

Australian Evidence-Based Clinical Guidelines for Diabetes

SELECTED RECOMMENDATIONS FOR:

- Medical device technology for the management of Type 1 Diabetes
- Medications for blood glucose management in adults with Type 2 Diabetes



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Disclaimer

These clinical guidelines are a general guide to appropriate practice, to be followed subject to the clinician's judgement and the patient's preference in each individual case. The guidelines are not intended to be prescriptive. They are designed to provide information to assist decision making and have been informed by the highest quality evidence available at the time of compilation. Accordingly, the parties involved in the development of these guidelines shall have no liability to any users of the information contained in this publication for any loss or damage, cost or expense incurred or arising from reliance on the information contained in this publication.

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Summary of recommendations

1 - Reading guide

2 - Introduction

3 - Medical device technology for the management of type 1 diabetes

3.1 - Continuous glucose monitoring devices (CGM)

Conditional recommendation

We suggest continuous glucose monitoring rather than self-monitoring of blood glucose alone for all adults with type 1 diabetes treated with multiple daily injections.

Remark: The decision on whether to use continuous glucose monitoring or self-monitoring of blood glucose alone is highly dependent on personal preference. Health professional discussions with people with type 1 diabetes should include the use and potential benefits of CGM and considerations of personal preferences, the value of alarms and data trends, available resources, and the importance of high level engagement with the technology and health services.

Current CGM devices enable real-time measurement of interstitial fluid glucose concentrations via a subcutaneous glucose sensor. Interstitial fluid glucose measures are recognised as closely correlating with blood glucose concentrations. CGM devices are available with a variety of functions including alarms for hypoglycaemic and hyperglycaemic thresholds and as intermittently scanned devices (also known as 'flash' continuous glucose monitoring). CGM devices provide a large amount of real-time data and summary glycaemic data (e.g. modal day reports) which can be highly valuable for both the person with diabetes and their healthcare providers. Higher proportions of time spent actively using and responding to CGM data are consistently associated with glycaemic improvements such as lower HbA1c concentrations and increased time within an appropriate glucose range (3.9-10.0 mmol/L). A conditional recommendation for use of CGM in type 1 diabetes was based on low-moderate certainty of evidence for favourable outcomes.

3.2 - Continuous subcutaneous insulin infusion pump devices (CSII)

Conditional recommendation

We suggest CSII or MDI treatment for children and adolescents with type 1 diabetes based on the preference of the person with diabetes (and carer).

Remark: The timing of initiating CSII following diagnosis of type 1 diabetes should be determined by the clinician in consultation with the person with diabetes and their carer. CSII treatment consists of continuous subcutaneous insulin infusion pump devices with various options including: manual CSII systems either without or with CGM (including low glucose suspend and predictive low glucose suspend) or automated CSII systems (AutoCSII), also known as 'hybrid closed loop' systems. MDI consists of daily administration of basal insulin in combination with prandial rapid-acting insulin injection treatment. CSII improves glycaemia (lowers HbA1c) which could ultimately lead to decreased microvascular complications. However, there is a paucity of studies examining the long term impact of CSII on microvascular complications, diabetic ketoacidosis, mortality and quality of life. There is also little current evidence to demonstrate that CSII decreases weight. Variation in preference for CSII is anticipated in light of the higher treatment intensity required and costs associated with its use to manage type 1 diabetes.

Conditional recommendation

We suggest CSII rather than MDI treatment for adults with type 1 diabetes based on the preference of the person with diabetes.

Remark: The decision on whether to use CSII or MDI is highly dependent on personal preference. Health professional discussions with people with type 1 diabetes should include the use and potential benefits of CSII and considerations of personal preferences, the value of the different options, available resources, and the importance of high level engagement with the technology and health services.

CSII treatment consists of continuous subcutaneous insulin infusion pump devices with various options including: manual CSII systems either without or with CGM (including low glucose suspend and predictive low glucose suspend) or AutoCSII, also known as 'hybrid closed loop' systems. MDI consists of daily administration of basal insulin in combination with prandial rapid-acting insulin injection treatment. CSII improves glycaemia (lowers HbA1c) which could ultimately lead to decreased microvascular complications. However, there is little current evidence examining the impact of CSII on microvascular complications, diabetic ketoacidosis, and mortality. There is also little current evidence to demonstrate CSII decreases severe hypoglycaemia and weight gain or improves quality of life. Variation in preference for CSII is anticipated in light of the higher treatment intensity required and costs associated with its use to manage type 1 diabetes.

3.3 - Automated continuous subcutaneous insulin infusion (AutoCSII)

Conditional recommendation

We suggest automated continuous subcutaneous insulin infusion (AutoCSII) treatment rather than non-automated CSII treatment to optimise glycaemia for children, adolescents and adults with type 1 diabetes.

Remark: The decision on whether to use AutoCSII or non-automated CSII is highly dependent on personal preference. Health professional discussions with people with type 1 diabetes (and carers) should include the use and potential benefits of AutoCSII and considerations of personal preferences, the value of the different options, available resources, and the importance of high level engagement with the technology and health services. Automated continuous subcutaneous insulin infusions (AutoCSII), also known as 'hybrid closed loop insulin pumps', are insulin delivery systems consisting of three linked components functioning continuously: a subcutaneous glucose sensor device, a subcutaneous insulin infusion pump device and a computerised algorithm which determines insulin delivery based on ambient glucose. AutoCSII enables basal and some correctional insulin to be automatically adjusted based on CGM measures, while insulin bolus doses for meals require initiation by the user. These AutoCSII technologies are relatively new, with the first randomised clinical trial being reported in 2014, and are distinct to previous non-automated CSII systems which function solely using manual insulin pump settings with or without suspension of basal insulin in response to actual or predicted low glucose (also known as '(Predictive) Low Glucose Suspend' systems). Use of AutoCSII results in further improvements to glycaemia compared to non-automated CSII. It was not possible to evaluate the age groups separately as most trials incorporated people across both paediatric and adult age ranges. The generalisability of benefits from AutoCSII to children under six years old is limited given the lack of evidence in this young group. It is anticipated that future AutoCSII systems may use more refined automated insulin delivery algorithms (including automatic bolus delivery in addition to automatic basal delivery) and potentially dual hormone treatment (e.g. insulin and glucagon).

4 - Medications for blood glucose management in adults with type 2 diabetes

4.1 - Optimal initial medication

Conditional recommendation

We suggest the use of metformin as first-line monotherapy in adults with type 2 diabetes.

Remark: This recommendation is based on the relative low cost and ease of administration of metformin. There is no convincing evidence of clinically significant differences in treatment effectiveness, serious adverse outcomes or all-cause mortality between the different classes when used as monotherapy. For individuals, there may be other factors that require consideration such as adverse effect potential, weight management strategy, frailty or comorbidities, which may contribute to clinician decision making when prescribing an alternative initial medication.

4.2 - Optimal add-on medication

Recommended

We recommend the addition of an SGLT-2 inhibitor to other glucose lowering medication(s) in adults with type 2 diabetes who also have cardiovascular disease, multiple cardiovascular risk factors and/or kidney disease.

Remark: This recommendation applies to adults with type 2 diabetes who have cardiovascular disease, multiple cardiovascular risk factors and/or kidney disease and are unable to achieve optimal blood glucose levels using their current baseline therapy. The evidence base for this recommendation includes studies with people with kidney disease, who had an estimated glomerular filtration rate as low as 30 mL per minute per 1.73 m² of body-surface area. We define multiple cardiovascular risk factors as men 55 years of age or older or women 60 years of age or older with type 2 diabetes who have one or more additional traditional risk factors, including hypertension, dyslipidaemia, or smoking.

Recommended

We recommend the addition of a GLP-1 receptor agonist to other glucose lowering medication(s) in adults with type 2 diabetes who have cardiovascular disease, multiple cardiovascular risk factors and/or kidney disease, and are unable to be prescribed an SGLT-2 inhibitor due to either intolerance or contraindication.

Remark: This recommendation applies to adults with type 2 diabetes who have cardiovascular disease, multiple cardiovascular risk factors and/or kidney disease, are unable to achieve optimal blood glucose levels on their current baseline therapy, and are unable to be prescribed an SGLT-2 inhibitor due to either intolerance or contraindication. The evidence base for this recommendations include studies on people with kidney disease who had an estimated glomerular filtration rate as low as 30 mL per minute per 1.73 m² of body-surface area. We define multiple cardiovascular risk factors as men 55 years of age or older or women 60 years of age or older with type 2 diabetes who have one or more additional traditional risk factors, including hypertension, dyslipidaemia, or smoking.

Conditional recommendation

We suggest the addition of a DPP-4 inhibitor to other glucose lowering medication(s) in adults with type 2 diabetes who have cardiovascular disease, multiple cardiovascular risk factors and/or kidney disease, and are unable to be prescribed an SGLT-2 inhibitor or a GLP-1 receptor agonist due to either intolerance or contraindication.

Remark: This recommendation applies to individuals with type 2 diabetes who have cardiovascular disease, multiple cardiovascular risk factors and/or kidney disease and are unable to achieve optimal blood glucose levels on their current baseline therapy. DPP-4 inhibitors were inferior to SGLT-2 inhibitors and GLP-1 receptor agonists with regard to cardiovascular and renal benefits and all-cause mortality. However, certain people are unable to tolerate SGLT-2 inhibitors due to side effects such as genitourinary infections, or GLP-1 receptor agonists due to gastrointestinal upset. Similarly, these medications may be contraindicated in people with kidney failure. In these instances, people with type 2 diabetes would benefit from the addition of a DPP-4 inhibitor as an alternative add on therapy.

Conditional recommendation

We suggest the addition of either an SGLT-2 inhibitor, GLP-1 receptor agonist or a DPP-4 inhibitor to metformin in adults with type 2 diabetes who do not have cardiovascular disease, multiple cardiovascular risk factors or kidney disease, and are unable to achieve optimal blood glucose levels.

Remark: This recommendation applies to people without established cardiovascular disease, multiple cardiovascular risk factors or kidney disease. In these people, the addition of an SGLT-2 inhibitor, GLP-1 receptor agonist or DPP-4 inhibitor is equally efficacious in lowering blood glucose. The choice of agent should be based on personal preference, side effect tolerance and comorbidities.

Conditional recommendation against

We suggest that a sulphonylurea should not be the first choice medication to add to metformin as dual therapy in adults with type 2 diabetes as it may increase the risk of severe hypoglycaemia.

Conditional recommendation against

We suggest that a thiazolidinedione should not be the first choice medication to add to metformin as dual therapy in adults with type 2 diabetes as it may increase the risk of hospitalisation for heart failure.

5 - Methods and processes

5.1 - Steering Committee - membership and terms of reference

5.2 - Guideline Development Groups - membership and terms of reference

5.3 - Conflicts of interest

5.4 - Clinical questions (PICO)

5.5 - Search strategies and PRISMA

5.6 - Guideline development methodology

5.7 - Abbreviations and acronyms

1 - Reading guide

The guideline is made up of two layers:

1. The Recommendation

Recommendation for (Green)

A strong recommendation is given when there is high-quality evidence showing that the overall benefits of the intervention are clearly greater than the disadvantages. This means that all, or nearly all, people with diabetes will want the recommended intervention.

Recommendation against (Red)

A strong recommendation against the intervention is given when there is high-quality evidence showing that the overall disadvantages of the intervention are clearly greater than the benefits. A strong recommendation is also used when the examination of the evidence shows that an intervention is not safe.

Conditional Recommendation for (Yellow)

A conditional recommendation is given when it is considered that the benefits of the intervention are greater than the disadvantages, or the available evidence cannot rule out a significant benefit of the intervention while assessing that the adverse effects are few or absent. This recommendation is also used when people with diabetes' preferences vary.

Conditional Recommendation against (Orange)

A conditional recommendation is given against the intervention when it is judged that the disadvantages of the intervention are greater than the benefits, but where this is not substantiated by strong evidence. This recommendation is also used where there is strong evidence of both beneficial and harmful effects, but where the balance between them is difficult to determine. Likewise, it is also used when people with diabetes' preferences vary.

2. The basis of the recommendation

Click on the recommendation to learn more about the basis of the recommendation

Evidence profile: The overall effect estimates and references to the studies.

Summary: Overview and brief review of the underlying evidence.

The certainty of the evidence:

High: We are very sure that the true effect is close to the estimated effect.

Moderate: We are moderately sure of the estimated effect. The true effect is probably close to this one, but there is a possibility that it is significantly different.

Low: We have limited confidence in the estimated effect. The true effect may be significantly different from the estimated effect.

Very low: We have very little confidence in the estimated effect. The true effect is likely to be significantly different from the estimated effect.

Evidence to decision: Brief description of beneficial and harmful effects, quality of evidence and considerations of people's preferences.

Rationale: Description of how the above elements were weighted in relation to each other and resulted in the current recommendation direction and strength.

Practical information: Practical information regarding the treatment and information on any special considerations.

Adaption: If the recommendation is adapted from another guideline, this is where you would describe any changes.

Discussion: If you are logged in as a user, you can comment here on specific recommendations.

References: Reference list for the recommendation.

The gradation of evidence quality and recommendation strength used is based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. For a quick and informative introduction to GRADE, the article 'Understanding GRADE: an introduction' by G.Goldet & J.Howick is recommended (*Journal of Evidence-Based Medicine* 2013;6:50-54). See also: <http://www.gradeworkinggroup.org>.

2 - Introduction

Introduction

Diabetes is a complex chronic condition that affects approximately 1.4 million Australians[1] and represents an estimated \$14.6 billion per annum in direct and indirect costs to the Australian economy[2]. Although clinical guidelines are integral to ensuring that healthcare decisions are based on the best available evidence, only one Australian clinical guideline relating to diabetes was current as of November 2019. Due to the high burden of disease associated with diabetes, significant research is directed at improving the prevention, diagnosis and treatment of diabetes through the refinement of existing methods and development of novel methods. The consistent and sustained generation of new evidence means that clinical recommendations are at risk of becoming outdated quickly, potentially resulting in suboptimal decisions by healthcare professionals and people living with diabetes.

The recommendations contained within this resource were generated as a result of collaboration between the Australian Diabetes Society, the Australian Diabetes Educators Association, the Australasian Paediatric Endocrine Group and Diabetes Australia, with representation from the Royal Australian College of General Practitioners, the Australian Government Department of Health and Cochrane Australia (the Australian Living Evidence Consortium). The objective of the Consortium is to develop a demonstration project in which the methods of Living Evidence are applied to select, priority areas of diabetes prevention, diagnosis and treatment. Resulting recommendations will be updated when new, relevant and impactful evidence is available.

Purpose The purpose of these recommendations is to provide an up-to-date, evidence-based resource that health professionals and people living with diabetes can use to guide shared decision making in the treatment of diabetes.

This guideline contains only specific actionable instructions for selected, well-defined clinical problems (i.e. what needs to be done and who it is relevant to). It does not define the individuals responsible for providing care, nor does it consider the detailed socio-economic consequences of adherence to the recommendations presented within.

Delineation of interventions and population groups

The recommendations within this resource are specific to population groups detailed within each individual clinical question on which the recommendation is based (see Section 5.4) and are applicable only to those population groups for which relevant evidence is available. In no instance should recommendations be extrapolated to population groups outside of this scope; for example, no included studies provide evidence on the safety and effectiveness of automated continuous subcutaneous insulin infusion pumps (AutoCSII) in children under 6 years of age and thus, the associated recommendation does not apply to this population.

Medical device technology for the management of type 1 diabetes:

Recommendations within this clinical area are specific to either adults (>18 years of age), children and adolescents (minimum age with regulatory approval for use to <18 years of age) or - where evidence shows no difference with respect to these populations - all age groups with type 1 diabetes. The recommendations do not apply to individuals with type 2 diabetes or individuals who are pregnant or are planning pregnancy. The recommendations do not take into account the complexities of individuals with multimorbid conditions, and the decision of whether to apply the recommendation should be made in consideration of existing multimorbidities in partnership with the person with type 1 diabetes.

The clinical questions addressed are:

- Should you use continuous glucose monitoring (CGM) with/without alerts or self-monitored blood glucose (SMBG) alone in conjunction with multiple daily injections (MDI) in adults?
- Should you use CSII pumps (with or without continuous glucose monitoring) or MDI (with or without continuous glucose monitoring) in children, adolescents and adults?
- Should you use non-automated continuous subcutaneous insulin infusion (CSII) pumps with CGM (including low-glucose insulin suspend systems), or automated CSII pumps with closed-loop systems in children, adolescents and adults?

For more details on the clinical questions see Section 5.4.

Therapeutics for blood glucose management in adults with type 2 diabetes:

Recommendations within this clinical area are specific to adults (>18 years of age) with type 2 diabetes. The recommendations do not apply to individuals with type 2 diabetes who are under the age of 18 years, individuals with type 1 diabetes, or individuals who are pregnant or are planning pregnancy. The recommendations do not take into account the complexities of individuals with multimorbid conditions, and the decision of whether to apply the recommendation should be made in consideration of existing multimorbidities in partnership with the person with type 2 diabetes.

The clinical questions addressed are:

- Monotherapy: Should you use metformin or a different blood glucose lowering medication (sulphonylurea, thiazolidinedione, DPP-4 inhibitor, SGLT-2 inhibitor or GLP-1 receptor agonist) as first line treatment in adults with type 2 diabetes?
- Dual therapy: Which blood glucose lowering medication (sulphonylurea, thiazolidinedione, DPP-4 inhibitor, SGLT-2 inhibitor or GLP-1 receptor agonist) should be used in combination with metformin as dual treatment in adults with type 2 diabetes?
- Add-on to standard care: Should you use a GLP-1 receptor agonist, SGLT-2 inhibitor, sulphonylurea or DPP-4 inhibitor as add-on in adults with type 2 diabetes? Will it differ by cardiovascular risk groups?

Target audience

The recommendations within this resource are applicable to individuals responsible for both treating diabetes (e.g. general practitioners) and individuals providing auxiliary services (e.g. support and education). These include but are not limited to health professionals (i.e. endocrinologists, general physicians, general practitioners, diabetes educators, diabetes nurse practitioners, nurses), people living with diabetes and parents of children with type 1 diabetes (for the medical device recommendations).

Individuals such as policy makers, practice managers, researchers and students may elect to use or adopt these recommendations or supporting information contained therein for purposes other than the treatment of diabetes; however these individuals do not represent the target audience. Additional considerations not addressed within this resource are required when using these recommendations for any purpose other than for the treatment or support of people living with diabetes.

Subject demarcation

This resource contains information specific to select areas of diabetes treatment, as defined by the Living Evidence for Diabetes (LED) Steering Committee, established by the Consortium to lead this project, and two Guideline Development Groups (GDGs). Complete lists of LED and GDG members are presented in Sections 5.1 and 5.2.

In phase one of the program, the LED Steering Committee identified eleven key priority areas in the prevention, diagnosis and treatment of diabetes that fulfilled the three key criteria for living recommendations: (1) the topic represents a priority area; (2) there is uncertainty in the strength or direction of evidence; and (3) there is a likelihood of new evidence being available in the near future. Two topics were selected by consensus: Technology for the management of type 1 diabetes and therapeutics for blood glucose management in adults with type 2 diabetes. For each topic, a separate GDG was established, the first responsibility of which was to define a select number of specific clinical questions within their designated topic that also fulfilled the three key criteria for living recommendations (see Section 5.4).

The populations, interventions, comparators and outcomes of interest (PICO) and included study designs are explicitly stated within each clinical question and define the boundaries of that question. The assessment of benefits and harms of the selected interventions is based on randomised trials. We acknowledge that observational data potentially could add information but is currently considered outside the scope of this guideline. Abbreviations, acronyms and definitions of key terms within this resource are presented in Section 5.7.

The perspective of people living with diabetes

The Consortium believes that forming and maintaining partnerships with people who have diabetes and those that support them is integral to ensuring that the guidelines appropriately address their needs. Both GDGs are responsible for defining clinical questions and developing recommendations and included individuals with diabetes, who actively shared their knowledge and advice throughout all stages of the process. Key areas in which people living with diabetes were involved include:

- Developing clinical questions and defining outcomes of greatest importance to people living with diabetes
- Reviewing included studies and assisting researchers in interpreting the evidence from a consumers perspective
- Co-developing each recommendation, including setting the strength and direction of the recommendation and formulating the associated rationale
- Developing key information for each recommendation relating to equity, acceptability, feasibility, and resources and other considerations

In addition, an active effort was made to distribute the draft guideline to a broad range of people with diabetes and those that care for and support them as part of the public consultation process, feedback of which has been incorporated into the final draft of the guideline.

A research project is currently being undertaken by researchers from La Trobe University to identify how to best involve consumers in living guidelines for diabetes. The project has been granted ethics approval and several consumer forums were held during July and August 2020. Results from this project will guide consumer involvement in this guideline moving forward.

Publication Approval



Australian Government

National Health and Medical Research Council

These guideline recommendations were approved by the Chief Executive Officer of the National Health and Medical Research Council (NHMRC) on the 23rd of November 2020, under Section 14A of the National Health and Medical Research Council Act 1992. In approving the guideline recommendations, NHMRC considers that they meet the NHMRC standard for clinical practice guidelines. This approval is valid for a period of 5 years.

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

This publication reflects the views of the authors and not necessarily the views of the Australian Government.

Updating and public consultation

A considerable volume of research related to the care of people with diabetes is ongoing and will potentially impact clinical recommendations. To ensure these guidelines are updated rapidly in response to new and important evidence, the underpinning knowledge syntheses and recommendations will be reviewed and updated on an ongoing basis. This will be reflected in the publication of a new version in which changes made to a specific recommendation or supporting information are highlighted in order to emphasise the update.

The consortium will seek NHMRC approval of the guideline under section 14A of the National Health and Medical Research Council Act 1992 on an ongoing basis as new recommendations are added or existing recommendations are changed. As part of the approval process (and for the lifetime of the guidelines), public consultation is required. We welcome your feedback and suggestions. Comments can be submitted via the feedback function under each recommendation in MAGIC, see the reading guide in the above section for guidance, or by emailing livingguidelines@diabetessociety.com.au.

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Disclaimer

These Clinical Guidelines are a general guide to appropriate practice, to be followed subject to the clinician's judgment and the patient's preference in each individual case. The Clinical Guidelines are designed to provide information to assist decision-making and are based on the best evidence available at the time of development.

3 - Medical device technology for the management of type 1 diabetes

Medical device technologies are transforming the care of people with diabetes and are increasingly used for the management of type 1 diabetes in the developed world. The two main medical device systems used to treat diabetes include continuous subcutaneous insulin infusions (CSII), also known as 'insulin pumps', and continuous glucose monitoring (CGM). CSII systems have been in use for over 25 years and CGM systems for over 15 years, with the last decade heralding rapid technological development and the availability of numerous different devices. Current CGM systems measure interstitial fluid glucose and have the capacity to improve blood glucose management given CGM provides real-time glucose data to people with diabetes, which can lead to immediate behavioural change and also adjustments to the delivery of insulin by CSII. CSII and CGM devices aim to improve the safety and efficacy of treating diabetes to ultimately improve quality of life and health outcomes for more people, especially individuals with type 1 diabetes.

CSII devices consist of an insulin pump which delivers insulin via a subcutaneous cannula. The broad classification of CSII devices can be in two categories according to the method used for determining the insulin delivered. Manual (or non-automated CSII) insulin delivery means the basal and bolus insulin doses are pre-determined by inputting settings in to the CSII device and are not adjusted in an ongoing, immediate manner according to real-time CGM. However, manual CSII also includes systems that have the feature of basal insulin suspension with sensor-detected hypoglycaemia (low-glucose suspend) or sensor-predicted hypoglycaemia (predictive low-glucose suspend). Automated insulin delivery (AutoCSII) systems, also known as 'hybrid closed loop insulin pumps', consist of three linked components functioning continuously: a continuous glucose monitoring device; a subcutaneous insulin infusion pump device; and a computerised algorithm which determines insulin delivery based on ambient glucose. AutoCSII enables basal insulin delivery to be automatically adjusted based on CGM measures. Insulin boluses for meals with AutoCSII may require initiation by the user to manually input the total carbohydrate content into the pump, or automated bolus adjustment based on CGM measures. Currently, there are few studies which have investigated devices providing automated basal and bolus insulin delivery, with a majority of current AutoCSII systems using automated basal insulin delivery alone.

CGM devices enable real-time measurement of interstitial fluid glucose concentrations via a subcutaneous glucose sensor. CGM can be performed in a blinded manner, typically for research purposes, whereby the user is blinded to the collection of 'real-time' glucose measures. This guideline has excluded the analysis of studies investigating the utility of blinded CGM. Alternatively, CGM may be performed in an open manner whereby real-time CGM data are instantly available to the user either on a CGM device with a read-out or on a smart phone or tablet application. Such real-time CGM may also include devices requiring intermittent scanning to obtain live glucose data and also devices which may alert for low and high blood glucose. This guideline has investigated the efficacy of all real-time CGM systems including those with and without alert capability and those which require intermittent scanning.

In regard to specific groups of people with type 1 diabetes, it is important to note that women in pregnancy and young children (under 6 years of age) were not assessed given the lack of studies in these specific populations. Where feasible, paediatric populations (i.e. children and adolescents) were analysed separately to adults. This guideline focuses on registered medical device technologies that have been subjected to a regulatory process, and thus does not incorporate 'Do It Yourself' (DIY) device technology solutions for the treatment of type 1 diabetes.

The trials included in the present analyses were not fully representative of the type 1 population, particularly of the frail elderly and persons with both diabetes and complex comorbidities. Clinical judgement should be exercised when applying these guidelines to these underrepresented subgroups

3.1 - Continuous glucose monitoring devices (CGM)

In this chapter we address the effectiveness of continuous glucose monitoring (CGM) compared to self-monitoring of blood glucose (SMBG) in adults with type 1 diabetes treated with multiple daily injections (MDI).

While there are increasingly advanced systems integrating CGM with insulin pumps, the majority of people with type 1 diabetes still use MDI due to a number of factors including personal preference, high acquisition costs, funding, and not wanting to be attached to a device. Furthermore, from an evidence synthesis perspective, we felt the comparison of CGM with SMBG among adults using MDI would be important in order to separate treatment effects from insulin delivery systems and better address the relative clinical efficacy of the various categories of diabetes management technology.

Conditional recommendation

We suggest continuous glucose monitoring rather than self-monitoring of blood glucose alone for all adults with type 1 diabetes treated with multiple daily injections.

The decision on whether to use continuous glucose monitoring or self-monitoring of blood glucose alone is highly dependent on personal preference. Health professional discussions with people with type 1 diabetes should include the use and potential benefits of CGM and considerations of personal preferences, the value of alarms and data trends, available resources, and the importance of high level engagement with the technology and health services.

Current CGM devices enable real-time measurement of interstitial fluid glucose concentrations via a subcutaneous glucose sensor. Interstitial fluid glucose measures are recognised as closely correlating with blood glucose concentrations. CGM devices are available with a variety of functions including alarms for hypoglycaemic and hyperglycaemic thresholds and as intermittently scanned devices (also known as 'flash' continuous glucose monitoring). CGM devices provide a large amount of real-time data and summary glycaemic data (e.g. modal day reports) which can be highly valuable for both the person with diabetes and their healthcare providers. Higher proportions of time spent actively using and responding to CGM data are consistently associated with glycaemic improvements such as lower HbA1c concentrations and increased time within an appropriate glucose range (3.9-10.0 mmol/L). A conditional recommendation for use of CGM in type 1 diabetes was based on low-moderate certainty of evidence for favourable outcomes.

Practical Info

Given CGM devices measure interstitial fluid glucose concentrations there can be a discrepancy in values when compared to capillary blood glucose concentrations obtained via self-monitoring with a point-of-care glucose meter. The discrepancy between interstitial fluid and capillary glucose measures may be greater in situations where the blood glucose is rapidly rising or falling. As there can be occasional significant discrepancies in these two types of glucose measures it is important to appreciate CGM may need to be used in combination with SMBG.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

In adults with type 1 diabetes using MDI, CGM with alerts probably decreases HbA1c, increases time within target glucose range, and may decrease the frequency of severe hypoglycaemic events in comparison to SMBG. Therapy with CGM and alerts may also decrease the number of nocturnal hypoglycaemic episodes and probably decreases the percent time spent with sensor glucose levels <50-54mg/dL (2.8-3.0mmol/L) overnight (22:00-06:00). It appeared that CGM had little or no impact on quality of life, however scores on the WHO-5 Well Being Index were high for both treatment groups in the two included studies. CGM without alerts had inadequate evidence, however flash CGM without alerts may make little or no difference to quality of life, but probably increases time in range and reduces time below range overnight.

There was no consistent evidence to suggest harm was directly related to glucose monitoring with CGM. The CGM and alerts probably makes little or no difference to weight, and any slight increase of weight may be related to additional insulin doses or dietary changes.

The evidence analyses and reference list for CGM with alerts is contained within the associated Review Manager 5 (RevMan 5) file which can be found [here](#).

The evidence analyses and reference list for CGM without alerts is contained within the associated Review Manager 5 (RevMan 5) file which can be found [here](#).

The evidence analyses and reference list for Flash CGM is contained within the associated Review Manager 5 (RevMan 5) file which can be found [here](#).

Certainty of the Evidence

Moderate

CGM with alerts: For the critical outcomes of HbA1c and percent time in range, the overall certainty of evidence was moderate due to inconsistency. For the critical outcome of rates of severe hypoglycaemia, the overall certainty of evidence was low due to imprecision.

CGM without alerts: For critical outcomes, certainty of evidence was low for HbA1c, very low for severe hypoglycaemia, and low for time in range due to very serious imprecision.

Flash CGM without alerts: For critical outcomes, certainty of evidence was low for HbA1c, very low for severe hypoglycaemia, and moderate for time in range due to imprecision.

Preference and values

Substantial variability is expected or uncertain

Therapy with CGM offers greater insight into glucose patterns to assist people with diabetes and their care providers in adjusting therapy. However, effective implementation of such therapy requires users to undertake appropriate training in both diabetes self-management and the use of CGM systems. Users also require a high degree of motivation and engagement in order to synthesise and act upon the large volume of information. Glucose monitoring alarms may detract from the user experience for some individuals and all interstitial glucose monitoring systems require a subcutaneous needle for application and an adhesive patch. CGM also represents a considerable additional expense for most adults. We therefore believe that while most people could gain glycaemic benefit from CGM and that therapy is usually well accepted, for some individuals the particular practical aspects of implementation may outweigh these potential benefits.

Resources

Important issues, or potential issues not investigated

The cost of CGM to people with type 1 diabetes varies depending on how much time they spend using this therapy and the various packages offered through manufacturer websites. The annual retail cost of daily CGM therapy exceeds \$5,000 AUD, and flash CGM may cost up to \$2,500 AUD per year. The ongoing expense of these devices is expected to be a significant barrier for people to access CGM therapy.

From a government funding perspective, our review of international economic evaluations found that CGM with MDI may be cost-effective in comparison to SMBG particularly among those who gain significant improvement in blood glucose management and quality of life.

In more detail, cost-effectiveness analyses aim to assess the differences between costs of therapy balanced against the differences in health outcomes. Incremental cost-effectiveness ratios are used in cost-effectiveness analyses and represent the difference in costs of treatments and outcomes between two interventions divided by the difference in quality adjusted life years over a predefined period of time, or time horizon. While the acquisition costs of CGM therapy are significantly larger than SMBG, for example, economic evaluations assess whether fewer complications of diabetes due to glycaemic improvement from CGM might offset these costs. We found four economic evaluations that compared CGM and MDI therapy against SMBG and MDI. Two studies concluded CGM was cost-effective while the other two did not. Where insulin delivery could be either MDI or continuous subcutaneous insulin infusion (CSII), we found four out of five studies reported that CGM was cost-effective, reduced costs, or had minimal budget impact when compared to SMBG. One economic evaluation reported that flash CGM was cost-effective compared to SMBG among a population using CSII or MDI therapy. Furthermore, apart from differences across funding systems, it appeared that key determinants of cost-effectiveness comprised the treatment effect of CGM on HbA1c and rates of hypoglycaemia, as well as the utility score associated with fear of hypoglycaemia. In summary, it appeared that CGM may be cost-effective particularly among those who gain significant improvement in blood glucose management and quality of life. However, economic evaluations are needed in the Australian healthcare system. [21]

Equity

Important issues, or potential issues not investigated

People with type 1 diabetes aged 21 years and older who have concessional status can access fully subsidised continuous and flash glucose monitoring systems[18]. Access to CGM is not expected to be equitable in the absence of universal government funding among adults with type 1 diabetes.

Acceptability

No important issues with the recommended alternative

No significant concerns were raised although acceptability of CGM was not consistently reported across studies from our systematic review. A small proportion of people using CGM may develop local reactions to adhesive patches, find alarms to be intrusive, find the volume of information to be burdensome, or prefer not having devices attached to them. Acceptability may be influenced by the level of knowledge regarding different options.

Feasibility

No important issues with the recommended alternative

No significant concerns were raised, although feasibility of CGM was not reported in studies from our systematic review. Access to education and health services with adequate resources, capacity, and expertise to optimally implement CGM may limit feasibility in some areas.

Rationale

In formulating this recommendation, the working group placed emphasis on the favourable findings regarding critical outcomes of HbA1c, time in range, and rates of severe hypoglycaemia. The improvement in important outcomes of nocturnal hypoglycaemia and time below range overnight was also largely consistent across studies. The improvements in glycaemic outcomes were clinically relevant although imprecision and inconsistency led to a downgrading for certainty of evidence. CGM with alerts had moderate certainty for reduction in HbA1c and improved time in range, and low certainty for reduced severe hypoglycaemia. Flash CGM without alerts had moderate certainty for improved time in range, however the certainty of evidence for flash CGM without alerts was otherwise low to very low.

From a clinical perspective, there was consistent evidence for glycaemic benefit and no strong evidence for adverse outcomes directly related to CGM. That being said, there exists variation in personal preference, and resource requirements will result in inequity in the absence of universal government funding. Based on our review of international data, CGM may be cost-effective among actively engaged people with type 1 diabetes who stand to achieve glycaemic and quality of life improvements. As a result, people willing to engage with this therapy should be provided the opportunity to access it.

Clinical Question/ PICO

Population:	Adults with type 1 diabetes
Intervention:	CGM with alerts + MDI
Comparator:	SMBG + MDI

Summary

In adults with type 1 diabetes using MDI therapy, CGM with alerts probably improves critical outcomes of HbA1c, time in range, and may decrease severe hypoglycaemia when compared to SMBG. CGM with alerts may reduce the frequency of nocturnal hypoglycaemia and probably decreases time spent with sensor glucose below 2.8/3.0 mmol/L. The improvements in the critical outcomes of HbA1c, time in range, and severe hypoglycaemia were judged to be clinically relevant. Imprecision and inconsistency lead to a moderate grading for certainty of evidence. Nocturnal hypoglycaemia frequency had low certainty and the percentage of time spent below 2.8/3.0mmol/L (overnight) had moderate certainty due to very serious imprecision and serious inconsistency, respectively.

Despite a high certainty of the evidence concluding CGM with alerts had little impact on quality of life, we felt that the generalisability may have been limited by high baseline quality of life scores in study populations. We found event rates were too low to make conclusions regarding diabetic ketoacidosis or mortality, although the limited evidence favoured CGM with alerts. Serious adverse events during trials were also infrequent and were not routinely reported for relatedness to interventions. We did find that CGM with alerts probably had little or no impact on weight, although only two studies reported this outcome, and slight differences in weight could be related to altered behaviours such as additional use of insulin or dietary adjustments. Due to the short duration of studies comparing CGM to SMBG, the impact on long term complications such as diabetic retinopathy, neuropathy, and nephropathy could not be determined.

The evidence analyses and reference list for CGM with alerts are contained within the associated Review Manager 5 (RevMan 5) file, which can be found [here](#).

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		SMBG + MDI	CGM with alerts + MDI		
<p>Severe hypoglycaemic events (rate ratio) End of treatment</p> <p>9 Critical</p>	<p>0.6 (CI 95% 0.29 - 1.26) Based on data from 349 patients in 4 studies. (Randomized controlled) Follow up Rate ratio based on a total of 101 events</p>			<p>Low Due to very serious imprecision ¹</p>	<p>CGM with alerts + MDI may decrease the number of severe hypoglycaemic events</p>
<p>No. of patients experiencing diabetic ketoacidosis End of treatment</p> <p>6 Important</p>	<p>Relative risk 0.31 (CI 95% 0.01 - 7.46) Based on data from 650 patients in 4 studies. ² (Randomized controlled)</p>			<p>Low Due to very serious imprecision ³</p>	<p>As only one person experienced diabetic ketoacidosis, it was not possible to determine whether CGM with alerts + MDI made a difference (1/294 SMBG; 0/356 CGM)</p>
<p>Serious adverse events End of treatment</p> <p>6 Important</p>	<p>Relative risk 1.7 (CI 95% 0.82 - 3.52) Based on data from 591 patients in 3 studies. ⁴ (Randomized controlled)</p>			<p>Low Due to very serious imprecision ⁵</p>	<p>As only 29 people experienced serious adverse events, it was not possible to determine whether CGM with alerts + MDI made a difference (10/269 SMBG; 19/322 CGM)</p>
<p>All cause mortality End of treatment</p> <p>6 Important</p>	<p>Relative risk 0.33 (CI 95% 0.03 - 3.16) Based on data from 433 patients in 2 studies. ⁶</p>			<p>Low Due to very serious imprecision ⁷</p>	<p>As only two people died, it was not possible to determine whether CGM with alerts + MDI made a difference (2/216 SMBG; 0/217 CGM)</p>
<p>Retinopathy End of treatment</p> <p>6 Important</p>					<p>No studies were found that looked at retinopathy</p>
<p>Nephropathy End of treatment</p> <p>6 Important</p>					<p>No studies were found that looked at nephropathy</p>

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		SMBG + MDI	CGM with alerts + MDI		
Neuropathy End of treatment					No studies were found that looked at neuropathy
6 Important					
Hospitalisation End of treatment					No studies were found that looked at hospitalisation
6 Important					
HbA1c % End of treatment	Based on data from: 832 patients in 7 studies. ⁸ (Randomized controlled)	8.35 (Median)	8	Moderate Due to serious inconsistency ⁹	CGM with alerts + MDI probably decreases HbA1c %
9 Critical		Difference: MD 0.35 lower (CI 95% 0.61 lower - 0.08 lower)			
Time within target glucose range End of treatment	Measured by: Minutes per day Based on data from: 496 patients in 4 studies. ¹⁰ (Randomized controlled)	814 Minutes per day (Median)	880 Minutes per day	Moderate Due to serious inconsistency ¹¹	CGM with alerts + MDI probably increases time within target glucose range
9 Critical		Difference: MD 66.37 higher (CI 95% 3.66 higher - 129.08 higher)			
No. of nocturnal hypoglycaemic events End of treatment	Measured by: Per patient per 28 days Based on data from: 141 patients in 1 studies. ¹² (Randomized controlled)	2.7 (Mean)	1 (Mean)	Low Due to very serious imprecision ¹³	CGM with alerts + MDI may decrease no. of nocturnal hypoglycaemic events
6 Important		Difference: MD 1.7 lower (CI 95% 2.41 lower - 0.99 lower)			
Percentage of time spent at <2.75-3.0 mmol/L between 10 PM and 6 AM End of treatment	Based on data from: 400 patients in 2 studies. ¹⁴ (Randomized controlled)	2.08 (Median)	1.31	Moderate Due to serious inconsistency and resulting imprecision ¹⁵	CGM with alerts + MDI probably decreases percentage of time spent at <2.75-3.0 mmol/L between 10 PM and 6 AM slightly
6 Important		Difference: MD 0.77 lower (CI 95% 1.73 lower - 0.19 higher)			

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		SMBG + MDI	CGM with alerts + MDI		
Quality of life End of treatment 6 Important	Measured by: WHO-5 Well Being Index Scale: 0-100 High better Based on data from: 434 patients in 2 studies. ¹⁶	63 points (Median) Difference: MD 3.31 higher (CI 95% 0.01 higher - 6.61 higher)	66 points	High ¹⁷	CGM with alerts + MDI has little or no impact on quality of life
Weight End of treatment 6 Important	Measured by: Kilograms Based on data from: 439 patients in 2 studies. ¹⁸ (Randomized controlled)	82.5 (Median) Difference: MD 0.76 higher (CI 95% 0.02 higher - 1.51 higher)	83.3	Moderate Due to serious imprecision ¹⁹	CGM with alerts + MDI probably has little or no impact on weight

- Risk of bias: No serious.** Lack of blinding of participants and personnel, however this is unlikely to introduce bias for this outcome.. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Wide confidence intervals. **Publication bias: No serious.**
- Systematic review [4] with included studies: Lind 2017, Tamborlane 2008 >24, DIAMOND 2017, Tamborlane 2008 15-24. **Baseline/comparator:** Control arm of reference used for intervention.
- Risk of bias: No serious.** Lack of blinding of participants and personnel, however this shouldn't introduce bias into the outcome. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Low number of patients. **Publication bias: No serious.**
- Systematic review [4] with included studies: Heinemann 2018, DIAMOND 2017, Lind 2017. **Baseline/comparator:** Control arm of reference used for intervention.
- Risk of bias: No serious.** Lack of blinding of participants and personnel, however this is unlikely to introduce bias for this outcome.. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Wide confidence intervals due to few events. **Publication bias: No serious.**
- Systematic review [4] with included studies: Lind 2017, Heinemann 2018. **Baseline/comparator:** Control arm of reference used for intervention.
- Risk of bias: No serious.** Lack of blinding of participants and personnel, however this is unlikely to introduce bias for this outcome.. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Low number of patients. **Publication bias: No serious.**
- Systematic review [4] with included studies: Sequeira 2013, DIAMOND 2017, Tumminia 2015, Lind 2017, Tamborlane 2008 >24, Tamborlane 2008 15-24, Heinemann 2018. **Baseline/comparator:** Control arm of reference used for intervention.
- Risk of bias: No serious.** Lack of blinding of participants and personnel, however this shouldn't introduce bias; Some loss to follow up. **Inconsistency: Serious.** The magnitude of statistical heterogeneity was high, with I²: 86%.. **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
- Systematic review [4] with included studies: DIAMOND 2017, Tamborlane 2008 15-24, Heinemann 2018, Tamborlane 2008 >24. **Baseline/comparator:** Control arm of reference used for intervention.
- Risk of bias: No serious.** Lack of blinding of participants and personnel, however this is unlikely to introduce bias. **Inconsistency: Serious.** The magnitude of statistical heterogeneity was high, with I²:69%.. **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
- Systematic review [4] with included studies: Heinemann 2018. **Baseline/comparator:** Control arm of reference used for intervention.
- Risk of bias: No serious.** Lack of blinding of participants and personnel, however this is unlikely to introduce bias.. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Only data from one study. **Publication bias:**

No serious.

- 14. Systematic review [4] with included studies: Lind 2017. **Baseline/comparator:** Control arm of reference used for intervention.
- 15. **Risk of bias: No serious.** Lack of blinding of participants and personnel, however this is unlikely to introduce bias. **Inconsistency: Serious.** The magnitude of statistical heterogeneity was high, with I²:82%.. **Indirectness: No serious.** **Imprecision: Serious.** Wide confidence intervals partly due to inconsistency. **Publication bias: No serious.**
- 16. Systematic review [4] with included studies: Lind 2017, DIAMOND 2017. **Baseline/comparator:** Control arm of reference used for intervention.
- 17. **Risk of bias: No serious.** Lack of blinding of participants and personnel, however this is unlikely to introduce bias. **Inconsistency: No serious.** **Indirectness: No serious.** **Imprecision: No serious.** Wide confidence intervals, but does not cross 10 points (minimal important difference). **Publication bias: No serious.**
- 18. Systematic review [4] with included studies: DIAMOND 2017, Lind 2017. **Baseline/comparator:** Control arm of reference used for intervention.
- 19. **Risk of bias: No serious.** Lack of blinding of participants and personnel, however this is unlikely to introduce bias. **Inconsistency: No serious.** **Indirectness: No serious.** **Imprecision: Serious.** Low number of patients. **Publication bias: No serious.**

Clinical Question/ PICO

- Population:** Adults with type 1 diabetes
- Intervention:** CGM without alerts + MDI
- Comparator:** SMBG+MDI

Summary

In adults with type 1 diabetes using MDI therapy, CGM without alerts was compared to SMBG by only one study.[6] The randomised controlled trial was of parallel design, spanned 100 days, and included 42 participants with type 1 diabetes in the intention to treat analysis. For the critical outcomes of our review comprising HbA1c, time in range, and rates of severe hypoglycaemia, the level of evidence was low due to very serious imprecision. Time in range, HbA1c, and weight were not significantly different between groups, and only one episode of severe hypoglycaemia occurred during the trial period. The other important outcomes of diabetic ketoacidosis, serious adverse events, mortality, retinopathy, nephropathy, neuropathy, hospitalisation, nocturnal hypoglycaemia, and quality of life were not reported.

The evidence analyses and reference list for CGM without alerts are contained within the associated Review Manager 5 (RevMan 5) file, which can be found [here](#).

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		SMBG+MDI	CGM+MDI without alerts		
Severe hypoglycaemia End of treatment 9 Critical	Relative risk 1.4 (CI 95% 0.06 - 32.25) Based on data from 42 patients in 1 studies. ¹ (Randomized controlled)			Very Low Due to very serious imprecision ²	As only one person experienced severe hypoglycaemia, it was not possible to determine whether CGM+MDI without alerts made a difference (SMBG 0/13; CGM 1/ 29)

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		SMBG+MDI	CGM+MDI without alerts		
Diabetic ketoacidosis 6 Important					No studies were found that looked at diabetic ketoacidosis
Serious adverse events 6 Important					No studies were found that looked at serious adverse events
All cause mortality 6 Important					No studies were found that looked at all cause mortality
Retinopathy 6 Important					No studies were found that looked at retinopathy
Nephropathy 6 Important					No studies were found that looked at nephropathy
Neuropathy 6 Important					No studies were found that looked at neuropathy
Hospitalisation 6 Important					No studies were found that looked at hospitalisation
HbA1c %³ End of treatment 9 Critical	Based on data from: 41 patients in 1 studies. ⁴	8.9 (Mean)	8.7 (Mean)	Low Due to very serious imprecision ⁵	CGM + MDI without alerts may improve HbA1c % slightly
		Difference: MD 0.2 lower (CI 95% 0.95 lower - 0.55 higher)			

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		SMBG+MDI	CGM+MDI without alerts		
Time in range ⁶ End of treatment 6 Important	Measured by: Hours per day Based on data from: 40 patients in 1 studies. ⁷ (Randomized controlled)	11.5 (Mean)	10.8 (Mean)	Low Due to very serious imprecision ⁸	CGM + MDI without alerts may increase HbA1c time in range slightly
Weight ⁹ End of treatment 6 Important	Measured by: Kilograms Based on data from: 42 patients in 1 studies. ¹⁰	80.4 (Mean)	81.8 (Mean)	Low Due to very serious imprecision ¹¹	CGM + MDI without alerts may have little or no impact on weight
Nocturnal hypoglycaemia	Based on data from: 0 patients in 0 studies.				No studies were found that looked at nocturnal hypoglycaemia
Quality of life	Based on data from: 0 patients in 0 studies.				No studies were found that looked at quality of life

1. Systematic review [3] with included studies: Ajjan 2016. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: No serious.** Lack of blinding of participants and personnel, however this would not affect the objective measure of hypoglycaemic events.. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Only data from one study, Low number of patients and only one event. **Publication bias: No serious.**
3. Absolute glycated haemoglobin % at end of treatment
4. Systematic review [3] with included studies: Ajjan 2016. **Baseline/comparator:** Control arm of reference used for intervention.
5. **Risk of bias: No serious.** Lack of blinding of participants and personnel, however this would not affect the objective value of HbA1c %.. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Only data from one study, Low number of patients. **Publication bias: No serious.**
6. Time spent in range of euglycaemia (>3.9 to <10.0 mmol/l), hours per day
7. Systematic review [3] with included studies: Ajjan 2016. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Only data from one study, Low number of patients. **Publication bias: No serious.**
9. Absolute weight at end of treatment (kg)
10. Systematic review [3] with included studies: Ajjan 2016. **Baseline/comparator:** Control arm of reference used for intervention.
11. **Risk of bias: No serious.** Lack of blinding of participants and personnel, however this would not affect the objective measure of hypoglycaemic events.. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Only data

from one study, Low number of patients. **Publication bias: No serious.**

Clinical Question/ PICO

Population: Adults with type 1 diabetes
Intervention: Flash + MDI
Comparator: SMBG + MDI

Summary

Only one study was found that compared flash CGM without alerts to SMBG in adults with type 1 diabetes using MDI.[7] The randomised controlled trial was of parallel design, spanned six months, and included 161 participants. Imprecision reduced the certainty of the critical outcomes HbA1c, time in range, and rates of severe hypoglycaemia. HbA1c was not significantly different between groups at the end of the study, however we noted that HbA1c at baseline was low in both treatment arms (6.7%(0.5) and 6.7%(0.6) in the flash CGM and SMBG groups respectively). Participants using flash CGM without alerts probably spent more time (an additional 1.4 hours, 95% confidence interval 0.5, 2.3) in range per day with moderate quality evidence. Rates of severe hypoglycaemia were too low to determine if flash CGM made a difference, although time spent <2.5mmol/L overnight was probably lower among participants using flash CGM.

Quality of life related to diabetes may have been little or no better among participants using flash CGM without alerts, although serious imprecision and a small magnitude of difference in scores raised uncertainty. The worry subscale of the hypoglycaemia fear survey may have been little or no different between groups.

None of the study participants experienced diabetic ketoacidosis and rates of serious adverse events were too low to determine whether flash CGM made a difference. There may have been little or no difference in weight between the treatment groups. The other important outcomes of mortality, retinopathy, nephropathy, and neuropathy were not reported.

The evidence analyses and reference list for CGM without alerts are contained within the associated Review Manager 5 (RevMan 5) file, which can be found [here](#).

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		SMBG + MDI	Flash + MDI		
No. of patients with a hypoglycaemic SAE 6 months 9 Critical	Relative risk 0.33 (CI 95% 0.03 - 3.1) Based on data from 163 patients in 1 studies. ¹ (Randomized controlled)	37 per 1000	12 per 1000	Very Low Due to very serious imprecision ²	As only four people experienced a hypoglycaemic SAE, it was not possible to determine whether flash made a difference (SMBG 3/81; Flash 1/ 82)
Difference: 25 fewer per 1000 (CI 95% 36 fewer - 78 more)					
No. of patients experiencing diabetic ketoacidosis 6 months	Based on data from 160 patients in 1 studies. ³ (Randomized controlled)			Very Low Due to very serious imprecision ⁴	There were no patients experiencing diabetic ketoacidosis in the trial

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		SMBG + MDI	Flash + MDI		
6 Important					
No. of patients who experienced one or more serious adverse events 6 months	Relative risk 0.99 (CI 95% 0.26 - 3.82) Based on data from 163 patients in 1 studies. ⁵ (Randomized controlled)	49 per 1000	49 per 1000	Very Low Due to very serious imprecision ⁶	As only eight people experienced a serious adverse events, it was not possible to determine whether flash made a difference (SMBG 4/81; flash 4/82)
6 Important					
All cause mortality					No studies were found that looked at all cause mortality
6 Important					
Retinopathy					No studies were found that looked at retinopathy
6 Important					
Nephropathy					No studies were found that looked at nephropathy
6 Important					
Neuropathy					No studies were found that looked at neuropathy
6 Important					
Hospitalisation					No studies were found that looked at hospitalisation
6 Important					
HbA1c % 6 months	Based on data from: 160 patients in 1 studies. ⁷ (Randomized controlled)	6.91 % (Mean)	7 % (Mean)	Low Due to very serious imprecision ⁸	Flash may have little impact on average HbA1c
9 Critical		Difference: MD 0.09 higher (CI 95% 0.11 lower - 0.29 higher)			

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		SMBG + MDI	Flash + MDI		
Time spend in range hours/ day 6 months 9 Critical	Based on data from: 160 patients in 1 studies. ⁹ (Randomized controlled)	14.3 hours (Mean)	15.7 hours (Mean)	Moderate Due to serious imprecision ¹⁰	Flash probably increases time spend in range
Hours in hypoglycaemic range (<2.5 mmol/L) between 23:00 and 6:00 6 months 6 Important	Based on data from: 160 patients in 1 studies. ¹¹ (Randomized controlled)	0.5 Hours (Mean)	0.15 Hours (Mean)	Moderate Due to serious imprecision ¹²	Flash probably decreases hours in nocturnal severe hypoglycaemic range (<2.5 mmol/L) slightly
Hypoglycaemia Fear Survey, worry subscale 6 months 6 Important	Scale: 0-52 Lower better Based on data from: 148 patients in 1 studies. ¹³ (Randomized controlled)	18.4 points (Mean)	14.9 points (Mean)	Low Due to serious risk of bias, Due to serious imprecision ¹⁴	Flash may make little difference regarding hypoglycaemia worry
Diabetes Quality of Life 6 months 6 Important	Scale: 1-5 Lower better Based on data from: 148 patients in 1 studies. ¹⁵ (Randomized controlled)	2.1 points (Mean)	1.9 points (Mean)	Low Due to serious risk of bias, Due to serious imprecision ¹⁶	Flash may make little impact on diabetes quality of life
Weight 6 months 6 Important	Based on data from 148 patients in 1 studies.	At the end of the study, weight (p = 0.34) and BMI (p= 0.32) were comparable between the groups.		Low Due to very serious imprecision ¹⁷	Flash may have little or no difference on weight

1. Systematic review [5] with included studies: Oskarsson 2018. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Only data from one study with few events. **Publication bias: No serious.**
3. Systematic review [5] with included studies: Oskarsson 2018. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Only data from one study with no events. **Publication bias: No serious.**

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5. Systematic review [5] with included studies: Oskarsson 2018. **Baseline/comparator:** Control arm of reference used for intervention.
 6. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Only data from one study with few events.
 7. Systematic review [5] with included studies: Oskarsson 2018. **Baseline/comparator:** Control arm of reference used for intervention.
 8. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Only data from one study, Wide confidence intervals. **Publication bias: No serious.**
 9. Systematic review [5] with included studies: Oskarsson 2018. **Baseline/comparator:** Control arm of reference used for intervention.
 10. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Only data from one study. **Publication bias: No serious.**
 11. Systematic review [5] with included studies: Oskarsson 2018. **Baseline/comparator:** Control arm of reference used for intervention.
 12. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Only data from one study. **Publication bias: No serious.**
 13. Systematic review [5] with included studies: Oskarsson 2018. **Baseline/comparator:** Control arm of reference used for intervention.
 14. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Only data from one study. **Publication bias: No serious.**
 15. Systematic review [5] with included studies: Oskarsson 2018. **Baseline/comparator:** Control arm of reference used for intervention.
 16. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Only data from one study. **Publication bias: No serious.**
 17. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Only data from one study, Wide confidence intervals. **Publication bias: No serious.**

3.2 - Continuous subcutaneous insulin infusion pump devices (CSII)

In this chapter we will address continuous subcutaneous insulin infusions (CSII) compared to multi-dose insulin injections (MDI) in children, adolescents and adults with type 1 diabetes.

CSII pumps are becoming increasingly used to manage type 1 diabetes, however a number of factors associated with CSII use, including high acquisition costs, funding, and not wanting to be attached to a device, result in many individuals preferring to administer insulin via intensive insulin therapy, or MDI.

Conditional recommendation

We suggest CSII or MDI treatment for children and adolescents with type 1 diabetes based on the preference of the person with diabetes (and carer).

The timing of initiating CSII following diagnosis of type 1 diabetes should be determined by the clinician in consultation with the person with diabetes and their carer. CSII treatment consists of continuous subcutaneous insulin infusion pump devices with various options including: manual CSII systems either without or with CGM (including low glucose suspend and predictive low glucose suspend) or automated CSII systems (AutoCSII), also known as 'hybrid closed loop' systems. MDI consists of daily administration of basal insulin in combination with prandial rapid-acting insulin injection treatment. CSII improves glycaemia (lowers HbA1c) which could ultimately lead to decreased microvascular complications. However, there is a paucity of studies examining the long term impact of CSII on microvascular complications, diabetic ketoacidosis, mortality and quality of life. There is also little current evidence to demonstrate that CSII decreases weight. Variation in preference for CSII is anticipated in light of the higher treatment intensity required and costs associated with its use to manage type 1 diabetes.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

Evidence demonstrates neither significant benefits nor significant harms are associated with the use of CSII pumps compared to MDI. Slight benefits associated with the use of CSII include a reduction in incidence of hospitalisation and lower HbA1c levels. There were no significant differences observed with regards to weight, quality of life, severe hypoglycaemia, diabetic ketoacidosis, serious adverse events and nocturnal hypoglycaemia. No studies reported data relating to mortality, nephropathy, neuropathy, retinopathy or blood glucose time in range (3.9-10 mmol/L).

The evidence analyses and reference list are contained within the associated Review Manager 5 (RevMan 5) file, which can be found [here](#).

Certainty of the Evidence

Low

The certainty of evidence was high for HbA1c and moderate for weight (BMI) due to serious imprecision. Certainty in evidence was low for all remaining outcomes for which data were available due to very serious imprecision (hospitalisation, serious adverse events and nocturnal hypoglycaemia) and a combination of serious imprecision and serious inconsistency (severe hypoglycaemia and diabetic ketoacidosis). Three studies presented quality of life data; however, each used a separate performance measure (KINDL-DM, PedsQL and DQOLY) for which an inconsistent direction of effect was observed.

Preference and values

Substantial variability is expected or uncertain

As there is no clear evidence demonstrating superior safety and effectiveness of insulin pumps over the use of multiple daily injections, preferences and values are an important consideration when determining whether to adopt this technology. One key consideration is the steep learning curve associated with commencing pump therapy. In addition, children are often unable to manage their pump and thus a parent or carer is required at all times to assist. Children may also have an aversion to wearing the pump due to limitations in some types of physical activity and/or in order to avoid judgement from other children.

Resources

Important issues, or potential issues not investigated

The Insulin Pump Program provides fully subsidised insulin pumps to eligible young people under 18 years of age without access to other means of reimbursement such as private health insurance. This program is administered by JDRF Australia on behalf of the Commonwealth.

For the majority of young people who are ineligible for fully subsidised pumps and who are not covered by private health insurance, the costs associated with insulin pump use can be high. The cost of an insulin pump within Australia ranges from \$6,994 to \$8,574 (4-year warranty). In addition, insulin pump consumables cost the person with diabetes ~\$340 per year above the 91% subsidy through the NDSS. The annual cost of insulin varies based on requirements. Individuals who

administer insulin via MDI are required to pay the costs of insulin only, as syringes and pen needles are provided at no cost through the NDSS.

Equity

Important issues, or potential issues not investigated

The predominant ways in which children and adolescents with type 1 diabetes can access the use of an insulin pump include the Insulin Pump Program (administered by the JDRF), their parents' private health insurer, or else full payment for the device.

The availability of fully subsidised insulin pumps through the Government's means-tested Insulin Pump Program is limited, resulting in the majority of children and adolescents being ineligible for access through this avenue. Restricted availability of pumps through the subsidy program and lack of private health insurance in many families can greatly inhibit the use of insulin pumps, particularly in families with limited financial capacity or those located in rural/remote communities.

Acceptability

No important issues with the recommended alternative

Population level meta-analyses demonstrate that although insulin pumps do not provide significant benefits over and above the use of MDI, they provide equal or better management of type 1 diabetes in children and adolescents. No moral or ethical considerations were identified that are likely to render the use of insulin pumps as unacceptable.

Feasibility

Important issues, or potential issues not investigated

The implementation of insulin pump therapy in children and adolescents is feasible from an availability perspective, as many insulin pumps are approved by the Therapeutic Goods Administration (TGA) and included on the prostheses list. Access may be limited due to the cost price of the insulin pump for those ineligible for subsidisation through the Insulin Pump Program. Also, the requirement of constant parent/caregiver support can reduce the feasibility of insulin pump use in some individuals.

Rationale

In formulating the recommendation to consider the use of CSII in children and adolescents, the working group acknowledged the highly consistent and favourable improvement in the key glycaemic outcome of HbA1c. It was our impression that improvements in glycaemic outcomes were clinically relevant (HbA1c reduction of 0.3%) compared to control groups who already displayed better than average blood glucose management (mean HbA1c 8.1%). There is moderate certainty for CSII resulting in little or no impact on weight, and low certainty that CSII has little or no impact on quality of life and severe hypoglycaemia. The effect of CSII on diabetic ketoacidosis and hospitalisation is uncertain. The low certainty regarding its impact on key clinical outcomes, together with expected variability in preferences and values of people (and carers) led to a conditional recommendation for CSII. Given the potential benefits of CSII it is anticipated many people with type 1 diabetes on MDI treatment will seek to adopt CSII. Variability in preference for CSII is anticipated given the greater commitment to treatment intensity required and increased costs associated with ongoing use of CSII. Equity of access to CSII in Australia remains an issue given the high retail cost of CSII devices, which are predominantly funded through private health insurance in the presence of an appropriate level of cover, or publicly funded for a limited number of individuals under 18 years of age without access to private health insurance. The feasibility of CSII also needs to be considered given the initial increased training time required for both health professionals and people with type 1 diabetes, although this may ultimately be offset over time through improved quality of life for children and adolescents (and carers) due to more stable glycaemia and potentially fewer vascular complications. The working group also acknowledged that economic evaluations should be performed to clarify the cost-effectiveness of CSII in the Australian context.

Clinical Question/ PICO

- Population:** Children with type 1 diabetes
- Intervention:** CSII
- Comparator:** MDI

Summary

Thirteen studies informed the critical outcome of glycosylated haemoglobin (HbA1c), improvements which were borderline clinically relevant and of low certainty. There was probably a slight reduction in weight, as determined by decrease in BMI, in people using CSII; however, this was not considered clinically relevant. It was not possible to draw any conclusions regarding the remaining two critical outcomes of severe hypoglycaemia and diabetic ketoacidosis due to very serious imprecision based on the low number of events - although an additional measure of severe hypoglycaemia was reported (incidence rate ratio), it was not possible to determine whether there was a difference between people using CSII and those using MDI due to inconsistency in direction of effect and serious imprecision.

The results may demonstrate a slight increase in the rate of hospitalisation in children and adolescents within the CSII group, however this was only based on two studies and as a result was regarded as having low certainty of evidence. Uncertainty remains regarding serious adverse events and nocturnal hypoglycaemia due to very serious imprecision based on the low number of events. No studies reported data on incidence of all-cause mortality, nephropathy, neuropathy, retinopathy or time in glycaemic range. Three separate tools provided data relating to quality of life. Although these couldn't be pooled for analysis, CSII may have little or no effect on quality of life, although this measure was low certainty due to serious inconsistency and serious imprecision.

The evidence analyses and reference list are contained within the associated Review Manager 5 (RevMan 5) file, which can be found [here](#).

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		MDI	CSII		
Severe hypoglycaemia End of treatment (range 4 - 12 months) 9 Critical	Relative risk 0.97 (CI 95% 0.48 - 1.94) Based on data from 740 patients in 7 studies. ¹ (Randomized controlled)			Low Due to very serious imprecision ²	As only 34 people experienced severe hypoglycaemia, it was not possible to determine whether CSII made a difference (16/ 368 CSII; 18/372 MDI)
Diabetic ketoacidosis End of treatment (range 6 - 24 months) 9 Critical	Relative risk 1.21 (CI 95% 0.49 - 3) Based on data from 901 patients in 11 studies. ³ (Randomized controlled)			Low Due to very serious imprecision ⁴	As only 20 people experienced diabetic ketoacidosis, it was not possible to determine whether CSII made a difference (11/449 CSII; 9/452 MDI)
Serious adverse events End of treatment (12 months) 6 Important	Relative risk 1.16 (CI 95% 0.46 - 2.93) Based on data from 293 patients in 1 studies. ⁵ (Randomized controlled)			Low Due to very serious imprecision ⁶	As only 17 people experienced serious adverse events, it was not possible to determine whether CSII made a difference (9/ 144 CSII; 8/149 MDI)
Nocturnal	Relative risk 4.71 (CI 95% 0.24 - 90.69)			Low Due to very	As only two people experienced nocturnal

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary						
		MDI	CSII								
<p>hypoglycaemia End of treatment (4 months)</p> <p>6 Important</p>	<p>Based on data from 31 patients in 1 studies. ⁷ (Randomized controlled)</p>			<p>serious imprecision ⁸</p>	<p>hypoglycaemia, it was not possible to determine whether CSII made a difference (2/16 CSII; 0/15 MDI)</p>						
<p>Retinopathy End of treatment</p> <p>6 Important</p>						<p>No studies were found that looked at retinopathy</p>					
<p>Mortality (all cause) End of treatment</p> <p>6 Important</p>							<p>No studies were found that looked at mortality</p>				
<p>Hospitalisation End of treatment (range 4 - 12 months)</p> <p>6 Important</p>	<p>Relative risk 1.43 (CI 95% 0.91 - 2.25) Based on data from 324 patients in 2 studies. ⁹ (Randomized controlled)</p>	<p>159 per 1000</p>	<p>227 per 1000</p>	<p>Low Due to very serious imprecision ¹⁰</p>	<p>CSII may increase hospitalisation slightly</p>						
<p>Nephropathy End of treatment</p> <p>6 Important</p>		<p>Difference: 68 more per 1000 (CI 95% 14 fewer - 199 more)</p>				<p>No studies were found that looked at nephropathy</p>					
<p>Neuropathy End of treatment</p> <p>6 Important</p>							<p>No studies were found that looked at neuropathy</p>				
<p>HbA1c (% absolute) End of treatment (range 4 - 24 months)</p> <p>9 Critical</p>		<p>Based on data from: 671 patients in 13 studies. ¹¹ (Randomized controlled)</p>	<p>8.1 (Median)</p>					<p>7.81</p>	<p>High</p>	<p>CSII slightly improves HbA1c</p>	
			<p>Difference: MD 0.29 lower (CI 95% 0.41 lower - 0.16 lower)</p>								

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		MDI	CSII		
<p>Weight End of treatment (range 7 - 24 months)</p> <p>6 Important</p>	<p>Measured by: BMI change</p> <p>Based on data from: 135 patients in 3 studies.¹² (Randomized controlled)</p>	<p>0.3 (Median)</p> <p>Difference: MD 0.15 lower (CI 95% 0.26 lower - 0.03 lower)</p>	<p>0.15</p>	<p>Moderate Due to serious imprecision¹³</p>	<p>CSII may have little or no impact on weight</p>
<p>Time within range End of treatment</p> <p>6 Important</p>					<p>No studies were found that looked at time within range</p>
<p>Quality of life End of treatment</p> <p>6 Important</p>	<p>Based on data from 231 patients in 3 studies.</p>	<p>Three separate tools were used in one study each (KINDL-DM, PedsQL and DQOLY). Data could not be combined due to incompatibilities between scales. The PedsQL (n=38) and DQOLY (n=28) scores were mean 6.5 and 6.3 points higher in CSII patients, favouring MDI (lower score represents higher QoL); The KIND-DM (n=165) score was mean 5.9 points higher in CSII patients, favouring CSII (higher score represents higher QoL).</p>		<p>Low Due to serious inconsistency, Due to serious imprecision¹⁴</p>	<p>CSII may have little or no impact on quality of life</p>
<p>Severe hypoglycaemia (IRR) End of treatment</p> <p>6 Important</p>	<p>Based on data from 332 patients in 5 studies.</p>	<p>Five studies presented severe hypoglycaemia rate data (Nuboer 2008, Cohen 2003, Bergenstal 2010, Skogsberg 2008, Weintrob 2004); however only Weintrob 2004 provided 95% CI values and thus they cannot be combined. Three of the five studies demonstrated a reduced rate of severe hypoglycaemia in patients treated with CSII (Nuboer 2008: CSII 0.29, MDI 1.1 (n=38); Cohen 2003: CSII 0.13, MDI 0.61 (n=24); Weintrob 2004: CSII 0.13, MDI 0.39 (n=44) per patient year) whereas the other two demonstrated an increased rate in CSII patients (Bergenstal 2010: CSII 8.98, MDI 4.95 (n=159); Skogsberg 2008: CSII 19, MDI 17 (n=67) per 100 patient years).</p>		<p>Low Due to serious inconsistency, Due to serious imprecision¹⁵</p>	<p>There were too few who experienced severe hypoglycaemia, to determine whether CSII made a difference</p>

1. Systematic review [19] with included studies: Fox 2005, Doyle 2004, Bergenstal 2010, DiMeglio 2004, Blair 2018, Wilson 2005, Mueller Godeffroy 2018. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: No serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** due to too few events. **Publication bias: No serious.**
3. Systematic review [19] with included studies: Weintrob 2004, Bergenstal 2010, Fox 2005, Skogsberg 2008, Wilson

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- 2005, DiMeglio 2004, Nuboer 2008, Cohen 2003, Blair 2018, Thrailkill 2011, Mueller Godeffroy 2018. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of bias: No serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** due to very few events. **Publication bias: No serious.**
5. Systematic review [19] with included studies: Blair 2018. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of bias: No serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Only data from one study, Low number of patients. **Publication bias: No serious.**
7. Systematic review [19] with included studies: Doyle 2004. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Risk of bias: No serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Low number of patients, Only data from one study. **Publication bias: No serious.**
9. Systematic review [19] with included studies: Doyle 2004, Blair 2018. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Risk of bias: No serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Low number of patients, low number of events. **Publication bias: No serious.**
11. Systematic review [19] with included studies: Weintrob 2004, Skogsberg 2008, Opiari Arrigan 2007, Wilson 2005, Doyle 2004, Thrailkill 2011, Nuboer 2008, Fox 2005, Mueller Godeffroy 2018, Cohen 2003, Davies 1984, DiMeglio 2004, Bergenstal 2010. **Baseline/comparator:** Control arm of reference used for intervention.
12. Systematic review [19] with included studies: Skogsberg 2008, Weintrob 2004, Cohen 2003. **Baseline/comparator:** Control arm of reference used for intervention.
13. **Risk of bias: No serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Low number of patients. **Publication bias: No serious.**
14. **Risk of bias: No serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: Serious.** The direction of the effect is not consistent between the included studies. **Indirectness: No serious. Imprecision: Serious.** Data from only one study per QoL tool. **Publication bias: No serious.**
15. **Risk of bias: No serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: Serious.** The direction of the effect is not consistent between the included studies. **Indirectness: No serious. Imprecision: Serious.** due to lack of 95% CI data, resulting in the inability to pool data. **Publication bias: No serious.**

Conditional recommendation

We suggest CSII rather than MDI treatment for adults with type 1 diabetes based on the preference of the person with diabetes.

The decision on whether to use CSII or MDI is highly dependent on personal preference. Health professional discussions with people with type 1 diabetes should include the use and potential benefits of CSII and considerations of personal preferences, the value of the different options, available resources, and the importance of high level engagement with the technology and health services.

CSII treatment consists of continuous subcutaneous insulin infusion pump devices with various options including: manual CSII systems either without or with CGM (including low glucose suspend and predictive low glucose suspend) or AutoCSII, also known as 'hybrid closed loop' systems. MDI consists of daily administration of basal insulin in combination with prandial rapid-acting insulin injection treatment. CSII improves glycaemia (lowers HbA1c) which could ultimately lead to decreased microvascular complications. However, there is little current evidence examining the impact of CSII on microvascular complications, diabetic ketoacidosis, and mortality. There is also little current evidence to demonstrate CSII decreases severe hypoglycaemia and weight gain or improves quality of life. Variation in preference for CSII is anticipated in light of the higher treatment intensity required and costs associated with its use to manage type 1 diabetes.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

For critical outcomes, there were observed benefits in HbA1c levels with CSII. Incidence of severe hypoglycaemia was similar between groups and there were too few diabetic ketoacidosis events to determine whether insulin pumps made a difference with regards to this outcome. No studies were found that reported results for time in range.

For the majority of important outcomes, there were either too few events to determine whether insulin pumps made a difference (all cause mortality, hospitalisation) or no studies reporting on the outcome (retinopathy, nephropathy, neuropathy). For the remaining important outcomes, there was little or no difference in net benefit using insulin pumps compared to MDI (serious adverse events, weight, hypoglycaemia fear survey [total and worry subscales] and quality of life using DQoL, SF-36 general health and SF-36/SF-12 physical subscales).

The evidence analyses and reference list are contained within the associated Review Manager 5 (RevMan 5) file, which can be found [here](#).

Certainty of the Evidence

Low

The certainty of evidence for critical outcomes ranged from high (HbA1c), to moderate (severe hypoglycaemia, due to serious imprecision) and low (diabetic ketoacidosis, due to very serious imprecision).

Important outcomes with a moderate certainty of evidence consisted of quality of life (measured by the SF-36 general health and hypoglycaemia fear survey total score), weight (kg), and serious adverse effects. All other important outcomes were either low certainty due to serious inconsistency and serious imprecision due to inconsistent direction of effect (quality of life (measured by the DQoL questionnaire, SF-36/SF-12 physical subscale or hypoglycaemia fear survey worry subscale). Certainty was considered very low for all cause mortality and hospitalisation due to very serious imprecision based on low number of study participants and/or low event rate.

Preference and values

Substantial variability is expected or uncertain

Many individuals would consider the use of insulin pumps over injections; however there is a steep learning curve associated with commencing pump therapy, some individuals may have an aversion to wearing the pump due to limitations in mobility, and some individuals prefer the use of injections as it can provide greater autonomy over insulin administration.

Resources

Important issues, or potential issues not investigated

There is a significant expense associated with the use of insulin pumps. The purchase price for individual pumps range from

\$6,994 to \$8,574, with consumables purchased through the NDSS costing the consumer an average of over ~\$340 per year above the 91% Government subsidy provided through NDSS. The annual cost of insulin varies based on requirements. Individuals who administer insulin via MDI are required to pay the costs of insulin only, as syringes and pen needles are provided at no cost through the NDSS.

From a government funding perspective, review of international economic evaluations found that CSII with SMBG may be cost-effective in comparison to MDI particularly among those who gain significant improvement in blood glucose management and quality of life.

In more detail, cost-effectiveness analyses aim to assess the differences between costs of therapy balanced against the differences in health outcomes. Incremental cost-effectiveness ratios are used in cost-effectiveness analyses and represent the difference in costs of treatments and outcomes between two interventions divided by the difference in quality adjusted life years over a predefined period of time, or time horizon. While the acquisition costs of CSII therapy are significantly larger than SMBG for example, economic evaluations assess whether fewer complications of diabetes due to glycaemic improvement from CSII might offset these costs. We found nine economic evaluations that compared CSII and SMBG therapy against MDI and SMBG. Five studies concluded CSII was cost-effective while the other four did not.

Apart from differences across funding systems, it appeared that key determinants of cost-effectiveness comprised the treatment effect of CSII on HbA1c and rates of hypoglycaemia, as well as the utility score associated with fear of hypoglycaemia. In summary, it appeared that CSII may be cost-effective particularly among those who gain significant improvement in glycaemic blood glucose management and quality of life. However, economic evaluations are needed in the Australian healthcare system. [21]

Equity

Important issues, or potential issues not investigated

Coverage for insulin pumps is a minimum requirement for the most comprehensive level of cover (the Gold tier) under the Australian Governments new private health insurance hospital tier arrangements. Adults with private health insurance that includes cover for insulin pumps, may have the full cost of their insulin pump covered by their insurance provider. However, adults without private health insurance or who do not have the appropriate level of private health insurance cover may be unable to afford the cost of an insulin pump.

Individuals in remote and regional areas may also have insufficient access to training and support for optimal implementation of insulin pump therapy

Acceptability

No important issues with the recommended alternative

The use of insulin pumps in adults with type 1 diabetes demonstrates improved reductions in HbA1c without any increase in detrimental effects compared to MDI. Insulin pumps have the potential to provide improved blood glucose management. No moral or ethical considerations were identified that are likely to render the use of insulin pumps as unacceptable.

Feasibility

Important issues, or potential issues not investigated

Potential barriers to the widespread adoption of insulin pumps include the initial cost price of the pump (for those individuals without private health insurance or appropriate cover), sensitivity to topical adhesives and the limitations (perceived or real) associated with wearing an insulin pump throughout the day. Factors that facilitate the widespread use of insulin pumps include the availability of devices (several insulin pumps have been approved for use in Australia by the TGA and are included on the Prostheses List), access to training and support in the use of pumps through diabetes educators, diabetes nurse practitioners, endocrinologists and general practitioners, and the increased control and autonomy many people are likely to experience when using insulin pumps compared to MDI.

Rationale

The GDG suggests using CSII rather than MDI treatment in adults as CSII decreases glycosylated haemoglobin and improving glycaemia is known to reduce microvascular complications. In formulating the recommendation to promote use of CSII over MDI, the working group placed emphasis on the favourable consistent findings of high certainty regarding the critical glycaemic outcome of HbA1c. It was our impression that improvements in glycaemic outcomes were clinically relevant (HbA1c reduction of 0.4% [4.4mmol/mol]) compared to control groups who already displayed better than average blood glucose management (mean HbA1c 7.6% [60mmol/mol]). There is moderate certainty for CSII resulting in little or no difference in severe

hypoglycaemia, and weight and some measures of quality of life. There was low certainty for the effect of CSII on diabetic ketoacidosis, hospitalisation and other measures of quality of life. The low certainty regarding its impact on key outcomes such as severe hypoglycaemia together with expected variability in personal preferences and values led to a conditional recommendation for CSII. Given the potential benefits of CSII it is anticipated many people with type 1 diabetes on MDI treatment will seek to adopt CSII. Variability in preference for CSII is anticipated given the greater commitment to treatment intensity required and increased costs associated with ongoing use of CSII. Equity of access to CSII in Australia remains an issue given the high retail cost of CSII devices which are predominantly funded through private health insurance in the presence of an appropriate level of cover, or publicly funded for a limited number of individuals under 18 years of age without access to private health insurance. The feasibility of CSII also needs to be considered given the initial increased training time required for both health professionals and people with type 1 diabetes, although this may ultimately be offset over time by decreased utilisation of health professional resources and improved quality of life due to more stable diabetes and potentially fewer vascular complications. The working group also acknowledged that economic evaluations should be performed to clarify the cost-effectiveness of CSII in the Australian context.

Clinical Question/ PICO

Population: Adults with type 1 diabetes
Intervention: Insulin pump (CSII)
Comparator: Multiple daily injections (MDI)

Summary

There was a clinically relevant reduction in HbA1C in adults using CSII compared to those using MDI. For the remaining critical outcomes, the incidence of diabetic ketoacidosis was too low, leading to very serious imprecision in the absolute effect estimate. Although eight studies reported the number of patients experiencing severe hypoglycaemic events, incidence rates were very similar, suggesting that CSII will probably have little effect on this outcome compared with MDI. Serious adverse events were similar between treatment arms.

Quality of life was measured using five different scales (including two measures of hypoglycaemia fear). All five measures were of either a low or moderate (hypoglycaemia fear survey, total score) certainty of evidence, and it was concluded that CSII probably has little or no impact on quality of life. CSII also has an uncertain impact on all-cause mortality and hospitalisation (very low certainty due to low event rate), and probably has little or no impact on weight (moderate certainty due to serious imprecision). No studies reported data for nephropathy, neuropathy, retinopathy or time within target glucose range.

The evidence analyses and reference list are contained within the associated Review Manager 5 (RevMan 5) file, which can be found [here](#).

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		MDI	CSII		
Diabetic ketoacidosis End of treatment (range 2 - 48 months) 9 Critical	Relative risk 2.67 (CI 95% 1.22 - 5.83) Based on data from 1,469 patients in 13 studies. ¹ (Randomized controlled)	8 per 1000 Difference: 13 more per 1000 (CI 95% 2 more - 39 more)	21 per 1000	Low Due to very serious imprecision ²	As only 29 people experienced diabetic ketoacidosis, it was not possible to determine whether CSII made a difference (23/734 CSII; 6/735 MDI)
Severe hypoglycaemia End of treatment	Relative risk 1.06 (CI 95% 0.7 - 1.61) Based on data from	87 per 1000	92 per 1000	Moderate Due to serious imprecision ⁴	CSII and MDI probably have around the same no. of patients

Outcome Timeframe	Study results and measurements	Absolute effect estimates MDI CSII		Certainty of the Evidence (Quality of evidence)	Plain text summary
(range 5.5 - 48 months) 9 Critical	968 patients in 8 studies. ³ (Randomized controlled)	Difference: 5 more per 1000 (CI 95% 26 fewer - 53 more)			experiencing severe hypoglycaemia
Serious Adverse Events End of treatment (range 3.5 - 24 months) 6 Important	Relative risk 0.97 (CI 95% 0.67 - 1.41) Based on data from 834 patients in 4 studies. ⁵ (Randomized controlled)	138 per 1000 Difference: 4 fewer per 1000 (CI 95% 46 fewer - 57 more)	134 per 1000	Moderate Due to serious imprecision ⁶	CSII and MDI probably have the same no. of patients experiencing serious adverse events
All cause mortality End of treatment (12 months) 6 Important	Relative risk 1.02 (CI 95% 0.11 - 9.64) Based on data from 386 patients in 2 studies. ⁷ (Randomized controlled)			Very Low Due to very serious imprecision ⁸	As only two people died it was not possible to determine whether CSII made a difference (1/194 CSII; 1/192 MDI)
Hospitalisation End of treatment (6.5 months) 6 Important	Based on data from 71 patients in 1 studies. ⁹ (Randomized controlled)			Very Low Due to very serious imprecision ¹⁰	As only one person required hospitalisation, it was not possible to determine whether insulin pump (CSII) made a difference (1/ 36 CSII; 0/35 MDI)
Retinopathy End of treatment 6 Important					No studies were found that looked at retinopathy
Nephropathy End of treatment 6 Important					No studies were found that looked at nephropathy
Neuropathy End of treatment 6 Important					No studies were found that looked at neuropathy

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		MDI	CSII		
<p>HbA1c (%) End of treatment (range 3.5 - 48 months)</p> <p>9 Critical</p>	<p>Based on data from: 1,798 patients in 18 studies. ¹¹ (Randomized controlled)</p>	<p>7.67 (Median)</p>	<p>7.23</p>	<p>High ¹²</p>	<p>CSII improves HbA1c</p>
<p>Time within target glucose range</p> <p>9 Critical</p>					<p>No studies were found that looked at time within target glucose range</p>
<p>Quality of Life End of treatment (range 6-12 months)</p> <p>6 Important</p>	<p>Measured by: SF-36 General Health Items Scale: 0-100 High better</p> <p>Based on data from: 451 patients in 3 studies. ¹³ (Randomized controlled)</p>	<p>63.1 (Median)</p>	<p>67.7</p>	<p>Moderate Due to serious risk of bias ¹⁴</p>	<p>CSII probably has little or no impact on quality of life</p>
<p>Quality of Life End of treatment (range 5.5 - 6 months)</p> <p>6 Important</p>	<p>Measured by: Diabetes Quality of Life Questionnaire Scale: 0-100 High better</p> <p>Based on data from: 52 patients in 2 studies. ¹⁵ (Randomized controlled)</p>	<p>81.39 (Median)</p>	<p>77.87</p>	<p>Low Due to very serious imprecision ¹⁶</p>	<p>CSII may have little or no impact on quality of life</p>
<p>Quality of Life End of treatment (range 12 - 24 months)</p> <p>6 Important</p>	<p>Measured by: Change in SF-36 and SF-12 Physical subscales High better</p> <p>Based on data from: 568 patients in 2 studies. ¹⁷ (Randomized controlled)</p>			<p>Low Due to serious inconsistency, Due to serious imprecision ¹⁸</p>	<p>CSII may have little or no impact on quality of life</p>
<p>Quality of Life End of treatment (range 5.5 - 12 months)</p> <p>6 Important</p>	<p>Measured by: Hypoglycaemia Fear Survey - total score High better</p> <p>Based on data from: 317 patients in 2 studies. ¹⁹ (Randomized</p>	<p>83 (Median)</p>	<p>82.57</p>	<p>Moderate Due to serious risk of bias ²⁰</p>	<p>CSII probably has little or no impact on quality of life</p>

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		MDI	CSII		
Quality of Life End of Treatment (range 6 - 24 months) 6 Important	controlled) Measured by: Hypoglycaemia Fear Survey; Worry subscore High better Based on data from: 300 patients in 2 studies. ²¹ (Randomized controlled)	20.3 (Median) Difference: MD 0.1 lower (CI 95% 0.57 lower - 0.38 higher)	20.2 Difference: MD 0.1 lower (CI 95% 0.57 lower - 0.38 higher)	Low Due to serious inconsistency, Due to serious imprecision ²²	CSII may have little or no impact on quality of life
Weight (kg) End of Treatment (range 5.5 - 48 months) 6 Important	Based on data from: 942 patients in 10 studies. ²³ (Randomized controlled)	76.05 kg (Median)	75.61 kg Difference: MD 0.44 lower (CI 95% 1.93 lower - 1.05 higher)	Moderate Due to serious inconsistency ²⁴	CSII probably has little or no impact on weight

1. Systematic review [20] with included studies: DeVries 2002, Rosenlund 2015, Lee 2007, Lecavalier 1987, Peyrot 2009, Brinchmann Hansen 1985, Hoogma 2006, Beck 2017, Bergenstal 2010, Thomas 2007, Saurbrey 1988, Schmitz 1989, ReposeStudyGroup 2017. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: No serious.** Inadequate/lack of blinding of participants and personnel, however this should not have introduced bias.. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** due to few events. **Publication bias: No serious.**
3. Systematic review [20] with included studies: DeVries 2002, ReposeStudyGroup 2017, Rosenlund 2015, Bergenstal 2010, Bolli 2009, Hanaire Broutin 2000, Brinchmann Hansen 1985, Hermanides 2011. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of bias: No serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Wide confidence intervals. **Publication bias: No serious.**
5. Systematic review [20] with included studies: Bruttomesso 2008, Hoogma 2006, ReposeStudyGroup 2017, Lee 2007. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of bias: No serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Wide confidence intervals. **Publication bias: No serious.**
7. Systematic review [20] with included studies: Rosenlund 2015, Bergenstal 2010. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Risk of bias: No serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Only data from one study, Low number of patients. **Publication bias: No serious.**
9. Systematic review [20] with included studies: Beck 2017. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Risk of bias: No serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Low number of patients, Only data from one study. **Publication bias: No serious.**
11. Systematic review [20] with included studies: Bruttomesso 2008, Brinchmann Hansen 1985, Beck 2017, Chiasson

- 1984, Hanaire Broutin 2000, Peyrot 2009, ReposeStudyGroup 2017, Bolli 2009, Lepore 2003, Hermanides 2011, Hoogma 2006, DeVries 2002, Hermanides 2011, Schmitz 1989, Thomas 2007, Bergenstal 2010, Lee 2007, Ruiz De Adana 2016, Rosenlund 2015. **Baseline/comparator:** Control arm of reference used for intervention.
12. **Risk of bias: No serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
13. Systematic review [20] with included studies: Hermanides 2011, Bergenstal 2010, DeVries 2002. **Baseline/comparator:** Control arm of reference used for intervention.
14. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
15. Systematic review [20] with included studies: Thomas 2007, Ruiz De Adana 2016. **Baseline/comparator:** Control arm of reference used for intervention.
16. **Risk of bias: No serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Low number of patients. **Publication bias: No serious.**
17. Systematic review [20] with included studies: ReposeStudyGroup 2017, Bergenstal 2010. **Baseline/comparator:** Control arm of reference used for intervention.
18. **Risk of bias: No serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: Serious.** The direction of the effect is not consistent between the included studies. **Indirectness: No serious. Imprecision: Serious.** Low number of patients. **Publication bias: No serious.**
19. Systematic review [20] with included studies: Bergenstal 2010, Thomas 2007. **Baseline/comparator:** Control arm of reference used for intervention.
20. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
21. Systematic review [20] with included studies: ReposeStudyGroup 2017, Hermanides 2011. **Baseline/comparator:** Control arm of reference used for intervention.
22. **Risk of bias: No serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: Serious.** The direction of the effect is not consistent between the included studies. **Indirectness: No serious. Imprecision: Serious.** Low number of patients. **Publication bias: No serious.**
23. Systematic review [20] with included studies: Rosenlund 2015, Schmitz 1989, Brinchmann Hansen 1985, Beck 2017, Thomas 2007, Peyrot 2009, Hanaire Broutin 2000, Bergenstal 2010, DeVries 2002, ReposeStudyGroup 2017. **Baseline/comparator:** Control arm of reference used for intervention.
24. **Risk of bias: No serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: Serious.** The direction of the effect is not consistent between the included studies and all of the 95%CI do not overlap. The magnitude of statistical heterogeneity was high, with $I^2:67\%$. **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**

3.3 - Automated continuous subcutaneous insulin infusion (AutoCSII)

Automated continuous subcutaneous insulin infusion (AutoCSII) treatment compared to non-automated CSII treatment in children, adolescents and adults with type 1 diabetes.

AutoCSII device systems have the potential to increase time in euglycaemia and reduce many of the complications associated with type 1 diabetes. Of interest is whether AutoCSII improves outcomes in individuals with type 1 diabetes compared to non-automated CSII systems and if other considerations such as preference, resource requirements and equity affect the implementation and adoption of AutoCSII device technologies.

Conditional recommendation

We suggest automated continuous subcutaneous insulin infusion (AutoCSII) treatment rather than non-automated CSII treatment to optimise glycaemia for children, adolescents and adults with type 1 diabetes.

The decision on whether to use AutoCSII or non-automated CSII is highly dependent on personal preference. Health professional discussions with people with type 1 diabetes (and carers) should include the use and potential benefits of AutoCSII and considerations of personal preferences, the value of the different options, available resources, and the importance of high level engagement with the technology and health services. Automated continuous subcutaneous insulin infusions (AutoCSII), also known as 'hybrid closed loop insulin pumps', are insulin delivery systems consisting of three linked components functioning continuously: a subcutaneous glucose sensor device, a subcutaneous insulin infusion pump device and a computerised algorithm which determines insulin delivery based on ambient glucose. AutoCSII enables basal and some correctional insulin to be automatically adjusted based on CGM measures, while insulin bolus doses for meals require initiation by the user. These AutoCSII technologies are relatively new, with the first randomised clinical trial being reported in 2014, and are distinct to previous non-automated CSII systems which function solely using manual insulin pump settings with or without suspension of basal insulin in response to actual or predicted low glucose (also known as 'Predictive) Low Glucose Suspend' systems). Use of AutoCSII results in further improvements to glycaemia compared to non-automated CSII. It was not possible to evaluate the age groups separately as most trials incorporated people across both paediatric and adult age ranges. The generalisability of benefits from AutoCSII to children under six years old is limited given the lack of evidence in this young group. It is anticipated that future AutoCSII systems may use more refined automated insulin delivery algorithms (including automatic bolus delivery in addition to automatic basal delivery) and potentially dual hormone treatment (e.g. insulin and glucagon).

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

Compared to non-automated CSII systems, adults and children using AutoCSII technologies experienced a clinically important improvement in blood glucose percentage time in range (3.9-10.0mmol/L [70-180 mg/dL]) for all three time ranges analysed (day only, night only and day + night), and may have had improvement in the number of nights in which blood glucose fell below 3.5 mmol/L for 20 minutes or longer. Slight benefits were observed with regards to reduction in HbA1c levels and percentage of time spent in hypoglycaemia (<3.5/3.9 mmol/L) at night. There was probably little or no difference was observed with regards to weight (kg), and there may have been little or no difference in Body Mass Index (BMI) and the hypoglycaemia fear survey score. It was uncertain whether there was an effect on severe hypoglycaemia, diabetic ketoacidosis, serious adverse events, hospitalisation or quality of life (as measured by the PedsQL questionnaire). No studies were identified that reported on nephropathy, neuropathy or retinopathy.

The evidence analyses and reference list are contained within the associated Review Manager 5 (RevMan 5) file, which can be found [here](#).

Certainty of the Evidence

Low

There was a high certainty of evidence for the critical outcomes of HbA1c and time in range (for day only, night only and day + night). Certainty was low for the remaining critical outcomes due to very serious imprecision (diabetic ketoacidosis) and serious imprecision and serious inconsistency (severe hypoglycaemia) based on low event rates for these outcomes.

The majority of non-critical outcomes were based on low certainty of evidence due to very serious imprecision as a result of a low event rate among subjects (serious adverse events, hospitalisation) and having been based on a single study (number of nights with >20 minutes spent in hypoglycaemia <3.5 mmol/L, BMI, Quality of Life) or too few study participants (hypoglycaemia fear survey); the exceptions were percentage of time spent in hypoglycaemia (<3.5/3.9 mmol/L) at night (high certainty) and weight (kg; moderate certainty due to serious imprecision). No studies were identified that reported on nephropathy, neuropathy and retinopathy.

Preference and values

Substantial variability is expected or uncertain

Qualitative evidence^[25] suggests that not all individuals with type 1 diabetes will prefer the use of AutoCSII technologies over traditional non-automated CSII systems. Factors that contribute to this variability include the desire for greater autonomy offered by non-automated CSII systems compared with AutoCSII systems, and the technological difficulties of using AutoCSII systems, including high frequency of alarms, forced exit from auto-mode, calibration requirements and

premature sensor failure.

Resources

Important issues, or potential issues not investigated

AutoCSII device systems require additional training and support for both the individual with diabetes and the carers, as well as the health professionals responsible for supporting them in order for AutoCSII to be used effectively compared with non-automated CSII systems. Geographically remote individuals may experience limited access to these resources.

From a government funding perspective, review of international economic evaluations found that AutoCSII treatment may be cost-effective in comparison to CSII with capillary glucose monitoring. A subsequent Australian cost-effectiveness analysis by a member of the Medical Device Technology Guideline Development Group reported that AutoCSII systems were cost effective compared to the MDI with capillary glucose monitoring.

In more detail, cost-effectiveness analyses aim to assess the differences between costs of therapy balanced against the differences in health outcomes. Incremental cost-effectiveness ratios are used in cost-effectiveness analyses and represent the difference in costs of treatments and outcomes between two interventions divided by the difference in quality adjusted life years over a predefined period of time, or time horizon. Economic evaluations assess whether fewer complications of diabetes due to glycaemic improvement from AutoCSII might offset their acquisition costs. We found one cost-effectiveness analysis that concluded AutoCSII was cost-effective compared to CSII therapy in Sweden. In the Australian setting, an additional cost-effectiveness analysis was published subsequent to our review. Study authors reported that AutoCSII was cost-effective compared to the least expensive comparator of MDI with capillary glucose testing over a lifetime with the key clinical determinant of cost-effectiveness comprising the rate of severe hypoglycaemia[21].

Equity

No important issues with the recommended alternative

Equity of access to AutoCSII technologies should not differ significantly from non-automated CSII systems, in that both delivery modes involve the same insulin pump and continuous glucose monitor (CGM) devices; however, individuals from rural or remote regions may experience greater difficulty accessing the training and support required when commencing use of AutoCSII technologies. In Australia, the Insulin Pump Program provides access to insulin pumps for a proportion of eligible people under 18 years of age. In addition, the CGM Initiative provides broad access to people with type 1 diabetes under 21 years of age and some adults with concessional status or of Aboriginal or Torres Strait Islander origin. People outside of these funding criteria require additional private health insurance to access insulin pumps, and must self-fund CGM[20].

Acceptability

Important issues, or potential issues not investigated

No randomised controlled trials were identified that assess the comparative safety or effectiveness of AutoCSII treatment in children under the age of 6 years. Randomised controlled trials suggest little or no net benefit is likely to be realised in individuals who have high baseline time in range and HbA1c levels (e.g. 6.5-7.0%) through the additional use of AutoCSII treatment. However, among those individuals with appropriate glycaemia through intensive self-management, it is unclear if automation will result in glycaemic or quality of life improvements. It is also unclear if the improvements reported within included trials will be reflected in clinical conditions that do not match that of the trials.

Feasibility

Important issues, or potential issues not investigated

AutoCSII medical device technologies have only recently been approved for use in Australia. Use of this technology has had insufficient time to expand and access may be limited for individuals in remote geographical regions. The requirement of additional training and education for optimal implementation of AutoCSII treatment, for the person living with diabetes and also for health professionals, may also reduce their potential for widespread use.

Rationale

In formulating the recommendation supporting the use of AutoCSII treatment, the working group placed emphasis on the favourable and consistent findings of high certainty regarding critical glycaemic outcomes of HbA1c, time in range (both day and night) and nocturnal hypoglycaemia. It was our impression that improvements in glycaemic outcomes were clinically relevant and modest compared to control groups who already displayed better than average blood glucose management (mean HbA1c 7.7% [61mmol/mol]). There is moderate certainty for AutoCSII having little or no effect on weight. There was low certainty for the

effect of AutoCSII on severe hypoglycaemia, diabetic ketoacidosis, hospitalisation, quality of life and fear of hypoglycaemia. The low certainty evidence regarding its impact on key outcomes such as severe hypoglycemia together with expected variability in individual preferences and values led to a conditional recommendation for AutoCSII. Given the potential benefits of AutoCSII it is anticipated that many people with type 1 diabetes already on CSII treatment will seek to adopt AutoCSII. Variability in preference for AutoCSII is anticipated given the greater commitment to treatment intensity required and increased costs associated with ongoing use of CGM, a necessary component of AutoCSII. The feasibility of treatment with AutoCSII also needs to be considered given the initial increased training time required for both health professionals and people with type 1 diabetes, although this may ultimately be offset over time through improved quality of life due to more stable glycaemia and potentially fewer vascular complications. The working group also acknowledged that economic evaluations should be performed to clarify the cost-effectiveness of AutoCSII in the Australian context.

Clinical Question/ PICO

Population: Children, adolescents and adults with type 1 diabetes
Intervention: AutoCSII
Comparator: CSII

Summary

It was not possible to determine whether AutoCSII reduced the incidence of severe hypoglycaemia or diabetic ketoacidosis. Although reported in twelve studies each, the number of events was too low, which resulted in low certainty of evidence. A slight reduction in glycosylated haemoglobin (HbA1c) was observed. The small size of the reduction may be due to the short duration of many included studies.

In addition to HbA1c, severe hypoglycaemia and diabetic ketoacidosis, time in range was considered a critical outcome for studies in which AutoCSII data were reported. For all reported measures of time in range (day, night and day+night), clinically relevant improvements were observed in patients using AutoCSII compared to non-automated CSII systems. A clinically relevant reduction in time spent below 3.5/3.9 mmol/L was also observed in AutoCSII patients. The certainty for each of these critical outcomes were considered high.

For the important outcomes, there were too few severe adverse events and hospitalisations to determine whether AutoCSII reduces the incidence of these outcomes. There is probably little or no difference in weight, and there may be little or no difference with regards to BMI, quality of life and hypoglycaemia fear survey scores. There may be a slight reduction in the number of nights in which patients spent 20 minutes or more in hypoglycaemia (<3.5 mmol/L), however certainty of evidence was low for this outcome. No studies reported incidence of nephropathy, neuropathy or retinopathy.

The evidence analyses and reference list are contained within the associated Review Manager 5 (RevMan 5) file, which can be found [here](#).

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		CSII	AutoCSII		
Severe hypoglycaemia End of treatment (range 1 - 6 months) 9 Critical	Relative risk 1.35 (CI 95% 0.52 - 3.53) Based on data from 871 patients in 12 studies. ¹ (Randomized controlled)			Low Due to very serious imprecision ²	As only 15 people experienced severe hypoglycaemia it was not possible to determine whether AutoCSII made a difference (9/467 AutoCSII; 6/404 CSII)
Diabetic	Relative risk 1.99			Low	As only two people

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		CSII	AutoCSII		
<p>ketoacidosis End of treatment (range 1 - 6 months)</p> <p>9 Critical</p>	<p>(CI 95% 0.21 - 18.86) Based on data from 866 patients in 12 studies. ³ (Randomized controlled)</p>			<p>Due to very serious imprecision ⁴</p>	<p>experienced diabetic ketoacidosis it was not possible to determine whether AutoCSII made a difference (2/ 414 AutoCSII; 0/352 CSII)</p>
<p>Serious adverse events End of treatment (range 1 - 6 months)</p> <p>6 Important</p>	<p>Relative risk 3.53 (CI 95% 0.19 - 67.2) Based on data from 562 patients in 9 studies. ⁵ (Randomized controlled)</p>			<p>Low Due to very serious imprecision ⁶</p>	<p>As only three people experienced serious adverse events it was not possible to determine whether AutoCSII made a difference (3/309 AutoCSII; 0/253 CSII)</p>
<p>Hospitalisation End of treatment (3 months)</p> <p>6 Important</p>	<p>Relative risk 0.5 (CI 95% 0.05 - 5.25) Based on data from 116 patients in 1 studies. ⁷ (Randomized controlled)</p>			<p>Low Due to very serious imprecision ⁸</p>	<p>As only three were hospitalised, it was not possible to determine whether AutoCSII made a difference (1/ 58 AutoCSII; 2/58 CSII)</p>
<p>Nephropathy End of treatment</p> <p>6 Important</p>					<p>No studies were found that looked at nephropathy</p>
<p>Neuropathy End of treatment</p> <p>6 Important</p>					<p>No studies were found that looked at neuropathy</p>
<p>Retinopathy End of treatment</p> <p>6 Important</p>					<p>No studies were found that looked at retinopathy</p>
<p>HbA1c % End of treatment (range 1 - 6 months)</p> <p>9 Critical</p>	<p>Based on data from: 606 patients in 5 studies. ⁹ (Randomized controlled)</p>	<p>7.7 (Median)</p>	<p>7.48</p>	<p>High ¹⁰</p>	<p>AutoCSII improves HbA1c slightly</p>
		<p>Difference: MD 0.22 lower (CI 95% 0.33 lower - 0.11 lower)</p>			

Outcome Timeframe	Study results and measurements	Absolute effect estimates CSII AutoCSII		Certainty of the Evidence (Quality of evidence)	Plain text summary
<p>% Time in range, day+night End of treatment (range 1 - 6 months)</p> <p>9 Critical</p>	<p>Based on data from: 729 patients in 9 studies. ¹¹ (Randomized controlled)</p>	<p>59 (Median)</p>	<p>69.43</p>	<p>High ¹²</p>	<p>AutoCSII improves time in range, day+night</p>
<p>% Time in range, day End of treatment (range 1 - 6 months)</p> <p>9 Critical</p>	<p>Based on data from: 426 patients in 6 studies. ¹³ (Randomized controlled)</p>	<p>56 (Median)</p>	<p>65.72</p>	<p>High ¹⁴</p>	<p>AutoCSII improves time in range during the day</p>
<p>% Time in range, night End of treatment (range 1 - 6 months)</p> <p>9 Critical</p>	<p>Based on data from: 547 patients in 8 studies. ¹⁵ (Randomized controlled)</p>	<p>59.5 (Median)</p>	<p>74.16</p>	<p>High ¹⁶</p>	<p>AutoCSII improves time in range during the night</p>
<p>% Time below 3.5/3.9 mmol/L or 60/63 mg/dL, night End of treatment (range 1 - 6 months)</p> <p>9 Critical</p>	<p>Based on data from: 367 patients in 5 studies. ¹⁷ (Randomized controlled)</p>	<p>2.2 (Median)</p>	<p>1.44</p>	<p>High ¹⁸</p>	<p>AutoCSII decreases time spend below 3.5/3.9 mmol/l or 60/63 mg/dl at night</p>
<p>Nights with glucose <3.5 mmol/L (min 20 min) End of treatment (1 month)</p> <p>6 Important</p>	<p>Measured by: Number of nights</p> <p>Based on data from: 48 patients in 1 studies. ¹⁹ (Randomized controlled)</p>	<p>58 (Mean)</p>	<p>36 (Mean)</p>	<p>Low Due to very serious imprecision ²⁰</p>	<p>AutoCSII may decrease number of nights with glucose <3.5 mmol/l (min 20 min)</p>

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		CSII	AutoCSII		
BMI End of treatment (6 months) 6 Important	Based on data from: 166 patients in 1 studies. ²¹ (Randomized controlled)	26.1 (Mean)	26.2 (Mean)	Low Due to very serious imprecision ²²	AutoCSII may have little or no difference on bmi
Hypoglycaemia Fear Survey, total score End of treatment (range 1.5 - 2 months) 6 Important	Based on data from: 84 patients in 2 studies. ²³ (Randomized controlled)	Difference: SMD 0.36 higher (CI 95% 0.41 lower - 1.13 higher)		Low Due to very serious imprecision ²⁴	AutoCSII may have little or no difference on hypoglycaemia fear survey, total score
Weight (kg) End of treatment (range 3 - 6 months) 6 Important	Based on data from: 252 patients in 2 studies. ²⁵ (Randomized controlled)	76 (Median)	76.86	Moderate Due to serious imprecision ²⁶	AutoCSII probably has little or no impact on weight
Quality of life End of treatment (3 months) 6 Important	Measured by: PedsQL, total score Based on data from: 22 patients in 1 studies. ²⁷ (Randomized controlled)	77 (Mean)	76 (Mean)	Low Due to very serious imprecision ²⁸	We are uncertain whether AutoCSII improves or worsens quality of life

1. Systematic review [24] with included studies: Thabit 2015, Brown 2019, Bally 2017, Thabit 2015, Thabit 2014, Kropff 2015, Hovorka 2014, Spaic 2017, Nimri 2014, Tauschmann 2016, [26], Tauschmann 2018. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: No serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Low number of events. **Publication bias: No serious.**
3. Systematic review [24] with included studies: Thabit 2015, Thabit 2014, Tauschmann 2018, Spaic 2017, Nimri 2014, Kropff 2015, Brown 2019, [26], Bally 2017. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of bias: No serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** low number of events. **Publication bias: No serious.**
5. Systematic review [24] with included studies: Tauschmann 2016, Thabit 2015, Kropff 2015, Thabit 2014, Brown 2019, Spaic 2017, [26], Hovorka 2014, Bally 2017. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of bias: No serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** low number of events, Low number of

patients. **Publication bias: No serious.**

7. Systematic review [24] with included studies: Thabit 2015, Thabit 2015. **Baseline/comparator:** Control arm of reference used for intervention.

8. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Only data from one study, Low number of patients, low number of events. **Publication bias: No serious.**

9. Systematic review [24] with included studies: Thabit 2014, Tauschmann 2018, Brown 2019, Kropff 2015, Thabit 2015, Thabit 2015. **Baseline/comparator:** Control arm of reference used for intervention.

10. **Risk of bias: No serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**

11. Systematic review [24] with included studies: Bally 2017, Thabit 2015, Brown 2019, Tauschmann 2018, Thabit 2015, Tauschmann 2016, Thabit 2014, Kropff 2015. **Baseline/comparator:** Control arm of reference used for intervention.

12. **Risk of bias: No serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**

13. Systematic review [24] with included studies: [26], Brown 2019, Thabit 2015, Tauschmann 2016, Tauschmann 2018, Bally 2017. **Baseline/comparator:** Control arm of reference used for intervention.

14. **Risk of bias: No serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**

15. Systematic review [24] with included studies: Hovorka 2014, Brown 2019, Tauschmann 2018, Spaic 2017, Bally 2017, Nimri 2014, [26], Kropff 2015. **Baseline/comparator:** Control arm of reference used for intervention.

16. **Risk of bias: No serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**

17. Systematic review [24] with included studies: Hovorka 2014, Tauschmann 2016, [26], Brown 2019, Tauschmann 2018, Bally 2017. **Baseline/comparator:** Control arm of reference used for intervention.

18. **Risk of bias: No serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**

19. Systematic review [24] with included studies: Thabit 2014. **Baseline/comparator:** Control arm of reference used for intervention.

20. **Risk of bias: No serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Low number of patients, Only data from one study. **Publication bias: No serious.**

21. Systematic review [24] with included studies: Brown 2019. **Baseline/comparator:** Control arm of reference used for intervention.

22. **Risk of bias: No serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Low number of patients, Only data from one study. **Publication bias: No serious.**

23. Systematic review [24] with included studies: Barnard 2014, Kropff 2015. **Baseline/comparator:** Control arm of reference used for intervention.

24. **Risk of bias: No serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** due to only two studies, Low number of patients. **Publication bias: No serious.**

25. Systematic review [24] with included studies: Brown 2019, Tauschmann 2018. **Baseline/comparator:** Control arm of reference used for intervention.

26. **Risk of bias: No serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Wide confidence intervals. **Publication bias: No serious.**

27. Systematic review [24] with included studies: Tauschmann 2018. **Baseline/comparator:** Control arm of reference used for intervention.

28. **Risk of bias: No serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Low number of patients, Only data from one study. **Publication bias: No serious.**

4 - Medications for blood glucose management in adults with type 2 diabetes

Glucose lowering medications are used in conjunction with lifestyle modifications in the management of type 2 diabetes. While the following guidelines focus on the pharmaceutical management of type 2 diabetes, it is important to emphasise that lifestyle interventions including dietary education, increased physical activity and weight management strategies are typically the initial approach for people with type 2 diabetes and remain important when glucose-lowering medication is required.

There are currently several classes of medications that can be prescribed for the management of type 2 diabetes. These classes work via different mechanisms to lower blood glucose levels and improve overall glycaemic management. Reducing hyperglycaemia has been associated with a lower risk of long-term diabetes-related complications, in particular the microvascular complications of retinopathy, neuropathy and nephropathy. The medications and glycaemic targets used to manage type 2 diabetes need to be individualised for each person based on age, comorbidities and risk of adverse events (e.g. severe hypoglycaemia). The recommendations in this section are focused on a selection of the available medications. For the question regarding monotherapy and the preferred drug to add to monotherapy in adults with type 2 diabetes, the following medications were selected and compared: metformin, sulphonylurea, thiazolidinedione, DPP-4 inhibitor, SGLT-2 inhibitor and GLP-1 receptor agonist. For the question of which medication to add-on to any existing medication(s) in adults with type 2 diabetes, the following were selected and compared: GLP-1 receptor agonist, SGLT-2 inhibitor, sulphonylurea or DPP-4 inhibitor. Insulin will be considered in future updates of the guideline.

Newer classes of glucose lowering medications have also demonstrated benefits in reducing the risk of atherosclerotic cardiovascular disease, kidney disease, heart failure and mortality. The challenge that practitioners face in managing type 2 diabetes is knowing when, and in what order, to initiate and up-titrate treatment regimens. Below, we briefly describe the mechanism of action and adverse effect profile of the glucose lowering medication classes.

Metformin decreases hepatic gluconeogenesis and increases insulin sensitivity in tissues, such as skeletal muscle and adipose tissue. The most common adverse event is gastrointestinal upset, with the more serious adverse event of lactic acidosis being relatively rare. Metformin should not be used in individuals with severe renal or hepatic impairment.

Sulphonylureas stimulate increased insulin secretion from pancreatic islet beta cells. The most common adverse events are hypoglycaemia and modest weight gain. As this class acts directly on insulin production, it cannot be used in individuals with a loss of pancreatic islet beta cells, such as in type 1 diabetes, and in pancreatic deficiency, as in people who have undergone pancreatectomy.

Sodium-glucose co-transporter 2 (SGLT-2) inhibitors prevent the reabsorption of glucose from glomerular filtrate by blocking the action of the sodium-glucose co-transporter 2 proteins located in the kidney's proximal convoluted tubules. They result in reduced threshold for glycosuria, which improves overall glycaemic management, however this mechanism contributes to the most common adverse events of genitourinary infections, polyuria and volume depletion. Euglycaemic ketoacidosis and Fournier gangrene are serious, yet rare adverse events associated with SGLT-2 inhibitor use. In addition to improving glycaemic management, SGLT-2 inhibitors also reduce blood pressure and body weight.

Glucagon-like peptide-1 (GLP-1) receptor agonists activate the receptor of GLP-1, an incretin that stimulates glucose-dependent insulin secretion. GLP-1 activation also decreases pancreatic islet glucagon secretion, and delays gastric emptying leading to earlier satiety, resulting in weight loss. The most common adverse event following GLP-1 use is gastrointestinal upset. There is also a rare association with pancreatitis and a theoretical increased risk of medullary thyroid cancer. Therefore, this class of medication should be avoided in patients with either of these conditions.

Dipeptidyl peptidase-4 (DPP-4) inhibitors block the activity of dipeptidyl peptidase-4, the enzyme responsible for the breakdown of incretins such as GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), thereby prolonging their activity, as described above. Infrequent adverse events include nasopharyngitis and headache. There is also a possible rare association with pancreatitis in patients with a history of this condition.

Less frequently used glucose lowering medication classes include thiazolidinediones (TZD) which activate peroxisome proliferator-activated receptor gamma (PPAR γ) leading to increased insulin sensitivity, and acarbose, an alpha-glucosidase inhibitor that reduces carbohydrate absorption from the small intestine. Adverse events related to TZD use include weight gain, cardiac failure and osteoporotic fractures. Adverse events related to acarbose include gastrointestinal upset.

Recommendations within this guideline are based on the results of network meta-analyses of a broad range of medications. For these analyses, members of each class of medication were pooled and no subgroups of any class were considered separately. For example, data relating to the use of SGLT-2 inhibitors were derived from all trials in which an SGLT-2 inhibitor was included (whether dapagliflozin, empagliflozin or canagliflozin). While there may be class differences between agents with respect to some outcomes, this has not been considered in the network meta-analysis underpinning these guidelines. The best choice of agent within each class of glucose lowering medications should be based on factors such as cost, individual patient preference and the available within class clinical trial evidence. The trials included in the network meta analysis were not fully representative of the type 2 population, particularly of the frail elderly and persons with diabetes and complex comorbidities. Clinical judgement should be exercised when applying these guidelines to these underrepresented subgroups. The reference list for included studies can be found [here](#).

4.1 - Optimal initial medication

Conditional recommendation

We suggest the use of metformin as first-line monotherapy in adults with type 2 diabetes.

This recommendation is based on the relative low cost and ease of administration of metformin. There is no convincing evidence of clinically significant differences in treatment effectiveness, serious adverse outcomes or all-cause mortality between the different classes when used as monotherapy. For individuals, there may be other factors that require consideration such as adverse effect potential, weight management strategy, frailty or comorbidities, which may contribute to clinician decision making when prescribing an alternative initial medication.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

There were no clinically relevant differences in any outcome when comparing SGLT-2 inhibitors, GLP-1 receptor agonists, DPP-4 inhibitors, sulphonylureas or thiazolidinediones as monotherapies to metformin alone.

No studies reported results with regards to the major adverse cardiovascular events (MACE) composite outcome.

Certainty of the Evidence

Low

There was no evidence of serious heterogeneity or inconsistency in the network with the exception of HbA1c, in which severe inconsistency was observed. For all outcomes, there was no evidence of incoherence in direct and indirect estimates or evidence of serious small-study effects.

Certainty of the evidence for all outcomes was low or moderate due to serious or very serious imprecision (based on wide confidence intervals and/or estimates not overlapping), with the exception of HbA1c, in which certainty was low due to very serious inconsistency within the network.

Preference and values

Substantial variability is expected or uncertain

The World Health Organization (WHO) conducted a narrative review exploring preferences and values relating to treatment decisions in people living with type 2 diabetes[29]. When deciding between treatment regimens, important considerations included route of administration, avoiding or reducing the number of injections, side effects (in particular nausea), glycaemic management and avoiding hypoglycaemia, supporting the person's weight management strategy, reducing the risk of cardiovascular disease and reducing the frequency of blood glucose monitoring.

Resources

No important issues with the recommended alternative

Metformin, sulphonylureas and acarbose are currently the only medications approved for use as initial therapy for people with type 2 diabetes under the Australian Government's Pharmaceutical Benefits Scheme (PBS). Acarbose is infrequently used and is not within the scope of these clinical guidelines. Prescription of metformin for initial therapy results in minimal out of pocket expense from the individual's perspective.

The cost of medications to manage blood glucose differ depending on whether the individual is covered under the Australian Government's Pharmaceutical Benefits Scheme (PBS) or not.

Although prices can vary, as of 22 July 2020 the PBS listed Dispensed Price for Maximum Quantity (DPMQ) of metformin was \$14.71. DPMQs for other medications ranged from \$12.99 to \$23.81 for sulphonylureas, \$19.78 to \$27.55 for the thiazolidinedione pioglitazone, \$52.78 to \$60.54 for DPP-4 inhibitors, \$56.85 to \$60.04 for SGLT-2 inhibitors and \$66.93 to \$132.83 for GLP-1 receptor agonists. SGLT-2 inhibitors, GLP-1 receptor agonists and DPP-4 inhibitors and thiazolidinediones are not reimbursed by PBS when used as monotherapy for diabetes. The maximum price payable by the consumer covered under the PBS allowing brand substitution was \$22.01 for metformin and \$24.94 for sulphonylureas,

whereas all listed medications incur a maximum cost of \$6.60 for concession card holders.

Equity

No important issues with the recommended alternative

No equity issues have been identified regarding the availability of metformin for blood glucose management in people with type 2 diabetes in Australia.

Acceptability

No important issues with the recommended alternative

In the absence of contraindications, metformin is likely to be acceptable to all people with type 2 diabetes who require medication for blood glucose management.

Feasibility

No important issues with the recommended alternative

Metformin is approved for use in Australia and is listed on the PBS. No feasibility issues have been identified.

Rationale

In formulating this recommendation, the Guideline Development Group placed emphasis on the low to moderate certainty of evidence. No medication class demonstrated statistically or clinically significant superiority when used as monotherapy. Metformin and sulphonylureas are both relatively inexpensive options for blood glucose management in people with type 2 diabetes. Presently, they are the only two therapeutics of interest approved as first-line therapy under the Pharmaceutical Benefits Scheme (PBS). Acarbose is also approved as initial therapy, however it is infrequently used due to frequent gastrointestinal side-effects. When comparing treatments, the cost to the individual and community was considered to be a significant factor. Metformin, as the cheapest medication class, was therefore recommended as first-line monotherapy.

In the absence of any high certainty evidence to prescribe one class over the other as first-line monotherapy, there is also no evidence to avoid a different glucose lowering agent as first-line monotherapy instead of metformin, if an individual has comorbidities where treatment with another medication would be beneficial or preferred.

Clinical Question/ PICO

- Population:** Adults with type 2 diabetes
- Intervention:** Therapeutics for blood glucose control
- Comparator:** Metformin or standard care

Summary

For details of the evidence used to develop the recommendations, please see the summaries and associated tables [here](#).

Outcome Timeframe	Study results and measurements	Absolute effect estimates Metformin or standard care Therapeutics		Certainty of the Evidence (Quality of evidence)	Plain text summary
Please see Summary					

4.2 - Optimal add-on medication

Recommended

We recommend the addition of an SGLT-2 inhibitor to other glucose lowering medication(s) in adults with type 2 diabetes who also have cardiovascular disease, multiple cardiovascular risk factors and/or kidney disease.

This recommendation applies to adults with type 2 diabetes who have cardiovascular disease, multiple cardiovascular risk factors and/or kidney disease and are unable to achieve optimal blood glucose levels using their current baseline therapy. The evidence base for this recommendation includes studies with people with kidney disease, who had an estimated glomerular filtration rate as low as 30 mL per minute per 1.73 m² of body-surface area. We define multiple cardiovascular risk factors as men 55 years of age or older or women 60 years of age or older with type 2 diabetes who have one or more additional traditional risk factors, including hypertension, dyslipidaemia, or smoking.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

When added to other glucose lowering medications, SGLT-2 inhibitors resulted in reductions in all-cause mortality, heart failure, kidney failure, serious adverse events, events within the 4-item MACE composite outcome and mean HbA1c amongst people with type 2 diabetes and HbA1c ≥53 mmol/mol (7%). Some trials also found benefit amongst people with type 2 diabetes and HbA1c <53 mmol/mol (7%). The effect on all-cause mortality, heart failure and kidney failure were most clinically significant amongst people with established cardiovascular disease, multiple cardiovascular risk factors and/or kidney disease. No clinically relevant differences were observed when adding SGLT-2 inhibitors to other glucose lowering medications with regard to severe hypoglycaemia or events within the 3-item MACE composite outcome.

Certainty of the Evidence

Moderate

With regard to the addition of SGLT-2 inhibitors to other glucose lowering medication, there was no evidence of serious heterogeneity or inconsistency in the network - or incoherence in the direct and indirect estimates across all outcomes.

The certainty of evidence for SGLT-2 inhibitors added to other glucose lowering medication was high across all outcomes, with the exception of MACE, in which certainty was downgraded to moderate due to suspicion of selective outcome reporting.

Preference and values

No substantial variability expected

The World Health Organization (WHO) conducted a narrative review exploring preferences and values relating to treatment decisions in people living with type 2 diabetes[21]. When deciding between treatment regimens, important considerations included route of administration, avoiding or reducing the number of injections, side effects (in particular nausea), glycaemic management and avoiding hypoglycaemia, supporting the person's weight management strategy, reducing the risk of cardiovascular disease and reducing the frequency of blood glucose monitoring.

Resources

Important issues, or potential issues not investigated

SGLT-2 inhibitors are provided to the majority of people with HbA1c $\geq 7\%$ as add-on medication at reduced cost as part of the Australian Government's Pharmaceutical Benefits Scheme (PBS). As a result, there is little difference in out of pocket expense from the individual's perspective.

Although prices can vary, as of 22 July 2020, the PBS listed DPMQ of SGLT-2 inhibitors ranged from \$56.85 to \$60.04. For all SGLT-2 inhibitors, the maximum price payable by the person covered under the PBS was \$41, whereas all listed medications incur a maximum cost of \$6.60 for concession card holders. For those people who are not covered under the PBS, prices can vary considerably. This may impact the decision regarding which medication to use.

Equity

No important issues with the recommended alternative

No equity issues have been identified regarding the availability of SGLT-2 inhibitors for the management of type 2 diabetes. Equity may be affected in people who are not eligible for subsidies through the PBS.

Acceptability

No important issues with the recommended alternative

In people with type 2 diabetes who have cardiovascular disease, multiple cardiovascular risk factors and/or kidney disease, SGLT-2 inhibitors are likely to be acceptable for the management of blood glucose.

Feasibility

No important issues with the recommended alternative

SGLT-2 inhibitors are approved for use in Australia and listed on the PBS. The Therapeutic Goods Administration currently only approves the use of SGLT-2 inhibitors in patients with an eGFR of 45 or higher.

Rationale

In formulating this recommendation, the Guideline Development Group placed emphasis on the high certainty of evidence across all outcomes, with the exception of 3-item MACE outcomes in people with moderate to very high cardiovascular risk. SGLT-2 inhibitors when used as add-on therapy, demonstrated clinically relevant improvements in all-cause mortality, heart failure, kidney failure, serious adverse events, HbA1c and 4-item MACE outcomes over GLP-1 receptor agonists, DDP-4 inhibitors and sulphonylureas. There were also no significant accessibility or acceptability issues associated with SGLT-2 inhibitor use, making them an appropriate addition to baseline therapy for people living with type 2 diabetes.

Clinical Question/ PICO

- Population:** Adults with type 2 diabetes
- Intervention:** Therapeutics for blood glucose control
- Comparator:** Metformin or standard care

Summary

For details of the evidence used to develop the recommendations, please see the summaries and associated tables [here](#).

Outcome Timeframe	Study results and measurements	Absolute effect estimates Metformin or standard care Therapeutics		Certainty of the Evidence (Quality of evidence)	Plain text summary
Please see Summary					

Recommended

We recommend the addition of a GLP-1 receptor agonist to other glucose lowering medication(s) in adults with type 2 diabetes who have cardiovascular disease, multiple cardiovascular risk factors and/or kidney disease, and are unable to be prescribed an SGLT-2 inhibitor due to either intolerance or contraindication.

This recommendation applies to adults with type 2 diabetes who have cardiovascular disease, multiple cardiovascular risk factors and/or kidney disease, are unable to achieve optimal blood glucose levels on their current baseline therapy, and are unable to be prescribed an SGLT-2 inhibitor due to either intolerance or contraindication. The evidence base for this recommendations include studies on people with kidney disease who had an estimated glomerular filtration rate as low as 30 mL per minute per 1.73 m² of body-surface area. We define multiple cardiovascular risk factors as men 55 years of age or older or women 60 years of age or older with type 2 diabetes who have one or more additional traditional risk factors, including hypertension, dyslipidaemia, or smoking.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

When added to other glucose lowering medications, GLP-1 receptor agonists resulted in clinically relevant reductions in mean HbA1c, all-cause mortality, kidney failure and events within the 3-item MACE composite outcome amongst people with type 2 diabetes and an HbA1c ≥ 53 mmol/mol (7%). Some trials also found benefit amongst people with type 2 diabetes and HbA1c < 53 mmol/mol (7%).

When added to other glucose lowering medications, the use of GLP-1 receptor agonists resulted in greater reductions in mean HbA1c compared with SGLT-2 inhibitors, however the use of SGLT-2 inhibitors resulted in clinically relevant improvements with regards to heart failure and all-cause mortality compared with GLP-1 receptor agonists.

Certainty of the Evidence

High

With regard to the addition of a GLP-1 receptor agonist to other glucose lowering medications, there was no evidence of serious heterogeneity or inconsistency in the network, incoherence in the direct and indirect estimates or evidence of serious small-study effects for all outcomes.

The certainty of evidence for GLP-1 receptor agonists was high for all outcomes. As a result, we are confident that the true effect reflects the data used to formulate the recommendation.

Preference and values

Substantial variability is expected or uncertain

The World Health Organization (WHO) conducted a narrative review exploring preferences and values relating to treatment

decisions in people living with type 2 diabetes[21]. When deciding between treatment regimens, important considerations included route of administration, avoiding or reducing the number of injections, side effects (in particular nausea), glycaemic management and avoiding hypoglycaemia, supporting the person's weight management strategy, reducing the risk of cardiovascular disease and reducing the frequency of blood glucose monitoring.

As GLP-1 receptor agonists require administration via subcutaneous injection, some people may prefer the use of other medications over GLP-1 receptor agonists.

Resources

Important issues, or potential issues not investigated

GLP-1 receptor agonists are available as add-on medication at reduced cost as part of the Australian Government's Pharmaceutical Benefits Scheme (PBS) to people with an HbA1c ≥ 53 mmol/mol (7%). However, there are some PBS restrictions on the use of GLP-1 receptor agonists when added to other blood glucose lowering medication.

Although prices can vary, as of 22 July 2020 the PBS listed DPMQ of GLP-1 receptor agonists ranged from \$66.93 to \$132.83. For all GLP-1 receptor agonists, the maximum price payable by the person covered under the PBS was \$41, whereas all listed medications incur a maximum cost of \$6.60 for concession card holders. For those people who are not covered under the PBS, prices can vary considerably. This may impact the decision regarding which medication to use.

Equity

No important issues with the recommended alternative

No equity issues have been identified regarding the availability of GLP-1 inhibitors for the management of type 2 diabetes. Equity may be affected in individuals who are not eligible for subsidies through the PBS.

Acceptability

No important issues with the recommended alternative

In people living with type 2 diabetes who also have cardiovascular disease, multiple cardiovascular risk factors and/or kidney disease, GLP-1 receptor agonists are likely to be acceptable for the management of blood glucose.

Feasibility

Important issues, or potential issues not investigated

GLP-1 receptor agonists are approved for use in Australia and listed on the PBS, however there are some restrictions on the use of GLP-1 receptor agonists as add-on to other glucose lowering medication and this may affect feasibility.

Rationale

In formulating this recommendation, the Guideline Development Group placed emphasis on the high certainty of evidence with regard to all outcomes in people with cardiovascular disease and/or kidney disease. The use of GLP-1 receptor agonists resulted in clinically relevant reductions in mean HbA1c, all-cause mortality, kidney failure and events within the 3-item MACE composite outcome, compared to baseline therapy; however, the use of SGLT-2 inhibitors resulted in clinically relevant improvements with regard to heart failure and all-cause mortality compared to GLP-1 receptor agonists.

Clinical Question/ PICO

- Population:** Adults with type 2 diabetes
Intervention: Therapeutics for blood glucose control
Comparator: Metformin or standard care

Summary

For details of the evidence used to develop the recommendations, please see the summaries and associated tables [here](#).

Outcome Timeframe	Study results and measurements	Absolute effect estimates Metformin or standard care Therapeutics		Certainty of the Evidence (Quality of evidence)	Plain text summary
Please see Summary					

Conditional recommendation

We suggest the addition of a DPP-4 inhibitor to other glucose lowering medication(s) in adults with type 2 diabetes who have cardiovascular disease, multiple cardiovascular risk factors and/or kidney disease, and are unable to be prescribed an SGLT-2 inhibitor or a GLP-1 receptor agonist due to either intolerance or contraindication.

This recommendation applies to individuals with type 2 diabetes who have cardiovascular disease, multiple cardiovascular risk factors and/or kidney disease and are unable to achieve optimal blood glucose levels on their current baseline therapy. DPP-4 inhibitors were inferior to SGLT-2 inhibitors and GLP-1 receptor agonists with regard to cardiovascular and renal benefits and all-cause mortality. However, certain people are unable to tolerate SGLT-2 inhibitors due to side effects such as genitourinary infections, or GLP-1 receptor agonists due to gastrointestinal upset. Similarly, these medications may be contraindicated in people with kidney failure. In these instances, people with type 2 diabetes would benefit from the addition of a DPP-4 inhibitor as an alternative add on therapy.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

When added to other glucose lowering medication, DPP-4 inhibitors provided clinically significant reductions in HbA1c compared to baseline medications alone. There were no differences in all-cause mortality, heart failure, 3-item MACE, severe hypoglycaemia, kidney failure or serious adverse events. There were no data comparing DPP-4 inhibitors to other glucose lowering medications with regard to 4-item MACE.

When added to other glucose lowering medications, SGLT-2 inhibitors demonstrated superior safety for all-cause mortality, heart failure, 4-item MACE, kidney failure and serious adverse events, and GLP-1 demonstrated superior safety for all-cause mortality, 3-item MACE and kidney failure, and clinically significant improvements in HbA1c compared to DPP4 inhibitors.

When added to metformin only, DPP-4 inhibitors had better safety profiles compared with sulphonylureas (clinically relevant increase in severe hypoglycaemia) and thiazolidinediones (clinically relevant increase in heart failure).

Certainty of the Evidence

High

With regard to the addition of a DPP-4 inhibitor to other glucose lowering medications, there was no evidence of serious heterogeneity or inconsistency in the network, incoherence in the direct and indirect estimates or evidence of serious small-study effects for all outcomes.

The certainty of evidence for DPP-4 inhibitors was high for all outcomes. As a result, we are confident that the true effect reflects the data used to formulate the recommendation.

Preference and values

Substantial variability is expected or uncertain

The World Health Organization (WHO) conducted a narrative review exploring preferences and values relating to treatment decisions in people living with type 2 diabetes[21]. When deciding between treatment regimens, important considerations included route of administration, avoiding or reducing the number of injections, side effects (in particular nausea), glycaemic management and avoiding hypoglycaemia, supporting the person's weight management strategy, reducing risk of cardiovascular disease and reducing the frequency of blood glucose monitoring.

Resources

Important issues, or potential issues not investigated

DPP-4 inhibitors are provided as add-on medication to the majority of people with type 2 diabetes and an HbA1c ≥ 53 mmol/mol (7%) at reduced cost as part of the Australian Government's Pharmaceutical Benefits Scheme (PBS). As a result, there is little difference in out of pocket expense from the person's perspective.

Although prices can vary, as of 22 July 2020 the PBS listed Dispensed Price for Maximum Quantity (DPMQ) ranged from \$52.78 to \$60.54 for DPP-4 inhibitors. For DPP-4 inhibitors, the maximum price payable by the consumer covered under the PBS was \$41, whereas all listed medications incur a maximum cost of \$6.60 for concession card holders. For those people who are not covered under the PBS, prices can vary considerably. This may impact the decision regarding which medication to use.

Equity

No important issues with the recommended alternative

No equity issues have been identified regarding the availability of DPP-4 inhibitors for the management of type 2 diabetes. Equity may be affected in individuals who are not eligible for subsidies through the PBS.

Acceptability

No important issues with the recommended alternative

In people for whom SGLT-2 inhibitors and GLP-1 receptor agonists are contraindicated or not tolerated and who also have cardiovascular disease, multiple cardiovascular risk factors and/or kidney disease, DPP-4 inhibitors are likely to be an acceptable alternative for the management of blood glucose.

Feasibility

No important issues with the recommended alternative

DPP-4 inhibitors are approved for use in Australia and are listed on the PBS. No feasibility issues have been identified.

Rationale

In formulating this recommendation, the Guideline Development Group placed emphasis on the low certainty of evidence of benefit of DPP-4 inhibitors when compared to SGLT-2 inhibitors and GLP-1 receptor agonists, as add-on therapy. DPP-4 inhibitors did demonstrate a clinically relevant reduction in HbA1c as add-on therapy, however they did not demonstrate any benefit for all cause-mortality, heart failure or kidney failure. While this class is not recommended as first choice of add-on therapy in adults with type 2 diabetes who have cardiovascular disease, multiple cardiovascular risk factors and/or kidney disease, it does have an important role in people who are unable to be prescribed either an SGLT-2 inhibitor or GLP-1 receptor agonist. There were also no significant accessibility or acceptability issues with DPP-4 inhibitors use, making them well tolerated amongst people living with type 2 diabetes.

Clinical Question/ PICO

Population:	Adults with type 2 diabetes
Intervention:	Therapeutics for blood glucose control
Comparator:	Metformin or standard care

Summary

For details of the evidence used to develop the recommendations, please see the summaries and associated tables [here](#).

Outcome Timeframe	Study results and measurements	Absolute effect estimates Metformin or standard care Therapeutics	Certainty of the Evidence (Quality of evidence)	Plain text summary
Please see Summary				

Conditional recommendation

We suggest the addition of either an SGLT-2 inhibitor, GLP-1 receptor agonist or a DPP-4 inhibitor to metformin in adults with type 2 diabetes who do not have cardiovascular disease, multiple cardiovascular risk factors or kidney disease, and are unable to achieve optimal blood glucose levels.

This recommendation applies to people without established cardiovascular disease, multiple cardiovascular risk factors or kidney disease. In these people, the addition of an SGLT-2 inhibitor, GLP-1 receptor agonist or DPP-4 inhibitor is equally efficacious in lowering blood glucose. The choice of agent should be based on personal preference, side effect tolerance and comorbidities.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

When added to metformin, SGLT-2 inhibitors, GLP-1 receptor agonists and DPP-4 inhibitors all resulted in clinically relevant reductions in mean HbA1c. In people without cardiovascular disease, multiple cardiovascular risk factors or kidney disease, no clinically relevant differences were observed between SGLT-2 inhibitors, GLP-1 receptor agonists or DPP-4 inhibitors with regard to all-cause mortality, heart failure, severe hypoglycaemia and serious adverse events. There were no data comparing SGLT-2 inhibitors, GLP-1 receptor agonists or DPP-4 inhibitors with regard to 3-item MACE, 4-item MACE or kidney failure. SGLT-2 inhibitors, GLP-1 receptor agonists and DPP-4 inhibitors had better safety profiles compared with sulphonylureas (clinically relevant increase in severe hypoglycaemia) and thiazolidinediones (clinically relevant increase in heart failure).

When added to any other glucose lowering medications, SGLT-2 inhibitors, GLP-1 receptor agonists and DPP-4 inhibitors all resulted in clinically relevant reductions in mean HbA1c. In people without multiple cardiovascular risk factors, no clinically relevant differences were observed between SGLT-2 inhibitors, GLP-1 receptor agonists or DPP-1 inhibitors with regard to all-cause mortality, heart failure, severe hypoglycaemia, serious adverse events, 3-item MACE or kidney failure. SGLT-2 inhibitors, GLP-1 receptor agonists and DPP-4 inhibitors had better safety profiles compared with sulphonylureas (clinically relevant increase in severe hypoglycaemia).

Certainty of the Evidence

Moderate

With regard to the addition of SGLT-2 inhibitors, GLP-1 receptor agonists or DPP-4 inhibitors to any other glucose lowering medications including metformin, there was no evidence of serious heterogeneity or inconsistency in the network, incoherence in the direct and indirect estimates or evidence of serious small-study effects for all outcomes.

When added to metformin, the certainty of evidence was high for SGLT-2 inhibitors, GLP-1 receptor agonists and DPP-4 inhibitors with regard to change in mean HbA1c and serious adverse events, and moderate for severe hypoglycaemia due to imprecision. Certainty was low for all-cause mortality, heart failure and kidney failure due to serious imprecision with the exception of GLP-1 receptor agonists and DPP-4 inhibitors, for which certainty was moderate due to imprecision.

When added to any other glucose lowering medications, the certainty of evidence was moderate for SGLT-2 inhibitors, GLP-1 receptor agonists and DPP-4 inhibitors for all outcomes due to indirectness. The exception was 3-item MACE in people treated with SGLT-2, in which certainty was low due to both indirectness and suspicion of selective outcome reporting.

Preference and values

Substantial variability is expected or uncertain

The World Health Organization (WHO) conducted a narrative review exploring preferences and values relating to treatment decisions in people living with type 2 diabetes[21]. When deciding between treatment regimens, important considerations included route of administration, avoiding or reducing the number of injections, side effects (in particular nausea), glycaemic management and avoiding hypoglycaemia, supporting the person's weight management strategy, reducing the risk of cardiovascular disease and reducing the frequency of blood glucose monitoring.

As GLP-1 receptor agonists require administration via subcutaneous injection, some people may prefer the use of other medications over GLP-1 receptor agonists.

Resources

Important issues, or potential issues not investigated

SGLT-2 inhibitors and DPP-4 inhibitors are provided as second-line therapy to the majority of people with type 2 diabetes and an HbA1c ≥ 53 mmol/mol (7%) at reduced cost as part of the Australian Government's Pharmaceutical Benefits Scheme (PBS). As a result, there is little difference in out of pocket expense from the person's perspective. There are some PBS restrictions on the use of GLP-1 receptor agonists when added to other blood glucose lowering medications.

Although prices can vary, as of 22 July 2020 the PBS listed DPMQ ranged from \$52.78 to \$60.54 for DPP-4 inhibitors, \$56.85 to \$60.04 for SGLT-2 inhibitors and \$66.93 to \$132.83 for GLP-1 receptor agonists. For all SGLT-2 inhibitors, GLP-1 receptor agonists and DPP-4 inhibitors, the maximum price payable by the person covered under the PBS was \$41, whereas all listed medications incur a maximum cost of \$6.60 for concession card holders. For those people who are not covered under the PBS, prices can vary considerably. This may impact the decision regarding which medication to use.

Equity

No important issues with the recommended alternative

No equity issues have been identified regarding the availability of SGLT-2 inhibitors and DPP-4 inhibitors for the management of type 2 diabetes. PBS restrictions on the use of GLP-1 receptor agonists when added to other blood glucose lowering medication may affect equity.

Acceptability

No important issues with the recommended alternative

In people living with type 2 diabetes who do not have multiple cardiovascular risk factors, SGLT-2 inhibitors, GLP-1 receptor agonists and DPP-4 inhibitors are all likely to be acceptable for the management of blood glucose. As GLP-1 receptor agonists require administration via subcutaneous injection, this may affect acceptability for some people.

Feasibility

No important issues with the recommended alternative

DPP-4 inhibitors, GLP-1 receptor agonists and SGLT-2 inhibitors are approved for use in Australia and are listed on the PBS. No feasibility issues have been identified regarding the use of DPP-4 inhibitors. There are some restrictions on the use of GLP-1 receptor agonists as add-on to other glucose lowering medications, and the Therapeutic Goods Administration

currently only approves the use of SGLT-2 inhibitors in people with an eGFR of 45 or higher which may affect feasibility.

Rationale

In formulating this recommendation, the Guideline Development Group placed emphasis on the high certainty of evidence with regard to mean change in HbA1c and serious adverse events for SGLT-2 inhibitors, GLP-1 receptor agonists and DPP-4 inhibitors. In people without established cardiovascular and/or kidney disease SGLT-2 inhibitors, GLP-1 receptor agonists and DPP-4 inhibitors are equally efficacious in these outcomes, and therefore none could be recommended over the others. All three classes are also equally accessible to Australian residents from a cost perspective. Individuals may prefer the use of an SGLT-2 inhibitor or DPP-4 inhibitor over a GLP-1 receptor agonist given its ease of administration as a tablet compared with a subcutaneous injection.

The working group also acknowledge the low certainty of evidence with regard to all-cause mortality, heart failure and kidney failure in people without established cardiovascular and/or kidney disease, which may potentially limit the interpretation of cardiovascular benefit in this lower risk population.

Clinical Question/ PICO

- Population:** Adults with type 2 diabetes
- Intervention:** Therapeutics for blood glucose control
- Comparator:** Metformin or standard care

Summary

For details of the evidence used to develop the recommendations, please see the summaries and associated tables [here](#).

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		Metformin or standard care	Therapeutics		
Please see Summary					

Conditional recommendation against

We suggest that a sulphonylurea should not be the first choice medication to add to metformin as dual therapy in adults with type 2 diabetes as it may increase the risk of severe hypoglycaemia.

Evidence To Decision

Benefits and harms

Important harms

When added to metformin as dual therapy, sulphonylureas resulted in a clinically relevant increase in severe hypoglycaemia and decrease in mean HbA1c compared to metformin alone. No clinically relevant differences were observed between sulphonylurea plus metformin compared with metformin alone with regard to all-cause mortality, heart failure or serious adverse events. There were no data comparing sulphonylurea plus metformin to metformin alone within the network meta-analysis for 3-item MACE, 4-item MACE or kidney failure.

Certainty of the Evidence

Moderate

For all outcomes, there was no evidence of serious heterogeneity or inconsistency in the network, incoherence in the direct and indirect estimates or evidence of serious small-study effects.

Certainty of evidence was high for mean change in HbA1c and serious adverse events, moderate for severe hypoglycaemia and all-cause mortality due to imprecision, and low for heart failure and kidney failure due to serious imprecision.

Preference and values

No substantial variability expected

The World Health Organization (WHO) conducted a narrative review exploring preferences and values relating to treatment decisions in people living with type 2 diabetes[29]. When deciding between treatment regimens, important considerations included route of administration, avoiding or reducing the number of injections, side effects (in particular nausea), glycaemic control and avoiding hypoglycaemia, supporting the person's weight management strategy, reducing the risk of cardiovascular disease and reducing the frequency of blood glucose monitoring.

In the absence of increased benefits of using sulphonylureas compared to metformin and other blood glucose lowering medications, and due to the increased risk of severe hypoglycaemic episodes, most people would prefer to avoid the use of sulphonylureas.

Resources

Important issues, or potential issues not investigated

All therapeutic alternatives to sulphonylureas are provided to the majority of people as add-on medication at reduced cost as part of the Australian Government's Pharmaceutical Benefits Scheme (PBS). As a result, there is little difference in out of pocket expense from the person's perspective.

Although prices can vary, as of 22 July 2020 the PBS listed Dispensed Price for Maximum Quantity (DPMQ) of sulphonylureas ranged from \$12.99 to \$23.81. DPMQs for other medications ranged from \$19.78 to \$27.55 for the thiazolidinedione pioglitazone, \$52.78 to \$60.54 for DPP-4 inhibitors, \$56.85 to \$60.04 for SGLT-2 inhibitors and \$66.93 to \$132.83 for GLP-1 receptor agonists. The maximum price payable by the consumer covered under the PBS allowing brand substitution was \$24.94 for sulphonylureas, \$33.23 for pioglitazone and \$41.00 for SGLT-2 inhibitors, GLP-1 receptor agonists and DPP-4 inhibitors, whereas all listed medications incur a maximum cost of \$6.60 for concession card holders. For those people who are not covered under the PBS, prices can vary considerably.

Equity

No important issues with the recommended alternative

No equity issues have been identified regarding the availability of alternative medications for blood glucose management in Australians with type 2 diabetes. Equity may be affected in individuals who are not eligible for subsidies through the PBS.

Acceptability

No important issues with the recommended alternative

There are no acceptability issues identified related to avoiding the administration of sulphonylureas to people with type 2 diabetes who are at increased risk of severe hypoglycaemia.

Feasibility

No important issues with the recommended alternative

No feasibility issues have been identified.

Rationale

In formulating this recommendation, the Guideline Development Group placed emphasis on the high certainty of evidence for serious adverse events and moderate certainty of evidence for severe hypoglycaemia. When added to metformin as dual therapy, sulphonylureas resulted in a statistically and clinically relevant increased risk of severe hypoglycaemia and serious adverse events, which outweighs their potential reduction in HbA1c. For this recommendation, sulphonylureas were analysed as a single class. While there are in class differences between sulphonylureas in their propensity to cause hypoglycaemia, all sulphonylurea agents are known to cause hypoglycaemia.

Clinical Question/ PICO

- Population:** Adults with type 2 diabetes
- Intervention:** Therapeutics for blood glucose control
- Comparator:** Metformin or standard care

Summary

For details of the evidence used to develop the recommendations, please see the summaries and associated tables [here](#).

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		Metfomin or standard care	Therapeutics		
Please see Summary					

Conditional recommendation against

We suggest that a thiazolidinedione should not be the first choice medication to add to metformin as dual therapy in adults with type 2 diabetes as it may increase the risk of hospitalisation for heart failure.

Evidence To Decision

Benefits and harms

Important harms

When added to metformin as dual therapy, thiazolidinediones resulted in a clinically relevant increase in hospitalisation due to heart failure and a decrease in mean HbA1c compared to metformin alone. No clinically relevant differences were observed between thiazolidinediones plus metformin compared with metformin alone with regard to all-cause mortality, severe hypoglycaemia or serious adverse events. There were no data comparing thiazolidinediones plus metformin to metformin alone within the network meta analysis with regard to severe hypoglycaemia, 3-item MACE, 4-item MACE or kidney failure.

Certainty of the Evidence

Moderate

For all outcomes, there was no evidence of serious heterogeneity or inconsistency in the network, incoherence in the direct and indirect estimates or evidence of serious small-study effects.

Certainty of evidence was high for mean change in HbA1c, and moderate for all-cause mortality, heart failure and serious adverse events due to imprecision.

Preference and values

No substantial variability expected

The World Health Organization (WHO) conducted a narrative review exploring preferences and values relating to treatment decisions in people living with type 2 diabetes[29]. When deciding between treatment regimens, important considerations included route of administration, avoiding or reducing the number of injections, side effects (in particular nausea), glycaemic control and avoiding hypoglycaemia, supporting the person's weight management strategy, reducing the risk of cardiovascular disease and reducing the frequency of blood glucose monitoring.

In the absence of increased benefits of using thiazolidinediones compared to metformin and other blood glucose lowering medications, and due to the increased risk of hospitalisation due to heart failure, most people would prefer to avoid the use of thiazolidinediones.

Resources

Important issues, or potential issues not investigated

All therapeutic alternatives to thiazolidinediones are provided to the majority of people with type 2 diabetes and an HbA1c ≥ 53 mmol/mol (7%) as add-on therapy at reduced cost as part of the Australian Government's Pharmaceutical Benefits Scheme (PBS). As a result, there is little difference in out of pocket expense from the person's perspective.

Although prices can vary, as of 22 July 2020 the PBS listed Dispensed Price for Maximum Quantity (DPMQ) of the thiazolidinedione pioglitazone ranged from \$19.78 to \$27.55. DPMQs for other medications ranged from \$12.99 to \$23.81 for sulphonylureas, \$52.78 to \$60.54 for DPP-4 inhibitors, \$56.85 to \$60.04 for SGLT-2 inhibitors and \$66.93 to \$132.83 for GLP-1 receptor agonists. The maximum price payable by the consumer covered under the PBS allowing brand substitution was \$24.94 for sulphonylureas, \$33.23 for pioglitazone and \$41.00 for SGLT-2 inhibitors, GLP-1 receptor agonists and DPP-4 inhibitors, whereas all listed medications incur a maximum cost of \$6.60 for concession card holders. For those people who are not covered under the PBS, prices can vary considerably.

Equity

No important issues with the recommended alternative

No equity issues have been identified regarding the availability of alternative medications for blood glucose management in people with type 2 diabetes. Equity may be affected in individuals who are not eligible for subsidies through the PBS.

Acceptability

No important issues with the recommended alternative

There are no acceptability issues identified related to avoiding the administration of thiazolidinediones to people with type 2 diabetes who are at risk of hospitalisation due to heart failure.

Feasibility

No important issues with the recommended alternative

No feasibility issues have been identified.

Rationale

In formulating this recommendation, the Guideline Development Group placed emphasis on the moderate certainty of evidence of harm in people with type 2 diabetes due to an increase risk of hospitalisation for heart failure. When added to metformin as dual therapy, thiazolidinediones resulted in a statistically and clinically relevant increase in hospitalisations due to heart failure, which outweighs their potential reduction in HbA1c. For this recommendation, thiazolidinediones were analysed as a single class and no subgroup analyses of specific thiazolidinediones was performed.

Clinical Question/ PICO

Population: Adults with type 2 diabetes
Intervention: Therapeutics for blood glucose control
Comparator: Metformin or standard care

Summary

For details of the evidence used to develop the recommendations, please see the summaries and associated tables [here](#).

Outcome Timeframe	Study results and measurements	Absolute effect estimates Metformin or standard care Therapeutics	Certainty of the Evidence (Quality of evidence)	Plain text summary
Please see Summary				

5 - Methods and processes

These Clinical Guidelines were developed according to the procedures and requirements for meeting the 2011 NHMRC standard for clinical practice guidelines. The recommendations are based on clinically relevant questions taking into consideration the population to whom the recommendation should apply, the specific interventions and outcomes addressed. Based on those focused questions, a search for studies answering those questions was performed and the resulting citations were screened, the studies that ended up being included were assessed and synthesised.

A recommendation was then formed based on the following key information: benefit and harms, certainty of the evidence, preferences and values of people living with diabetes, resource considerations, health equity impact, acceptability and feasibility. More details on the different steps are given in the following sections.

This is a living guideline. As such, each recommendation contained herein is a living recommendation that will be updated in accordance with the methods of living evidence [31]. By necessity, each of the recommendations is based on a living systematic review.

For living recommendations the evidence will be surveyed monthly and any new studies will be added to the evidence base, allowing us to continually update the living systematic reviews used to inform the recommendations. When the evidence is considered strong enough to possibly warrant a change in one or more recommendations, the panel will re-convene, review the key information and update the recommendation if deemed appropriate.

Instances which may warrant a change to a recommendation include but are not limited to:

- the identification of a new study or studies that shift the benefit to harm ratio, potentially leading to a change in the direction of the recommendation;
- the identification of a new study or studies that shift the certainty of the evidence, potentially leading to a conditional recommendation becoming a strong, non-conditional recommendation or vice versa; or
- a marked drop in the price of an intervention.

5.1 - Steering Committee - membership and terms of reference

The Living Evidence for Diabetes Steering Committee is responsible for overseeing the processes of organisation and budgeting for the development of clinical recommendations within a series of demonstration projects, including this clinical guideline. Membership is comprised of individuals from each of the collaborating organisations and other experts, as listed below.

Members of the Living Evidence for Diabetes Steering Committee as at 26th July, 2020

Name	Position
Sophia Zoungas (Chair)	Head, School of Public Health and Preventative Medicine, Monash University
Brett Fenton	President, Australian Diabetes Educators Association
Britta Tendal	Research Fellow, Cochrane Australia
Christopher Lee	Manager, Aboriginal and Torres Strait Islander Engagement, Diabetes Australia
Elizabeth Davis	Vice President, Australasian Paediatric Endocrine Group
Esko Wiltshire	President, Australasian Paediatric Endocrin Group; Associate Professor of Paediatrics, University of Otago, Wellington, NZ
Gary Deed	Chair, Diabetes Specific Interest Network, Royal Australian College of General Practitioners
Giuliana Murfet	Past President, Australian Diabetes Educators Association
Glynis Ross	President, Australian Diabetes Society
Greg Johnson	CEO, Diabetes Australia

Jerry Wales	Treasurer, Australasian Paediatric Endocrine Group
Renza Scibilia	Manager, Type 1 Diabetes & Consumer Voice, Diabetes Australia
Sof Andrikopoulos	CEO, Australian Diabetes Society
Ex-Officio members	
Heath White	Senior Research Officer, Cochrane Australia
Jacinta McDonald	Chronic Diseases Policy Section, Australian Government Department of Health
Jonathan Shaw	Head, Clinical Diabetes and Epidemiology, Baker Heart and Diabetes Institute
Sally Green	Co-Director, Cochrane Australia
Tanya Millard	Project Coordinator, Australian Diabetes Society

A copy of the Steering Committee Terms of Reference can be found [here](#).

5.2 - Guideline Development Groups - membership and terms of reference

Individual Guideline Development Groups were established for each of the topics within the demonstration project. The full list of members for each group is presented below. The criteria for selection of Guideline Development Group members is provided in section 2.2 of the Administration Report.

Members of the Medical Device Technology Guideline Development Group *as at 22 July 2020*

Name	Position	Organisation
A/Prof Spiros Furlanos (Chair)	Endocrinologist; Director Department of Diabetes and Endocrinology	Royal Melbourne Hospital; University of Melbourne
Alexander Meredith	Paralegal (*consumer representative)	Bupa, Melbourne
Dr Anthony Pease	Endocrinologist; PhD candidate	School of Public Health and Preventive Medicine, Monash University
Brett Fenton	Nurse Unit Manager	Central Coast Local Health District
Dr Carmel Smart	Senior Paediatric Diabetes Dietician	John Hunter Children's Hospital
David Burren	Software eEngineer (*consumer representative)	Baker Heart and Diabetes Institute
A/Prof Glynis Ross	Endocrinologist	Royal Prince Alfred Hospital; Bankstown-Lidcombe Hospital; private practice
A/Prof Jane Holmes-Walker	Endocrinologist	Westmead Hospital
Dr Mark Forbes	Senior Staff Specialist, General Medicine and Endocrinology	Gold Coast Hospital and Health Service

Dr Mary Abraham	Paediatric Endocrinologist	Perth Children's Hospital
A/Prof (Peter) Shane Hamblin	Endocrinologist	Western Health, Melbourne

Members of the therapeutics Guideline Development Group as at 22 July 2020

Name	Position	Organisation
Prof Chris Nolan (Co-chair)	Endocrinologist	ANU Medical School
A/Prof (Peter) Shane Hamblin (Co-chair)	Endocrinologist	Western Health
Cheryl Steele	Credentialed Diabetes Educator; Clinical Nurse Consultant (*consumer representative)	Western Health
Dr Gary Deed	General Practitioner, Chair, Diabetes Specific Interest Group	Mediwell; Royal Australian College of General Practitioners
Giuliana Murfet	Nurse Practitioner; PhD candidate	Tasmanian Health Service
Prof Jonathan Shaw	Consultant Physician; Deputy Director, Clinical and Population Health; Head, Clinical Diabetes and Epidemiology.	Baker Heart and Diabetes Institute; La Trobe University; Monash University
A/Prof Marg McGill	Assistant Director, Diabetes Centre	Royal Prince Alfred Hospital
Michelle Robbins	Nurse Practitioner; Credentialed Diabetes Educator	Northern Health
Nicole Frayne	Pharmacist; Diabetes Educator	St John of God Hospital
Dr Susan Gray	Pharmacist	Pharmaceutical Society of Australia; University of Queensland
Prof Tim Davis	Professor of Medicine; Endocrinologist	University of Western Australia; Fremantle Hospital
Prof N Wah Cheung	Endocrinologist	Westmead Hospital; University of Sydney

A copy of the Guideline Development Group Terms of Reference can be found [here](#).

5.3 - Conflicts of interest

The NHMRC Act 1992 defines a conflict of interest as '*any direct or indirect pecuniary or non-pecuniary interest*'. A conflict of interest does not preclude an individual's involvement within a particular group; however, to avoid the introduction of bias into decision making processes and for transparency, all potential conflicts of interest must be declared and managed appropriately.

For further information on conflicts of interest, please visit the NHMRC 'Guidelines for Guidelines' website at <https://www.nhmrc.gov.au/guidelinesforguidelines/plan/identifying-and-managing-conflicts-interest>.

The Diabetes for Living Evidence conflicts of interest policy, declarations of interest template and current summary of the conflicts of interest of GDG members can be found [here](#).

5.4 - Clinical questions (PICOs)

Clinical questions are formulated using the framework of population, intervention, comparator and outcome (PICO).

Medical device technologies to manage Type 1 Diabetes PICOs

Following discussion among the Guideline Development Group, six PICO questions were chosen for which to develop clinical recommendations. Detailed information regarding PICO criteria can be found [here](#).

PICO 1a Should you use continuous glucose monitoring (CGM) with alerts or self-monitored blood glucose (SMBG) in conjunction with multiple daily injections (MDI) in adults with type 1 diabetes?

PICO 1b Should you use continuous glucose monitoring (CGM) without alerts or self-monitored blood glucose (SMBG) in conjunction with multiple daily injections (MDI) in adults with type 1 diabetes?

PICO 1c Should you use flash glucose monitoring (FGM) or self-monitored blood glucose (SMBG) in conjunction with multiple daily injections (MDI) in adults with type 1 diabetes?

PICO 3 Should you use non-automated continuous subcutaneous insulin infusion (CSII) pumps with CGM (including low glucose insulin suspend systems), or automated continuous subcutaneous insulin infusion (CSII) pumps with closed-loop systems in children, adolescents and adults with type 1 diabetes?

PICO 6a Should you use continuous subcutaneous insulin infusion (CSII) pumps (with or without continuous glucose monitoring) or multiple daily injections (MDI) (with or without continuous glucose monitoring) in children with type 1 diabetes?

PICO 6b Should you use continuous subcutaneous insulin infusion (CSII) pumps (with or without continuous glucose monitoring) or multiple daily injections (MDI) (with or without continuous glucose monitoring) in adults with type 1 diabetes?

Medications for blood glucose management in Type 2 Diabetes PICOs

Following discussion among the guideline development group, three PICO questions were chosen for which to develop clinical recommendations. Detailed information regarding PICO criteria can be found [here](#).

PICO 10 Should you use metformin or a different blood glucose lowering medication as first line treatment in adults with type 2 diabetes?

PICO 11 Which blood glucose lowering medication should be used in combination with metformin as dual therapy in adults with type 2 diabetes?

PICO 13 Should you use GLP-1 RA, SGLT-2, sulphonylurea or DPP-4 as add-on medication in adults with type 2 diabetes? Will it differ by cardiovascular risk groups?

5.5 - Search strategies and PRISMA

Medical device technology for the management of type 1 diabetes

The search strategy for medical device technology clinical questions involved (a) the use of existing search results for clinical questions focused on adult populations (the full search strategy can be found [here](#)), and (b) a confirmation of these search results through a truncated PubMed search, and a combined search specific to the two paediatric clinical questions.

The PubMed search strategy used to confirm search results can be found [here](#).

The search strategy developed for paediatric clinical questions can be found [here](#).

The PRISMA flow diagram, outlining the potentially relevant studies identified by the search and screening results for all medical device technology clinical questions can be found [here](#).

Medications for blood glucose management in type 2 diabetes

An information specialist developed the search strategy and conducted the literature search. MEDLINE, Embase and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched to 1st May 2020 without

language restriction.

The search strategy used for the medications for type 2 diabetes management can be found [here](#).

The PRISMA flow diagrams for all medication questions are awaiting publication and will be made available as soon as possible.

5.6 - Guideline development methodology

These living recommendations were developed in accordance with the procedures and requirements for meeting the 2011 NHMRC standards for clinical practice guidelines. They focus on a specific subset of clinical questions from priority areas in prevention, diagnosis and treatment of diabetes as determined by the Living Evidence for Diabetes Steering Committee and Guideline Development Groups. Established and validated methods of GRADE were used to formulate clinical questions, prioritise outcomes, summarise the evidence, assess the quality of evidence and translate this evidence into actionable recommendations.

Details of the methods used in developing clinical recommendations can be found [here](#).

The Technical Report can be found [here](#).

The Administration Report can be found [here](#).

The purpose of this document is to outline the methods employed during the process of developing clinical recommendations as part of the Living Evidence for Diabetes project. This includes but is not limited to defining scope, formulation of clinical questions, search strategies, evidence synthesis and formulation of recommendations.

5.7 - Abbreviations and acronyms

AUD	Australian dollar
Auto CSII	Automated continuous subcutaneous insulin infusions
BMI	Body mass index
CGM	Continuous glucose monitoring
CSII	Continuous subcutaneous insulin infusion
DIY	Do it yourself
DPMQ	Dispensed price for maximum quantity
DPP-4	Dipeptidyl peptidase-4
eGFR	estimated glomerular filtration rate (mL/min/1.73m ²)
GDG	Guideline Development Group
GIP	Glucose-dependent insulintropic polypeptide
GLP-1	Glucagon like peptide-1
GP	General practitioner
HbA1c	Glycosylated haemoglobin A1c
JDRF	Juvenile Diabetes Research Foundation

LED	Living Evidence for Diabetes
MACE	Major adverse cardiovascular events
MDI	Multiple daily injections
NDSS	National Diabetes Services Scheme
NHMRC	National Health and Medical Research Council
PPARY	Peroxisome proliferative-activated receptor gamma
PBS	Pharmaceutical Benefits Scheme
PICO	Population, intervention, comparator, outcome
SGLT-2	Sodium-glucose transporter-2
SMBG	Self-monitoring of blood glucose
TGA	Therapeutic Goods Administration
TZD	Thiazolidinediones
WHO	World Health Organization

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