to Verdecchia et al's. Though there is no study especially targeting individuals with preserved left ventricular systolic function, actually those individuals were included in some of the trials in the meta-analysis.
<table>
<thead>
<tr>
<th>Individual 1</th>
<th>rcvd 22/06/2015</th>
<th>Overall I think this is an excellent document. There is however one glaring omission related to peripheral vascular disease. As you would be aware this is major problem that affects diabetics with significantly higher amputation rates within this group. Currently there are no national guidelines (that I am aware of) looking at use of antiplatelets +/- statins in the reduction of diabetic foot disease. This is especially</th>
</tr>
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<tr>
<td></td>
<td></td>
<td>Trials on prevention of amputation were not specifically sought, as there is a separate guideline on diabetic foot disease.</td>
</tr>
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</table>
important with the rapid increase in the use of drug elluting balloons and stents used in the periphery to treat these problems. Currently our patients have to pay for their clopidogrel as there is no PBS indication (negatively affecting compliance), even though there is clear evidence that the results post drug elluting balloon and stent is far superior when combined with clopidogrel (as in the coronary tree). It would be great if a section related to this could be included.

In CBR2, JH commented that there is a trend now for 10mg of Atorvastatin - I think this is a waste of time.

| Org 4 | National Heart Foundation | Comment 1: Definition of Vascular vs Cardiovascular Disease
Developers may consider being clear on the definition between vascular and cardiovascular disease. It would be helpful to have a definition of cardiovascular disease upfront in the guidelines to avoid confusion around which patient groups the evidence refers too (i.e. stroke, TIA, post MI, angina, atrial fibrillation, peripheral arterial disease, and or congenital cardiovascular disease).

Comment 2: Section on Management of Blood Pressure.
In addition to the comments provided within the NVDPA submission, the strong reliance on the 2009 meta-analysis by Law et al throughout the blood pressure management section raises two additional concerns. Firstly, the authors use their data to suggest that routine measurement of BP is not necessary. This is at odds with the position of the Heart Foundation and with recent literature where there is strong evidence that more accurate measurement of BP, particularly the use of ABPM and HBPM, are better predictors of cardiovascular outcome. |

The title of the guideline has been changed to use the word ‘cardiovascular’ instead of ‘vascular’. The issue of definition was already addressed in the last paragraph of the section entitled ‘Vascular Disease in People with Diabetes’ on page 11, as well as being briefly referred to at the beginning of the guideline summary.

The guideline does not specifically make any statement about whether or not, or how, blood pressure should be measured. However, the presence of a blood pressure target in CBR1 indicates the need to measure blood pressure.
Secondly, there are a number of more recent systematic reviews on BP management for people with diabetes than Law et al 2009 that are not referenced.

- **a)** Edmin et al 2015 is the largest and more recent review. It examined the impact of BP drug choice and treatment targets in 100,345 patients with diabetes. Consistent with the literature listed below this review of 40 trials found no effect of drug class on cardiovascular outcome in patients with diabetes and no improvement on mortality if BP is treated to <140mmHg systolic.

- **b)** Wu et al 2013 is a systematic review of 63 trials and 36,197 patients with diabetes, albuminuria and with/without prior cardiovascular disease.

- **c)** Lv et al 2012 is a Cochrane systematic review of 26 trials including 61,264 diabetic participants of which a percentage had established cardiovascular disease.

- **d)** Redon et al 2013 is a systematic review that evaluates the efficacy of combination therapy in a subgroup of patients with diabetes and hypertension.

- **e)** Turnbull et al 2005 is further support to the papers listed here that consistently show that choice of drug choice and intense BP lowering (<130mmHg) has limited effect on cardiovascular and all-cause morbidity and mortality.

This was published after cut-off for the literature review. Nevertheless, it shows a benefit of blood pressure lowering for stroke reduction irrespective of whether baseline SBP is above or below 140, and irrespective of whether achieved SBP is above or below 130.

The population in this study was patients with any type of diabetes and any level of albuminuria, but provided no information on the prior CVD status of participants.

The endpoint of this study was diabetic kidney disease which is not included in our PICO. The focus of this guideline is studies reporting on vascular events as outcomes.

Assuming that this refers to the paper in *Expert Opinion Pharmacother*, this did not provide information on the group with diabetes and prior CVD. Its focus was diabetes and hypertension.

Turnbull et al was included (page 16, ref 106). It reports benefits for more vs less intensive BP-lowering in regard to the outcomes of stroke and major cardiovascular events.
We would suggest that this more recent evidence be included in guideline and recommendations and targets for initiating treatment be reviewed accordingly.

Comment 3: Drug recommendations for all patients with prior CVD and prior MI.
The Heart Foundations 2012 Reducing Risk in Heart Disease Guide currently supports the recommendations for

a) Prescribing ACEIs for everyone with coronary heart disease, especially in patients at high risk of recurrent events, unless contraindicated.

b) Prescribing beta-blockers in all patients post MI, especially in patients at high risk of recurrent events, unless contraindicated.

The current draft guideline does not clearly define ‘prior CVD’ in the ACEI recommendation and EBR6 EBR7 and EBR2 seem to be blanket statements for all patients with the removal of contraindications. Some obvious contraindications are of course, age, pregnancy, heart failure, angioedema, intolerance to ACEI etc.

It should be considered to both clearly define the patients groups reviewed and classed as prior CVD within the guideline, and to allow for health professionals to consider contraindications and clinically inappropriate prescription.

A general precaution about consideration of factors such as contra-indications has now been added to the beginning of the guideline summary.

CVD is already defined at the beginning of the summary of recommendations, specified as prior acute MI in EBR 6 and 7, and discussed in more detail on page 11.

EBR 6 and 7 refer to those with prior MI, rather than to ‘all patients’. While there is strong evidence for each, and many of the trial participants would have been on combinations of the two, we are not aware of specific trial data on the combination. We note that the Heart Foundation 2012 secondary prevention guideline also recommends ACEI and beta blockers in this population.
Comment 5: Combination treatment of ACEI and beta-blockers in all patients.
EBR6 and EBR7 in combination suggests that ACEI and beta-blocker combination therapy provides the best protection against recurrent events and cardiovascular outcome in patients with diabetes, irrespective of their blood pressure. Is there direct evidence to support this?

Comment 6: Lifestyle advice
Whilst it was noted that lifestyle advice was not reviewed in the current draft and readers are directed elsewhere, there are opportunities to discuss the measured effect of lifestyle risk factor modification, in particular mental health and cardiac rehab programs, in the implementation section. The importance of lifestyle advice and reference to RACGPs SNAP and HF resources may also be incorporated into the figure on page 5.

Comment 7: PP5 - Strategies to improve adherence should be considered, as there will frequently be a requirement to use multiple drugs.
This is an important point and indeed applies to all sections within the drafted guideline. Currently PP5 sits under the management of antiplatelet therapy. We would suggest that adherence and medication review are important issues for all sections of the drafted guideline.

EBR 6 and 7 apply, as stated in the EBRs, only to those with diabetes and prior MI. These recommendations are consistent with the Heart Foundation 2012 secondary prevention guideline, which recommends ACEI and beta blockers in all those with prior MI, and makes no mention of a blood pressure threshold. The general precaution about consideration of contraindications for all recommendations that has been added, makes the current EBRs 6 and 7 entirely consistent with the NHF position.

A practice point (PP6) has now been added, and a note added to the flowchart, to highlight the importance of lifestyle change.

PP5, as well as PP3 have now been moved out of the anti-platelet section into a general section.
<table>
<thead>
<tr>
<th>Comment 8: Table 4 – Adverse effects of blood pressure lowering medications. We kindly inform developers that this Heart Foundation resource has been significantly updated as a part of the soon to be released hypertension guidelines, and as it is in its current form will soon be rescinded. Another resource for adverse effects of antihypertensive drugs should be considered.</th>
<th>Once an update is available, we will be happy to replace the current table.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Org 5</td>
<td>SA Health rcvd 01/07/2015</td>
</tr>
</tbody>
</table>

[Cover email] Guidelines, along with other resources, are important in contemporary medical practice, to maintain currency of practice, and ensure optimum effectiveness of interventions with minimisation of harms. The increasing complexity of practice, large number of medical publications and rate of change in the therapeutic landscape have ensured that guidelines are increasingly important. In this complex environment, confidence in robustness of a guideline, and its evidence base is essential.

The presence of a guideline, not supported by an appropriate clinical evidence base, has the potential to undermine confidence of both the public and health professionals, not only in that particular guideline, but also in guidelines more broadly.

As a result of reviewing the DDG, and associated literature, we believe we have identified a number of significant concerns. These are outlined in detail below, together with supporting evidence for our concerns. In summary, these relate predominantly to levels of blood pressure at which use of blood pressure lowering therapy is recommended, potential for adverse effects and comments in relation to the application of the guideline in the Australian Indigenous population.
We ask that these concerns be considered in the process of review of the draft guideline.

**EBR 1** All adults with type 2 diabetes and known prior cardiovascular disease and BP > 110/70 mmHg should receive blood pressure lowering therapy unless contraindicated by symptomatic hypotension.

The process for the development of explicit, evidence-based guidelines has been developed and established over many years. Central to this process is the formulation of the clinical question, within the framework of a structure that defines the population of interest, the intervention, the comparison and the outcome (PICO). This DDG defines the population as adults with type 2 diabetes and known vascular disease.

The key reference for EBR 1 however, defines the studies included within it, on the basis of the intervention provided, that being blood pressure lowering drugs (Law et al 2009) with studies being included ‘irrespective of…disease status’. As such, this is an inappropriate reference to use as a basis for a clinical guideline. Many other international guidelines relating to blood pressure management have identified this weakness with this reference (see summary Appendix 1) and have not used it as a basis for their recommendations, despite it being available prior to the development of their guideline.

In relation to the Law study, given the absence of a clearly defined population group, it is difficult to know how the interpretation of this study, applies to a population of diabetics with known prior cardiovascular disease. Additionally, a large number of the subjects

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Although reliance on secondary prevention studies in people with diabetes would be ideal, the expert panel had to go beyond them. It was noted at the onset of the literature review process that evidence specifically secondary prevention populations of type 2 diabetes would be scant. It was therefore necessary to search in a broader population which included mixed populations. Nevertheless, many studies and meta-analyses contain large numbers of participants with diabetes and prior CVD, and frequently report results separately for the relevant sub-group or report whether or not outcomes differed according to baseline diabetes or prior CVD status. The broader populations used to develop recommendations have been taken into consideration when rating the generalisability of the evidence, and thus has been
included in the Law paper had no vascular disease (108 297 of 464 164 subjects). Again, there is no clear relationship between this paper, and the patient population being considered for this guideline.

This lack of clear relationship between the populations included in the cited references, and the population to which the DDG is intended to apply is not limited to the Law paper, but extends to a number of other references as outlined in the table below. As indicated by this selection of references, many of the references do not relate to populations with a predominance of diabetics with a history of vascular disease. A complete analysis of the references, in relations to the populations considered has not been conducted. However we believe that the deficiencies outlined in these references, which are regarded as key, mean that the conclusions that have been drawn are not supported by appropriate literature and raise serious questions about the validity of the draft guideline.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Diabetes</th>
<th>Non-diabetic*</th>
<th>History of Vascular Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>106</td>
<td>33 395</td>
<td>125 314</td>
<td></td>
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<tr>
<td>30</td>
<td>36</td>
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<td>23,25</td>
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<td></td>
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<tr>
<td>ACCOMPLISH</td>
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</tr>
<tr>
<td>ASCOT-BPLA</td>
<td>36</td>
<td>64</td>
<td>36</td>
</tr>
</tbody>
</table>

reflected in the overall grading of the recommendation. The guideline developers also took into account the concern that since the population as defined for the guideline is relatively narrow, there is a risk that the restricted evidence available for this specific group could lead to a series of low-level recommendations, even when recommendations for the general diabetes population or the general secondary prevention population would have had a much higher level.
*a large number of cited studies do not consist of a diabetic population with vascular disease

**Page 1** PP1 .....there should be no concern that implementing EBR1 will increase risks for patients

**Page 17** Paragraph 2 Therapies used for blood pressure lowering are generally safe and well tolerated

This assertion is not supported by references within the DDG in addition to clinical experience as outlined below. Therapies used for blood pressure lowering are a frequent contributor to hospitalisation, often with hypotension, suggesting the advice to use blood pressure lowering therapy if BP >110/70 is likely to be dangerous for many people.

The ACCORD study (reference 112 of the DDG) was a RCT examining the effects of targeting SBP less than 120 mmHg vs less than 140 mmHg in patients with type 2 diabetes who had cardiovascular disease or who were at high risk for cardiovascular events (Cushman et al 2010). This study found no significant benefit for more intensive therapy for both primary and secondary outcome measures, however found significantly more serious adverse effects including hypotension, syncope, bradycardia, arrhythmia, hyper and hypokalaemia, angioedema and renal failure. This finding suggests that the assertion in PP1 as outlined above are not supported and that

The specific context of the original PP1 indicated that PP1 is not asserting that implementation of EBR1 will be without risk, but that since EBR1 does not differ materially from previous guidelines, there will be no increase in risk. However, EBR1 and PP1 have now been modified in response to other comments.

The guideline does in fact address this issue. Page 19 reproduces the adverse event reporting from the ACCORD trial of intensive vs standard blood pressure lowering. In this trial, serious adverse events (which include all events leading to hospitalization) attributed to blood pressure medications occurred in 3.3% of the intensively-treated group and 1.27% of the standard group. Given that the intensive SBP target in ACCORD of 120 was below the suggested target of 130 in this guideline, the data support the assertion of being ‘generally safe’.

ACCORD showed a stroke benefit for lower BP, and therefore supports EBR1. Cushman (ACCORD) reports for the composite outcome that the mean BP achieved in intensive v standard therapy group was 119.3 v 133.5. Greater benefit was seen for the intensive group in terms of stroke reduction only, no difference was seen for the primary outcome of fatal and non-fatal CVD events.

As noted elsewhere, EBR1 and PP1 have now been modified in response to other comments.
the advice to use blood pressure lowering therapy if BP >110/70 will result in increased harms, without additional benefits.

McLachlan et al (2014) prospectively reviewed acute medical admissions to a General Medicine service in New Zealand and found that 28.6% of admissions were related to adverse drug events. Many of these medications are those considered in the DDG. The most common medications involved were vasodilators, psychotropics and diuretics, with the most common adverse event being postural hypotension, syncope, acute renal failure and dehydration. The adverse drug events occurred in a population of patients with a high prevalence of hypertension (45.8 %), ischaemic heart disease (29.2 %) and diabetes (22.9%)

Table 3 Medications responsible for adverse drug event (ADE)-associated admissions (from McLachlan 2014)

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
<th>Events % of ADE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasodilators</td>
<td>ACE inhibitors, alpha receptor blockers, angiotensin receptor blockers, felodipine, isosorbide mononitrate</td>
<td>36.23%</td>
</tr>
<tr>
<td>Psychotropics</td>
<td>Benzodiazepines, bupropion, chlorpromazine, methylphenidate, phenytoin, quetiapine, selective noradrenaline reuptake inhibitors, selective serotonin reuptake inhibitors, sodium valproate, tricyclic antidepressants</td>
<td>28.18%</td>
</tr>
</tbody>
</table>

This paper by McLachlan has all medical admissions as the denominator. It is not possible to determine the risk of an adverse event for a person commencing BP lowering therapy in such an analysis. Only analyses including all those starting therapy, such as reported for ACCORD, can do this. Furthermore, data from uncontrolled and non-randomised studies such as McLachlan et al are a weak basis for guideline recommendations, especially when data from RCTs are available.
Diuretics  
Furosemide, spironolactone, thiazide diuretics  
25.16%

Chronotropes  
Amiodarone, beta blockers, diltiazem, digoxin  
18.11%

Opiates  
Codeine, fentanyl, morphine, oxycodone  
12.8%

Others  
Adalimumab, alcohol, alendronate, amantidine, antibiotics, aspirin, carbidopa/levodopa, chemotherapy for malignancy, domperidone, ferrous fumarate, heroin, IV contrast, lisuride, omeprazole, paracetamol, phenylephrine, prednisone, promethazine, sulfasalazine, trial medication (MIS 416), unknown recreational drug, warfarin

The recent report of the Chief Public Health Officer in South Australia has found that injury is a leading cause of mortality and morbidity in South Australia. Of the total Hospital Separations attributed to injury over a 2 year period, 43.2% or 78,018 were assigned a code of Y40 to Y84 indicating they were due to complications of medical and surgical care. While a specific breakdown of these injuries is not available, in light of the information provided above, it reasonable to presume that many of these injuries could be attributed to the effects of commonly used medications such as blood pressure lowering therapies, lipid lowering therapies and antiplatelet agents.

Page 6  The recommendations and consensus-based statements in this guideline apply equally to Aboriginal and Torres Strait Islander
people and non-Indigenous Australians

Page 2 CBR 2 and 3 re lipid control. Only atorvastatin has good evidence for safety and efficacy at the maximum available dose

Ramamoorthy et al (2015) reviewed new drugs approved by the FDA between 2008 and 2013. Of 167 new molecular entities (NME) reviewed, 35 (21%) had some racial or ethnic difference in relation to pharmacokinetics, safety, efficacy or need for additional post-marketing studies in specific racial groups. Thus this study demonstrates that race and ethnicity can contribute to inter-individual differences in drug exposure and/or response, which may alter risk–benefit in certain populations. Population-specific prescribing recommendations may be appropriate in some cases. It cannot be presumed that information derived from one population group is necessarily applicable or appropriate to another population group.

Specific studies in the Australian Indigenous populations, regarding the majority of the medications listed in the Secondary Prevention of Vascular Disease in Type 2 Diabetes have not been conducted. Therefore there is an absence of evidence in relation to use of medications in this population group. This absence of evidence, does not equate to evidence of absence of harms, therefore the above recommendations are potentially dangerous and/or may be ineffective. It is essential that health care professionals are aware of these limitations, and the uncertainties around drug use in Aboriginal and Torres Strait Islander populations.

In addition to general evidence of the potential effect of racial status and/or ethnicity on the effect of drugs, there is some specific evidence

The issue of use in Aboriginal and Torres Straits Islanders was carefully considered. No evidence from CV outcomes trials was available on this population, nor is it likely to become available in the near future. Given the high CVD risk in this population, the Expert Panel did not believe that there should be any weakening of the recommendations to this group. With regard to the issue of statin myopathy, it is noted that the data referred to by the reviewer in Aboriginal and Torres Strait Islander populations are from case series, with no evidence of ethnic differences. Furthermore, even though the 2010 observation noted by the reviewer about increased risks in Caribbean and Black African patients was from the UK, the 2014 NICE guideline on lipids makes no mention of special precautions for any ethnic group.
of an increased risk of statin myotoxicity according to racial status. Hippisley-Cox et al (2010) found that Caribbean and Black African patients had a six to eightfold increased risk (men), and four to fivefold increased risk (women) compared with the white reference population in a large UK cohort study for statin myotoxicity. There have been no equivalent studies in Aboriginal and Torres Strait Islander populations, but the strong evidence for an increased risk according to racial status observed in other populations, raises concerns in relation to the Australian Indigenous population. This information does not support the assertions listed above, that this DDG should apply equally to Aboriginal and Torres Strait Islander populations, without additional attention to safety issues.

There have been a number of case reports and case series of serious statin myotoxicity in Aboriginal and Torres Strait Islanders (Gabb 2013, Wood 2015, Haysom 2015), including some resulting in death or permanent disability. Atorvastatin was the most frequently used medication, the dose range in one case series was 20 to 80 mg (Gabb 2013), suggesting the advice to use ‘maximum’ dose of atorvastatin may be dangerous for this population, as is the advice that the recommendations apply equally to the non-indigenous and indigenous populations.

**Part G Related Australian and International Guidelines and Resources Page 50**

This section states that the guideline developers are confident that the recommendations developed for this DDG are consistent with international guidelines, or sensible variations in instances where new evidence has become available.
However, EBR 1 recommending blood pressure lowering therapy for adults with a blood pressure of >110/70 is not consistent with international guidelines. While there is some variation between international guidelines, the recommendation of blood pressure lowering therapy in diabetics is in the range of >130-150 systolic, and >80-90 diastolic (NICE 2011, Scotland 2010, ASH\_ISH 2013, JNC 8 2014).

As a result of this inconsistency with international guidelines we looked for references within the DDG to new evidence in support of the lower threshold. A review of references in the DDG identified that there were 63 references regarding blood pressure lowering therapy. The majority of these were published in 2010 or earlier with only one reference regarding hypertension from 2011, and one reference from 2013. Therefore, the body of evidence used to reference this DDG was largely available to authors of earlier guidelines. (Appendix 2)

The 2011 paper (Nakagomi et al 2011) was a small study of 120 Japanese patients post-myocardial infarction, comparing outcomes with use of calcium channel blocker with beta-blocker. This paper would not constitute sufficient evidence to support the low threshold of BP 110/70 for use of blood pressure lowering therapy.

The 2013 reference (Benavente OR et al 2013) compared a systolic BP target of 130-149 mmHg to a target of <130 in a sub-group of about 1000 patients with diabetes who had recently had a lacunar stroke. There was no statistically significant difference between BP targets. Again, this paper would not constitute sufficient new evidence for the recommendation of blood pressure lowering therapy at a blood pressure of 110/70 mmHg.

It is important to recognise the difference between the treatment of ‘hypertension’, which implies a definition of hypertension, and the prevention of CVD in high risk patients, which often involves blood pressure lowering agents. In many guidelines about CVD prevention, the use of specific blood pressure lowering agents is recommended though not necessarily in the context of aiming for lowering of blood pressure. Typically, such recommendations make no reference to the need to have an elevated blood pressure before commencing therapy. EBR1 is consistent with these. Elsewhere, in the same guideline or in another guideline from the same organisation, there may be recommendations about how to treat hypertension, which involve both a threshold and a target blood pressure. This philosophical difference needs to be recognised when comparing CVD prevention guidelines with hypertension guidelines. It is notable that the NVDPA 2009 guideline moves away from seeing hypertension as a disease to be defined and treated, to seeing it as one of several risk factors that should be considered in initiating cardioprotective therapy (directed at lipids, BP and platelet function).

The concept of recommending blood pressure lowering drugs in those with prior CVD or in other high risk patients who do not have elevated blood pressure is not new. It is consistent with, for example, the NVDPA guideline on primary prevention (2009), the National Heart Foundation guideline on secondary prevention of CHD (2012), the NICE guideline on secondary
The assertions that the recommendations within the DDG are consistent with international guidelines, or sensible variations where new evidence has become available are not supported by the references provided. In addition, in view of earlier comments, this recommendation may result in increased harms.

**Appendix 1**

Reference to *Law, Morris & Wald (2009)* meta-analysis within other recent guidelines

**NICE Guidelines (2011)**

- [reference 351]
  - pp.168-169 “The GDG noted that the results of a meta-analysis and systematic review of 248,445 people in 108 RCTs (Law et al.) had shown that BP lowering reduced the risk of CVD and stroke irrespective of the patients’ pre-treatment blood pressure, even when pre-treatment pressures were as low as 110/70mmHg – suggesting that blood pressure lowering treatment could be offered to any person at high risk of CVD, not just those with hypertension. The GDG concluded that such a hypothesis was consistent with the continuous relationship between BP and clinical outcomes. **However, it remains a hypothesis that requires prospective testing to properly define the balance between efficacy and safety, especially in people with low baseline blood pressure, as well as the cost-effectiveness of such a strategy.**”
  - i.e. they acknowledge the conclusions of the paper, but

prevention of MI (2013), and the ESC guideline on CVD management for people with diabetes (2013). In each of these guidelines, blood pressure lowering agents (e.g. ACE inhibitors and beta blockers) are recommended without reference to a threshold or target blood pressure. Nevertheless, EBR1 and the associated PP1 have now been modified.
have not adopted them into their recommendation about threshold for initiating treatment

- p.608 “This meta analysis was reviewed as part of the guideline update in relation to the question of what the treatment initiation threshold should be. This analysis asserts that cardiovascular risk reduction is obtained at all levels of pre-treatment BP. However, the GDG noted that the analysis included studies with a range of populations…”
  
  o i.e. they did not use the conclusions to guide specific recommendations for the general hypertensive population due to heterogeneity across the analysis sub-populations

| National Stroke Foundation guidelines (2010) – not referenced |
| SIGN guidelines (2010) – not referenced |
| ASH / ISH (2013) – not referenced |
| JNC 8 (2013) – not referenced |

Not referenced in these guidelines (presumably because the populations in the meta-analysis are too broad to justify specific guideline recommendations)

| ESH-ESC Hypertension Guideline 2013 |
| - [reference 284] |
| - p.23 – referenced in discussion of recommendations for BP |
initiation; specifically for patients in the ‘High normal blood pressure’ category

- discussion recognised the limitations of the results, in terms of applicability to recommendations for high/normotensive patients, due to a lack of truly normotensive patients in the study populations (i.e. like other guidelines, acknowledging the heterogeneity between subpopulations”

- “This consideration also applies to recent large meta-analyses showing the benefits of BP-lowering therapy also in individuals with baseline SBP above and below 140mmHg, since the great majority of the individuals had been involved in trials in which antihypertensive agents were present at baseline.”

- p.23 – referenced in support of two recommendations regarding initiation of drug therapy:

- “Prompt initiation of drug treatment is recommended in individuals with grade 2 and 3 hypertension with any level of CV risk, a few weeks after or simultaneous with initiation of lifestyle changes”

- “Lowering BP with drugs is also recommended when total CV risk is high because of organ damage, diabetes, CVD or CKD, even when hypertension is in the grade 1 range”

  ▪ Relevant to secondary prevention of CVD in...
diabetics – recommends that grade 1 hypertension (140-159 / 90-99) is the threshold for initiating treatment in high-risk diabetic patients

PLUS two tables?

Org 6
Royal Melbourne Hospital
rcvd 01/07/2015

The document is comprehensive and clear, and literature review is extensive. However, I do have some reservations about the interpretation of the data to widespread applicability without some caveats. I think this is especially true of EBR1, the recommendation which will be read first. By their nature, evidence-based clinical guidelines are limited in applicability by the entry criteria limitations on participant patients in the studies underpinning them. In my opinion this should be acknowledged – for example, few clinicians would treat an 85 year old T2 diabetic with a BP of 115/80 with an antihypertensive, but that is the recommendation. Needing to prove symptomatic hypotension before treatment is NOT started does not seem sensible to me. The guidelines may not be generalisable.

EBR 1 has now had several modifications. This includes the removal of the 110/70 threshold, and the addition of a precaution stating ‘unless contraindicated or considered clinically inappropriate’.

A general precaution about consideration of factors such as age and contra-indications has now been added to the beginning of the guideline summary.

The text on Paragraph 3 Page 17 can answer this question:

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
For specific drugs, some comment on the need (or not) to dose reduce in renal impairment would also be pertinent.  

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

The specific precautions (for renal and other conditions) for individual drugs is beyond the scope of the guideline. However, a general precaution about the need to consider the presence of renal disease as well as other factors that impact on therapeutic choices has been added to the beginning of the summary document.

<table>
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<th>Org 7</th>
<th>Kidney Health Australia rcvd 01/07/2015</th>
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<tr>
<td></td>
<td>Have read through the review, impressively comprehensive and authoritative.</td>
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<td>A few quick comments:</td>
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<td></td>
<td>- The method of BP reading is not specified - <strong>home BP monitoring</strong> can reduce the risk of dangerous over-treatment of &quot;white-coat&quot; BP, especially in diabetic patients with autonomic neuropathy</td>
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<td></td>
<td>- The (small extra) benefit of <strong>ezetimibe</strong> has recently been shown in the IMPROVE-IT trial (add to pg. 36)</td>
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<td></td>
<td>- The lack of benefit (and in some cases real harm) of <strong>intensive glucose control</strong> should be mentioned as a strategy to avoid</td>
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<td></td>
<td>- There seems to be an extra &quot;l&quot; inserted after ketaseril and sulocitil (see pg. 49)</td>
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<td></td>
<td>Other guidelines should be referred to for advice on methods of BP measurement.</td>
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<td>See previous comments.</td>
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<td>Org 8 Rcvd via email on 2/07</td>
<td>WA Health Rcvd 03/07/2015</td>
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earlier documents and therefore not included in this draft document, it is recommended that the guideline still acknowledges the importance of these factors. It is recommended this acknowledgement is made in the executive summary in addition to within the body of the document.

- The feedback recommended the inclusion of specific acknowledgement related to the advantages of bariatric surgery in patients with a BMI of 36 or more and of the ‘Absolute Cardiovascular Risk Guidelines’ as endorsed by Diabetes Australia and Heart Foundation.

WA Health hopes you will consider these suggestions positively and we look forward to the release of this document.

<table>
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<tr>
<th>Org 9 Rcvd</th>
<th>CRANA</th>
<th>Have distributed Guideline link to their networks and have nothing specific to add but would welcome wide distribution in all formats to suit a range of clinicians and settings. They have offered to provide links through their professional resources on their site!</th>
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We are not aware of any RCTs demonstrating that bariatric surgery prevents CVD events. The ‘Absolute Cardiovascular Risk Guidelines’ specifically apply to those without prior CVD events.

<table>
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<tr>
<th>Org 10</th>
<th>The Royal Australasian College of Physicians (RACP) Rcvd 07/07/2015</th>
<th>The Royal Australasian College of Physicians (RACP) thanks the Baker IDI Heart &amp; Diabetes Institute for the opportunity to provide feedback on the draft National Evidence-Based Guideline on Secondary Prevention of Vascular Disease in Type 2 Diabetes. The prevalence of type 2 diabetes is increasing in Australia, and most people with diabetes are at risk of developing various vascular complications such as cardiovascular disease and stroke. These complications, which represent the major cause of morbidity and mortality in diabetic patients, can have a significant impact on their health.</th>
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quality of life and decrease life expectancy. It is vital that clinicians are aware of effective interventions for secondary prevention for these complications. The RACP considers a national, evidence-based guideline as a useful resource for our members, as it would be a therapeutic standard for secondary prevention of vascular disease in type 2 diabetes once endorsed by the National Health and Medical Research Council (NHMRC). A clinical-practice Guideline would support clinicians in their decision-making on optimal treatments for their patients with type 2 diabetes.

The College’s submission draws from consultation with our Fellows. Our main points of concern for consideration are:

**Recommendation of EBR1 - blood pressure management**
The RACP regards that setting a blood pressure target at 110/70 mmHg in all adults with type 2 diabetes and known prior cardiovascular disease as unsuitable, discordant with the literature of the past several years, and potentially dangerous for patients over the age of 50. It is also out of step with contemporary evidence-based guidelines for the management of high blood pressure in adults around the globe.

Some clinical evidence such as the ADVANCE and the ACOORD BP studies do not support this recommendation. A revision on this recommendation is needed, given that the evidence on this target is lacking. It is critically important that blood pressure targets and management recommendations in the Guideline are based on clinical evidence of patients with type 2 diabetes, rather than clinical trials of cardiovascular disease specifically. Otherwise, unnecessary harm may be caused to a patient.

**Recommendation of EBR 8 - lipid control**
The Guideline advocates the use of the maximum tolerated doses of a statin, which is misleading, as it can be interpreted as stating that

The figure of 110/70 was not a target. Nevertheless, in response to a number of comments, EBR1 and the associated PP1, have been changed, and there is no longer a BP value referred to in the recommendation.

As noted in the guideline (CBR3), the strongest evidence
80mg atorvastatin is the most desirable dose for most patients with type 2 diabetes. Clarification is needed to prevent misinterpretation. Moreover, this recommendation fails to acknowledge the risk of dose-dependent drug interactions between statins and commonly prescribed medicines such as diltiazem and clarithromycin. Furthermore, Aboriginal and Torres Strait Islander patients are highly sensitive to statins and often experience severe myositis on usual recommended doses.

To ensure appropriate decisions are made about drug combination therapy by clinicians, the RACP proposes that this recommendation should come with a note that higher doses of statins can potentially induce more pronounced drug interactions and adverse effects. This will help clinicians better anticipate the adverse outcomes of drug combination therapy.

**Overuse of medications**

If the Guideline is followed completely, the RACP is concerned that patients with type 2 diabetes would be on too many medications, elderly patients particularly. The issue of polypharmacy in the elderly is a growing problem. It is well recognised that there are a number of clinical problems associated with polypharmacy, including decreased physical and social functioning, increased risk of falls, delirium, hospital admissions and death.

The Guideline should improve the quality of patients’ care and health outcomes, and avoid promoting over-prescribing of medicines, which can lead to reduced compliance, and increase the risk of adverse drug effects and poor medication outcomes.

The College would like to see the next revision of the draft Guideline with consideration of the evidence presented in our feedback. Should you require any further information regarding this response, please contact Bella Wang, Policy Officer at Bella.Wang@racp.edu.au or on +61 2 9256 5432.

does, in fact, exist for atorvastatin 80 mg. CBR2 already advises caution in regard to high-dose statins and side-effects. This has been broadened to include drug interactions.

In regard to Aboriginal and Torres Strait Islander patients, see response above to SA Health.

The literature suggests similar efficacy for older people however as the commentators state, the adverse events may be greater in older people, and clinical judgement will be brought to bear depending on the individual circumstances. PP3 and PP5 specifically address these challenges, and advise caution.
<table>
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<tr>
<th>The Australian Primary Health Care Nurses Association (APNA) rcvd 08/07/2015</th>
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<tr>
<td>The Australian Primary Health Care Nurses Association (APNA) welcomes the opportunity to contribute to Baker IDI Heart and Diabetes Institute’s consultation on the draft Guideline on Secondary Prevention of Vascular Disease in Type 2 Diabetes. We are providing this submission on behalf of our membership, Australian primary health care nurses.</td>
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<tr>
<td><strong>APNA Submission</strong></td>
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<tr>
<td>As an overall comment on the draft Guideline on Secondary Prevention of Vascular Disease in Type 2 Diabetes (the Guideline) it is APNA’s view that the Guideline is extremely comprehensive and its authors appear to have considered all relevant and available evidence. It is also APNA’s general view that, without knowing the proposed methods of delivering the Guideline, the document could be made clearer and more ‘user-friendly’ for healthcare professionals.</td>
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<td>Our specific comments on the Guideline are listed below:</td>
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<tr>
<td>- Although the Guideline covers secondary prevention [of Vascular Disease in type 2 diabetes], and there are separate guidelines for primary prevention, APNA notes there is no reference to the continuation of primary interventions, such as ongoing education. It is our view that the Guideline should reference primary interventions.</td>
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<tr>
<td>- In order for the Guideline to be as accessible and available as possible to all health professionals, it is important that the elements of the Guideline are clearly presented. APNA suggests clarity could be improved with the use of algorithm charts covering all the considered 'key evidence based recommendations for adults with type 2 diabetes and cardiovascular disease'. An example of this in another context is the algorithm charts developed by the Royal Australian</td>
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<tr>
<td>We are not aware of any trials showing that ‘ongoing education’ prevents CVD events.</td>
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<tr>
<td>This is already provided in the flow chart on page 5.</td>
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College of General Practitioners (RACGP) for its ‘Clinical guidelines for musculoskeletal diseases’ (see www.racgp.org.au/your-practice/guidelines/musculoskeletal).

AMA comment re National Guideline on Secondary Prevention of Vascular Disease in Type 2 Diabetes

Thank you for your letter of 5 June 2015 seeking the AMA’s views on the draft Evidence-Based Guideline on Secondary Prevention of Vascular Disease in Type 2 Diabetes and its implementation.

The AMA welcomes the opportunity to give feedback on the Guideline, which, on the whole, it considers acceptable, well evidence based and useful. In particular, the guideline was useful in reinforcing that calcium channel blockers (CCBs) should not be used in heart failure (EBR 4) and that statins should not be used with haemorrhagic stroke (CBR 4).

It is important to remember, however, that guidelines are simply a guide and must always be used with an understanding that every patient is an individual and should be treated as such. By their very nature, guidelines can only be used to assist, and not dictate to, clinicians in determining the most appropriate treatment options for their patients. For this reason, the AMA would be very concerned if any guidelines were to be used to measure patient outcomes.
Of course, the guidelines must also be clear, consistent with other guidelines, and as flexible as possible to accommodate differing comorbidities, risks and ages. A recognised problem with many guidelines is the degree to which they are applicable to real life and its complex multi morbidities and comorbidities. Patients with such complexities may not be represented in research studies and hence may not be well served by the resulting guidelines. In this respect, the degree of applicability of any guidelines or recommendations should always be stated.

The AMA would like to provide the following specific comments:

It is suggested that the flow chart is the first item presented in the Guideline, with the summary of evidence-based recommendations (EBR) following for explanation. The flow chart is the action item which a busy clinician would want to see first and from which they would work.

Although research on health lifestyle strategies was not included in the literature review for this guideline because it has been extensively reviewed elsewhere, the AMA nevertheless considers it very important that the recommendations and the flow chart include the provision of lifestyle advice, particularly smoking cessation, as it is a vital component of any treatment plan.

This extensive document is unlikely to be read by most practitioners. We intend to produce the list of recommendations and the flowchart as a standalone document.

See previous comment.
# Blood Pressure Management

Although it is stated in the summary of EBR that the threshold of 110/70 mmHg is not intended to be a treatment target, there is nevertheless an implication that it is. The studies suggest lowering the BP but not to this target, and it is likely that this subtlety will be lost when busy GPs are attempting to achieve best practice. It is suggested that the goal for blood pressure control (130/80mmHg or less) should be stated first and the recommendation that those with a BP greater than 110/80mmHg would benefit from treatment be placed further down in the flow chart. In other words, the blood pressures in the boxes in the flow chart should be reversed. Furthermore, feedback from some AMA GP members indicated reservations regarding the recommendation to treat a BP level as low as between 130/80 to 110/70mmHg, particularly given that BP measurements taken during a consultation are generally higher than those recorded at home or over 24 hours.

In relation to patients living in the tropics, particularly remote indigenous patients, there is some concern with the recommendation for the use of thiazides (EBR 2), as the side effects can be very significant. These are dehydration, gout and stone disease particularly, along with potential hypokalaemia relating to poor access to fresh fruit, the major source of K+. It is questionable to give a diabetic something that makes the diabetes worse, despite the evidence of cardiovascular protection. It would be worthwhile determining if there is any evidence of the benefits of thiazides for people living in the tropics.

EBR1 and the associated PP1 have now been changed. The specific threshold of 110/70 mmHg has been removed from the text and from the flowchart. No evidence from CV outcomes trials was available on the population of people living in the tropics. Nevertheless, a general precaution about consideration of factors such as the environment and contra-indications has now been added to the beginning of the guideline summary.
tropics.

Lipid Management

EBR 8 recommends using a statin at the highest tolerated dose yet the studies highlight that side effects are likely with maximum doses. It is difficult to maintain compliance given the risk of side effects. This is a gold standard EBR, but it lacks a common-sense understanding for implementation.

Regarding CBR 5, the AMA has received representation from AMA GP members that there is not enough evidence to recommend reducing the fasting LDL cholesterol goal from 2.0mmol/L (as stated in General Practice Management of Type 2 Diabetes 2014-15) to 1.8mmol/L. Making this change without good reason could be counterproductive.

There are also reservations about the recommendation in CBR 5 to add bile acid binding resins, ezetimibe or nicotinic acid when fasting LDL cholesterol levels remain greater than or equal to 1.8mmol/L. These are stated without evidence and might do more harm, with poor compliance leading to cessation of proven treatments if they are administered. Feedback from some AMA GP members reported that when nicotinic acid or bile acid binding resins were tried, no patient could tolerate the side effects beyond a short period of time.

The concept of the ‘highest tolerated dose’ explicitly recognises the limitations imposed by side-effects. It means the highest dose that a person can take without suffering side effects. For many people, this will be less than the highest available dose.

The General Practice guideline referred to does not provide a lipid target for the ‘HIGH RISK’ group. The target of 2.0 mmol/l applies to those at ‘MODERATE RISK’ and is therefore not directly applicable to the current guideline, nor is there evidence provided as to the basis for selecting this value of 2.0. The current guideline recommends 1.8 mmol/l based on evidence from the PROVE-IT trial (page 31).

Multiple references are provided for combination therapy of statins and ezetimibe, eg 70, 132, 133, 134, 142. The available data with references for nicotinic acid and resins is described on page 32-33. CBR 5 only notes these drugs for consideration, and specifically refers to risk of side-effects. CBR 5 has now been amplified to to note that nicotinic acid is often poorly tolerated.
Antiplalet Therapy

The recommendations for antiplatelet therapy are in line with existing guidelines and the AMA agrees with them.

Thank you for providing the AMA an opportunity to comment on the guideline.

| Org 13 | NVDPA rcvd on 08/07/2015 | **NVDPA SUBMISSION ON DRAFT NATIONAL EVIDENCE-BASED GUIDELINE ON SECONDARY PREVENTION OF VASCULAR DISEASE IN TYPE 2 DIABETES**  The NVDPA (an alliance of the National Heart Foundation, National Stroke Foundation, Kidney Health Australia and Diabetes Australia) welcomes the opportunity to comment on these draft guidelines which address an important aspect of management of people with type 2 diabetes, many of whom are affected by both macro and microvascular disease.  **Point 1: Title of Guideline**  Since it is stated that the recommendations in this guideline apply to “secondary prevention of cardiovascular disease in 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”, the title of the guideline could be amended to reflect this by amending “vascular disease” to “cardiovascular disease” to remove any implication that it deals with microvascular disease which is addressed in other NHMRC guidelines. | The title has been changed to use the word ‘cardiovascular’, instead of ‘vascular’. |
| Point 2: Section on Management of Blood Pressure.  
EBR1 All adults with type 2 diabetes and known prior cardiovascular disease and BP >110/70 mmHg should receive blood pressure lowering therapy unless contraindicated by symptomatic hypotension. (Grade A)[1, 2]  
The major support for this recommendation is the 2009 meta-analysis by Law et al. This publication reports a consistent benefit for stroke and coronary heart disease across all BP ranges reported. The meta-regression analysis found a constant proportional effect with the authors noting BP therapy has “a proportional reduction in risk that is constant over all measured levels”. The authors did concede “there were too few data” below 110/70 mmHg but refer to existing epidemiological cohort studies that include very low levels.  
It should also be noted that Law et al concluded that “there is medical benefit in lowering a person’s blood pressure whatever the blood pressure, with the logically inescapable conclusion that there is then little or no gain in routinely measuring a person’s blood pressure”. Law et al’s conclusion is in conflict with the evidence for more accurate BP measurement. It is increasing clear that ABPM and HBPM are stronger predictors of cardiovascular outcome.  

Comment 1:  
The strong support for Law et al throughout the guideline should be reconsidered.  
The evidence in the Law et al paper does not support this conclusion for sBP for stroke. Box 2 of the guideline (a reproduction of Fig 5 of the publication) shows that there is no evidence for a reduction in stroke for a sBP 110-119 mm Hg and the reduction for sBP 120-129 mm Hg is not significant. Also for sBP ≥ 170 mm Hg there is no significant | We agree with the on-going need to monitor BP, and while Law et al suggested this was not necessary, this does not form a part of any recommendation in the current guideline.  
The relevant figure from Law et al shows clear benefit of BP lowering in regard to CHD prevention at all BP strata examined, including SBP 120-129 and 110-119. For stroke, the confidence intervals overlap 1.0 for 120-129, but the point estimate is similar to the other BP strata; there are no stroke outcome data for SBP 110-119. Since all individuals at risk of stroke are also at risk of CHD, EBR1 is supported for all secondary prevention |
reduction in coronary events. In addition it does not seem that analyses have also been performed separately for people with and without a previous event.

Most international guidelines seem to be aware of this paper’s significant limitations and either do not reference it, or acknowledge it’s limitations. For example:
- Stroke Foundation guidelines (2010) – not referenced
- SIGN guidelines (2010) – not referenced
- ASH / ISH (2013) – not referenced
- JNC 8 (2013) – not referenced
- NICE – acknowledged study but outline its limitations and why it was not used to influence recommendations.
- ESH Hypertension guidelines also discuss its limitations, especially the diverse population analysed.

Comment 2:
The ADVANCE study is also referenced to support benefits across a wide range of pre-treatment blood pressure. However it should be noted that only one third of subjects had a history of macrovascular disease and ADVANCE did not show any benefit in reducing macrovascular events.

Comment 3:
The Law et al study did not perform a sub-group analysis of people with diabetes. While it may be argued that there is no logical reason for there to be a difference between people with and without diabetes, this assumption is not necessarily valid. The ACCORD BP study did not find any overall benefit from achieving a target sBP of 119 mmHg v 134 mmHg in people with type 2 diabetes (one third with previous macrovascular disease). There was no difference in pre-specified cardiac secondary outcomes (nonfatal myocardial infarction, individuals, if only on the basis of CHD prevention. Table 2 of Law et al reports results for those with and without prior CVD, and shows no difference in the proportionate effect of BP lowering.

ADVANCE showed statistically significant benefits of BP lowering for CVD death and all-cause mortality. The ADVANCE trial reported in text that these findings were not different for those with and without prior CVD.

We agree that ACCORD showed increased adverse events as well as reduced stroke incidence. However, the Expert Panel considered that the benefit of a reduction in stroke incidence was not offset by an increase in adverse events such as hypotension, since the overall impact of a stroke is generally much greater than that of an episode of hypotension or hyperkalaemia, even if hospital admission were required. Furthermore, ACCORD was pursuing a BP
death from cardiovascular cause, major coronary disease event, fatal or nonfatal heart failure). However there was a significant reduction in annual rates of stroke with the lower sBP, but an increase in serious adverse events attributed to antihypertensive treatment. These findings are not consistent with the Law et al meta-analysis which did not differentiate people with and without diabetes.

**Comment 4:**
A number of systematic reviews on BP management for people with diabetes are not referenced. Evidence for patients with diabetes and prior CVD that have direct impact on the recommendations for drug choice and BP targets are Wu et al 2013, Lv et al 2012, Redon et al 2013, Edmon et al 2015, Turnbull et al 2005. These systematic reviews report effect of drug classes and intensity of BP treatment on cardiovascular outcome in patients with diabetes and seem not to be included within the references or considered during development of recommendations.

**Comment 5:**
This draft guideline states that "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". As summarized below, this unqualified statement is not the case with many current guideline recommendations:

The **American Diabetes Association** states that:
"In patients with known CVD (and diabetes), use aspirin and statin therapy (if not contraindicated) [Level A] and consider ACE inhibitor therapy [Level C] to reduce the risk of cardiovascular events”.

The **International Diabetes Federation guideline** statement is:
"People with a previous CVD event should be treated with lifestyle modification, low-dose aspirin (or clopidigrel), statins and blood pressure lowering medications, unless contraindicated or considered clinically inappropriate”.

target of <120, and the current guideline refers to a target of 130. ACCORD and Law asked slightly different questions. ACCORD was a single RCT comparing two specific BP targets, while the meta analysis by Law asked much broader questions. Law et al did not report on adverse events.

See previous comments about these specific reviews.

Three of the guidelines cited here by the NVDPA (Canadian, NICE, ESC) make unqualified recommendations about ACEI use, and are therefore more aggressive than the original EBR1. Nevertheless, EBR1 and the associated PP1 have now been modified, removing the reference to 110/70 mmHg, and incorporating the phrase ‘unless contraindicated or considered clinically inappropriate’. 
The *Canadian guidelines* state the following:
ACE inhibitor or ARB, at doses that have demonstrated vascular protection, should be used to reduce cardiovascular risk in adults with type 1 or type 2 diabetes with any of the following:
- Clinical macrovascular disease [Grade A, Level 1]
- Age >55 years [Grade A, Level 1] for those with an additional risk factor or end organ damage; Grade D, Consensus, for all others
- Age <55 years and microvascular complications [Grade D, Consensus]

*SIGN Guidelines*
People with diabetes and established CVD as follows:
Myocardial infarction - Patients with clinical MI should be commenced on long term ACE inhibitor therapy within the first 36 hours.
Stable angina - *Consider* treatment with ACE inhibitors.
Note: no specific mention of stroke

*NZ Guideline*
After myocardial infarction:
Treat all people post-MI with a beta-blocker (eg, metoprolol, propranolol or timolol). *Consider* adding an ACE inhibitor long-term (regardless of BP level) especially if any significant left ventricular impairment

*NICE Guideline 2013*
ACE inhibitors:
1.3.5 Offer people who present acutely with an MI an ACE inhibitor as soon as they are haemodynamically stable. Continue the ACE inhibitor indefinitely.
1.3.8 Offer people after an MI who are intolerant to ACE inhibitors an ARB instead of an ACE inhibitor.

*European Society of Cardiology*
Treatment with ACE-I or ARB should be started during hospitalization for ACS and continued thereafter in patients with diabetes and left ventricular ejection fraction (LVEF) <40%, hypertension, or chronic kidney disease, and considered in all patients with ST-elevation MI (STEMI). Patients with diabetes and stable CAD are also recommended
Therefore, we suggest propose that the inclusion of a blood pressure number is not supported by strong evidence and may lead to inappropriate prescribing of therapy by clinicians. It is our opinion that it is better to use the wording of the current International Diabetes Federation guideline statement: “People with a previous CVD event should be treated with lifestyle modification, low-dose aspirin (or clopidigrel), statins and blood pressure lowering medications, unless contraindicated or considered clinically inappropriate”. The text could elaborate on situations which might be considered clinically inappropriate (including those with already low blood pressure).

Comment 5: Implications of EBR 6 and 7.
These recommendations are as follows:

EBR 6: All adults with type 2 diabetes and prior acute myocardial infarction should receive long-term treatment with beta blockers.
EBR 7: All adults with type 2 diabetes and prior acute myocardial infarction should receive long-term treatment with ACE inhibitors.

Combining these and EBR1 mean that all people with MI with a BP ≥ 110/70 will be treated with both an ACEI and a beta blocker (unless they have symptomatic hypotension). What is the evidence to support a benefit of combined ACEI and beta blocker in people with a previous MI – with or without diabetes?

Summary:
In view of the above comments, the NVDPA would ask the committee to review the essentially unqualified recommendation of treating all people with diabetes who have established cardiovascular disease with an ACEI.

Specifically the NVDPA suggests that EBR1:
- is qualified to state that ACEI should be considered rather than a blanket recommendation
- the lower sBP target be reviewed and the level recommended for considering therapy be not specified or increased
- the qualification be broadened to include “if considered clinically inappropriate”

EBR1 and the associated PP1 have now been modified, removing the reference to 110/70 mmHg, and incorporating the phrase ‘unless contraindicated or considered clinically inappropriate’.
<table>
<thead>
<tr>
<th>Org 14</th>
<th>Dietitians Association of Australia</th>
<th>As noted above, we do not know of specific data on the combination of ACEI and BB. However, many of the trials of each agent (especially ACEI trials) included participants on both agents. We note that the 2012 NHF guideline on secondary prevention recommends both ACEI and BB for those with prior MI, and therefore by implication the combination. Thus, this is not a change of practice.</th>
</tr>
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<tbody>
<tr>
<td>Referral for medical nutrition therapy</td>
<td>Referral for medical nutrition therapy</td>
<td>An additional PP has been added referring to the need for lifestyle advice, and includes reference to healthy nutrition.</td>
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<tr>
<td>DAA notes that diet and physical activity interventions were out of scope for this project, and readers are referred to a number of other guidelines. However, DAA considers that individuals living with Type 2 Diabetes and cardiovascular disease, including hypertension and hyperlipidaemia, have complex nutrition needs which are not served well by disparate guidelines. It is recommended individuals living with diabetes be referred to a dietitian for individual nutrition advice1,2. Given diet is fundamental to the self management of diabetes with co morbidities, DAA recommends the inclusion of a Practice Point within the Guidelines i.e. “Clinicians should refer all people with Type 2 Diabetes to an APD to receive individualised medical nutrition therapy. This is consistent with the advice that consumers receiving a lipid-lowering medication as concurrent nutrition therapy is required as part of treatment under the Pharmaceutical Benefits Scheme3”. APDs are the professionals who are qualified and credentialed to provide nutrition advice to individuals living with Type 2 Diabetes. APDs are recognised by Medicare, Department of Veterans’ Affairs, and private health funds. Consumers can search for an APD online or by calling 02 6163 5200. Non-functioning links</td>
<td>These will be updated and corrected.</td>
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</tr>
<tr>
<td>DAA would like to advise that links within the document do not currently work and should be amended prior to publishing the</td>
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| Org 15 | Department of Health Queensland rcvd 30/07 | With regard to hypertensive medications, Queensland recommends a first line agent such as ACEi be promoted given the guideline refers to diabetic patients and there is some suggestion of worsened glycaemic control and lipid control in diabetic patients on thiazides.

In relation to the statement about anticoagulants and atrial fibrillation (AF). Queensland suggests that antiplatelet therapies are generally not appropriate as first line agents in patients, and an anticoagulant is preferred.

Queensland clinicians have also suggested making note that fixed dose combination medications may improve adherence to therapy.

The document includes significant discussion about antiplatelet therapies that are simply not available in Australia. This may cause unnecessary distraction from the key messages you are trying to promote with the guideline.

There is no evidence that was found to show that CVD outcomes differ between the major classes of anti-hypertensive agents. Furthermore, the recent CVD outcomes trials in diabetes, which show only a very small effect of glucose lowering on CVD outcomes would suggest that any worsening of glycaemic control with thiazides would have no more than a trivial effect.

PP3 already specifically recommends that anticoagulation be considered for those with AF.

PP5 already specifically advises the clinician to consider means of improving adherence in the setting of multiple therapies. As this wasn’t a focus of the literature review, specific advice on the many options available to address this are not given.

The full description document needs to address everything found in the literature review, which does include some drugs not currently available. We do not expect that most practitioners will read beyond the summary. Nevertheless, we can consider noting in the text those drugs not currently available.
Appendix 4

Dissemination & Implementation Plan
Dissemination & Implementation Plan for the

Secondary Prevention of Cardiovascular Disease in Type 2 Diabetes Guideline

“Guidelines do not implement themselves.” Field and Lohr (1992)

Version: final

Date: August 2015
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Background
The NHMRC “A guide to the development, implementation and evaluation of clinical practice guidelines” states that “If guidelines are to be effective, their dissemination and implementation are to be vigorously pursued.” The NHMRC guide also emphasises the importance of a multidisciplinary panel responsible for:

- overseeing the various steps of the dissemination and implementation of the guidelines;
- identifying any barriers with the acceptance and implementation of the guidelines;
- working with members of target groups to develop ways of overcoming barriers;
- adapting guidelines to local conditions;
- assist local groups with the adaption process if applicable; and
- ensuring a range of dissemination and implementation strategies are employed.

Objective of the Implementation Plan
Given the broader goal for the ‘Secondary Prevention of Cardiovascular Disease in Type 2 Diabetes Guidelines’ [the Guidelines] to have an impact on the health outcomes of people with diabetes, the objective is to have the guidelines taken up into practice as quickly and effectively as possible. This Guideline Implementation Plan aims to map out the strategies for uptake of the Guidelines into practice. It will include, but not be limited to, engagement with stakeholder organisations, use of web-based and other information technologies, use of the mainstream and professional media, use of opinion leaders where possible and incorporation into existing quality assurance processes.

Defining Target Audiences
The target audiences for the Guidelines are largely defined by the requirements of the Contract with the Department of Health. However the Project Executive, Guidelines Advisory Committee (GAC) and Implementation Committee (IC) have further defined the target groups in terms of the primary groups to be targeted by the Guidelines and those who are a secondary audience. Defining audiences as primary and secondary was discussed at length by the Implementation Committee and assists in determining the different formats of the Guidelines. The types of audiences are outlined below:

Primary audiences
Primary audiences consist of the following groups:

- GPs
- Endocrinologists
- Other specialist clinicians
- Diabetes educators
- Pharmacists
- Nurses, including Remote Area Nurses & Practice Nurses
- Aboriginal Health Workers
- Dietitians
Exercise Physiologists
Adults with type 2 diabetes

Secondary audiences
Secondary audiences include the following:

- Carers of people with type 2 diabetes
- Consumers
- Policy makers
- Standards setting bodies
- Postgraduate training bodies
- Continuing professional education groups
- Health insurance funds
- Tertiary education institutions
- Teaching hospitals

Informing the Target Audiences

GAC Nominating Organisations
The Guidelines Advisory Committee has representatives from many of the above organisations. In seeking nominations for the GAC, these organisations were advised of the development of the Guidelines, the timeframe and the role that they are expected to play in the process, especially public consultation.

T2DGR Website
A website has been created specifically for the project [http://t2dgr.bakeridi.edu.au/](http://t2dgr.bakeridi.edu.au/) and is fully functional. The website provides the vehicle for posting up to date information on the Guidelines development process and has assisted with public consultation. It will be a key portal for the final Guideline resources.

Public Consultation
Wide consultation on the draft Guideline has taken place. An advertisement was placed in The Australian on 6 June regarding the draft guideline. The advertisement met the requirements of the NHMRC. A broad mail out to key stakeholders was undertaken. This alerted organisations to the commencement of the consultation and ensured they were appropriately directed to the website to download the draft Guideline to access the on-line feedback tool or make a written submission.

Designing Accessible Formats
The guidelines should be available in a variety of formats and it is the responsibility of the Implementation Committee in consultation with the defined audiences to determine the appropriate formats. Suggested formats should consider print and electronic formats, a full technical report and
overview, summaries for GPs, and for other health care professionals, consumer guides and be available on various websites.

**Publishing the guidelines**

Approval from the NHMRC for their approval and endorsement of the guideline will be sought. Links to the guideline will also be available on various websites, particularly organisations represented on the Committees. The Guideline will be published as booklets (comprehensive information) or in summary form (main findings and recommendations). Summaries of the guideline could be published in:

- Professional journals
- Professional association newsletters and magazines
- Trade publications and industry newspapers
- Institutional newsletters
- Popular media
- Brochures
- Posters
- Websites

The IC will provide input to the GAC about accessibility of the final guidelines. Issues of budget will need to be considered.

**Dissemination**

The Dissemination Plan covers a limited period following approval of the Guideline by NHMRC and approval by the Department of Health to publish the Guideline and associated products. Dissemination will commence in December 2015. We will work with each of the targeted stakeholders to identify and develop the most appropriate strategy (e.g. messages and channels) to maximize the guidelines uptake and implementation. Although all of the recommendations are important, EBRs 1, 2, 8 and 10 are critical in terms of improving outcomes, and will be highlighted in the dissemination.

Dissemination has been designed to take into account the views of stakeholders provided through the consultation process and the input of the end users brought together in the Implementation Committee. The key drivers of decisions about dissemination were:

- Preferences for digital information easily accessed when needed
- Interest in some print material for health professionals
- Preference for using existing mechanisms for dissemination through respected sources/organisations
- Preferences for reference guides or brief summaries for quick access

The feedback from Public Consultation was that a downloadable version of the Guideline and quick reference guide were essential for successful dissemination.
Some particular printed resources will be targeted:

- The RACGP Green Book will be targeted as a key resource for GPs.
- The CARPA Standard Treatment Manual will be targeted for inclusion [in the upcoming 7th edition] as it is a key resource for rural and remote settings.

We anticipate printing a small run of the full guideline that will be available via the special 'Type 2 Diabetes Guidelines' website that has been established by Baker IDI. This website will be updated via Google Ad Words so online traffic will be directed to this website upon searching. The focus will be on downloadable versions of the summary and consumer guide. The Technical Report will not be printed but will be made available on the website.

The guidelines will be disseminated via the broad range of Stakeholder web sites, and trade media will be pursued wherever possible. Additional dissemination will occur through presentations at conferences, such as medical education conferences, and through articles published in peer-reviewed journals.

**Implementation**

It has been suggested that the most effective means to implement the guidelines is to develop a concrete plan that utilises an analysis of the localised factors necessary for clinical behaviour change, including multiple barriers and enablers. Recent systematic reviews suggest that: modest improvements can be derived from audits and feedback; educational meeting can influence complex behaviours when used in conjunction with other interventions; inter-professional collaboration may have a positive effect in patient outcomes; professional practice is more likely to improve with interventions tailored to identified barriers than with no intervention or dissemination of guidelines alone; the presence of printed education materials and quality improvement collaboratives have both shown benefits, though limited and unclear in nature; effect is unclear compared with other interventions, whilst the opinions of local leaders can successfully reduce non-compliance with evidence-based practice. This approach has been successfully utilised by the Australian Primary Care Collaboratives (APCC) to improve best-practice care for diabetes and chronic heart disease in general practice.

The Implementation Committee members have discussed appropriate strategies they consider to be of most value for ensuring the implementation of the guidelines. They considered:

- Use of opinion leaders and champions
- Endorsement by clinical groups
- Education of patients and patient-mediated intervention
- Educational materials
- Seminars and conferences
- Reminder systems incorporated into clinicians’ daily practice
Strategies
The Implementation Committee felt that a mix of the following strategies should be utilised for implementation and dissemination of the guideline:

- Short summaries and links to full documents for relevant websites
- Professional journals, bulletins and magazines
- Use of communication links developed by clinical colleges, allied health organisations, speciality societies, State and regional medical societies, consumers, consumer groups, medical libraries and health education facilities
- Asking respected clinical leaders to promote the guidelines
- Use of educational processes of colleges, professional organisations and consumer groups, including conferences, workshops, seminars and specialist journals
- For institutions and organisations that provide care, ensure the guidelines are incorporated into routine procedures, such as quality assurance and review processes
- Use information technology and e-health
- Arrange for credible health care providers of training to visit practitioners in the clinical setting

National Prescribing Service MedicineWise
Discussions have been had with the National Prescribing Service Ltd (NPS MedicineWise) and it is anticipated that they will be able to assist in disseminating the Guideline through their existing channels of education and decision support for health professionals and consumers. We are very pleased that they will be able to provide support for the implementation of the guideline via their educational one-to-one format visiting program. This national program involves visiting approximately 18,000 GPs and we hope to be able to print a resource for doctors, funding permitting. We will also be targeting their online learning modules as part of the National Prescribing Curriculum which provide information on quality use of medicines for health professional students.

Timeline
The timeline for guideline development are broadly outlined in the Implementation Committee Terms of Reference. The implementation process will formally commence after final endorsement by NHMRC.

Stakeholder Organisations
There is a broad range of stakeholder organisations that have been consulted prior and particularly during public consultation. They represent our target audience and include organizations focusing on
policy, advocacy, professional association, standard setting, and research and are the peak organisations. Some of these organisations will be targeted for possible endorsement.

Australian Diabetes Educators Association (ADEA)

Australian Diabetes Society (ADS)

Australian General Practice Network (AGPN)

Australian Indigenous Doctors Association (AIDA)

Australian Medical Association (AMA)

Australian Practice Nurses Association (APNA)

Central Australian Rural Practitioners Association (CARPA) Standard Treatment Manual

Cardiac Society of Australia and New Zealand (CSANZ)

Congress of Aboriginal Torres Strait Islander Nurses (CATSIN)

Consumers’ Health Forum (CHF)

Diabetes Australia Ltd (DA) and NDSS

Dietitians Association of Australia (DAA)

Kidney Health Australia (KHA)

National Aboriginal Community Controlled Health Organisation (NACCHO)

National Heart Foundation (NHF)

National Prescribing Services (NPS)

National Stroke Foundation (NSF)

Pharmaceutical Society of Australia (PSA)

Pharmacy Guild of Australia (PGA)

Royal Australian College of General Practitioners (RACGP)

Royal Australian College of Physicians (RACP)

Royal College of Nursing Australia (RCNA)

Teaching Hospitals and Universities

Implementation Committee, July 2015
Disclosures of Conflict of Interest
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