National Evidence Based Guideline for Blood Glucose Control in Type 2 Diabetes

Prepared by:
The Boden Institute of Obesity, Nutrition and Exercise
The University of Sydney

In collaboration with:
The Diabetes Unit
Menzies Centre for Health Policy
The University of Sydney

For the:
Diabetes Australia Guideline Development Consortium

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Diabetes Australia Guideline Development Consortium

The Diabetes Australia Guideline Development Consortium comprises Diabetes Australia; Australian Diabetes Society; the Australian Diabetes Educators' Association; the Royal Australian College of General Practitioners; and The Diabetes Unit, Menzies Centre for Health Policy, The University of Sydney.

A link to the guideline can be found on the Diabetes Australia website:
www.diabetesaustralia.com.au/For-Health-Professionals/Diabetes-National-Guidelines/

The National Health and Medical Research Council

The National Health and Medical Research Council (NHMRC) is Australia's leading funding body for health and medical research. The NHMRC also provides the government, health professionals and the community with expert and independent advice on a range of issues that directly affect the health and well being of all Australians.

The guideline was approved by the Chief Executive Officer of the NHMRC on 14 July 2009 under section 14A of the National Health and Medical Research Council Act 1992. Approval for the guideline by NHMRC is granted for a period not exceeding five years, at which date the approval expires. The NHMRC expects that all guidelines will be reviewed no less than once every five years.

A link to the guideline can be found on the National Health and Medical Research Council website:
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Disclaimer

This document is 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 guidelines are designed to provide information to assist decision-making and are based on the beset evidence available at the time of development.

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Glossary of Acronyms

ABS	Australian Bureau of Statistics
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation
ADA	American Diabetes Association
AusDiab	Australian Diabetes, Obesity and Lifestyle Study
CI	Confidence Interval
BMI	Body Mass Index
CAD	Coronary artery disease
CVD	Cardiovascular disease
DALY	Disability adjusted life year
FBG	Fasting blood glucose
FPG	Fasting plasma glucose
HbA1c	Glycated haemoglobin
HDL	High density lipoprotein
HR	Hazard ratio
IDF	International Diabetes Federation
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
LDL	Low density lipoprotein
NHMRC	National Health and Medical Research Council
OGTT	Oral glucose tolerance test
OR	Odds ratio
PVD	Peripheral vascular disease
QALY	Quality adjusted life year
RCT	Randomised controlled trial
RR	Relative risk
UKPDS	United Kingdom Prospective Diabetes Study
VADT	Veterans' Affairs Diabetes Trial
VA-CSDM	Veterans Affairs Cooperative Study on Glycaemic Control
WHO	World Health Organization
WHR	Waist to hip ratio

Blood Glucose Control
Expert Advisory Group

Chair	Professor Stephen Colagiuri Institute of Obesity, Nutrition and Exercise Faculty of Medicine The University of Sydney NSW 2006
Australian Diabetes Society	A/Professor Jeff Flack Director, Diabetes Centre Bankstown-Lidcombe Hospital NSW 2200
ADEA	Mr George Barker Diabetes Services Hornsby Ku-ring-gai Hospital & Community Health Services NSW 2077
RACGP	Professor Mark Harris Centre for Primary Health Care and Equity School of Public Health and Community Medicine University of NSW NSW 2052
Consumer	Mr Robert Guthrie Mosman NSW 2088
Content Expert	Professor Peter Colman Department, Diabetes and Endocrinology Royal Melbourne Hospital VIC 3050
Research Officer	Dr Scott Dickinson Institute of Obesity, Nutrition and Exercise Faculty of Medicine The University of Sydney NSW 2006

Guideline for Blood Glucose Control

Introduction

Aim of the Guideline

This Guideline addresses the topic of blood glucose control in people with type 2 diabetes and provides guidance on a number of issues relating to the assessment and management of blood glucose levels in people with type 2 diabetes.

Methods

The methods used to identify and critically appraise the evidence to formulate the guideline recommendations are described in detail in the *Overview of Guideline Development Process and Methods* (Appendix 2).

Guideline Format

Questions identified by the Expert Advisory Group (EAG) for blood glucose control in type 2 diabetes are shown on the next page.

Each of these issues is addressed in a separate section in a format presenting:

- ***Recommendation(s)***
- ***Practice Point (s) –*** *including experts' consensus in absence of gradable evidence*
- ***Evidence Statements –*** supporting the recommendations
- ***Background –*** to issues for the guideline
- ***Evidence –*** detailing and interpreting the key findings
- ***Evidence tables –*** summarising the evidence ratings for the articles reviewed

For all issues combined, supporting material appears at the end of the guideline topic and includes:

- ***Evidence references***
- ***Search Strategy and Yield Tables*** documenting the identification of evidence sources

Questions for Blood Glucose Control

- What is the effect of improving blood glucose control on:
  a) microvascular complications (retinopathy, neuropathy, nephropathy)?
  b) macrovascular complications (heart disease, stroke, peripheral vascular disease)?
  c) quality of life?

- Are there any potentially harmful effects of improving blood glucose control?

- How should blood glucose control be assessed?

- What are the targets for blood glucose control?

- What lifestyle modification and therapeutic interventions can be used to improve blood glucose control in people with type 2 diabetes?

- What are the economic consequences of and socio-economic influences on blood glucose control?

Summary of Recommendations and Practice Points

Recommendations

- Blood glucose control should be optimised because of its beneficial effects on the development and progression of microvascular complications. (Grade A)
- The potential harmful effects of optimising blood glucose control in people with type 2 diabetes should be considered when setting individual glycaemic targets. (Grade A)
- Glycated haemoglobin (HbA1c) measurement should be used to assess long term blood glucose control. (Grade A)
- Self monitoring of blood glucose (SMBG) should be considered in all people with type 2 diabetes but the decision to perform SMBG, and the frequency and timing of testing, should be individualised. (Grade C)
- The general HbA1c target in people with type 2 diabetes is ≤ 7%. Adjustment to diabetes treatment should be considered when HbA1c is above this level. (Grade A)
- Targets for self-monitored blood glucose levels are 6–8 mmol/L fasting and preprandial, and 6–10 mmol/L 2 h postprandial. (Grade C)
- Interventions to achieve target glycated haemoglobin should begin with lifestyle modification followed by pharmacological options selected on the basis of individual clinical circumstances, side effects and contraindications. (Grade A)
- Routine care of people with type 2 diabetes should address disparities associated with socio-economic status and ethnicity. (Grade C)

Practice Points

- Glycated haemoglobin should be measured at least twice a year in people with type 2 diabetes and stable blood glucose control. More frequent testing is required in people with sub-optimal control and following changes to therapy.
- Health professionals should be aware of factors which interfere with accurate measurement of glycated haemoglobin.
- Laboratory glycated haemoglobin measurement should be aligned to the DCCT method.
- An HbA1c target above 7% may be appropriate in people with type 2 diabetes who have a history of severe hypoglycaemia, a limited life expectancy, co-morbidities or who are elderly.
- People with newly diagnosed type 2 diabetes should routinely be offered a trial of lifestyle modification. However, pharmacotherapy may also be required in people presenting with significant hyperglycaemia.
- Treatment should be intensified if diabetes control is not at target and is not improving or is worsening after 3–6 months of a specific treatment strategy. However, this time interval should be shortened in the presence of significant hyperglycaemia.
- It is preferable to add a second oral anti-diabetic medication rather than using a maximum dose of one medication alone.
- Metformin is contraindicated in people with an eGFR < 30 ml/min/1.73 m^2 and should be used with caution in people with an eGFR of 30-45 ml/min/1.73 m^2.
- People who are not responding to usual diabetes management should be assessed for other conditions (e.g. Latent Autoimmune Diabetes of Adults [LADA], malignancy).
- Disparities in diabetes control may require additional efforts to improve accessibility of services.

Section 1: Blood Glucose Control

Question

What is the effect of improving blood glucose control on
a) Microvascular complications (retinopathy, neuropathy, nephropathy)
b) Macrovascular complications (heart disease, stroke, peripheral vascular disease)
c) Quality of life

Recommendation

Blood glucose control should be optimised because of its beneficial effects on the development and progression of microvascular complications. (Grade A)

Evidence Statements

- Improving blood glucose control in people with type 2 diabetes reduces the development or progression of microvascular complications.
  Level of Evidence I

- No clear independent effect of improving blood glucose control on macrovascular complications has been demonstrated in people with type 2 diabetes.
  Level of Evidence I

- The effect of tight blood glucose control on premature mortality in people with type 2 diabetes remains uncertain.
  Level of Evidence I

- There is an association between blood glucose control and quality of life in people with type 2 diabetes.
  Level of Evidence II

Background – Improving blood glucose control in people with type 2 diabetes

Type 2 diabetes is associated with reduced life expectancy, significant morbidity due to the specific diabetes related microvascular complications (retinopathy, nephropathy and neuropathy), and the increased risk of macrovascular complications (ischemic heart disease, stroke and peripheral vascular disease). The development of these complications impacts on quality of life.

In Australia, type 2 diabetes results in premature death and irreversible long term complications including myocardial infarction, stroke, retinopathy and blindness, renal disease requiring dialysis or transplantation, neuropathy, foot ulcer, amputation, and erectile dysfunction.

In 2004, diabetes was among the top ten leading causes of death being the direct cause of 2.7% of deaths in Australia, and being associated with another 6% of deaths (Australian Bureau of Statistics, 2006). Cardiovascular disease is the major cause of death in people with diabetes, accounting for approximately 50% of all fatalities (International Diabetes Federation, 2006). In 2005, diabetes was associated with cause of death in nearly 11,900 Australian deaths or 9% of all deaths that year. Approximately half of these deaths involved CHD (48%), stroke (16%), and PVD in 6% of diabetes deaths (Diabetes: Australian Facts 2008).

Over 81,000 hospitalisations occurred in 2004-05 where both diabetes and CHD were present, which accounted for 15.3% of all diabetes hospitalisations. In the same years, stroke from diabetes amounted to 2.2% of all diabetes hospitalisations and peripheral vascular disease accounted for 5.9% of all diabetes hospitalisations (Diabetes Australian Facts, 2008).

Age at diagnosis has an important influence on the occurrence of outcomes. People who were older at diagnosis had more complications at baseline (1997). However, a recent study reported an increased inherent susceptibility to retinopathy with earlier onset diabetes (Wong et al., 2008). Even after adjusting for glycaemic exposure, age of diagnosis was an independent predictor of long term retinopathy. Furthermore, young adults with early-onset diabetes are at a much greater risk of CVD relative to matched controls (Hillier and Pedula, 2003). Hanefeld et al (1996) found that all-cause mortality in newly diagnosed type 2 diabetes followed for 12 years was increased 5.1-fold in males and 7-fold in women aged 36-45 and 2-fold in males and 3.5-fold in women aged 46-55 years.

While there is evidence in the general population that mortality from heart disease is decreasing, the pattern in people with diabetes is different. In representative cohorts of people with and without diabetes followed for 8 to 9 years from the First National Health and Nutrition Examination Survey (NHANES I) and the NHANES I Follow-up Survey (NHEFS), there was a 36.4% decline in age-adjusted heart disease mortality in men without

diabetes compared with a 13.1% decline in men with diabetes for the two periods. For women, the situation was worse with a decline of 27% in non-diabetic women, but an increase of 23% in diabetic women (Gu et al., 1999).

Over the past decade intervention studies have examined the effect of lowering blood glucose levels in people with type 2 diabetes. This section examines the evidence of the relationship between blood glucose control and diabetes vascular complications and the impact on quality of life.

Evidence – Improving blood glucose control in people with type 2 diabetes and complications

Improving blood glucose control in people with type 2 diabetes reduces the development or progression of microvascular complications

A number of systematic reviews have examined the relationship between blood glucose control and long term complications in people with type 2 diabetes (Gaster and Hirsch, 1998; O'Connor et al., 1998; Vaaler, 2000; Woolf et al., 2000). These studies concluded that improved glycaemic control can reduce retinopathy, renal disease and neuropathy in people with type 2 diabetes are largely based on the results of the Kumamoto study in Japan and the UKPDS study.

The Kumamoto study (Ohkubo et al., 1995) was a prospective study conducted in 110 non obese insulin-requiring Japanese people with type 2 diabetes. Subjects included 55 people without evidence of retinopathy or urinary albumin excretion < 30 mg/24 h at baseline (primary prevention cohort) and 55 who showed "simple" retinopathy and urinary albumin excretion < 300 mg/24 h at baseline (secondary prevention cohort). Participants were randomly allocated to intensive treatment with multiple insulin injections (≥ 3) or conventional treatment with 1-2 injections daily. The intensive treatment group achieved a mean HbA1c of 7.1% and the conventionally treated group a mean HbA1c of 9.4% during the 6-year study period. There were significantly less people in the multiple injection group compared with the conventional group who developed retinopathy in the primary (7.7 vs 32% respectively, p = 0.04) and secondary prevention (19.2 vs 44% respectively, p = 0.05) groups. Similar results were found for primary prevention of nephropathy (7.7 vs 28% respectively, p = 0.03) and secondary prevention of nephropathy (11.5 vs 32% respectively, p = 0.04). The odds ratio (OR and 95% CI) for the development or progression of nephropathy was 0.26 (CI 0.09-0.76) and the number needed to treat was 5 (CI 4-19). Intensive glycaemic control delayed the onset and the progression of the early stages of retinopathy, nephropathy and neuropathy in people with type 2 diabetes. These results were confirmed in an 8-year follow-up report of the Kumamoto study (Shichiri et al., 2000) where intensive glycaemic control in people with type 2 diabetes effectively continued to delay the onset and progression of microvascular complications including retinopathy, nephropathy, and neuropathy.

The UKPDS was a randomised controlled trial which compared the effects of intensive blood-glucose control with either sulphonylurea or insulin and conventional treatment on the risk of microvascular and macrovascular complications in 3,867 people with newly diagnosed type 2 diabetes (median age 54 years) (UKPDS Study Group, 1998). After 3 months of diet treatment, subjects were randomly assigned to an intensive treatment policy with a sulphonylurea (chlorpropamide, glibenclamide, or glipizide) or with insulin, or to conventional treatment. The aim in the intensive group was to achieve a fasting plasma glucose (FPG) of < than 6 mmol/L while in the conventional group, the aim was the best

achievable FPG with diet alone and pharmacotherapy was added only if there were hyperglycaemic symptoms or the FPG was > 15 mmol/L. Aggregate endpoints were any diabetes-related endpoint (sudden death, death from hyperglycaemia or hypoglycaemia, fatal or non-fatal myocardial infarction, angina, heart failure, stroke, renal failure, amputation (of at least one digit), vitreous hemorrhage, retinopathy requiring photocoagulation, blindness in one eye, or cataract extraction); diabetes-related death (death from myocardial infarction, stroke, peripheral vascular disease, renal disease, hyperglycaemia or hypoglycaemia, and sudden death); all-cause mortality. Over 10 years, the median HbA1c was 7.0% in the intensive group compared with 7.9% in the conventional group – an 11% reduction ($p < 0.0001$). There was no difference in HbA1c among agents in the intensive group. Compared with the conventional group, the risk in the intensive group was 12% lower (95% CI 1–21, $p = 0.03$) for any diabetes-related endpoint; 10% lower (–11 to 27, $p = 0.34$) for any diabetes-related death; and 6% lower (–10 to 20, $p = 0.4$) for all-cause mortality. Most of the risk reduction in the any diabetes-related aggregate endpoint was due to a 25% risk reduction (7–40, $p = 0.01$) in microvascular endpoints, including the need for retinal photocoagulation. There was no difference for any of the three aggregate endpoints between the three intensive agents (chlorpropamide, glibenclamide, or insulin. In a 10-year follow-up, Holman et al (2008) monitored 3,277 people from the UKPDS. Over the first five years participants were asked to attend annual UKPDS clinics, but with no attempt made to maintain their previously assigned therapies. Annual questionnaires were used to follow participants who were able to attend the clinics, and all people in years 6 to 10 were assessed via questionnaires. At 10 years, there was a 24% risk reduction in the sulphonylurea–insulin group for microvascular disease ($p = 0.001$) compared with the conventional group. This difference was noted despite a lack of difference in HbA1c levels between the intensive and control groups following the conclusion to the randomized intervention in 1997, suggesting a continuing legacy effect of the prior period of improved blood glucose control. In the metformin-treated group, no significant risk reduction was observed for microvascular disease compared with the conventional group.

The first randomised control trial to examine the effects of different agents in diabetes outcomes (Smelo, 1971) – the University Group Diabetes Program (UGDP) – is invariably excluded from these reviews because it did not produce significant differences in glucose control in some treatment arms and lacked statistical power (Woolf et al., 2000). Furthermore, the study pre-dated the use of glycated haemoglobin to measure longer term diabetes control. This UGDP involved the recruitment of 823 people with newly diagnosed diabetes, with a mean age of 53 years, who were randomised to treatment with placebo, tolbutamide, a fixed amount of daily insulin and a variable dose of insulin. Subjects were followed up for 5 years. There was little evidence showing that insulin treatment was any better than diet alone in changing the course of vascular complications in stable type 2 diabetes. The only difference in outcomes observed in this study was increased cardiovascular mortality in the tolbutamide treated group.

The feasibility study for the Veterans Affairs Cooperative Study on Glycaemic Control and Complications in type 2 diabetes (VA-CSDM) study was conducted in 153 men with type 2 diabetes from five medical centres (mean age 60 years, mean duration of diabetes 7.8 years) (Emanuele et al., 1996). Participants were randomly assigned to receive standard insulin treatment (one injection in the morning) or intensified treatment (a stepped plan starting with one insulin injection in the evening ± glipizide up to multiple daily injections without glipizide) and were prospectively followed for a mean of 27 months. By 6 months the intensive blood glucose control group achieved a mean HbA1c of 7.1% (9.8% at baseline) while the standard treatment group had reached a baseline HbA1c of 9.5%. This level was maintained throughout the study period. The difference in HbA1c in the two groups was 2.1% ($p < 0.001$). Over this relatively short study period intensive therapy was not associated with either a worsening or improvement in retinopathy. This result was not unexpected and was consistent with results of the UKPDS where a difference in retinopathy with intensive treatment was not observed until after 3 years (UKPDS Study Group, 1998).

The effect of improved diabetes control on neuropathy has also been reported. The Kumamoto study reported that lowering blood glucose increased median nerve conduction velocity in the intensively treated group compared with the conventional group and reduced the arm vibration threshold ($p < 0.05$ for both), but other physiological measures were unaffected (Ohkubo et al., 1995). A follow up report of the Kumamoto study with 8 years of observation confirmed these findings and reported a significant deterioration in these parameters in the conventionally treated group (Shichiri et al., 2000). In the UKPDS there was no effect on the incidence of absent ankle and knee reflexes; however, although the number of subjects was small, abnormal biothesiometer (> 25 V) was significantly less in the intensive policy group ($p = 0.0052$) after 15 years of follow up (UKPDS Study Group, 1998).

A short-term study in 54 Japanese people with type 2 diabetes (mean age 49 years, mean duration of diabetes 10 years) was conducted to assess the reversibility of autonomic nerve function in relation to improved glycaemic control (Isotani and Fukumoto, 2000). The subjects were admitted to hospital for 4 weeks and placed on a strict diet and treatment. HbA1c improved from 9.9% to 8.6% and was associated with a significant improvement in dark-adapted pupillary area, an indicator of autonomic neuropathy, suggesting that autonomic neuropathy could be improved by rapid improvement in diabetes control.

An American study of 780 people with type 1 and type 2 diabetes examined the risk of death or renal failure with long-term intensive diabetes treatment (Hellman et al., 1997). The group was split into two groups: those with a longer duration of intensive therapy (median duration > 11 y, group 1), and 571 subjects with a shorter duration of intensive therapy (median duration < 1 y, group 2). The intensive treatment involved maintaining FPG between 3.9 and 6.3 mmol/L and having an HbA1c ≤ 6.4%, seeing a physician an average of five times a year, regular telephone contact with a diabetes educator and participating in a diabetes education program. Intensive insulin therapy (≥ three injections a day) was also

used in half of this group. Of the study population 113 people with type 2 diabetes maintained the intensive therapy long term (median > 11 y) and these were compared with the 377 people with type 2 diabetes who only achieved this short term (median < 1 y). Baseline HbA1c in the two groups was 10.5% and 10.9% respectively. Overall, despite the greater number of people with a higher initial comorbidity, group 1 subjects had a significant reduction in mortality (25.9 vs 33.3%, $p = 0.05$). People aged < 65 y were less likely to die in the intensive group than in the control group (17.2 vs 29.7%, $p = 0.04$). In the intensive group those who were on more intensive insulin therapy had a lower mortality, cardiac specific mortality and cardiac mortality with renal comorbidity than those who received conventional insulin therapy ($p = 0.02$, $p = 0.001$ and $p = 0.02$, respectively). There was no significant difference between the total number of renal events (dialysis, transplantation or death) in the two groups in people with type 2 diabetes who were under 65 years.

Intensified blood glucose control appears to reduce the incidence of albuminuria. In the Kumamoto study the cumulative development and progression in nephropathy (defined by increase in urinary albumin excretion) after 6 years was 7.7% in the intensively treated group and 28% in the conventionally treated group in the primary prevention group ($p = 0.03$) and 11.5% and 32% respectively in the secondary prevention group ($p = 0.04$) (Ohkubo et al., 1995). The UKPDS observed a lower incidence of microalbuminuria with intensified treatment which became statistically significant after three years and a lower incidence of gross proteinuria and increased plasma creatinine within nine years of follow-up (relative risk reduction = 17%, 33%, and 60%, respectively). The incidence rates of renal failure and death from renal disease did not differ significantly between the groups, but the absolute number of cases was small. (Levin et al., 2000) reported the effect of intensified insulin treatment on microalbuminuria in the VA-CSDM study. The intensively treated group had significantly less change in albumin:creatinine ratio than the standard treatment group (ACR change from baseline 0.045 vs 0.141, $p = 0.05$) but had a similar deterioration in creatinine clearance over the two years of follow up.

Blood glucose control appears to be important in people with end stage renal disease. Mortality and morbidity was assessed in a retrospective survey in 166 people with type 2 diabetes who were on dialysis for diabetic renal disease (Tzamaloukas et al., 1993). When the 57 people with type 2 diabetes and poor glycaemic control were compared with 109 people with good glycaemic control, those with good control had lower rates of myocardial infarction ($p < 0.001$), gangrene ($p = 0.001$), amputation ($p = 0.007$), heart failure ($p < 0.001$), gastroparesis ($p < 0.001$), enteropathy ($p < 0.001$) and significantly longer survival (mean survival 129 ± 8 vs 29.5 ± 5 months; $p < 0.0001$). There was no significant difference in cerebrovascular disease, retinopathy or blindness.

A multifactorial intervention that included improved glycaemic control is also associated with improved outcomes. In the STENO-2 Study, 160 people with type 2 diabetes (mean age 55.1 years) and persistent microalbuminuria were randomly assigned to receive either

intensive, target-driven therapy or conventional multifactorial treatment consistent with the Danish Medical Association guidelines (Gaede et al., 2008). Intensive treatment targets included HbA1c of < 6.5% and fasting total cholesterol of < 4.5 mmol/L and included a stepwise implementation of behaviour modification and pharmacological therapy that targeted hyperglycaemia, hypertension, dyslipidaemia, and microalbuminuria, along with secondary prevention of cardiovascular disease with aspirin. The mean treatment period was 7.8 years. Subjects were subsequently followed observationally for a mean of 5.5 years, until December 31, 2006. The primary endpoint in the follow-up trial (13.3 years) was time to death from any cause; secondary endpoints included death from a composite of cardiovascular disease events. The two study groups were similar at baseline but differed significantly at the end of the intervention period. Progression of microvascular complications was reduced after a mean of 3.8 years of intensified intervention and these changes were maintained at 13.3 years. The reduction translated into a significant absolute risk reduction in dialysis of 6.3%, a condition highly associated with death in many parts of the world. During the entire 13.3 years of follow-up, 24 subjects (30%) in the intensive-therapy group died compared with 40 (50%) in the conventional-therapy group (hazard ratio, 0.54; 95% confidence interval [CI], 0.32–0.89; p = 0.02). Diabetic nephropathy developed in 20 people in the intensive-therapy group compared with 37 in the conventional-therapy group (relative risk, 0.44; 95% CI, 0.25–0.77; p = 0.004); one subject in the intensive-therapy group progressed to end-stage renal disease compared with six people in the conventional-therapy group (p = 0.04). Diabetic retinopathy progression occurred in 41 people in the intensive-therapy group and in 54 people in the conventional-therapy group (relative risk, 0.57; 95% CI, 0.37–0.88; p = 0.01); autonomic neuropathy progressed in 39 people in the intensive-therapy group and in 52 people in the conventional-therapy group (relative risk, 0.53; 95% CI, 0.34–0.81; p = 0.004). Few major side effects were reported. Intensive intervention with multiple drug combinations and behaviour modification had sustained beneficial effects in at-risk people with type 2 diabetes.

A recent factorial randomised controlled trial (ADVANCE Collaborative Group, 2008) examined the effects of intensive glucose control on vascular outcomes in 11,140 people with type 2 diabetes. Subjects were assigned to either standard glucose control or intensive glucose control, defined as the use of gliclazide (modified release) plus other blood glucose lowering drugs as required to achieve a glycated haemoglobin value of 6.5% or less. Primary end points were composites of major macrovascular events (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) and major microvascular events (new or worsening nephropathy or retinopathy), assessed both jointly and separately. After 5 years of follow-up, the mean glycated haemoglobin level was lower in the intensive-control group (6.5%) than in the standard-control group (7.3%). Intensive control reduced the incidence of combined major macrovascular and microvascular events (18.1%, vs 20.0% with standard control; hazard ratio, 0.90; 95% confidence interval [CI], 0.82 to 0.98; p = 0.01), due to a reduction of major microvascular events (9.4% vs 10.9%; hazard ratio, 0.86; 95% CI, 0.77 to 0.97; p = 0.01). A 21% relative reduction in the risk of new or worsening nephropathy was the main contributor to the 10% overall relative

reduction in the primary outcome found with intensive blood glucose control. Compared with standard control, intensive treatment was associated with a significant reduction in renal events, including new or worsening nephropathy (hazard ratio, 0.79; 95% CI, 0.66 to 0.93; p = 0.006) and new-onset microalbuminuria (hazard ratio,0.91; 95% CI, 0.85 to 0.98; p = 0.02). There were no significant effect on retinopathy (p = 0.50), although the detailed analysis of the fundus photographs has not yet been completed. Intensive glucose control involving a modified release gliclazide and other drugs as required (which lowered HbA1c values to 6.5%) resulted in a 14% relative reduction in major microvascular events.

No clear independent effect of improving blood glucose control on macrovascular complications has been demonstrated in people with type 2 diabetes

While there are considerable data from prospective epidemiological studies and new epidemiological data from randomised controlled trials showing some association between glycaemic control and macrovascular outcomes (Stratton et al., 2000; Woolf et al., 2000; ACCORD Study Group, 2008; ADVANCE Collaborative Group, 2008; Gaede et al., 2008), the effect of improving glycaemic control on macrovascular complications remains unclear.

Systematic reviews which have examined this issue have predominantly relied on evidence from the UKPDS (Vaaler, 2000; Woolf et al., 2000). Vaaler examined evidence related to the effect of glycaemic control on the outcome of daily symptoms, microvascular and macrovascular complications, and concluded that surrogate endpoints reflecting CVD risk improve and that UKPDS evidence supported this view. The systematic review by Woolf et al concluded that while the evidence demonstrated a reduced reduction in microvascular complications with glycaemic control, the effect was not clear for macrovascular outcomes.

A systematic review by Gaster and Hirsch (1998) predated the UKPDS publications but considered data from the UDGP, VA-CSDM and Kumamoto studies. They concluded that the evidence was limited and equivocal for improved glycaemic control and its effect on coronary heart disease. The Kumamoto study had only one myocardial infarction in each of the intensive and conventional groups, probably because of excluding people with hypertension or hypercholesterolaemia (Ohkubo et al., 1995). In an 8-year follow-up, conventional insulin injection therapy showed twice the number of cardiovascular events, cerebrovascular and peripheral vascular diseases compared with subjects on the intensive insulin therapy (Shichiri et al., 2000). In the conventional group, three subjects died of cerebral vascular disease, and two subjects developed angina compared with one sudden death (likely MI), and two new cases of angina in the intensively-treated group. The VA-CSDM pilot study recorded 61 new predefined cardiovascular events over 27 months of which 35 occurred in 24 people in the intensive treatment group and 26 events in 16 people in the standard treatment group (p = NS). There was no difference in total and cardiovascular mortality (n = 5 for intensive vs n = 3 for standard). In a further analysis of the VA-CSDM, Pitale et al (Pitale et al., 2000) reported on cardiac scans in a subgroup of 104 people who were scanned twice and had not had any cardiac events which could have interfered with the scans. The HbA1c in the standard therapy group was 9.1% compared with 7.0% in the intensive therapy group ($p < 0.001$). There was no significant difference in left ventricular ejection fraction between the two groups at baseline (57.6% vs 58.3%, p = NS) or follow-up (58.0% vs 59.7%, p = NS). The UGDP found no significant difference in myocardial infarction between the intensive and conventional treatment groups 20.6% vs 20.2% (UGDP, 1982).

The UKPDS Study Group (1998) showed that compared with a conventionally-treated group, the intensive treatment group had a marginal 16% risk reduction for myocardial infarction (p = 0.052) and a non-significant effect on heart failure, angina, stroke, and amputation or death from peripheral vascular disease. However in the 10-year follow-up study (Holman et al, 2008), a highly significant 14% risk reduction for myocardial infarction (p=0.014) was observed. This has been assumed to be a legacy effect of prior improved diabetes control, other factors cannot be excluded.

The effect of metformin was evaluated in diet-treated overweight people with newly diagnosed type 2 diabetes (UKPDS Study Group, 1998). Of 4,075 subjects recruited in the UKPDS, 1,704 were overweight (> 120% ideal body weight, mean BMI 31.4 kg/m^2 (SD 4.6)) and had an elevated fasting plasma glucose (FPG; 6.1–15.0 mmol/L) after 3 months of initial diet therapy. Of these, 753 were included in a randomised controlled trial, median duration 10.7 years, of conventional policy, primarily with diet alone (n = 411) versus intensive blood glucose control with metformin, aiming for FPG below 6 mmol/L (n = 342). A secondary analysis compared the 342 people allocated metformin with 951 overweight people allocated intensive blood glucose control with chlorpropamide (n = 265), glibenclamide (n = 277), or insulin (n = 409). Primary outcome measures included diabetes-related death and all-cause mortality. The median HbA1c during the 10 years of follow-up was 7.4% in the metformin group and 8.0% in the conventional treatment group. People assigned intensive blood glucose control with metformin had a 32% lower risk (p = 0.002) of developing any diabetes-related endpoint than those allocated conventional blood-glucose control. Metformin produced a significantly greater risk reduction than those assigned intensive therapy with sulphonylurea or insulin (p = 0.003). There were no differences in microvascular complications alone (p = 0.39). The metformin group had a 39% lower risk (p = 0.01) of myocardial infarction than the conventional treatment group, but did not differ from the other intensive treatment group. This benefit could not entirely be explained on the basis of improved glycaemic control since the difference in glycaemic control between the two groups was not statistically significant. In the 10-year follow-up study (Holman et al., 2008), the risk reduction for any diabetes-related end point was 21% (p = 0.01), for diabetes-related death 30% (p = 0.01), for myocardial infarction 33% (p = 0.005), and for death from any cause 27% (p = 0.002) in the metformin group.

In the ADVANCE study (ADVANCE Collaborative Group, 2008) 11,140 people with type 2 diabetes were assigned to undergo either standard glucose control or intensive glucose control. Primary end point was a composites of macrovascular and microvascular events. Intensive control reduced the incidence of the primary end point (18.1% vs 20.0% with standard control; hazard ratio, 0.90; 95% confidence interval [CI], 0.82 to 0.98; p = 0.01). But there were no significant effect on major macrovascular events (hazard ratio with intensive control, 0.94; 95% CI, 0.84 to 1.06; p = NS), death from cardiovascular causes (hazard ratio with intensive control, 0.88; 95% CI, 0.74 to 1.04; p = NS), or death from any cause (hazard ratio with intensive control, 0.93; 95% CI, 0.83 to 1.06; p = NS).

ACCORD is a large randomised controlled trial investigating whether intensive therapy to target normal glycated haemoglobin levels would reduce cardiovascular events in people with type 2 diabetes who had either established cardiovascular disease or additional cardiovascular risk factors (ACCORD Study Group, 2008). Subjects (n = 10,251, mean age: 62 years) with a median glycated haemoglobin level of 8.1% were randomised to receive intensive therapy (targeting a glycated haemoglobin level below 6.0%) or standard therapy (targeting a level from 7.0 to 7.9%). Of these, 38% were women, and 35% had had a previous cardiovascular event. The primary outcome was a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes which occurred in 723 people. There were 460 deaths from any cause. At one year, stable median glycated haemoglobin levels of 6.4% and 7.5% were achieved in the intensive-therapy group and the standard-therapy group, respectively. The study was discontinued after a mean of 3.5 years of follow-up because higher mortality in the intensive-therapy group - 257 deaths in the intensive-therapy group compared with 203 deaths in the standard-therapy group (hazard ratio, 1.22; 95% CI, 1.01 to 1.46; p = 0.04). The primary outcome occurred in 352 people in the intensive-therapy group and 371 in the standard-therapy group (hazard ratio, 0.90; 95% confidence interval [CI], 0.78 to 1.04; p = 0.16). The rate of nonfatal myocardial infarction was significantly lower in the intensive therapy group compared with the standard-therapy group (3.6% vs 4.6%; hazard ratio, 0.76; 95% CI, 0.62 to 0.92; p = 0.004). This study provided conflicting outcome data – a significant increase in overall mortality but also a significantly lower rate of non-fatal myocardial infarction. The study did not identify any specific cause for the increased mortality.

As detailed under microvascular complications, the STENO-2 Study involved 160 people with type 2 diabetes (mean age 55.1 years) with persistent microalbuminuria who were randomly assigned to receive either intensive, target-driven therapy or conventional multifactorial treatment consistent with the Danish Medical Association guidelines (Gaede et al., 2008). The primary endpoint in the follow-up trial (13.3 years) was time to death from any cause; secondary endpoints included death from a composite of cardiovascular disease events. During the entire 13.3 years of follow-up, 24 subjects (30%) in the intensive-therapy group died compared with 40 (50%) in the conventional-therapy group (hazard ratio, 0.54; 95% confidence interval [CI], 0.32–0.89; p = 0.02). There were 51 cardiovascular events in 25 people in the intensive-therapy group and 158 events in 48 people in the conventional-therapy group. Intensive therapy was associated with a lower risk of death from cardiovascular causes (hazard ratio, 0.43; 95% CI, 0.19–0.94; p = 0.04) and of cardiovascular events (hazard ratio, 0.41; 95% CI, 0.25–0.67; p < 0.001).

A large multicentre US clinical trial examined whether intense blood glucose control could reduce the risk of cardiovascular disease in United States veterans with uncontrolled glucose on current insulin or oral hypoglycaemic agents (Duckworth, 2009 – during the review process this study was published and confirmed the reported findings at the 2008 ADA scientific meeting). The VA Diabetes Trial (VADT) enrolled 1,791 subjects (97% male, 16% African American, 16% Hispanic whites, 62% non-hispanic whites, and 5% for all

others). The average entry age was 60.4 years and median follow-up time 5.6 years. Most received two or three oral agents plus insulin; by the end of the first year, 90% of intensively-controlled subjects were using insulin. Primary endpoints included myocardial infarction, stroke, or death from cardiovascular disease, and severe congestive heart failure. Forty percent of subjects had already had a prior cardiovascular event. After the first two years, subjects in both groups were at or below targets for lipids and blood pressure. These targets were maintained over the six years of participation. The mean HbA1c in the groups was 9.4% at baseline and, after 6 months, the standard treatment group reached 8.4% and the intensive treatment group 6.9%. HbA1c levels were maintained throughout the trial allowing for a clear separation between the two groups. There were fewer cardiovascular events in both groups than predicted (standard group: 33.5%; intensive group: 29.5%; p = NS) and no significant differences between the two groups in any component of the primary outcome or in the rate of death from any cause.

Dormandy et al (2005) examined whether pioglitazone reduced macrovascular morbidity and mortality in high-risk people with type 2 diabetes in a prospective, randomised controlled trial in 5,238 subjects who had evidence of macrovascular disease. Included subjects were 35–75 years, had an HbA1c concentration > 6.5% and evidence of extensive macrovascular disease before recruitment. Subjects were assigned to pioglitazone titrated from 15 mg to 45 mg (n = 2,605) or matching placebo (n = 2,633), to be taken in addition to their glucose-lowering drugs and other medications. The primary endpoint was the composite of all-cause mortality, non fatal myocardial infarction (including silent myocardial infarction), stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle. Allocated subjects were given 15 mg of pioglitazone for the first month, 30 mg for the second month, and 45 mg thereafter with particular attention placed on the need to reach HbA1c levels below 6.5%. Mean baseline HbA1c levels were 7.8% in the pioglitazone group and 7.9% in the placebo group. The average time of observation was 34.5 months; 514 of 2,605 people in the pioglitazone group and 572 of 2,633 in the placebo group had at least one event in the primary composite endpoint (HR 0.90, 95% CI 0.80-1.02, p = 0.095). The main secondary endpoint was the composite of all-cause mortality, non-fatal myocardial infarction, and stroke. Significantly fewer people in the pioglitazone group compared with the placebo group experienced this endpoint (301 vs 358; 0.84, 0.72-0.98, p = 0.03). The reduction in HbA1c was -0.8 (-1.6 to -0.1) in the pioglitazone group and -0.3 (-1.1 to 0.4) in the placebo group (p < 0.0001). Six percent (149 of 2,065) and 4% (108 of 2,633) of those in the pioglitazone and placebo groups, respectively, were admitted to hospital with heart failure; mortality rates from heart failure did not differ between groups. In a follow-up analysis of the PROactive study, Erdmann et al (2007) examined the effects of pioglitazone on mortality and macrovascular morbidity in people with a previous myocardial infarction (MI). Of the total cohort, the subgroup who had a previous MI were as follows: n = 2,445 [46.7%]; n = 1,230 in the pioglitazone group and n = 1,215 in the placebo group. There was a significant beneficial effect of pioglitazone on the end points of fatal/nonfatal MI,

excluding silent MI (28% risk reduction [RR]; p = 0.045) and acute coronary syndrome (ACS) (37% RR; p = 0.04). There was a 19% RR in the cardiac composite end point of nonfatal MI (excluding silent MI), coronary revascularisation, ACS, and cardiac death (p = 0.03). The difference in the primary end point defined in the main PROactive study did not reach significance in the MI population (12% RR; p = 0.14). The rates of heart failure requiring hospitalisation were 7.5% (92 of 1,230) with pioglitazone and 5.2% (63 of 1,215) with placebo. Fatal heart failure rates were similar (1.4% [17 of the 92] with pioglitazone versus 0.9% [11 of the 63] with placebo).

Home et al (2007) compared glucose control over 18 months between rosiglitazone oral combination therapy and combination metformin and sulphonylurea. The RECORD study involves a total of 4,458 individuals with type 2 diabetes with inadequate control on metformin or sulphonylurea. Glycaemic control on the first 1,122 subjects was reported in this study. HbA1c was managed to ≤ 7.0% by dose titration; if HbA1c levels exceeded 7.0% after 8 weeks of treatment, the dose of rosiglitazone was increased to a maximum of 8 mg daily. The primary endpoint was change from baseline in HbA1c after 18 months of randomised treatment. At 18 months, and in subjects using background metformin, HbA1c reduction was similar with rosiglitazone and sulphonylurea [difference 0.07 (95% CI–0.09, 0.23)%], as was the change when rosiglitazone or metformin was added to background sulphonylurea [0.06 (–0.09, 0.20)%]. In a further interim analysis (3.75 years follow-up) the same group presented outcomes and deaths from cardiovascular causes in all 4,447 subjects (Home et al., 2007). A total of 217 people in the rosiglitazone group and 202 in the control group had the adjudicated primary end point (hazard ratio, 1.08; 95% confidence interval [CI], 0.89 to 1.31). After the inclusion of end points pending adjudication, the hazard ratio was 1.11 (95% CI, 0.93 to 1.32). There were no statistically significant differences between the rosiglitazone group and the control group regarding myocardial infarction and death from cardiovascular causes or any cause. There were more people with heart failure in the rosiglitazone group than in the control group (hazard ratio, 2.15; 95% CI, 1.30 to 3.57). The interim findings from this study were inconclusive regarding the effect of rosiglitazone on the overall risk of hospitalisation or death from cardiovascular causes.

Recently, the final results of the RECORD study were published (Home et al, 2009). Data were available for 4,447 people with type 2 diabetes. In the rosiglitazone group 321 people and in the active control group 323 people experienced the primary outcome during a mean 5.5-year follow-up (HR 0.99, 95% CI 0.85–1.16). HR was 0.84 (0.59–1.18) for cardiovascular death, 1.14 (0.80–1.63) for myocardial infarction, and 0.72 (0.49–1.06) for stroke. Addition of rosiglitazone to glucose-lowering therapy in people with type 2 diabetes was not associated with differences in risk of overall cardiovascular morbidity or mortality compared with standard glucose-lowering medications.

Hanefeld et al (2004) assessed the effect of the alpha-glucosidase inhibitor acarbose on cardiovascular events in people with type 2 diabetes via a meta-analysis of seven reports.

The meta-analysis included subjects randomised to either acarbose (n = 1,248) or placebo (n = 932) with a minimum treatment duration of 52 weeks. The primary outcome measure was time to develop a cardiovascular event; however, measures of glucose metabolism were also investigated. Long-term acarbose treatment significantly improved glycaemic control in the pooled study population with significant reductions in HbA1c (acarbose: baseline 8.5%, endpoint 7.9%; placebo: 8.5%, endpoint 8.5%, p <0.001), fasting and postprandial blood glucose levels. Favourable trends in risk reduction for all cardiovascular event categories with acarbose treatment were found. Overall, the number of adverse events was small but myocardial infarction and 'any cardiovascular event' were significantly reduced by 35 and 64% respectively (MI hazard ratio: 0.36 [95% CI 0.16–0.80], p = 0.012; any CV event: 0.65 [95% CI 0.48–0.88], p = 0.006). Triglyceride levels, body weight, systolic blood pressure and glycaemic control all showed significant improvement. Mean HbA1c levels were reduced from baseline by 0.57% (endpoint HbA1c = 7.9%), fasting blood glucose by 5.4%, and 2-h postprandial glucose by 21% (p < 0.001 for all).

The LOOK AHEAD study is a multi-centred, randomised, controlled trial of 5,145 individuals with type 2 diabetes which is examining the long-term effects of an intensive lifestyle intervention on the incidence of major CVD events (Look AHEAD Research Group, 2003). The Look AHEAD Research Group (2007) reported the one-year changes in CVD risk factors of an intensive lifestyle intervention (ILI) involving group and individual meetings to achieve and maintain weight loss through decreased caloric intake and increased physical activity compared with a diabetes support and education (DSE) condition. Participants assigned to ILI lost an average 8.6% of their initial weight vs 0.7% in the DSE group (p < 0.001). Mean fitness increased in ILI by 20.9 vs 5.8% in the DSE (p < 0.001). A greater proportion of ILI participants had reductions in diabetes, hypertension, and lipid-lowering medicines. During the 1st year, use of glucose-lowering medicines among ILI participants decreased from 86.5 to 78.6%, whereas it increased from 86.5 to 88.7% among DSE participants (p < 0.001). Despite this difference, mean fasting glucose declined more among ILI participants compared with DSE participants (p < 0.001), as did mean A1c. Mean HbA1c dropped from 7.3 to 6.6% in the ILI group (p < 0.001) vs from 7.3 to 7.2% in the DSE group. At one year, participants in the intensive lifestyle intervention showed clinically significant weight loss which was associated with improved cardiovascular risk factors. The intensively treated group achieved a 21% improvement in cardiovascular fitness.

The role of controlling postprandial glucose (PPG) in influencing macrovascular complications remains uncertain because of the lack of outcome studies which has specifically addressed this issue. This topic was recently reviewed (IDF, 2007). Two studies have attempted to compare outcomes in people treated to control post prandial hyperglycaemia.

The HEART 2D study (Milicevic et al., 2005) presented at the 2008 American Diabetes Association Scientific Meeting included 1,116 people with type 2 diabetes within 21 days of an acute myocardial infarction. Subjects were randomised to treatment with prandial insulin

aiming to control PPG or basal insulin. After 3 years 2-h PPG was significantly lower in the prandial insulin treated group (7.8 vs 8.6 mmol/L) but HbA1c was similar (7.7 vs 7.8%). There was no difference in CVD deaths in the two groups.

Esposito et al (2004) compared the effects of two insulin secretagogues, repaglinide and glyburide (known to have different efficacy on PPG) on carotid intima-media thickness (CIMT) and markers of systemic vascular inflammation in 175 drug-naive people with type 2 diabetes in a randomised, single-blind trial. Eighty-eight subjects were randomly assigned to receive repaglinide and 87 received glyburide, with a titration period of 6 to 8 weeks for optimisation of drug dosage and a subsequent 12-month treatment period. The effects of repaglinide (1.5 to 12 mg/d) and glyburide (5 to 20 mg/d) on CIMT were compared by using blinded, serial assessments. The targets of the intervention were HbA1c < 6.5%, fasting blood glucose < 6.1 mmol/L, and postprandial glucose < 7.8 mmol/L. Statins, ACE inhibitors, and aspirin were also used in 8, 18, and 15% of subjects, respectively. After 12 months, the postprandial glucose peak was 8.2 ± 1.6 mmol/L in the repaglinide group and 10 ± 1.8 mmol/L in the glyburide group ($p < 0.01$). HbA1c showed a similar decrease in both groups: repaglinide –0.9% ± 0.5, glyburide –0.8% ± 0.5, p = NS. CIMT regression, defined as a decrease of > 0.020 mm, was observed in 52% of subjects receiving repaglinide and in 18% of those receiving glyburide ($p < 0.01$). Interleukin-6 ($p = 0.04$) and C-reactive protein ($p = 0.02$) decreased more in the repaglinide group than in the glyburide group. The reduction in CIMT was associated with changes in postprandial but not fasting hyperglycaemia.

Table 1: Summary of microvascular and macrovascular outcome studies.

Study	Duration diabetes (I)	Duration diabetes (C)	Years follow-up	Baseline HbA1c (I)	Baseline HbA1c (C)	Final HbA1c (I)	Final HbA1c (C)	Outcome
ACCORD	10.0	10.0	3.5	8.3	8.3	6.4	7.5	Increased mortality; significant reduction in nonfatal MI
ADVANCE	7.9	8.0	5.0	7.5	7.5	6.5	7.3	10% reduction macro/ micro events; 21% reduction nephropathy
KUMAMOTO	6.2 / 10.2	6.7 / 10.3	6.0	9.3	9.0	7.1	9.4	25% less people developed retinopathy 20% less people developed nephropathy
Look AHEAD	6.8	6.8	1.0	7.3	7.3	6.6	7.2	Significant weight loss; improved BGC and CVD risk; reduced medication
RECORD	7.0	7.1	5.5	7.9	7.9	≤ 7.0	≤ 7.0	No significant difference in CV or all-cause mortality
STENO 2	5.5	6.0	13.3	8.4	8.8	7.7	8.0	20% risk reduction for death; 13% risk reduction for CV related death
UKPDS	new dx	new dx	10.0	7.1	7.1	7.0	7.9	25% risk reduction for microvascular endpoints; 16% risk reduction MI; no diff all-cause mortality
VADT	11.5	11.5	5.6	9.5	9.4	6.9	8.4	No significant differences between groups; significantly fewer CVD events in both groups than predicted.

The effect of tight blood glucose control on premature mortality in people with type 2 diabetes remains uncertain

Groeneveld et al (1999) conducted a systematic review on the relationship between blood glucose level and mortality in people with type 2 diabetes and found a weak but positive association between higher blood glucose concentrations in type 2 diabetes and mortality. In the six larger studies (more than 100 deceased people) where glycaemia was plotted as a continuous variable, the risk ratio per unit increase of glycaemic measure varied from 1.03 to 1.12. An increase in 6 units of HbA1c corresponded to a doubling of mortality risk.

Although there is epidemiological evidence of an association between premature mortality and glycaemic control, one systematic review highlights the lack of available data on the effects of improving glycaemic control on premature mortality in people with type 2 diabetes (Woolf et al., 2000) where conflicting information on all-cause mortality in both observational and randomised controlled trials was found.

The 8-year follow-up of the Kumamoto study cohort observed one death in the intensive treatment group and three deaths in the conventional treatment group (Shichiri et al., 2000).

In the UKPDS, the risk of any diabetes-related death and all-cause mortality was not significantly different between the intensive and conventional policy treatment groups (UKPDS Study Group, 1998). However reduced mortality was observed with metformin treatment in overweight people with newly diagnosed type 2 diabetes compared with conventional policy treatment and intensive blood-glucose control policy with other agents (UKPDS Study Group, 1998). Diabetes-related death was reduced by 42% (9–63, $p = 0.02$) and 36% for all-cause mortality (9–55, $p = 0.01$). However this effect could not be explained by differences in glycaemic control. In the 10-year follow-up study (Holman et al., 2008), a post-trial risk reduction emerged in the sulphonylurea–insulin group for diabetes-related death (17%, $p = 0.01$), and death from any cause (13%, $p = 0.007$). In the metformin group, the risk reduction for any diabetes-related end point was 21% ($p = 0.01$), for diabetes-related death 30% ($p = 0.01$), and death from any cause 27% ($p = 0.002$). The explanation for this difference is not clear.

The University Group Diabetes Program (Smelo, 1971) assessed people with newly diagnosed diabetes and compared treatment with placebo, tolbutamide, a fixed amount of daily insulin and a variable dose of insulin. People treated with tolbutamide had significantly increased cardiovascular death compared with placebo ($p = 0.005$) but there was no difference between placebo and the other treatments. All cause mortality was similar in all groups. Since the assessment of glycaemic control was limited in this study, the relationship of this finding and glycaemic control cannot be determined.

As detailed previously, the results of three large randomised controlled trial in people with diabetes have recently been released. The ACCORD study in 10,251 people with type 2

diabetes reported a significant increase in all-cause mortality (hazard ratio, 1.22; 95% CI, 1.01 to 1.46; p = 0.04) with intensive therapy (targeting a glycated haemoglobin level below 6.0%) compared with standard therapy (targeting a level from 7.0 to 7.9% (ACCORD Study Group, 2008). However neither the ADVANCE (ADVANCE Collaborative Group, 2008) or VADT studies (Duckworth, 2009) found increased mortality with intensive blood glucose control in people with type 2 diabetes.

Other studies have examined the effect of improving blood glucose control in people with diabetes who have had a myocardial infarction. The Diabetes and Insulin in Acute Myocardial Infarction (DIGAMI) study enrolled 620 people with type 2 diabetes admitted to hospital following a myocardial infarction (Malmberg et al., 1995). Participants were randomised to conventional treatment or to intensive treatment with an insulin infusion for 24 hours followed by 3 months of multiple daily subcutaneous insulin injections. After 1 year mean HbA1c was lower in the intensively treated group compared with the conventional group (7.3% vs 7.7%) and mortality was also lower 18.6% vs 26.1%, p = 0.03). However the DIGAMI 2 study did not replicate these findings (Malmberg et al., 2005). In this study, three treatment strategies were compared – acute insulin-glucose infusion followed by insulin-based long term glucose control, insulin-glucose infusion followed by standard glucose control, and routine metabolic management according to local practise. The corresponding fasting blood glucose values reached were 8.0, 8.3, and 8.6 mmol/L. None of the groups reached the target of 5–7 mmol/L. The mean study mortality was 18.4%, however, mortality did not differ significantly among the groups (acute group: 23.4%, standard group: 22.6%, routine group: 19.3%; p = NS). Similarly the HI-5 Study (Cheung et al., 2006) aimed to determine whether improving glycaemic control following an acute MI through an insulin/dextrose infusion would reduce mortality among 240 hyperglycaemic people. The infusion did not reduce mortality at the inpatient stage (4.8 vs conventional 3.5%, p = 0.75), 3 months (7.1 vs 4.4%, p = 0.42), or 6 months (7.9 vs 6.1%, p = 0.62). There was, however, a lower incidence of cardiac failure (12.7 vs 22.8%, p = 0.04) and reinfarction within 3 months (2.4 vs 6.1%, p = 0.05).

There is an association between blood glucose control and quality of life in people with type 2 diabetes

Several factors may influence quality of life in people with type 2 diabetes including the diabetes itself, the presence of complications, type of therapy, unwanted consequences of therapy (e.g. hypoglycaemia), and glycaemic control. The effects are often in different directions and determining the separate contribution of different factors can be difficult.

Testa et al (1998) performed a systematic review of quality of life and glycaemic control in people with type 2 diabetes. Five cross-sectional studies showed an overall positive association between glycaemic control and quality of life, although the results varied with the different instruments used to assess quality of life. Similar findings were observed in four prospective studies.

The report by Testa et al (1998) also presented the results of a 4-month randomised controlled trial comparing glipizide (n = 377) and placebo (n = 192) of whom 290 people completed the Health State Rating Questionnaire and quality of life questionnaires. The quality of life scales included an analogue scale of quality of life, cognitive functioning, mental health, general health perceptions and symptom distress. The mean health state rating of participants was 83% (full health = 100% and death = 0). Following the therapeutic intervention, changes in quality of life were linked with changes in diabetes control with an increase in HbA1c > 1.5% resulting in a decrease in quality of life and a reduction in HbA1c > 1.5% resulting in an improved quality of life rating.

Testa and Simonson (1998) examined short-term outcomes of glycaemic control in 569 male and female people with type 2 diabetes in a double-blinded, randomized, placebo-controlled, parallel trial in 62 sites within the United States. After a 3-week, single-blind placebo-washout period, participants were randomised to diet and titration with either 5 to 20 mg of glipizide gastrointestinal therapeutic system (GITS) (n = 377) or placebo (n = 192) for 12 weeks. The primary outcome measures were changes from baseline in glucose and HbA1c levels and symptom distress, QOL, and health economic indicators by questionnaires and diaries. After 12 weeks, mean (± SE) HbA1c and fasting blood glucose levels decreased with active therapy (glipizide GITS) vs placebo (7.5% 0.1% vs 9.3% ± 0.1% and 7.0 ± 0.1 mmol/L [126 ± 2 mg/dL] vs 9.3 ± 0.2 mmol/L [168 ± 4 mg/dL], respectively; $p < 0.001$). Quality of life treatment differences (SD units) for symptom distress (+0.59; $p < 0.001$), general perceived health (+0.36; $p = 0.004$), cognitive functioning (+0.34; $p = 0.005$), and the overall visual analog scale (VAS) (+0.24; $p = 0.04$) were significantly more favourable for active therapy. Subscales of acuity (+0.38; $p = 0.002$), VAS emotional health (+0.35; $p = 0.003$), general health (+0.27; $p = 0.01$), sleep (+0.26; $p = 0.04$), depression (+0.25; $p = 0.05$), disorientation and detachment (+0.23; $p = 0.05$), and vitality (+0.22; $p = 0.04$) were most affected. Favourable health economic outcomes for glipizide GITS included higher retained employment (97% vs 85%; $p < 0.001$), greater productive capacity (99% vs 87%; $p < 0.001$), less absenteeism (losses = $24 vs $115 per worker per month; $p < 0.001$),

fewer bed-days (losses = $1539 vs $1843 per 1000 person-days; p = 0.05), and fewer restricted-activity days (losses = $2660 vs $4275 per 1000 person-days; p = 0.01). Worsening of HbA1c levels in people with type 2 diabetes was shown to affect QOL and overall well-being negatively. For the employer, lost productivity, increased absenteeism, and an increased use of health resources associated with poor BG control provides a strong incentive for demanding comprehensive diabetes management. Improving glycaemic control in people with type 2 diabetes was associated with substantial short-term symptomatic, QOL, and health economic benefits.

In a Dutch study, 176 people with type 2 diabetes (mean age 63.6 years) were assigned to either strict glycaemic control (fasting capillary glucose < 6.5 mmol/L) or less strict control (fasting capillary glucose < 8.5 mmol/L) and followed for 1 year to assess well-being (van der Does et al., 1998). Positive effect and perceived treatment were both unfavourably altered in people allocated to the strict glycaemic control. At the end of the study there was no significant difference in HbA1c of people on the strict regimen compared with the less strict regimen. The effect of glycaemic control was assessed by subdividing participants into three subgroups: an HbA1c reduction of < 1%, a ≥ 1% decrease and those starting insulin. An HbA1c decrease of ≥ 1% was associated with a statistically significant better mood and a non-significant improvement in well-being scores after 1 year.

A component of the UKPDS determined the effects on quality of life of therapies for improving blood glucose control, diabetic complications, and hypoglycaemic episodes (UKPDS Study Group, 1999). Two cross–sectional samples were studied – 2,431 people (mean age 60, duration from randomisation 8 years) completed a "specific" questionnaire covering four aspects of QOL, and 3,104 people (mean age 62, duration from randomisation 11 years) completed a "generic" QOL measure (EQ-5D). A sample of 122 non-diabetic control subjects (average age 62) was also given the specific questionnaire. A longitudinal sample of 374 people randomised to either intensive or conventional blood glucose policies (mean age at randomisation 52), was given the specific questionnaire. The cross-sectional studies showed that allocated therapies were neutral in effect, with neither improvement nor deterioration in QOL scores for mood, cognitive mistakes, symptoms, work satisfaction, or general health. The longitudinal study also showed no difference in QOL scores for the specific domains assessed, other than showing marginally more symptoms in people allocated to conventional than to intensive policy (HbA1c at time of filling in the QOL questionnaire: conventional 8.3% ± 1.7, intensive: 7.8% ± 1.8). In the cross-sectional studies, subjects with a previous macrovascular complication in the last year had worse general health, as measured by the generic questionnaire, than those without complications: more problems with mobility, 64% and 36%, respectively (p < 0.0001); and more problems with usual activities, 48% and 28% respectively (p = 0.002). Subjects with a microvascular complication in the last year reported more tension (p = 0.008) and total mood disturbance (p = 0.005), as measured by the specific questionnaire, than subjects without complications. People treated with insulin with two or more hypoglycaemic episodes during the previous year reported more tension (p = 0.002), more overall mood disturbance (p = 0.0009), and

less work satisfaction (p = 0.004), as measured by the specific questionnaire, than those with no hypoglycaemic attacks, after adjusting for age, duration from randomisation, systolic blood pressure, HbA1c, and sex in a multivariate analyses. Therefore in people with type 2 diabetes, complications affected QOL, whereas therapeutic policies shown to reduce the risk of complications had no effect on QOL. It could not be determined whether frequent hypoglycaemic episodes affect QOL, or whether people with certain personality traits or many symptoms also reported increased numbers of hypoglycaemic episodes.

The impact of complications on quality of life was assessed in another UKPDS study (Clarke et al., 2002). The EuroQol EQ-5D instrument was administered in 1996 to 3667 UKPDS participants and data were available from 3,192 respondents. A visual analogue scale (VAS) and the EQ-5D utilities were assessed. The following effects were observed: myocardial infarction = –0.055 (95% CI –0.067, –0.042), blindness in one eye –0.074 (95% CI –0.124, –0.052), ischemic heart disease –0.090 (95% CI –0.126, –0.054), heart failure –0.108 (95% CI –0.169, –0.048), stroke –0.164 (95% CI –0.222, –0.105), and amputation –0.280 (95% CI = –0.389, –0.170). The impact on the VAS scores was smaller, but the ranking was identical. These results demonstrate the magnitude of the impact of six complications on utility based measures of quality of life, which can be used to estimate the outcome of interventions that reduce these diabetes related complications.

Goddijn et al (1999) investigated the association between improved glycaemic control on quality of life during 1 year of treatment in a sample of 94 people with type 2 diabetes referred for insulin therapy to an outpatient department. Treatment aimed to achieve acceptable glycaemic control (HbA1c ≤ 8%) by maximising oral therapy and if necessary commencing insulin therapy, and information and education provided by a diabetes specialist nurse and dietitian. QOL was measured using a disease-specific (Diabetes Health Profile (DHP)) and a generic questionnaire (RAND-36). After 1 year mean HbA1c was reduced from 10.4% to 7.8% and QOL improved in the total group. Subjects who achieved the good glycaemic control target after 1 year (61%) improved in a similar manner as the others. People who were started on insulin (65%) improved in a similar manner as the others, but experienced more problems with social functioning and pain. People with hyperglycaemic complaints at baseline (49%) improved more in QOL than those without. Symptoms of hyperglycaemia therefore predicted the strength of the association between improvement of glycaemic control and QOL.

The Veterans Affairs Cooperative Study in Diabetes Mellitus Type 2 Feasibility Trial included 153 male US veterans 40–69 years of age and with diabetes duration of 8 ± 4 years with suboptimally controlled diabetes (Pitale et al., 2005). Subjects were randomised to intensive and standard treatment groups achieving and maintaining for 27 months a difference in HbA1c of 2.1% (9.2% vs 7.1%, respectively). A sub-study examined health status as assessed by a health status questionnaire obtained at baseline and 24 months. Health-related qualify of life data were also assessed using a 20-question version of the Medical Outcome Study instrument. Baseline characteristics were similar between the

standard and intensive groups with respect to age (60 years in both), duration of diabetes (7.7 and 8 years, respectively), CV complications (27 and 31 subjects, respectively), HbA1c (9.5% and 9.3%, respectively), and reported physical activity. The intensive treatment group had more frequent, mandatory self-glucose monitoring (vs occasional measurement in the standard) and received two or more daily insulin injections (only one in the standard). This group had three times the number of clinic visits and 10-fold higher reported incidence of mild/moderate hypoglycaemia (intensive arm: 16 mild or moderate hypoglyceamic episodes/pt/year; the standard arm: 1.5 episodes/pt/year). There were no significant changes in the health status over time in either the standard or intensive treatment groups, nor was there a difference between the two groups. Intensive glucose control had no effect on health status over 2 years. Successful lowering of glycaemia did not improve health-related quality of life nor did the increased demands of an intensive therapy regimen make it worse.

A study from the Harvard School of Public Health conducted two analyses following a literature review to determine the absolute, relative, and operative quality-of-life ranges for people with type 2 diabetes (Testa and Simonson, 1998). Quality of life and fasting blood glucose and HbA1c concentrations were measured at baseline and at 4, 8, and 12 weeks of treatment in 569 men and women randomised to either glipizide gastrointestinal therapeutic system (GITS) or placebo in a double-blind, multicentre clinical trial. A subgroup of 290 people completed a diabetes-specific health states questionnaire at endpoint (week 12 or early termination) rating 10 health-state descriptions on a health thermometer scale ranging from 0 (death) to 100 (full health). Health losses at the higher end of the scale had a greater negative utility than did comparable losses at lower health states, indicating peoples' strong preferences for maintaining asymptomatic or mildly symptomatic conditions. Subjects rated their current health state at 83.4 ± 0.8% of full health and indicated that a loss of 27 points below this value would prevent them from living and working as they currently do. The calibration analysis applied to the quality-of-life scales suggested that the targeted range for clinical investigation and quality-of-care evaluation must be more narrowly focused. Effect sizes as small as 2% (0.25 responsiveness units) on the absolute scale corresponded to quality-of-life losses of 15-20% on the personal operative scale. Differences in glycaemic control clearly affected quality of life. Those with the best HbA1c responses (decreasing 1.5% or more from baseline) versus those with the worst responses (increasing 1.5% or more from baseline) were separated by 0.6 responsiveness units for the overall quality-of-life summary measure. The calibration analysis suggested that this degree of better glycaemic control provided a nearly 50% gain in quality of life according to personal expectations within the operative range. Quality of life measures may be too crude and insensitive to capture important gains in health outcomes due to new therapeutic interventions and programs in diabetes. Quality of care evaluations for diabetes may be at risk of favouring inferior programs with lower costs because gains or losses in health outcomes are undetected.

A sample of 1,348 Dutch people with type 2 diabetes were recruited by 29 general practitioners to estimate the health-related quality of life (HRQOL) and treatment

satisfaction and to examine which subject characteristics were associated with quality of life and treatment satisfaction (Redekop et al., 2002). The study was performed as part of a larger European study (Cost of Diabetes in Europe - Type 2 [CODE-2]) which involved 7,635 people in eight European countries. A generic instrument (Euroqol 5D) was used to measure HRQOL and treatment satisfaction was assessed using the Diabetes Treatment Satisfaction Questionnaire. The average age in the population was 65 years, and half of the subjects were women (50.2%). Subjects without complications had an HRQOL (0.74) only slightly lower than similarly aged persons in the general population. Insulin therapy, obesity, and complications were associated with a lower HRQOL, independent of age and sex. Although higher fasting blood glucose and HbA1c levels were negatively associated with HRQOL, these factors were not significant after adjustment for other factors using multivariate analysis. Overall treatment satisfaction was very high. However, the correlation between treatment satisfaction and HRQOL was modest although statistically significant ($p < 0.001$). Younger people, those using insulin, and those with higher HbA1c levels were less satisfied with the treatment than other people. Obesity and the presence of complications are important determinants of HRQOL in people with type 2 diabetes.

A Canadian study (Ménard et al., 2007) assessed the impact of an intensive multitherapy (IMT) on perceived quality of life (QOL), attitudes, knowledge and diabetes self-management in a 12-month randomised trial conducted in 72 people with poorly controlled type 2 diabetes (HbA1c $\geq$ 8%, blood pressure > 130/80 mmHg and dyslipidaemia). Half the group was randomised to the IMT or and half to the control group. IMT consisted of monthly visits including clinical and biochemical assessment, education sessions on diet, physical exercise, medical management of diabetes and associated diseases and adjustments in medication. Controls received usual care by their physicians. A diabetes-specific questionnaire assessing QOL, attitudes, knowledge, diabetes self-management and socio-demographic data was developed and validated for the study. Primary outcomes were measured at 0, 6 and 12 months. Subjects were 54.8 ± 8.1 years old with mean duration of diabetes 10.3 ± 7.2 years. Questionnaires showed no difference in QOL between the groups at baseline, however, over the course of the study (12 months), QOL improved significantly in the IMT group when compared to controls (+13.2 ± 10.3/+5.6 ± 13.2%, $p = 0.003$), particularly with respect to the satisfaction scale (+25.3 ± 13.9/+5.4 ± 21.7%, $p < 0.001$). QOL was not affected by complications or hypoglycaemic episodes. QOL scores improved in IMT subjects who began insulin therapy during the trial. Attitude scores, in the high normal range at baseline, did not change. Knowledge (+18.2 ± 26.3/+8.9 ± 30.4%, $p = 0.05$) and diabetes self-management (+22.6 ± 35.3/+6.8 ± 20.1%, $p < 0.001$) improved. Despite the inherent constraints imposed by intensive multitherapy, QOL improved statistically in poorly controlled subjects with type 2 diabetes.

The specific effect of insulin therapy on quality of life in people with type 2 diabetes has been assessed in a number of studies. The systematic review by Gaster & Hirsch (1998) on the effect of blood glucose control on complications in type 2 diabetes also considered quality of life. This review included only one randomised study which reported the effects

on quality of life of intensified insulin regimens to improve blood glucose control in people with type 2 diabetes. In the study, 153 people with type 2 diabetes were treated for 3 months with five different regimens. The mean (± SE) value for HbA1c decreased similarly in all four insulin-treatment groups (1.7 ± 0.3, 1.9 ± 0.2, 1.8 ± 0.3, and 1.6 ± 0.3 percent, respectively). The decrease was significantly greater in the four groups compared with the control group (0.5 ± 0.2 percent, $p < 0.001$). Subjective well-being significantly improved in the insulin-treatment groups compared with the controls ($p < 0.001$) (Yki-Jarvinen et al., 1992).

A Dutch study conducted in a general practice setting assessed the impact of insulin therapy on glycaemic control and quality of life in people with type 2 diabetic with secondary failure on maximal doses of oral medication. Participants were randomly allocated to insulin therapy on two different schedules: after a 12-week period with enhanced compliance to diet and oral therapy; or as soon as secondary failure was established. Of the 38 included, three dropped out and seven were not started on insulin. In people starting insulin therapy, mean HbA1c decreased from 9.5% to 7.6% ($p < 0.01$). Improved glycaemic control was accompanied by a decrease in hyperglycaemic complaints ($p = 0.01$) without an increase in hypoglycaemic complaints. There were no statistically significant changes in quality of life parameters. Insulin therapy in poorly controlled people with type 2 diabetes was accompanied by a reduction of hyperglycaemic complaints, without an increase in hypoglycaemic complaints or an adverse effect of quality of life (de Grauw et al., 2001).

In an Australian community-based, prospective and observational setting, Davis et al (2001) assessed the effect of insulin on quality of life (QOL) in 1,290 people with type 2 diabetes recruited from a region of 120,097 people and undergoing detailed annual assessments of metabolic control and complications. The average age of the cohort was 64 years, the median duration of diabetes was 4.4 years and 49% were males. A modified Diabetes Quality of Life (DQOL) questionnaire and a health measurement questionnaire providing the Rosser index was administered annually. At baseline, subjects on insulin had higher scores for all subscales ($p \leq 0.02$). The total DQOL score was significantly higher in the insulin-treated subjects compared to those on other therapeutic regimens ($p \leq 0.001$), indicating a lower overall QOL. Regression analyses were performed to determine whether insulin treatment was significantly associated with DQOL independently of confounding variables. There was no independent association between insulin treatment and satisfaction ($p = NS$), but there was a significant association between insulin treatment and worry ($p < 0.001$), impact ($p < 0.001$), and total score ($p < 0.001$). Insulin use remained an independent inverse predictor of the Rosser index (which defines health in two dimensions: namely disability and distress) ($p < 0.001$). The present study confirmed that, although QOL is associated with demographic variables, duration of diabetes, glycaemic control and macrovascular complications, established insulin treatment independently reduces diabetes-related and general QOL

Simon et al (2008) assessed quality adjusted life years and healthcare costs of SMBG alone or with additional training in incorporating the results into self care, in addition to standardised usual care for 453 people with non-insulin treated type 2 diabetes. The DiGEM trial covered 12 months before baseline and 12 months of trial follow-up. Primary outcome measures were quality adjusted life years and healthcare costs. An initial negative impact of self monitoring on quality of life occurred, averaging -0.027 (95% confidence interval-0.069 to 0.015) for the less intensive self monitoring group and -0.075 (-0.119 to -0.031) for the more intensive group. This trial confirmed that subjects in the SMBG group had a reduced self rated quality of life, perhaps as a result of increased anxiety and depression associated with SMBG.

The impact of SMBG on quality of life was studied in 2,855 people with type 2 diabetes (mean age 63 years) (Franciosi et al., 2001). SMBG was assessed by frequency of testing ranging from ≥ once daily to never tested combined with the number of times tested in the 2 weeks prior to assessment. Overall 471 people (17%) stated performing SMBG at least once a day, 899 (31%) at least once per week, 441 (14%) less than once per week, and 1071 (38%) never performed SMBG. Compared with people performing SMBG, people who never performed SMBG were more likely to be male ($p = 0.04$), older ($p = 0.001$), have a shorter diabetes duration ($p = 0.001$), lower HbA1c level ($p = 0.0001$), less likely to visit diabetes clinics or be treated with insulin ($p = 0.001$). Multivariate analysis showed that SMBG frequency ≥ once daily was significantly associated with higher levels of diabetes health distress ($p = 0.0001$), diabetes-related worries ($p = 0.0001$), and depressive symptoms ($p = 0.05$) in non-insulin-treated people, but not in insulin-treated people.

Evidence Table: Improving blood glucose control in people with type 2 diabetes reduces the development or progression of microvascular complications

Author (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of Effect*	*Relevance Rating*
	Level	*Study Type*			
ADVANCE Collaborative Group, 2008 (Australia)	II	RCT	High	High^{+}	High
Emanuele and Klein, 1996 (USA)	II	RCT	High	High^{+}	High
Gaede et al., 2008 (Denmark)	II	RCT	High	High^{+}	High
Gaster and Hirsch, 1998	I	Systematic review	High	High^{+}	High
Hellman et al., 1997	III-2	Prospective cohort	Medium	High^{+}	High
Holman et al., 2008 (UK)	II	RCT	High	High^{+}	High
Isotani and Fukumoto, 2000 (Japan)	III-2	Prospective cohort	Medium	High^{+}	Low
Levin et al., 2000 (USA)	II	RCT	High	High^{+}	High
O'Connor et al., 1998	I	Systematic review	Medium	High^{+}	High
Ohkubo et al., 1995 (Japan)	II	RCT	High	High^{+}	High
Shichiri et al., 2000 (Japan)	II	RCT	High	High^{+}	High
UGDP, 1971 (USA)	II	RCT	Medium	Low^{-}	Medium
Tzamaloukas et al., 1993 (USA)	III-2	Prospective Cohort	Medium	High^{+}	High
UKPDS Study Group 33, 1998	II	RCT	High	High^{+}	High
Vaaler, 2000	I	Systematic review	Medium	High^{+}	High
Woolf et al., 2000	I	Systematic review	High	High^{+}	High

$^{+}$ Improving blood glucose control in people with type 2 diabetes reduces the development or progression of microvascular complications.

Clinical importance rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

Evidence Table: No clear independent effect of improving blood glucose control on macrovascular complications has been demonstrated in people with type 2 diabetes

Author (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of Effect*	*Relevance Rating*
	Level	*Study Type*			
ACCORD Study Group, 2008 (USA)	II	RCT	High	High^{+}	High
ADVANCE Collaborative Group, 2008 (Australia)	II	RCT	High	High^{-}	High
Dormandy et al., 2005 (UK)	II	RCT	High	High^{+}	High
Duckworth et al., 2009 (USA)	II	RCT	High	High^{-}	High
Erdmann et al., 2007 (Germany)	II	RCT	High	High^{-}	High
Esposito et al., 2004 (Italy)	II	RCT	Medium	High^{+}	High
Gaede et al., 2008 (Denmark)	II	RCT	High	High^{+}	High
Gaster and Hirsch., 1998	I	Systematic review	High	High^{-}	High
Hanefeld et al., 2004	I	Systematic review	High	High^{+}	High
Home et al., 2007a (UK)	II	RCT	High	High^{+}	High
Home et al., 2007b (UK)	II	RCT	High	High^{-}	High
Holman et al., 2008 (UK)	II	RCT	High	High^{+}	High
Holman et al., 2009 (UK)	II	RCT	High	High^{-}	High
Look AHEAD Research Group, 2007 (USA)	II	RCT	High	High^{+}	High
Milicevic et al., 2005	II	RCT	High	High^{-}	High
Ohkubo et al., 1995 (Japan)	II	RCT	High	High^{-}	High
Pitale et al., 2000 (USA)	II	RCT	High	High^{-}	Low
Shichiri et al., 2000 (Japan)	II	RCT	High	High^{+}	High
Stratton et al., 2000	III-2	Prospective Cohort	Medium	High^{+}	High
UGDP Study Group, 1982	II	RCT	Medium	Low^{-}	Medium
UKPDS Study Group 33, 1998	II	RCT	High	Medium^{+}	High
UKPDS Study Group 34, 1998	II	RCT	High	Medium^{+}	High
Vaaler, 2000	I	Systematic review	Medium	Medium^{+}	High
Woolf et al., 2000	I	Systematic review	High	Low^{-}	High

[+] No clear independent effect of improving blood glucose control on macrovascular complications has been demonstrated in people with type 2 diabetes.

Clinical importance rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

Evidence Table: The effect of tight blood glucose control on premature mortality in people with type 2 diabetes remains uncertain

Author (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of Effect*	*Relevance Rating*
	Level	*Study Type*			
ACCORD Study Group, 2008 (USA)	II	RCT	High	High^{+}	High
ADVANCE Collaborative Group, 2008 (Australia)	II	RCT	High	High^{-}	High
Cheung et al., 2006 (Australia)	II	RCT	High	Medium^{-}	High
Duckworth et al., 2009 (USA)	II	RCT	High	High^{-}	High
Groeneveld et al., 1999 (Netherlands)	I	Systematic review	High	Medium^{+}	High
Holman et al., 2008 (UK)	II	RCT	High	High^{+}	High
Malmberg et al., 1995 (Sweden)	II	RCT	High	High^{+}	High
Malmberg et al., 2005 (Sweden)	II	RCT	High	Low^{-}	High
Shichiri et al., 2000 (Japan)	II	RCT	High	Low^{+}	High
UGDP, 1971 (USA)	II	RCT	Medium	Medium^{+}	Low
UKPDS Study Group 33, 1998	II	RCT	High	Low^{-}	High
UKPDS Study Group 34, 1998	II	RCT	High	Medium^{+}	High
Woolf et al., 2000	I	Systematic review	High	High$^{+/-}$	High

$^{+}$ The effect of tight blood glucose control on premature mortality in people with type 2 diabetes remains uncertain.

Clinical importance rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

Evidence Table: There is an association between blood glucose control and quality of life in people with type 2 diabetes

Author (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of Effect*	*Relevance Rating*
	Level	*Study Type*			
UKPDS Study Group 62, 2002	II	RCT	High	High^{+}	High
Davis et al., 2001 (Australia)	III-2	Prospective cohort	High	High^{+}	High
de Grauw et al., 2001 (Netherlands)	III-2	Prospective cohort	Medium	Low^{-}	High
Franciosi et al., 2001 (Italy)	IV	Cross-sectional	Medium	High^{+}	High
Goddijn et al., 1999 (Netherlands)	III-2	Prospective cohort	Medium	High^{+}	High
Menard et al., 2007 (Canada)	II	RCT	High	High^{+}	High
Pitale et al., 2005 (USA)	II	RCT	High	High^{-}	High
Redekop et al., 2002 (Netherlands)	IV	Cross-sectional	High	High^{+}	High
Simon et al., 2008 (UK)	III-2	Prospective cohort	High	High^{+}	High
Testa and Simonson., 1998 (USA)	II	RCT	High	High^{+}	High
UKPDS Study Group 37, 1999	IV	Cross-sectional	High	High^{+}	High
van der Does et al., 1998 (Netherlands)	II	RCT	Medium	High^{+}	High
Yki-Jarvinen et al., 1992 (Finland)	II	RCT	High	High^{+}	High

$^{+}$ There is an association between blood glucose control and quality of life in people with type 2 diabetes.

Clinical importance rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

Section 2: Blood Glucose Control

Question

Are there any potentially harmful effects of improving blood glucose control?

Recommendation

The potential harmful effects of optimising blood glucose control in people with type 2 diabetes should be considered when setting individual glycaemic targets. (Grade A)

Evidence Statements

- Improving blood glucose control increases the risk of hypoglycaemia
  Level of Evidence I

- Fear of hypoglycaemia is common in people with diabetes
  Level of Evidence I

- Improving blood glucose control is frequently associated with weight gain
  Level of Evidence I

Background – Harmful affects of improving blood glucose control in people with type 2 diabetes

Efforts to lower blood glucose in people with diabetes can be associated with potentially undesirable consequences.

Excessive lowering of glucose into the hypoglycaemic range can result in uncomfortable symptoms or more serious consequences including unconsciousness. Weight gain is also a concern with improved blood glucose control. An early study in people with type 1 diabetes also raised concerns that rapid improvements in blood glucose control could be associated with temporary deterioration in diabetic retinopathy (Kroc Collaborative Study Group, 1984).

Hypoglycaemia is one of the most feared acute complications of diabetes treatment. It can cause unpleasant symptoms, disrupt daily routines, increase the risk of accidents or injuries, create fear and anxiety, and lead to permanent neurological injury or death. As a result, it is the most formidable impediment to intensifying treatment and can prevent many people from achieving the benefits of improved glycaemic control (Murata et al., 2004).

Obtaining accurate population data on the incidence and prevalence of hypoglycaemia in people with type 2 diabetes is difficult. Murata et al (2004) reported that 51.2% of people with type 2 diabetes experienced at least 1 hypoglycaemic episode over a mean follow-up of 41 weeks, an overall incidence of hypoglycaemia of 610 events per 100 person years. Approximately 20% of episodes were asymptomatic, 77% were associated with mild-moderate symptoms and 3% were severe and associated with diminished mental state or requiring the assistance of another person.

There are important implications of these potential problems for improving glycaemic control (Thompson et al., 1996). People with insulin-treated diabetes were invited to complete a questionnaire to investigate their reaction to the results of Diabetes Control and Complications Trial (benefits in an intensively treated group associated with an increase in frequency of severe hypoglycaemia and weight gain). Of all respondents, 60% felt encouraged to improve glycaemic control. However people with longer diabetes duration, a history of more than one severe hypoglycaemic episode, or hypoglycaemia unawareness were less likely to want to improve their glycaemic control. Fear of hypoglycaemia and weight gain were common concerns.

In early studies in type 1 diabetes, improvement in diabetes control was associated with a transient worsening of diabetic retinopathy. However, there is no evidence from randomised controlled studies that improving blood glucose control in people with type 2 diabetes has any significant deleterious effects on retinopathy, even in the short term. On the contrary, improving diabetes control was associated with significantly less development or

progression of diabetic retinopathy in the Kumamoto study (Ohkubo et al., 1995), the UKPDS (UKPDS Study Group, 1998), and the STENO-2 Study (Gaede et al., 2008).

This Section reviews the evidence on the potential harmful effects of improving blood glucose control in people with type 2 diabetes.

Evidence – Harmful effects of improving blood glucose control in people with type 2 diabetes

Improving blood glucose control increases the risk of hypoglycaemia

All RCT studies which have included intensive treatment to improve glycaemic control have reported an increase in risk of hypoglycaemia.

A systematic review of the effect of improving glycaemic control on complications in type 2 diabetes (Gaster and Hirsch, 1998) included three randomised clinical trials which reported rates of hypoglycaemia. Among these studies rates of severe hypoglycaemia were found to be less common in type 2 diabetes than in type 1 diabetes. In the Kumamoto study there were no major episodes of hypoglycaemia requiring hospitalisation or the assistance of another person (Ohkubo et al., 1995). Rates of severe hypoglycaemia were also low in the feasibility study for the Veterans Affairs Cooperative Study on Glycaemic Control and Complications in Type II Diabetes (VA-CSDM) study (Abraira et al., 1995). The incidence of severe hypoglycaemia was not significantly different between the intensive and standard treatment groups (0.03 vs 0.01/patient-year). However, the incidence of mild or moderate hypoglycaemia was significantly higher with intensive therapy (16.5/patient-year) compared with standard therapy (1.5/patient-year) ($p < 0.001$). In addition, 19.2% of hypoglycaemic episodes with intensive therapy occurred during sleeping compared with 3.6% with standard therapy ($p < 0.001$). The 3-year results of the UKPDS showed higher rates than the other two studies (UKPDS Study Group, 1995). Major hypoglycaemic episodes occurred in 0.8%, 0.5% and 1.4% of participants per year allocated to treatment with sulphonylureas, metformin and insulin respectively, compared with 0.2% in the standard treatment group.

Woolf et al (2000) also performed a systematic review of controlling blood glucose levels in type 2 diabetes. This review included the same studies as the Gaster & Hirsch review but in addition included the final results of the UKPDS (UKPDS Study Group, 1998). The median HbA_{1c} values were significantly lower in the intensive group than in the conventional group over 10 years (7.0% vs 7.9%, $p < 0.0001$) and the median HbA1c values for treatment with chlorpropamide was 6.7%, with glibenclamide 7.2%, and with insulin 7.1%, each lower than in the conventional treatment group (7.9%, $p < 0.0001$). People in the intensive group experienced more hypoglycaemic episodes than those in the conventional group. By intention-to-treat analysis, the rates of major hypoglycaemic episodes per year were 0.7% with conventional treatment, 1.0% with chlorpropamide, 1.4% with glibenclamide and 1.8% with insulin ($p < 0.0001$). Any hypoglycaemic episode occurred in 10% of people treated with diet alone, 16% with chlorpropamide, 21% with glibenclamide and 28% with insulin.

The UKPDS also examined the effect of metformin and other therapies in overweight people (> 120% ideal body weight) (UKPDS Study Group, 1998). Over 10 years of follow-up the proportions of people per year who had one or more major hypoglycaemic episode in the conventional, chlorpropamide, glibenclamide, insulin, and metformin groups were 0.7%, 0.6%, 2.5%, 0.3%, and 0% respectively; for any hypoglycaemic episode the corresponding

proportions were 0.9%, 12.1%, 17.5%, 34.0%, and 4.2%. Among all people, major hypoglycaemic episodes occurred in 0.7%, 1.2%, 1.0%, 2.0%, and 0.6%, respectively, of the conventional, chlorpropamide, glibenclamide, insulin, and metformin groups, and any hypoglycaemic episodes in 7.9%, 15.2%, 20.5%, 25.5%, and 8.3%, respectively.

Wright et al (2006) examined the occurrence of hypoglycaemia and its contributing factors in people with type 2 diabetes from the UKPDS who were randomised to 6 years on diet, sulphonylurea, metformin (overweight subjects only), or insulin monotherapy. Self-reported hypoglycaemic episodes were graded on a 4-point scale by physicians as (1) transient, (2) temporarily incapacitated, (3) requiring third-party assistance, and (4) requiring medical attention, recording the most severe episode each quarter. Proportions of subjects reporting at least one episode per year were calculated in relation to therapy, HbA1c, and clinical characteristics. Of 5,063 people aged 25-65 years, the overall proportion reporting at least one Grade 1–4 hypoglycaemic episode (95% CI) per year was 11% (10.7–11.2), for Grade 2–4 episode 2.5% (2.4–2.7), and for Grade 3 or 4 episode 0.55% (0.50–0.60). Hypoglycaemia was more frequent in younger (4.0% < 45 years vs 2.2% ≥ 45 years), female (3.0% vs 2.2% male), normal weight (3.6% body mass index < 25 kg/m^2 vs 1.9% ≥ 25 kg/m^2), less hyperglycaemic (5.2% HbA1c < 7% vs 2.3% ≥ 7%), or islet autoantibody-positive subjects (4.3% vs 2.1% negative) (all $p < 0.0001$). Use of basal insulin was associated with more hypoglycaemia (3.8% per year) than diet (0.1%), sulphonylurea (1.2%), or metformin (0.3%) therapy, but less than on basal and prandial insulin (5.3%) (all $p < 0.0001$).

Akram et al (2006) conducted a literature review using Medline and EMBASE identifying 11 studies (5 retrospective and 6 prospective) to assess the risk of intensive treatment regimes and severe hypoglycaemia in people with type 2 diabetes. The incidence of severe hypoglycaemia in the retrospective studies were very diverse and varied from 15 to 73 episodes per 100 person-year with a proportion of the people having one or more episodes between 1.4 to 15%. In the prospective studies, both incidence rate and proportion of the people having one or more episodes of severe hypoglycaemia were lower than in the retrospective studies.

The recently reported ADVANCE study (ADVANCE Collaborative Group, 2008) examined the effects of intensive glucose control on vascular outcomes in 11,140 people with type 2 diabetes. After 5 years of follow-up, the mean glycated haemoglobin level was lower in the intensive-control group (6.5%) than in the standard-control group (7.3%). Severe hypoglycaemia occurred more frequently in the intensive-control group than in the standard-control group: 150 subjects (2.7%) in the intensive-control group had at least one severe hypoglycaemic episode compared with 81 subjects (1.5%) in the standard control group (hazard ratio, 1.86; 95% CI, 1.42–2.40; $p < 0.001$). In the standard control group there was one fatal hypoglycaemic episode, and in both groups one hypoglycaemic event which resulted in permanent disability. On average, the rate of severe hypoglycaemic events was

0.7 events per 100 person per year in the intensive group and 0.4 events per 100 person per year in the standard group. In the intensive-control group, minor hypoglycaemia occurred more often compared with the standard care (120 events per 100 person per year, vs 90 with standard control). Almost 50% of all people undergoing intensive control remained free from any hypoglycaemia – sever or minor – during the follow-up period.

In another large, randomised controlled trial involving 10,251 people with type 2 diabetes, (ACCORD Study Group, 2008) intensive therapy achieved an HbA1c of 6.4% compared with 7.5% in the standard-therapy group. There were significantly higher rates of hypoglycaemia (10.5% vs 3.5%) in the intensive therapy group compared with the standard-therapy group ($p < 0.001$). The annualised rate of hypoglycaemia where medical assistance was required was 3.1% in the intensive-therapy group and 1.0% in the standard-therapy group.

In the STENO-2 Study, 160 people with type 2 diabetes (mean age 55.1 years) and persistent microalbuminuria were randomly assigned to receive either intensive or conventional treatment (Gaede et al., 2008). The intensive blood glucose control group achieved a mean HbA1c of 7.7% while the standard treatment group had reached a mean HbA1c of 8.0%. Observations over 13.3 years revealed at least one reported minor episode of symptomatic hypoglycaemia in 80% of intensively controlled people compared with 70% in the conventional-therapy group ($p = 0.15$). There was no statistical difference in major hypoglycaemia episodes (13% in the intensive-therapy group and 17% in the conventional-therapy group, $p = 0.52$).

The VADT examined whether intense blood glucose control could reduce the risk of cardiovascular disease in United States veterans ($n = 1,791$) with uncontrolled glucose on current insulin or oral hypoglycaemic agents (Duckworth, 2009). Average HbA1c in the groups was 9.4% at baseline and, after 6 months, the standard treatment group reached 8.4% and the intensive treatment group 6.9%. Severe hypoglycaemia requiring medical assistance was reported in 21% of those in the intensively treated group versus 10% in the standard treatment group ($p < 0.001$).

Epidemiological data also provide information on hypoglycaemia prevalence and associated risk factors. Mild hypoglycaemia is common in people with type 2 diabetes treated with hypoglycaemic agents. Miller et al (2001) investigated the prevalence of hypoglycaemia in 1055 people `(mean age 61 years, diabetes duration 10.8 years) with type 2 diabetes. Hypoglycaemia was defined as typical symptoms which were relieved by eating and/or glucose level < 3.3 mmol/L. During the 7-month follow-up period, 24.5% reported at least one hypoglycaemic episode with glucose readings ranging from 0.9 to 4.2 mmol/L (median 3.1 mmol/L). The prevalence of reported hypoglycaemic episodes varied with type of treatment: 11.8% for diet alone, 16.2% with oral agents and 30.5% for insulin ($p < 0.001$ for trend). People treated with a combination of insulin, sulphonylurea and metformin had a

2-fold increase in prevalence of hypoglycaemia compared with people treated with insulin alone (61.5% vs 29.8%, p = 0.01). There was no difference in prevalence of hypoglycaemia between people treated with insulin alone or in combination with a single oral agent (31.0% vs 25.2%, p = 0.20). Although the rate of hypoglycaemia was higher in people treated with sulphonylurea compared with metformin (15.7% vs 8.6%), this was not significant (p = 0.28). In general, people treated with hypoglycaemic agents tended to have a lower glucose reading than people treated with diet alone (p = 0.06), and they had more glucose values of < 3.3 mmol/L (64.% vs 20.0%, p = 0.05). In a multiple regression analysis, lower follow-up HbA1c level (OR 0.87, 0.78–0.96; p = 0.006), use of insulin therapy (OR 3.44, 2.07–5.73; p < 0.001), younger age (OR 0.98, 0.97–1.00; p = 0.03) and report of hypoglycaemia at baseline (OR 2.65, 1.80–3.80; p < 0.001) were identified as independent predictors of any hypoglycaemia at follow-up; while race, gender, diabetes duration and BMI were not predictors of hypoglycaemia. Five people (0.5%) who were all insulin users reported severe hypoglycaemia (defined as treated by emergency medical services or losing consciousness) during the follow-up.

These studies demonstrate different rates of mild and severe hypoglycaemic episodes with different therapies; these finding have been confirmed in numerous studies comparing different therapies – these are reviewed in detail in Section 5.

Apart from therapy, other situations are associated with increased risk of hypoglycaemia including fasting and increasing age.

Holstein et al (2001) reported the incidence of severe hypoglycaemia in people with type 2 diabetes (mean age 79 years) in a 4-year prospective population based study. Hypoglycaemia was defined by the requirement for intravenous glucose or glucagon injection and blood glucose value of < 2.8 mmol/L. Of the 145 episodes of severe hypoglycaemia, 100 episodes involved insulin therapy and 45 sulphonylurea therapy. Glimepiride induced fewer episodes than glibenclamide (6 vs 38 episodes). The incidence of severe hypoglycaemia was 0.86/1000 person-years for glimepiride and 5.6/1000 person-years for glibenclamide. Forty-five people who experienced hypoglycaemia had an average age of 79 years and significant comorbidities - 62% had a creatinine clearance of < 60 mL/min; 36% had cardiac failure and 29% had coronary heart disease. In addition, this group was found to have HbA1c value of 5.4% (95% CI 5.1–5.7) indicating that their diabetes was well controlled.

Ben-Ami et al (1999) retrospectively studied 102 people with type 1 (10%) or type 2 diabetes (90%) who experienced an episode of drug-induced hypoglycaemic coma. The median age of the subjects was 72 years and treatment included insulin, glyburide, and combinations of insulin and glyburide, insulin and metformin, and glyburide and metformin. Ninety percent had at least one risk factor - age over 60 years, renal dysfunction, reduced energy intake, hypoglycaemia-potentiating medications, and infection. Forty subjects had a prolonged hypoglycaemia of 12–72 hours. Morbidity included physical injuries in seven

people, myocardial infarction in two, stroke in one, and death occurred in five people. These findings confirm that severe hypoglycaemia can be a serious problem, especially in elderly people with diabetes.

De Galan and Hoekstra (2001) conducted a systematic review into counterregulatory responses to hypoglycaemia in people with type 2 diabetes. They identified 12 studies which compared counterregulatory responses to hypoglycaemia induced by continuous insulin infusion, single bolus injection, or hyperinsulinaemic clamp in people with type 2 diabetes and healthy controls. The studies included 107 healthy controls and 137 people with type 2 diabetes (duration of diabetes 1 month to 28 years, mean HbA1c 5.6% to 10.4%, treated with diet or sulphonylureas (nine studies) and insulin (three studies)). Glucagon and growth hormone responses were decreased in seven studies compared with healthy controls, and cortisol responses (in four studies). In diet or sulphonylurea treated people (nine studies), counterregulatory impairments, mainly glucagon, were found in three studies, while insulin-treated people (three studies) had lower glucagon and adrenaline responses and experienced autonomic symptoms at lower glucose levels than those treated with sulphonylurea. Overall, there is impaired counterregulatory hormone responses and awareness of hypoglycaemia in some people with type 2 diabetes. This is more likely to be observed in people treated with insulin, either as a result of antecedent hypoglycaemia or better glycaemic control. However people with type 2 diabetes are less prone than people with type 1 diabetes to experience severe hypoglycaemia and this relative protection may be due to the preservation of some ß-cell function which is suppressed with falling blood glucose levels, and to diminished peripheral effects of insulin secondary to insulin resistance.

The effect of antecedent hypoglycaemia was confirmed by Segel et al (2002) who compared counterregulatory hormone responses to hypoglycaemia induced by hyperinsulinaemic clamps in 13 people with type 2 diabetes (n = 7 on oral agents; n = 6 on insulin) and 15 healthy controls on two consecutive days. On day one, compared with healthy controls, plasma glucagon was reduced and virtually absent in people on insulin (93 ± 15 vs 56 ± 5 pg/mL, p = 0.025), but not in people on oral agents (98 ± 16 pg/mL). Overall, glucagon (p = 0.002), adrenaline (p = 0.0002), and noradrenaline (p = 0.01) responses to hypoglycaemia; and autonomic (p = 0.02) and neuroglycopaenic (p = 0.002) symptom scores were reduced on day two after hypoglycaemia on day one in people with diabetes. The results support a reduced glucagon response in people treated with insulin and that recent antecedent hypoglycaemia results in reduced hypoglycaemia awareness in people with type 2 diabetes.

Murata et al (2004) conducted a prospective observational study to identify clinical factors affecting hypoglycaemia awareness in insulin-treated people with type 2 diabetes. Subjects (n = 344) were randomly selected from pharmacy records at three large medical centres; their blood glucose levels were monitored for up to 52 weeks. For blood glucose levels of ≤ 3.3 mmol/L, subjects recorded the severity of symptoms in a log book. Symptoms were scored "0" if they were asymptomatic, "1" for symptoms that were mild-to-moderate, and

"2" if the subject had a diminished level of consciousness or required the assistance of others. In all, 176 subjects (51.2%) experienced a median of 4.5 hypoglycaemic episodes during the follow-up. After adjusting for blood glucose, symptom scores were lower in the elderly and higher in subjects with higher diabetes knowledge scores, microvascular complications, and higher entry HbA1c. People with better long- and short-term glycaemic control were at higher risk of hypoglycaemia.

Fear of hypoglycaemia is common in people with diabetes

Fear of hypoglycaemia may have significant clinical implications for diabetes management and the unpleasant symptoms and negative consequences can result in significant increases in anxiety. In a literature review using Medline and EMBASE, Wild et al (2007) reviewed the research on fear of hypoglycaemia (FoH) in people with type 1 and type 2 diabetes. Twenty-eight papers were selected from a search limited to journal articles published in English from 1985 to 2007 inclusive; six additional papers were identified by further searches and were added to this review. FoH was measured primarily through the use of a specific scale, the Hypoglycaemic Fear Survey (HFS). FoH is a widespread phenomenon and its development related to a number of factors including a history of hypoglycaemia in an individual, length of time since first insulin treatment, and a higher level of variability in blood glucose level. One study found that 74% of those experiencing frequent hypoglycaemic events had exacerbated anxiety about hypoglycaemia (Costea et al., 1993). Similarly, Irvine et al (1992) showed that individuals with more psychological symptoms (using Hopkins' Symptom Checklist) experienced higher levels of FoH. In another study, 25% of the variance of "worry" on the HFS was accounted for by a history of previous severe hypoglycaemia (Gold et al., 1997). Evidence exists showing that FoH may have a significant negative impact on diabetes management, metabolic control and subsequent health outcomes and needs to be specifically addressed in education programs. Cox et al (1990) reported on an individual who acknowledged intentionally maintaining higher BG levels to avoid a reoccurrence of severe hypoglycaemia. Clarke et al (1998) found a positive linear relationship between HFS scores and HbA1c adding further support to the impact of FoH on glycaemic control. Blood glucose (BG) awareness training and cognitive behavioural therapy can reduce levels of fear and improve disease management, however, more research is needed to understand how FoH arises and the individual variables that predispose its development.

Improving blood glucose control is frequently associated with weight gain

Several recent studies have reported on weight gain being associated with improving diabetes control in people with type 2 diabetes. While weight gain is common, the magnitude of weight gain is related to the therapy used to improve glycaemic control.

A systematic review by Gaster & Hirsch (1998) reported that weight gain from intensified glucose lowering treatments was observed in some but not all studies. For example, in the Kumamoto study (Ohkubo et al., 1995) an increase in body mass index (BMI) was observed in both the intensively and conventionally treated groups from baseline over the 6-year study period (intensive group 20.5 to 21.2 kg/m^2; conventional group 20.3 to 21.9 kg/m^2, p = NS). It should be noted that in this cohort BMI was relatively low compared with a typical Australian with type 2 diabetes. However, in the feasibility study for the Veterans Affairs Cooperative Study on Glycaemic Control and Complications in Type II Diabetes (VA-CSDM) there was no statistically significant difference in weight between the intensive and standard treatment groups over the 27-month study period (Abraira et al., 1995).

The systematic review by Woolf et al (2000) included results from the UKPDS (UKPDS Study Group, 1998). Weight increased in the conventional group by approximately 2.5 kg over 10 years. Weight gain was significantly greater in the intensive group (mean 2.9 kg more that conventional group, $p < 0.001$). Compared with the conventionally treated group, those assigned insulin had a greater weight gain (4.0 kg, $p < 0.0001$) than those assigned chlorpropamide (2.6 kg, $p < 0.001$) or glibenclamide (1.7 kg, $p < 0.001$). The UKPDS also examined the effect of metformin with other therapies in overweight people (> 120% ideal body weight) (UKPDS Study Group, 1998). People treated with metformin gained a similar amount of weight to those in the conventional treatment group and less that the weight gain observed with the other intensive treatment therapies.

In the STENO-2 study people (n = 160) with type 2 diabetes (mean age 55.1 years) and persistent microalbuminuria were randomly assigned to receive either intensive, target-driven therapy or conventional multifactorial treatment (Gaede et al., 2008). Intensive treatment targets included HbA1c of < 6.5% and fasting serum total cholesterol of < 4.5 mmol/L and included a stepwise implementation of behaviour modification and pharmacological therapy that targeted hyperglycaemia, hypertension, dyslipidaemia, and microalbuminuria, along with secondary prevention of cardiovascular disease with aspirin. At the end of 13.3 years of follow-up there were some increases in BMI, however, they changes were not significant (baseline intensive men (kg/m^2 ± SEM): 29.3 ± 3.6, women: 31.1 ± 4.5; baseline conventional men: 30.3 ± 5.3, women: 28.9 ± 3.8; end of follow-up intensive men: 31.1 ± 4.6, women: 34.7 ± 7.0; end of follow-up conventional men: 30.2 ± 5.7, women: 33.4 ± 4.3).

In the ACCORD trial which involved 10,251 people with type 2 diabetes (ACCORD Study Group, 2008), intensive therapy was associated with a significantly greater 3.5 kg weight increase over 3 years compared with a 0.4 kg weight gain in the standard-therapy group.

The ADVANCE trial (ADVANCE Collaborative Group, 2008) in 11,140 people with type 2 diabetes reported that weight gain was not invariable with intensive glucose control. There were no significant differences reported in weight between the two treatment groups at 5 years of follow-up (baseline intensive control (kg ± SD): 78.2 ± 16.8, standard control: 78.0 ± 16.8; end of follow-up intensive control: 78.1 ± 17.5, standard control: 77.0 ± 16.7).

The VA Diabetes Trial (VADT) included 1,791 US veterans with type 2 diabetes from 20 medical centres around the United States (Duckworth, 2009). Most subjects received two or three oral agents plus insulin; by the end of the first year, 90% of intensively-controlled subjects were using insulin. Rosiglitazone was the most commonly prescribed drug and was used aggressively in the intensive arm to maintain the desired HbA1c levels. Mean BMI increased in the intensively-controlled group by 2.5 kg/m^2 compared with 1.1 kg/m^2 in the control group ($p = 0.01$).

Evidence Table: Improving blood glucose control increases the risk of hypoglycaemia

Author (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of Effect*	*Relevance Rating*
	Level	*Study Type*			
Abraira et al., 1995 (USA)	II	RCT	High	Medium^{+}	High
ACCORD Study Group, 2008 (USA)	II	RCT	High	High^{+}	High
ADVANCE Collabortive Group, 2008 (Australia)	II	RCT	High	High^{+}	High
Akram et al., 2006	I	Systematic review	High	Medium^{+}	High
Ben-Ami et al., 1999 (Israel)	III-2	Retrospective cohort	Medium	Medium^{+}	High
de Galan and Hoekstra, 2001	I	Systematic review	High	Low^{+}	High
Duckworth et al., 2009 (USA)	II	RCT	High	High^{+}	High
Gaede et al., 2008 (Denmark)	II	RCT	High	Low^{+}	High
Gaster and Hirsch, 1998	I	Systematic review	High	Medium^{+}	High
Holstein et al., 2001 (Germany)	III-2	Prospective cohort	High	High^{+}	High
Miller et al., 2001 (USA)	III-2	Prospective cohort	High	High^{+}	High
Murata et al., 2004 (USA)	III-2	Prospective cohort	Medium	Medium^{+}	High
Ohkubo et al., 1995 (Japan)	II	RCT	High	Low^{-}	High
Segel et al., 2002 (USA)	III-2	Case-control	Low	High^{+}	High
UKPDS Study Group 13, 1995	II	RCT	High	High^{+}	High
UKPDS Study Group 33, 1998	II	RCT	High	High^{+}	High
UKPDS Study Group 34, 1998	II	RCT	High	High^{+}	High
Woolf et al., 2000	I	Systematic review	High	High^{+}	High
UKPDS Study Group 73, 1998	II	RCT	High	High^{+}	High

$^{+}$ Improving blood glucose control increases the risk of hypoglycaemia

Clinical importance rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

Evidence Table: Fear of hypoglycaemia is common in people with diabetes

Author (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of Effect*	*Relevance Rating*
	Level	*Study Type*			
Clarke et al., 1998 (USA)	III-2	Retrospective cohort	Medium	High[+]	High
Costea et al., 1993 (Romania)	III-2	Prospective cohort	High	High[+]	High
Cox et al., 1990	III-2	Cross-sectional	Low	Low[+]	Medium
Gold et al., 1997 (UK)	III-2	Prospective cohort	Medium	Medium[+]	High
Irvine et al., 1992 (USA)	III-2	Cross-sectional	Medium	Medium[+]	High
Wild et al., 2007	I	Systematic review	High	Medium[+]	High

[+] Fear of hypoglycaemia is common in people with diabetes

Clinical importance rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

Evidence Table: Improving blood glucose control is frequently associated with weight gain

Author (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of Effect*	*Relevance Rating*
	Level	*Study Type*			
Abraira et al., 1995 (USA)	II	RCT	High	Low^{-}	High
ACCORD Study Group, 2008 (USA)	II	RCT	High	High^{+}	High
ADVANCE Collabortive Group, 2008 (Australia)	II	RCT	High	Low^{-}	High
Duckworth et al., 2009 (USA)	II	RCT	High	High^{+}	High
Gaede et al., 2008 (Denmark)	II	RCT	High	Low^{+}	High
Gaster and Hirsch, 1998	I	Systematic review	High	Medium^{+}	High
Ohkubo et al., 1995 (Japan)	II	RCT	High	Low^{+}	High
UKPDS Study Group 33, 1998	II	RCT	High	High^{+}	High
UKPDS Study Group 34, 1998	II	RCT	High	Low^{-}	High
Woolf et al., 2000	I	Systematic review	High	Medium^{+}	High

$^{+}$ Improving blood glucose control is frequently associated with weight gain

Clinical importance rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

Section 3: Blood Glucose Control

Question

How should blood glucose control be assessed?

Recommendations

Glycated haemoglobin (HbA1c) measurement should be used to assess long term blood glucose control. (Grade A)

Self monitoring of blood glucose (SMBG) should be considered in all people with type 2 diabetes but the decision to perform SMBG, and the frequency and timing of testing, should be individualised. (Grade C)

Practice Points

Glycated haemoglobin should be measured at least twice a year in people with type 2 diabetes and stable blood glucose control. More frequent testing is required in people with sub-optimal control and following changes to therapy.

Health professionals should be aware of factors which interfere with accurate measurement of glycated haemoglobin.

Laboratory glycated haemoglobin measurement should be aligned to the DCCT method.

Evidence Statements

- Glycated haemoglobin level correlates with diabetes complications and outcomes.
  Level of Evidence I

- An accurate and precise method is required for measuring glycated haemoglobin.
  Level of Evidence IV

- A number of clinical situations can affect the glycated haemoglobin result.
  Level of Evidence I

- The frequency of glycated haemoglobin testing is dependent on the clinical situation.
  Level of Evidence III

- Glycated proteins are an alternate measure of blood glucose control but there are no data on their relationship with chronic diabetes complications.
  Level of Evidence III

- Self measurement of blood glucose (SMBG) is a useful method for assessing real time blood glucose levels.
  Level of Evidence I

- There are limited data on the frequency and timing of SMBG testing.
  Level of Evidence III

Background – Assessment of blood glucose control

Glycaemic control is an important factor in the development of micro- and macrovascular complications and improvements in blood glucose levels are associated with reduced development and progression of microvascular complications. Therefore monitoring of glycaemic control is an important component of diabetes care.

Historically a number of methods have been used to monitor glycaemia in people with diabetes (Goldstein et al., 2004). Options are either based on laboratory testing or patient self-testing. Patient self-testing was initially based on urine glucose testing but has evolved to the use of portable meters which measure blood glucose, referred to as self-monitoring of blood glucose (SMBG).

While SMBG provides useful information for day-to-day management of diabetes, an objective measure of glycaemia over an extended period of time is also required. This is achieved by the measurement of glycated proteins which can estimate average glycaemia over weeks and months.

Glycated Haemoglobin

Glycated haemoglobin (HbA1c) refers to substances which are formed by any carbohydrate binding to haemoglobin in the red blood cell. Glycohaemoglobin is also used as an alternative term to glycated haemoglobin.

The major forms of adult haemoglobin (Hb) are:

- HbA (which consists of 2α and 2β chains) and makes up about 90% of adult Hb and includes:
    - HbA_0 – is the non-glycated fraction of HbA and
    - HbA_1 – is the glycated fraction of HbA which has the following subfractions:
        - HbA_{1a1} – in which fructose-1,6-biphosphate is bound to the β chain
        - HbA_{1a2} – in which gucose-6-phosphate is bound to the β chain
        - HbA_{1b} – in which unknown carbohydrate is bound to the β chain
        - HbA_{1c} – in which glucose is bound to the β chain

- HbA_2 (which consists of 2α and 2δ chains) and makes up about 2.5% of adult Hb

- HbF (foetal haemoglobin) consists of 2α and 2γ chains and is the major form of foetal haemoglobin and almost completely disappears within 6 months of birth and makes up < 1% of adult Hb.

The HbA1c fraction is the major part of glycated haemoglobin and is formed by the binding of glucose to the N valine terminal of the β chain of Hb. This occurs in a two-step process. The initial and rapid process takes minutes to hours to form an aldimine complex (Schiff

base), a reaction which is reversible. Over subsequent days to weeks this unstable aldimine complex undergoes an Amadori rearrangement to form the stable ketoamine HbA1c. Glucose binding (glycation) occurs slowly and continuously over the life span of a red blood cell (120 days) (Bunn et al., 1978).

Because erythrocytes are freely permeable to glucose, the level of HbA1c provides a glycaemic history of the previous 120 days, the average erythrocyte lifespan. HbA1c reflects the time averaged blood glucose over the preceding 1-3 months (Bunn et al., 1976) and is highly correlated to long-term complications of diabetes (retinopathy, nephropathy and neuropathy) (Dahl-Jorgensen et al., 1986; Klein et al., 1988; Molitch et al., 1993).

A number of different methods are used to routinely measure glycated haemoglobin. These fall into two major categories: those based on charge differences between glycated haemoglobin and non-glycated haemoglobin (these include cation-exchange chromatography, electrophoresis, and isoelectric focusing) and those based on structural characteristics of glyco groups on haemoglobin (these include affinity chromatography and immunoassay). Most methods quantifying HbA1c show excellent correlation; there are no convincing data to show that any one method is clinically superior to any other.

It is important that HbA1c laboratory assays produce the same numerical values and result in the same clinical information for both patients and clinicians throughout the world. HbA1c treatment goals are derived from the two major glycaemic control intervention studies, the DCCT (DCCT Study Group, 1993) and the UKPDS (UKPDS Study Group, 1998). However a number of studies have shown considerable variation in HbA1c results between various laboratories (Gilbert et al., 1996; Kullberg et al., 1996; Gibb et al., 1997).

As a result a number of national and international programs have been developed to standardise HbA1c assays. In the US in 1996, the National Glycohemoglobin Standardisation Program (NGSP) was initiated to standardise HbA1c test results among laboratories to DCCT-equivalent values (Goldstein et al., 2004). At an international level, the International Federation of Clinical Chemistry (IFCC) established a Global Reference System for HbA1c measurement (Hoelzel and Miedema, 1996). Although the same unit, % HbA1c, is used throughout the world, there are three National Schemes producing different numerical values for % HbA1c in the USA (NGSP), Japan and Sweden and in associated countries using these standardisation schemes. The feasibility of international harmonisation of HbA1c has been established (Hoelzel et al., 2004) by comparing programs from the US, Japan and Sweden with the IFCC Reference Method (RM). This has resulted in a set of Master Equations defining the relationship of the IFCC and national reference methods (Hoelzel et al., 2004):

US DCCT HbA1c	=	0.915	*	IFCC HbA1c	+	2.15% (r^2=0.998)
Japan HbA1c	=	0.927	*	IFCC HbA1c	+	1.73% (r^2=0.997)
Swedish HbA1c	=	0.989	*	IFCC HbA1c	+	0.88% (r^2=0.996)

By the use of these stable linear relationships, all past, present and future clinical trials and studies can be referenced to either old % HbA1c units or new IFCC units without any necessity to repeat any part of the studies.

Debate continues on which HbA1c units should be reported worldwide. As noted above IFCC units are 1–2% lower than currently used HbA1c results, resulting in a non-diabetic reference range of approximately 2.0–4.2%. Because of concern that these new figures would result in considerable confusion among people with diabetes, it has been suggested that in the future reporting of HbA1c should be abandoned and replaced by conversion to a mean blood glucose (MBG) equivalent.

To determine whether DCCT-aligned HbA1c could be expressed and reported in the same units as average glucose (AG) levels used in SMBG, an international multi-centre study involving 661 subjects from 10 clinical centres examined the mathematical relationship between HbA1c and AG (Nathan et al., 2008). In all, there were 507 people, including 268 with type 1 diabetes, 159 with type 2 diabetes, and 80 people without diabetes. Subjects had HbA1c measured every 4 weeks, and 4 x 48 hour periods of continuous glucose monitoring with a glucose sensor (CGMS Medtronic) and simultaneously measured eight point self measured capillary glucose using the HemoCue meter (SMBG HemoCue). Between the weeks of the CGMS measurements, a seven point self monitoring capillary glucose using the Lifescan meter (SMBG Lifescan) was also performed three days per week. Results of the study showed a close simple linear relationship between HbA1c levels and AG for both type 1 and type 2 diabetes in a clinically relevant range of glycaemia and supported the reporting of measured HbA1c as eAG. Ninety percent of estimates fell within the ± 15% range of the regression line and the criterion was realistic allowing for the imprecision of the HbA1c assay, CGM, and SMBG tests.

Ongoing deliberations involving a number of global peak bodies, including the International Diabetes Federation, continue on whether reporting HbA1c values along with the calculated eAG level should be adopted and implemented (International Diabetes Federation, 2007).

Glycated serum proteins

Measurement of glycation of serum proteins is another option for assessing longer term glycaemic control. Since human serum albumin has a half-life of approximately 14 days, the degree of glycation of albumin provides an index of glycaemia over a shorter period of time than glycated haemoglobin (Windeler and Kobberling, 1990). The term fructosamine was originally introduced as a general term for glycated protein. However the term is now used to refer to the specific analyte measured by the nitroblue tetrazolium (NBT) assay, which is known as the fructosamine assay (Goldstein et al., 2004). Measurements of total glycated serum proteins and glycated serum albumin have been suggested as alternative methods for routine monitoring of glycaemia in people with diabetes, however, there remain a number of unresolved problems with the assay.

Self monitoring of blood glucose (SMBG)

Many aspects of SMBG were reviewed at a consensus meeting (Bergenstal and Gavin, 2005). In general SMBG adds information which complements glycated haemoglobin data by providing real-time feedback to people with diabetes, their carers and health professionals. It allows detection of hypoglycaemia and hyperglycaemia which can improve safety and also helps to motivate people with diabetes to make appropriate treatment changes. In addition to evaluating blood glucose control, SMBG is an educational tool to inform both patient and health care professionals about the effects of lifestyle, behavioural and/or medication changes and to be fully effective requires ongoing education and reinforcement about the use of the data.

This Section reviews currently available options for routine assessment of blood glucose control.

Evidence – Assessment of blood glucose control

Glycated haemoglobin level correlates with diabetes complications and outcomes

Both epidemiological and intervention studies have shown a relationship between HbA1c and diabetes related complications, with lower levels of HbA1c being associated with fewer complications. While the evidence is stronger for microvascular complications, this relationship is also evident for macrovascular complications.

Epidemiological studies

Stratton et al (2000) reported epidemiological data from the UKPDS showing a significant association between mean updated HbA1c and clinical complications in people with newly diagnosed diabetes followed over 10 years. Each 1% increase in HbA1c was associated with a 21% (95% CI 17% to 24%, $p < 0.0001$) increased risk of any end point, 21% for deaths related to diabetes (15% to 27%, $p < 0.0001$), 14% for myocardial infarction (8% to 21%, $p < 0.0001$), and 37% for microvascular complications (33% to 41%, $p < 0.0001$). In people with type 2 diabetes the risk of diabetes complications was strongly associated with previous hyperglycaemia.

Selvin et al (2004) performed a systematic review and meta-analysis of observational studies reporting the association between glycated haemoglobin and incident cardiovascular disease (coronary heart disease and stroke) in prospective cohort studies in people with diabetes. The review included three studies in people with type 1 diabetes (n = 1,688) and 10 studies in people with type 2 diabetes (n = 7,435). A one percentage point increase in glycated haemoglobin level was associated with a pooled relative risk for cardiovascular disease of 1.18 (95% CI, 1.10–1.26) in people with type 2 diabetes and 1.15 (CI, 0.92–1.43) in people with type 1 diabetes. These data suggest that chronic hyperglycaemia as measured by HbA1c is associated with an increased risk for cardiovascular disease in people with type 2 diabetes.

In the Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR), Klein et al (1994) examined the relationship of glycated haemoglobin and incidence and progression of diabetic retinopathy over a 10-year period. In people older than 30 years at onset of diabetes (n = 834) glycated haemoglobin levels in the highest quartile at baseline were more likely to have progression of retinopathy than people with levels in the lowest quartile (RR 2.1; CI, 1.6–2.8 in people taking insulin; RR 4.3; CI, 3.0–6.2 in people not taking insulin; $p < 0.005$ in all groups after controlling for other risk variables).

Interventions studies

Intervention studies have been reviewed in Section 1 and are summarised here. The UKPDS compared the effects of intensive blood-glucose control and conventional treatment on the risk of microvascular and macrovascular complications in 3,867 people with newly

diagnosed type 2 diabetes (UKPDS Study Group, 1998). Over 10 years, an HbA1c of 7.0% in the intensive group compared with 7.9% in the conventional group was associated with 12% less (CI 1–21, p = 0.03) any diabetes-related endpoint, due mostly to 25% less (CI, 7–40, p = 0.01) microvascular endpoints, including the need for retinal photocoagulation.

The Kumamoto study included 110 non obese insulin requiring Japanese people with type 2 diabetes. The intensive treatment achieved a mean HbA1c of 7.1% compared with a mean HbA1c of 9.4% in the conventionally treated group. The lower HbA1c level was associated with less development or progression of retinopathy and nephropathy (Ohkubo et al., 1995).

Recent data from three major intervention studies where intensive versus standard glucose lowering were examined indicate benefits for improved blood glucose control on microvascular complications but remain equivocal for macrovascular outcomes.

The ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) trial involved 11,140 people with type 2 diabetes and showed a significant reduction in microvascular outcomes due to a reduction in renal complications with intensive blood glucose lowering (hazard ratio, 0.79; 95% CI, 0.66 to 0.93; p = 0.006) which achieved a mean HbA1c of 6.5% compared with standard therapy which achieved a mean HbA1c of 7.3% (ADVANCE Collaborative Group, 2008).

The other two recent major intervention studies (ACCORD and VADT), where intensive versus standard glucose lowering was examined, have not reported the results of microvascular outcomes.

ADVANCE and VADT (mean HbA1c in the intensive group 6.9% vs 8.4% in the conventional treated group) did not show any significant difference in cardiovascular outcomes or mortality. ACCORD (mean HbA1c in the intensive group 6.4% vs 7.5% in the conventional treated group) reported an increase in total mortality in the intensive treated group (257 subjects died in the intensive-therapy group compared with 203 subjects in the standard therapy group [hazard ratio, 1.22; 95% CI, 1.01 to 1.46; p = 0.04]) but a lower rate of non-fatal myocardial infarction compared with the conventional treated group (186 vs 235 non-fatal myocardial infarctions, respectively; hazard ratio 0.76; 95% CI, 0.62 to 0.92; p = 0.004).

An accurate and precise method is required for measuring glycated haemoglobin

The analytical requirements of HbA1c assays in terms of accuracy and precision are crucial to providing a reliable result to assess level of diabetes control and on which to base treatment changes.

There are 3 main sources which contribute to variations in HbA1c assay results:

Pre-analytical (e.g. specimen preparation etc)
Analytical
Within laboratory (intra-assay and inter-assay)
Between laboratory
Biological

Consideration of these is important because they can contribute to significant differences in HbA1c results which can lead to incorrect assessment of diabetes control and inappropriate therapeutic decisions.

Assay accuracy is defined as the true value of HbA1c in an individual specimen, irrespective of whether the HbA1c value is below, within or above the normal range. On the other hand, precision is the ability to obtain the same HbA1c result repeatedly, even if it is not accurate. Since HbA1c measurement is used clinically for long term monitoring of the person with diabetes, long term accuracy and tight analytical precision are essential.

Imprecision can occur within laboratories and between laboratories. Acceptable levels of imprecision are determined by consensus and take into account the effect of imprecision on HbA1c result which in turn influences clinical decision making. The review on tests of glycaemia in diabetes by Goldstein et al (2004) recommended that laboratories should use a HbA1c assay method with an intra-laboratory coefficient of variation (CV) of < 4% (ideally < 3%) and that laboratories should provide basic information about the assay method including type of assay method, non diabetic reference range, potential assay interference, and assay performance (e.g. some measure of assay imprecision, such as CV). The National Academy of Clinical Biochemistry guidelines recommend an intra-laboratory CV < 3% and inter-laboratory CV < 5% (Sacks et al., 2002). The Australian Diabetes Society, Royal College of Pathologists of Australasia and the Australasian Association of Clinical Biochemists group recommended intra-laboratory CV < 3% (Colman et al., 1997). The UK Association of Clinical Biochemistry recommends that an HbA1c assay should have a within-laboratory CV < 3.0% and between-laboratory CV < 5.0% (Marshall and Barth, 2000).

Biological variability in an individual's HbA1c is due to random fluctuations around that person's set-point and biological variation between individuals is due to individual specific factors, especially "high" or "low" glycation status. However it is difficult to distinguish

true biological variation from analytical variance in people without diabetes. In a study of 48 men without diabetes, Rohlfing et al (2002) collected serial samples for HbA1c analysis on a weekly basis for a total of 12 visits. Small between-subject variance of 0.20% HbA1c (CV = 4.0%) and within-subject variance of 0.08% HbA1c (CV = 1.7%) was observed. Distinguishing biological random and pathological variations in HbA1c in people with diabetes is also difficult. However biological variation appears to be greater in people with diabetes. A within-subject variance of 0.44% HbA1c was reported by Phillipov and Phillips (2001), 0.41% by Hyltoft Petersen et al (1990) and 0.17-0.29% by Kolatkar et al (1994).

Health professionals should be aware of the uncertainty surrounding the HbA1c result and the change in HbA1c result which truly represents a change in glycaemic status of a person with diabetes. Phillipov and Phillips (2001) presented data on the confidence ranges of reported HbA1c results. From their study which considered both biological and analytical variance, to be 80% confident that HbA1c was truly < 7%, the reported HbA1c concentration should be < 6.4% and to be 95% confident the required mean concentration (two specimens) < 6.3%. Expressed another way, there is only an 80% chance that an HbA1c result of 7% is actually between 6.4 and 7.6%. Similarly Koskinen et al (1993) reported that in their laboratory consecutive HbA1c results needed to have changed by > 0.65% for the results to be significantly different. With improvements in laboratory methods these ranges are likely to be smaller but cannot be totally eliminated. For example Tejani et al (2002), using an assay with an analytical CV of 1.8%, reported that taking into account biological variation in a group of people with stable diabetes control, an HbA1c of 7% would need to be < 6.6% or > 7.4% on subsequent testing to represent a clinically significant change.

In addition to laboratory measurement of HbA1c, point-of-care testing of HbA1c using a DCA 2000 is used in a number of clinical settings in Australia, particularly in diabetes centres. This instrument uses an immunoassay method for measuring HbA1c. The accuracy of this method has been assessed and has been found to be generally acceptable for clinical practice.

One hundred and fifty-seven people with type 2 diabetes, 80 with type 1 diabetes and 10 people without diabetes were studied to compare HbA1c measured by the DCA 2000 and the HPLC method (Matteucci et al., 1998). The HbA1c measured by the DCA was 7.8% (range 4.6–13.8%) and 8.2% (range 5–14.6%) by the HPLC method (correlation co-efficient 0.91) but the paired results were significantly different ($p < 0.001$) with DCA 2000 results being consistently lower.

The validity and reliability of HbA1c results obtained from the DCA 2000 when used under field conditions by nonmedical operators was assessed by Carter et al (1996). The absolute relative difference between the mean DCA 2000 and the reference laboratory HPLC method was 4.0 and 2.0% for 1994 and 1995 respectively. The mean coefficient of variation for paired measures was 3.0% in 1994 and 2.8% in 1995.

Arsie et al (2000) also assessed the DCA 2000 and HPLC in 171 people including 22 healthy controls, 78 people with type 2 diabetes, 11 women with gestational diabetes, 6 people with hyperlipidaemia, 38 people with chronic renal failure, 13 people with diabetes and renal failure and 3 people with haemoglobinopathies. HbA_{1c} values measured by the DCA 2000 were found to be significantly lower in all groups compared with the HPLC method - 5.0 v 5.7% ($p < 0.0001$) for controls, 5.2 v 6.0% ($p < 0.0001$) for gestational diabetes, 7.6 v 8.4% ($p < 0.0001$) for type 2 diabetes, 6.3 v 7.4% ($p < 0.0001$) for diabetes and chronic renal failure, 5.0 v 6.0% ($p < 0.0001$) for non diabetes and chronic renal failure; 5.9 v 6.8% for hyperlipidaemia and no results were obtained for the haemoglobinopathies group by the HPLC method although the DCA analyser gave a result of 6.0%. The reproducibility by the two methods was similar with CVs ranging from 1.9 to 3.0% for the HPLC method and 3.2 to 3.9% for the DCA 2000. The correlation between the two systems was 0.923.

A number of clinical situations can affect the glycated haemoglobin result

Apart from changes in blood glucose control, a number of clinical situations may compromise the HbA1c result. Unfortunately the interference effect may differ for different methods of measuring glycated haemoglobin and therefore laboratories should routinely report these situations with the method used in their laboratory.

Red cell survival

Any situation which shortens erythrocyte survival or decreases mean erythrocyte age falsely lowers HbA1c test results regardless of the assay method. Panzer et al (1982) showed that levels of HbA1c were significantly ($p < 0.0005$) lower in people with haemolytic anaemia ($n = 20$; mean = 3.9% ± 0.1 % SD) compared with people with non-haemolytic anaemia ($n = 20$; mean = 7.0% ± 0.7%) and normal controls ($n = 30$; mean = 6.7% ± 0.7%). They demonstrated a curvilinear correlation between HbA1c and red cell survival (0.88; $p < 0.001$).

Iron deficiency anaemia

Iron-deficiency anaemia increases HbA1c (Tarim et al., 1999). Thirty-seven people with type 1 diabetes (11 with iron deficient and 26 iron-sufficient) were studied and compared with two non-diabetic control groups. All people with iron deficiency were treated with iron at 6 mg/kg per day for 3 months. After iron therapy, HbA1c decreased from a mean of 10.1% to a mean of 8.2% ($p < 0.05$) in people with diabetes and from 7.6% to 6.2% ($p < 0.05$) in people without diabetes. Among people with type 1 diabetes, iron deficiency anaemia is associated with higher concentrations of HbA1c and iron replacement therapy leads to a drop in HbA1c in both patients with and without patients.

Blood transfusion

Blood transfusions which includes RBCs from a person who does not have diabetes will reduce the average level of glycation of circulating haemoglobin, and hence reduce the HbA1c (Panzer et al., 1982) and it can take 1–2 months before HbA1c level is restored to a level reflecting blood glucose control. However transfusions can also increase HbA1c. Weinblatt et al (1986) noted that 4 people without known diabetes who were being treated with chronic transfusions had significantly elevated HbA1c levels on several occasions. On further investigation, it was discovered that elevated levels of HbA1c were present in donor blood stored in dextrose solutions, leading to a higher level in the recipients and the authors concluded that HbA1c levels appear to be unreliable in people receiving large amounts of transfused blood.

Haemoglobin Variants

Bry et al (2001) performed a systematic review on the effects of haemoglobin variants and chemically modified derivatives on glycated haemoglobin assay methods. Genetic variants and chemically modified derivatives of haemoglobin can have profound effects on the accuracy of HbA1c measurement, but these effects vary considerably with the different

commercially available methods. Commonly encountered haemoglobin variants include HbS, HbC, HbE, and HbF and these variants are not uncommon in people with diabetes (Bry et al., 2001). Differing effects of common and uncommon haemoglobin variants illustrate the need for laboratories to report the effects for their particular assay and for health professionals to be aware of the potential effect. These effects are summarised in the Bry et al (2001) review and are also summarised on the National Glycohemoglobin Standardisation Program (NGSP) website at www.ngsp.org.

In general, affinity chromatography methods show no interference from any of these haemoglobin variants and derivatives and is the assay method of choice for people with haemoglobin variants. Abnormal haemoglobin variants interfere mainly with cation exchange methods in either a positive or negative way depending on the individual manufacturers separation system. The effect is less on immunological methods compared with many cation exchange methods but both positive and negative effects have been reported. HbF (generally at levels > 10% HbF) will effect immunoassays because the glycated HbF is not recognised by the antigenic site, but the non-glycated HbF is measured as part of the total haemoglobin assay and will therefore result in false lowering by a similar per cent to the elevation of the HbF level. Normal HbF is < 1.0% but increased levels occur in thalassaemias and late pregnancy and in people with abnormal Hb variants (Bry et al., 2001).

Uraemia

Urea spontaneously dissociates *in vivo* to form ammonia and cyanate and the latter forms isocyanic acid which can react with the N-terminal valine of the haemoglobin ß chain to form carbamylated haemoglobin. One mmol/L urea is associated with the formation of 0.063% carbamylated haemoglobin and some uraemic patients may have carbamylated HbA1c as high as 3% of total HbA1c. Carbamylated haemoglobin interfers with HbA1c assayed by HPLC and electrophoresis but not by affinity chromatography and immunoassay (Weykamp et al., 1993).

Vitamins C and E

Vitamin C can falsely lower HbA1c results, possibly by inhibiting glycation of haemoglobin. Davie et al (1992) studied 12 subjects without diabetes who consumed 1 g/day vitamin C for 3 months. Although there were no significant changes in fasting glucose, HbA1c measured by affinity chromatography decreased 18%, from 6.2% at the start to 5.1% ($p < 0.0001$) after 3 months, whereas, HbA1c measured by electrophoresis increased 16%, from 6.2% to 7.2% ($p < 0.0001$) over the 3 months. Glycosylated albumin decreased 33% ($p < 0.0001$).

Ceriello et al (1991) studied the effects of daily vitamin E supplementation of 600 mg and 1200 mg for 2 months in people with insulin-requiring diabetes and demonstrated reduced protein glycosylation independent of changes in plasma glucose, an effect that may be due to the inhibition of labile glycosylation.

Hypertriglyceridaemia

Falko et al (1982) reported in a person with diabetes that marked hypertriglyceridaemia resulted in a significant false increase in HbA1c measured by the cation-exchange chromatographic method. Conversely Garrib et al (2003) reported falsely low HbA1c in a person with diabetes and hypertriglyceridaemia measured by affinity chromatography but the result was unaffected when measured by HPLC and immunoturbidimetric methods.

Alcohol

The effect of alcohol on glycated haemoglobin was studied in four groups of 22 people categorised as having diabetes or not having diabetes and then according to drinking behaviour – normal (< 30 g of ethanol/day) or abusive (> 100 g of ethanol/day) (Ben et al., 1989). Each group was of similar age and gender except for the alcoholic group with diabetes which was all males. Fasting plasma glucose levels were not significantly different in people with diabetes with normal or excessive alcohol intake. In those without diabetes HbA1c were significantly lower in the alcoholic subgroup (6.3 vs 7.1%, $p < 0.01$ and 4.3 vs 4.8, $p < 0.001$ respectively). Although HbA1c levels were lower in heavy drinkers with diabetes (8.9 vs 9.5%) the difference was not significant.

Aspirin

Acetylated haemoglobin can interfere with HbA1c measured by HPLC and electrophoresis but not by affinity chromatography and immunoassay (Weykamp et al., 1993). However levels of acetylated haemoglobin formed from chronic use of small doses of acetylsalicylate (200–300 mg/day) or brief use of higher doses (2000 mg/day for one week) are not sufficient to interfere with HbA1c measurements.

The frequency of glycated haemoglobin testing is dependent on the clinical situation

Glycated haemoglobin is a measure of blood glucose levels over the previous 120 days and reflects the time averaged blood glucose over the preceding 1–3 months, depending on the rate of change of blood glucose levels.

Modelling and in vivo studies show that HbA1c is a "weighted" measure of mean blood glucose during the preceding 120 days, more recent past events contributing relatively more to the final result than earlier events. The mean level of blood glucose in the 30 days immediately preceding the HbA1c measurement (days 0–30) contribute approximately 50% to the final result, whereas days 90–120 contribute only approximately 10%. Regardless of the starting HbA1c level, the time required to reach a midpoint between the starting level and the new steady-state level is relatively constant at 30–35 days. Therefore, a large change in mean blood glucose is accompanied by a large change in HbA1c within a matter of 1–2 weeks, not 3–4 months (Beach, 1979; Tahara and Shima, 1993).

The dynamics of the change in blood glucose which is reflected in the HbA1c result should guide decisions about frequency of HbA1c measurement. In a person with type 2 diabetes and stable blood glucose, a minimum of two HbA1c measurements a year should be sufficient for routine assessment of diabetes control. In situations where blood glucose control is not optimal and/or therapeutic changes are made, HbA1c should be measured 3 months later to assess the response.

Glycated proteins are an alternate measure of blood glucose control but there are no data on their relationship with chronic diabetes complications

The relationship between fructosamine and HbA1c results has been assessed in a number of studies. Twenty one people with type 1 diabetes and 29 with type 2 diabetes with stable blood glucose control were assessed by three to five measurements of glycated albumin (fructosamine) and HbA1c over a 6-month period (Braatvedt et al., 1997). HbA1c and fructosamine were measured at the same time and stable blood glucose control was defined as three HbA1c results measured over 3–12 months where the value did not differ by more than 0.5%. Mean HbA1c was 8.4% (5.5–12.2%) and mean fructosamine was 333 μmol/L (203–487 μmol/L) and they were strongly correlated. ($r = 0.661$, $p < 0.0001$). For each fructosamine value a mean HbA1c (95% CI) was determined and found to be wide. For example for a fructosamine of 350 μmol/L, the mean HbA1c was 8.9% but the CI ranged from 6.6% (consistent with good glycaemic control) to 11.2% (consistent with poor control). Although fructosamine and HbA1c results correlate overall, individual results are poorly correlated and fructosamine cannot be used to predict HbA1c.

In a case-control study, 56 elderly people (age 66–95 years, 40 people with type 2 diabetes and 16 control subjects) were assessed to determine the correlation between fasting plasma glucose (FPG) , fructosamine and HbA1c (Cefalu et al., 1989). Over a 4-month period, FPG correlated well with fructosamine ($r =0.79$, $p < 0.001$) and HbA1c ($r = 0.78$, $p < 0.001$). In people with diabetes there was also a good correlation between the HbA1c and fructosamine ($r = 0.82$, $p < 0.001$).

Fructosamine and HbA1c were assessed in 450 people with diabetes (type 1 diabetes 45%, type 2 diabetes 53.5% and gestational diabetes 1.5%) (Hom et al., 1998). HbA1c and fructosamine were significantly correlated ($r = 0.80$, $p < 0.001$). Receiver operating characteristic (ROC) curves were used to assess the HbA1c and fructosamine prediction of blood glucose control into rankings of poor, fair, good, or excellent. Rankings were based on clinical symptoms, previous HbA1c results, home glucose monitoring results and, in some cases, laboratory measurement of fasting blood glucose. The area under the ROC curve was approximately 10% greater for HbA1c indicating a small but statistically significant advantage of HbA1c in predicting blood glucose control ($p < 0.05$).

The value of serum fructosamine in predicting blood glucose control measured by HbA1c was assessed in 98 people with type 2 diabetes (mean age 66 years) (Kruseman et al., 1992). Despite a significant correlation between the fructosamine and HbA1c ($p < 0.001$), the predictive value of fructosamine for an acceptable HbA1c ($\leq 7.6\%$) was 44%.

These studies indicate that although fructosamine and HbA1c are correlated, there are important differences between the two methods in assessing blood glucose control. HbA1c is considered the benchmark measure because all outcomes studies of blood glucose control

and diabetes complications have used this measure and there are no data on diabetes outcomes and blood glucose control assessed by fructosamine or other glycated proteins.

Self measurement of blood glucose (SMBG) is a useful method for assessing real time blood glucose levels

While HbA1c provides a measure of long-term blood glucose control and reliably predicts future complications of diabetes, it does not provide information or feedback on real-time blood glucose levels which are required to make short term adjustments to therapy. The availability of accurate methods for self monitoring of blood glucose provides people with diabetes and their carers with the means of obtaining real-time measurements of blood glucose readings, allowing confirmation of hypoglycaemia or hyperglycaemia and allowing action to be taken to correct these.

Numerous studies have been performed since the introduction of SMBG in the late 1980s demonstrating that available meters are sufficiently accurate for this purpose. Chen et al (2003) examined four brands of commonly used glucose meters using control materials, spiked whole blood specimens, and 461 heparinised whole blood specimens measured in triplicate by each of the four brands of meters compared with laboratory analysis. Testing with glucose meters was performed at three sites, with multiple operators, meters, and representative lots of reagents. Meters were precise with a coefficient of variation of < 4% across a wide range of glucose concentrations. Meters performed consistently throughout the study and, generally, were precise, although precision varied at extremely high or low glucose concentrations. Only a small number of the results showed clinically significant bias, mostly in the hypoglycaemic range.

SMBG is common among people with diabetes in developed countries, however its use is influenced by several factors. Karter et al (2000) examined the frequency and barriers to performing SMBG in 44,181 people with diabetes - type 1 (n = 2,818), insulin-treated (n = 12,090), OHA-treated (n = 29,273) and diet treated (6,762) type 2 diabetes. In people with type 2 diabetes, approximately 5% treated with insulin, 30% treated with OHA and 40% treated with diet did not perform SMBG. Sixty percent of people with type 1 diabetes and 67% with type 2 diabetes reported performing less frequently than the ADA recommendation (at least three times daily for type 1 and at least once daily for type 2 diabetes). After adjusting for multiple variables, in people with type 2 diabetes independent predictors of non-adherence to the ADA recommendation included: male gender (OR 1.3); being older than 65 years (OR 1.3); ethnic group - African-American (OR 1.2), Hispanic (OR 1.2), Asian or Pacific Islander (OR 1.5); lower education level (OR 1.1); higher out-of-pocket expenses for strips (OR 1.4): and having difficulties in English (OR 1.3).

Despite use of SMBG for over 25 years, a number of issues remain unresolved, including the frequency and timing of testing, whether SMBG per se is associated with improved diabetes outcomes, and which category of people with type 2 diabetes should perform SMBG.

Examining a possible relationship between blood glucose control and frequency of SMBG is difficult because of the interdependency of factors which influence blood glucose control and the limitations of cross-sectional studies. For example, SMBG is more likely to be recommended in people with poorer glycaemic control. Harris (2001) assessed the relationship between glycaemic control and frequency of SMBG in 1,480 people (mean age 62.5 years) with type 2 diabetes who had been instructed in SMBG. Of all subjects, 80% of people treated with diet alone, 65% treated with OHAs and 29% treated with insulin had either never performed SMBG or had tested less than once per month, while the percentage of people performing SMBG ≥ once per day was 6.5%, 4.6%, and 39.1%, respectively. The mean HbA1c value according to diabetes therapy was 6.4%, 8.0%, and 8.3% respectively. The percentages of people with a HbA1c ≥ 8.0% were 14.9% in people treated with diet alone, 42.2% in people treated with OHAs and 51.4% in people treated with insulin. The proportion of people who tested their glucose increased with higher HbA1c values – for HbA1c ≥ 8.0%, 14.9%, 42.2%, and 51.4%, respectively. The study failed to show a relationship between HbA1c values and the frequency of SMBG in people treated with diet alone, OHAs or insulin.

The frequency of SMBG (measured by the number of glucose strips dispensed) and glycaemic control was investigated over a 3-year period in 1,597 people with diabetes (807 with type 1 and 790 with insulin-treated type 2) (Evans et al., 1999). Overall, 20% of patients with type 1 diabetes and 17% with type 2 diabetes obtained more than 1,095 strips which was equivalent to one per day, while 16%, and 21%, respectively, obtained no strips at all. In people who had at least one HbA1c result during the study period (258 people with type 1 diabetes and 290 people with insulin-treated type 2 diabetes), after adjusting for age, gender, diabetes duration and socioeconomic status, strips dispensed was found to be a predictor of HbA1c in people with type 1 diabetes ($p = 0.002$), but not in people with type 2 diabetes ($p = 0.36$).

Karter et al (2001) examined frequency of SMBG and glycaemic control in 24,312 people with diabetes, including type 1 diabetes (n = 1,159), insulin-treated (n = 5,552), OHA-treated (n = 12,786), and diet-controlled (n = 4,815) type 2 diabetes. People with type 1 (34%) or insulin-treated type 2 diabetes (54%) were more adherent with the recommended frequency of SMBG (defined as at least 3 times daily in people with type 1 diabetes and at least daily in people with type 2 diabetes) than people with OHA-treated type 2 diabetes (20%, $p = 0.001$). After adjusting for age, sex, educational levels, annual income, diabetes duration, therapy type, and some behavioural and clinical variables, adherence (vs less frequent or no monitoring) was associated with lower HbA1c levels in all four groups: 7.7% vs 8.7% in type 1 ($p < 0.0001$), 8.2% vs 8.8% in insulin-treated type 2 ($p < 0.0001$), 8.1% vs 8.7% in OHA-treated type 2 ($p < 0.0001$), and 7.7% vs 8.1% in diet-controlled type 2 diabetes ($p < 0.0001$).

In an audit over a 3-year period of 228 people with type 2 diabetes (aged 35–65 years), 70% of "regular SMBG performers" (almost all visits with documented frequency of SMBG and

results) had an HbA1c ≤ 8% compared with only 22% in people who were not monitoring ($p < 0.0001$) (Blonde et al., 2002).

An Australian study examined whether or not SMBG was associated with better glycaemic control using cross-sectional and longitudinal data from people with type 2 diabetes in the community-based Fremantle Diabetes Study (FDS) (Davis et al., 2006). SMBG use was reported in 1,286 subjects at study entry and in 531 in annual reviews over 5 years. Most people (70%) were performing SMBG at baseline with a median of four tests per week (interquartile range two to seven). Subjects with shorter diabetes duration; who were attending diabetes education, diabetes-related clinics, or medical specialists; who were taking insulin with or without oral hypoglycaemic agents (OHAs); and who were self-reporting hypoglycaemic events were more likely to use SMBG. Both cross-sectional and longitudinal FDS data showed that HbA1c was not significantly different between SMBG users and nonusers, either overall or within diabetes treatment groups (diet, OHAs, and insulin with or without OHAs). There was also no independent cross-sectional relationship between HbA1c and SMBG frequency.

While SMBG is frequently used by people with diabetes to assess glycaemic control, there has been ongoing debate about whether its use is associated with improved short and longer term outcomes. Although the main purpose of this section of the Guideline is to consider the usefulness of SMBG as a means of assessing glycaemic control, the following is an overview of SMBG and clinical outcomes.

Two studies have examined whether SMBG is associated with improved clinical outcomes.

The ROSSO study (ROSSO study, (Martin et al., 2006)) used epidemiological data on SMBG in type 2 diabetes to investigate the relationship of SMBG with diabetes-related morbidity and mortality. The study followed 3,268 people from diagnosis of type 2 diabetes between 1995 and 1999 until the end of 2003 (mean follow-up 6.5 years). SMBG for at least one year was performed by 1,479 people (45.3%) including 808 people being treated with diet or oral hypoglycaemic medications. The total rate of nonfatal events, both micro- and macrovascular, was lower in the SMBG group than in the non-SMBG group (7.2 vs 10.4%, $p = 0.002$). A similar difference was found for the rate of fatal events (2.7 vs 4.6%, $p = 0.004$). SMBG was an independent predictor of morbidity and mortality, with adjusted hazard ratios of 0.68 (95% CI 0.51–0.91, $p = 0.009$) and 0.49 (95% CI 0.31–0.78, $p = 0.003$), respectively. A better outcome for both fatal and non-fatal endpoints was also observed in the SMBG cohort when only those people who were not receiving insulin were analysed. The reason for the observed association is unknown but may be related to a healthier lifestyle and/or better disease management.

Davis et al (2007) used longitudinal data from 1,280 people with type 2 diabetes in the observational Fremantle Diabetes Study where participants reported on SMBG and diabetes treatment status at entry to the study (1993–96) and from a subset of 531 people who

attended six or more annual assessments. Outcome measures were diabetes-related morbidity, cardiac death and all-cause mortality. In all, 898 subjects (70.2%) with type 2 diabetes were performing SMBG at baseline. Over 12,491 patient-years of follow-up (mean 9.8 ± 3.5 years), 486 (38%) died, of which 196 (15.3%) deaths were due to cardiac causes. In those who died, SMBG was significantly less prevalent during follow-up than in those who were alive. In an unadjusted survival analysis, SMBG was associated with a significant 24% reduction in all-cause mortality ($p = 0.004$); however, after adjusting for age, sex and duration of diabetes, the association was no longer significant although there was still an 11% increased risk. SMBG was not independently associated with all-cause mortality but was associated with a 79% increased risk of cardiovascular mortality in subjects not using insulin. There was a 48% reduced risk of retinopathy independently associated with SMBG for the 5-year cohort.

A number of systematic reviews have examined the influence of SMBG on diabetes control. Faas et al (1997) conducted a systematic review on the efficacy of SMBG in people with type 2 diabetes. Eleven studies were identified from a Medline search from 1976–1996, including six RCT studies, with follow-up ranging from 12 to 62 weeks. One RCT reported a positive effect of using SMBG on glycaemic control and weight loss, two studies showed non-significant positive results and three studies showed no significant differences. The reviewers concluded that SMBG in people with type 2 diabetes was questionable and more research with high quality studies was required.

A meta-analysis from the Netherlands evaluated the effectiveness of SMBG and HbA1c reductions in type 2 diabetes (Jansen, 2006). Medline, Embase, and the Cochrane Library (1966-Nov 2005) were searched and 13 RCTs were identified. The study populations in two of the 13 studies were a mixture of people using and not using insulin; insulin was not used in the other 11 studies. After adjusting for baseline HbA1c levels and internal validity, interventions with self-monitoring of blood glucose showed a reduction in HbA1c of 0.40 percentage-points (%) (95% credible interval [Crl] 0.07 to 0.70%) in comparison to interventions without self-monitoring. Regular feedback reduced HbA1c more than two times. The analysis gave comparable results for a subset of people with type 2 diabetes not requiring insulin (98% probability: 0.42% reduction); SMBG + feedback was more likely effective than no feedback [99% Crl -1.49; -0.13].

Welschen et al (2005) conducted a meta analysis with the aim to assess the effects of SMBG relative to usual care without SMBG on blood glucose control, quality of life and well-being, patient satisfaction, and hypoglycaemic episodes in people with type 2 diabetes who were not using insulin. Medline, The Cochrane Library, and EMBASE were searched from 1996 to September 2004. Six randomised controlled trials were identified. In a meta analysis, there was a small statistically significant decrease of 0.39% in HbA1c (95% CI -0.56 to -0.21) in favour of SMBG compared with the control group. Two studies which examined quality of life, well-being, and patient satisfaction showed no differences between SMBG and control groups.

Towfigh et al (2008) updated the review by searching for randomised controlled trials in PubMed from the 2004 to July 2007. Nine RCTs were identified ranging from 29 to 988 subjects. All people had type 2 diabetes with mean durations of 3 to 13 years. Mean age was 50 to 66 years and all trials included counselling and education with SMBG in the intervention groups. Five trials of SMBG of 6 month's duration yielded a pooled effect estimate of a decrease in mean HbA1c values of −0.21% (95% confidence interval [CI], −0.38% to −0.04%). Four trials that reported outcomes of 1 year or longer yielded a pooled effect estimate of a decrease in mean HbA1c values of −0.16% (95% CI, −0.38% to 0.05%).

McGeoch et al (2007) conducted a qualitative systematic review of randomised controlled trials and observational studies published from 1990 and November 2006. Included studies were those that reported SMBG in people with type 2 diabetes managed with oral hypoglycaemic agents and/or diet alone, HbA1c or clinical outcome, had at least 50 subjects and a duration of at least 6 months. Because of the clinical heterogeneity of the studies chosen, the authors did not perform any qualitative analysis. The two larger studies had statistically significantly lower HbA1c levels with SMBG. Thirteen observational studies had information on over 60,000 subjects. Smaller studies had lower initial HbA1c and showed no association between SMBG and laboratory or clinical improvement. Larger studies tended to have higher initial HbA1c levels and did show an association between SMBG and laboratory or clinical improvement. Studies where the initial HbA1c was higher than 8% tended to show the greatest improvements in overall glycaemic control.

McAndrew et al (2007) conducted a systematic review of relevant studies on the impact of self-monitoring of blood glucose (SMBG) on HbA1c levels in people with type 2 diabetes. Medline, PsychInfo, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, and CINAHL were searched for cross-sectional, longitudinal, and randomised control trials from 1990 to 2006, all of which included people with type 2 diabetes not using insulin. Twenty-nine studies met the inclusion criteria; nine cross-sectional studies, nine longitudinal studies, and 11 randomised controlled trials. Evidence from the cross-sectional and longitudinal studies was inconclusive; evidence from randomised controlled trials suggests that SMBG may lead to improved glycaemic control.

Sarol et al (2005) conducted a systematic review and meta analysis to determine if therapeutic management programs with SMBG would result in a greater reduction of HbA1c in people with type 2 diabetes not using insulin compared with programs without SMBG. Medline (1966-2004), The Cochrane Database, EMBASE (1950-2004), Centre for Reviews and Dissemination (CRD) and the Online Index Journals of the American Diabetes Association (ADA 1978-2004) were searched for randomised controlled trials comparing HbA1c reduction in therapies with and without SMBG. Eight RCTs with a total of 1,307 subjects were included in the analysis; heterogeneity among included studies was not statistically significant. There was no explicit description of medication criteria used in one RCT (Kwon et al., 2004) used in the meta analysis, and this may have influenced the results

by adding data from people treated with insulin. Therapies targeting diabetes that included SMBG as part of a multi-component management strategy produced a mean additional HbA1c reduction of -0.39% (95%CI: -0.54%, -0.23%) under the fixed effects model and -0.42% (95%CI: -0.63%, -0.21%) under the random effects model, when compared with therapies that did not. When three studies with a poor quality (C rating) were removed (Estey et al., 1990; Jaber et al., 1996; Kwon et al., 2004), the effect estimate was -0.31% (95% CI: -0.49%, -0.14%).

Two recent randomised controlled have also examined this question. Farmer et al (2007) examined whether self monitoring of blood glucose, alone or with instruction, and incorporating the results into self care, was more effective than usual care in improving glycaemic control in people with type 2 diabetes. Subjects were randomised to three interventions: standardised usual care with measurements of HbA1c by a professional every 3 months (control group, n = 152); use of a glucose meter, with advice for participants to contact a doctor for interpretation (less intensive, n = 150); and use of a glucose meter with training in interpretation and in the application of results (intensive group, n = 151). Median duration of diabetes was 3 years, mean age was 66 years, and mean HbA1c was 7.5%. At 12 months there was no difference in HbA1c levels among the groups after adjustment for baseline values (p = 0.12). The difference in unadjusted mean change in HbA1c level from baseline to 12 months between the control and less intensive self monitoring groups was −0.14% (95% confidence interval −0.35% to 0.07%) and between the control and more intensive self monitoring groups was −0.17% (−0.37% to 0.03%). There was no convincing evidence that more intensive efforts for SMBG were any better compared with usual care for improving glycaemic control.

O'Kane et al (2008) assessed the effect of SMBG on glycaemic control and psychological indices in 184 (111 men) people aged < 70 with newly diagnosed type 2 diabetes who were not using insulin. Subjects were randomised to self monitoring or no monitoring (control) groups for one year with follow-up at three monthly intervals. Both groups underwent an identical structured core education programme. There were no baseline differences in mean (SD) age (57.7 (11.0) in monitoring group vs 60.9 (11.5) in the control group) or HbA1c (8.8 (2.1)% vs 8.6 (2.3)%, respectively). There were no significant differences between groups at any time point in HbA1c (6.9 (0.8)% vs 6.9 (1.2)%, p = 0.69; 95% confidence interval for difference -0.25% to 0.38%), BMI (33.1 (6.4) vs 31.8 (6.0); adjusted for baseline BMI, p = 0.32), use of oral hypoglycaemic drugs, or reported incidence of hypoglycaemia.

There are no specific studies to inform a recommendation on who should perform SMBG. In Australia, the current practice is to include a discussion of SMBG as part of the diabetes education provided to people with type 2 diabetes with the final decision negotiated between the person with diabetes and their health care professionals. This decision takes into consideration the type of therapy, level of glycaemic control, risk of hypoglycaemia, and

need for short-term adjustment of treatment. Most people with medication treated diabetes, especially insulin users, are encouraged to routinely perform SMBG.

There are limited data on the frequency and timing of SMBG testing

There are few studies to inform recommendations on frequency or optimal testing times for SMBG. Hoffmann et al (2002) evaluated once- and twice-daily SMBG testing strategies compared with four-times daily testing in assessing glycaemic control and detecting hypoglycaemia or hyperglycaemia in people with stable insulin-treated type 2 diabetes (defined as not having insulin dose adjusted by >10%). One hundred and fifty people (mean age 66 years) measured their blood glucose levels each day before their three main meals and at bedtime for 8 weeks. The overall correlation of all glucose results and HbA1c was 0.79 ($p < 0.0001$). Mean blood glucose values for each of the four once-daily testing times (before each meal and at bedtime) were significantly correlated with HbA1c ($r = 0.65–0.70$, $p < 0.0001$). Similarly the six combinations of twice-daily testing strategies were also significantly correlated with HbA1c ($r = 0.73–0.75$, all $p < 0.0001$). The combination of prebreakfast and prelunch testings captured the largest proportion of hypoglycaemic (≤ 3.3 mmol/L) readings (63.6%), while the predinner and bedtime testing combination captured the largest proportion of hyperglycaemic (≥ 22.20 mmol/L) readings (66.2%), and the prelunch and predinner combination captured the largest proportion of all out-of-range readings (57.7%). For people performing once-daily testing, a rotating strategy (alternating testing times on successive days) explained more of the variance in HbA1c than any of the fixed once-daily testing strategies. The rotating once-daily testing strategy also captured nearly a quarter of the out-of-range readings, suggesting that people testing once daily should obtain readings from different times of day. Measuring prelunch and predinner readings was the best overall twice-daily testing strategy because the correlation with HbA1c was high ($r = 0.74$) and these measurements captured the statistically highest yield of hypoglycaemic and combined out-of-range readings. Rotating the timing of the twice-daily strategies explained more of the variance in HbA1c than any of the fixed twice-daily strategies, but the yield in capturing out-of-range readings decreased by approximately 10%. The authors concluded that twice-daily testing strategies, particularly prelunch and predinner, effectively assess glycaemic control and capture a substantial proportion of out-of-range readings. However, personal testing strategies will vary depending on an individual's risk for hypoglycaemia and hyperglycaemia.

Other studies have suggested that post-prandial measurement of blood glucose correlates better with diabetes control than preprandial testing but in these studies subjects were studied for only 1 day and in a controlled laboratory setting with collection of venous blood. Avignon et al (1997) measured HbA1c and four readings of plasma glucose (prebreakfast, prelunch, postlunch, and extended postlunch) during a single day in 66 non–insulin-treated outpatients with type 2 diabetes. The postlunch readings correlated best with HbA1c ($r = 0.81$, $p = 0.009$), followed by the extended postlunch readings ($r = 0.78$, $p = 0.032$). The prebreakfast readings were not significantly correlated ($r = 0.62$, $p = 0.079$). The authors concluded that the postlunch readings should be used to supplement or replace the fasting readings.

Soonthornpun et al (1999) investigated the relationship between HbA1c levels and postprandial glucose concentrations after a meal tolerance test in 35 people with type 2 diabetes. Two-hour postprandial glucose levels were more strongly correlated (r = 0.51) with HbA1c levels than 1-h postprandial glucose levels (r = 0.35) and fasting glucose (r = 0.46). People whose HbA_{1c} levels were high (HbA1c ≥ 7%) had significantly higher 2-h postprandial glucose than those whose HbA1c levels were lower. This study suggested that postprandial hyperglycaemia, particularly 2-h postprandial glucose concentrations, was associated with high HbA1c levels in people with type 2 diabetes whose fasting glucose levels were within normal or near-normal levels.

Guillausseau (1997) studied laboratory blood glucose profiles (8 am, 9.30 am after a 35 g carbohydrate breakfast and in the evening between 5 and 7 pm) in 58 people with type 2 diabetes (mean age 60, mean HbA1c 6.7%) treated with gliclazide alone or in combination with metformin. HbA1c was strongly correlated (p = 0.002 to 0.0001) in the whole group with 8 am (r = 0.39), 9.30 am (r = 0.56), and evening blood glucose values (r = 0.42). In 80% of subjects the lowest blood glucose values occurred in the evening more frequently than in the morning. The authors suggested that evening blood glucose determination should be performed routinely in the evaluation of patients with type 2 diabetes treated with oral hypoglycaemic agents.

Rohlfing et al (2002) studied the relationship between HbA1c and blood glucose in capillary samples collected at home in people with type 1 diabetes using data from the Diabetes Control and Complications Trial (DCCT). HbA1c was measured every 3 months and the seven-point capillary blood glucose profiles (premeal, 90 min postmeal, and bedtime) collected over 1 day every 3 months were analysed. Only data from complete profiles with corresponding HbA1c were used (n = 26,056). Mean plasma glucose (MPG) was estimated by multiplying capillary blood glucose by 1.11. Linear regression analysis weighted by the number of observations per subject was used to correlate MPG and HbA1c. The relationship of MPG and HbA1c was summarised by the following: MPG (mmol/L) = (1.98 X HbA1c) – 4.29. Among individual time points, afternoon and evening (postlunch, predinner, postdinner, and bedtime) showed higher correlations with HbA1c than the morning time points (prebreakfast, postbreakfast, and prelunch).

Bonora et al (2001) studied the following people with non-insulin treated diabetes – 371 who were willing to return to the outpatient clinic five times in 1 day to measure plasma glucose (mean HbA1c 6.6%), 30 who were requested to monitor blood glucose at home (mean HbA1c 7.0%) and 455 inpatients (mean HbA1c 8.4%). Subjects had a plasma/blood glucose assessment before and 2–3 h after breakfast, lunch, and dinner and HbA1c was also measured. Correlations between HbA1c and plasma/blood glucose at different times of the day ranged from 0.44 to 0.67. The strongest correlation was between HbA1c and mean daily glucose (r = 0.57–0.69). Multiple regression analyses showed that premeal but not postmeal plasma/blood glucose levels were independent predictors of HbA1c.

A study by Monnier et al (2003) suggested that the relationship between HbA1c and fasting and postprandial glucose varied depending on the absolute HbA1c result. In 290 non–insulin treated people with type 2 diabetes, plasma glucose (PG) concentrations were determined fasting (8:00 am) and during postprandial and postabsorptive periods (at 11:00 am, 2:00 pm, and 5:00 pm). The relative contribution of postprandial glucose decreased progressively from the lowest (69.7%) to the highest quintile of HbA1c (30.5%, $p < 0.001$), whereas the relative contribution of fasting glucose increased gradually with increasing levels of HbA1c: 30.3% in the lowest vs 69.5% in the highest quintile ($p < 0.001$). The authors concluded that the relative contribution of postprandial glucose excursions is predominant in fairly well controlled people, whereas the contribution of fasting hyperglycaemia increases gradually with worsening blood glucose control.

Another consideration in SMBG is what, if anything, people should do with the results of the tests. Bjorsness et al (2003) surveyed 815 people with type 2 diabetes for information about their current practice with SMBG. Among respondents using insulin, a larger proportion of those reporting a blood glucose target took some action (i.e. adjusted medication and/or ate more/less food) when their blood glucose values were low compared with those without a target (90 vs 71%, $p = 0.02$). However, there were no differences regarding actions taken when the glucose values were high. Similar findings were reported for respondents taking oral medications only. The median target blood glucose value reported was 6.7 mmol/L. Individuals using insulin reporting targets $\leq$ 6.7 mmol/L) had a significantly lower median HbA1c value (median 7.3%) compared with those with SMBG targets > 6.7 mmol/L and those with no target (8.7%, $p = 0.02$). There was a small but not significant difference in the median HbA1c values among respondents taking oral medications in those with targets $\geq$ 6.7 mg/dL (7.1%) compared with those reporting targets > 6.7 mmol/L (7.3%) or those with no target (7.0%, $p = 0.07$). Many people with diabetes who monitored did not know their blood glucose targets. Among those taking insulin, lower targets were associated with better metabolic control. The relationships between targets and metabolic control were not as clear among people taking only oral medications or those taking no medications.

Although further research is needed, the above studies suggest that measurement of both pre and post meal (1-2 hours after a meal) SMBG values provide useful information in people with type 2 diabetes. Taken together with data on which blood glucose values most influence different levels of HbA1c results, health professionals should determine the most appropriate testing schedule for individual patients. In general, once-daily testing should include readings from different times of the day while measuring prelunch and predinner readings is the best overall twice-daily testing strategy. Other testing times will depend on individual circumstances. Post meal testing should be included in people with HbA1c above target.

Evidence Table: Glycated haemoglobin level correlates with diabetes complications and outcomes.

Author (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of Effect*	*Relevance Rating*
	Level	*Study Type*			
ADVANCE Collaborative Group, 2008	II	RCT	High	High[+]	High
Klein et al., 1994	III-2	Prospective cohort	High	High[+]	High
Ohkubo et al., 1995 (Japan)	II	RCT	High	High[+]	High
Selvin et al., 2004	I	Systematic review	High	High[+]	High
Stratton et al., 2000	III-2	Prospective cohort	High	High[+]	High
UKPDS Study Group 33, 1998	II	RCT	High	High[+]	High

[+] Glycated haemoglobin level correlates with diabetes complications and outcomes.

Clinical importance rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

Evidence Table: An accurate and precise method is required for measuring glycated haemoglobin.

Author (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of Effect*	*Relevance Rating*
	Level	*Study Type*			
Arsie et al., 2000	IV	Cross-sectional	High	High[+]	High
Carter et al., 1996	IV	Cross-sectional	Low	High[+]	High
Hyltoft Petersen et al., 1990	IV	Cross-sectional	Medium	Medium[+]	High
Kolatkar et al., 1994	IV	Cross-sectional	Medium	Medium[+]	High
Koskinen et al., 1993	IV	Cross-sectional	Medium	Medium[+]	High
Matteucci et al., 1998	IV	Cross-sectional	High	High[+]	High
Rohlfing et al., 2002 (USA)	III-2	Prospective cohort	High	High[+]	High
Tejani et al., 2002	IV	Cross-sectional	Medium	Medium[+]	High

[+] An accurate and precise method is required for measuring glycated haemoglobin.

Clinical importance rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

Evidence Table: A number of clinical situations can affect the glycated haemoglobin result.

Author (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of Effect*	*Relevance Rating*
	Level	*Study Type*			
Ben et al., 1989	III-3	Prospective cohort	High	Low[+]	High
Bry et al., 2001	I	Systematic revew	High	High[+]	High
Ceriello et al., 1991	III-2	Prospective cohort	Medium	High[+]	High
Davie et al., 1992	III-2	Prospective cohort	Medium	High[+]	Medium
Falko et al., 1982	IV	Cross-sectional	Low	Low[+]	High
Garrib et al., 2003	IV	Cross-sectional	Low	Low[+]	High
Panzer et al., 1982	II	RCT	High	High[+]	High
Tarim et al., 1999	III-2	Prospective cohort	Low	High[+]	High
Weinblatt et al., 1986	III-2	Prospective cohort	Low	Medium[+]	Medium
Weykamp et al., 1993	III-2	Prospective cohort	High	Medium[+]	High

[+] A number of clinical situations can affect the glycated haemoglobin result.

Clinical importance rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

Evidence Table: The frequency of glycated haemoglobin testing is dependent on the clinical situation

Author (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of Effect*	*Relevance Rating*
	Level	*Study Type*			
Tahara and Shima, 1993	III-2	Prospective cohort	Medium	High[+]	High

[+] The frequency of glycated haemoglobin testing is dependent on the clinical situation

Clinical importance rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

Evidence Table: Glycated proteins are an alternate measure of blood glucose control but there are no data on their relationship with chronic diabetes complications.

Author (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of Effect*	*Relevance Rating*
	Level	*Study Type*			
Braatvedt et al., 1997	III-2	Prospective cohort	Low	Medium^{+}	High
Cefalu et al., 1989	III-2	Prospective cohort	Medium	High^{+}	High
Hom et al., 1998	IV	Cross-sectional	Medium	Medium^{+}	Medium
Kruseman et al., 1992	IV	Cross-sectional	Medium	Low^{-}	Medium

$^{+}$ Glycated proteins are an alternate measure of blood glucose control but there are no data on their relationship with chronic diabetes complications.

Clinical importance rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

Evidence Table: Self measurement of blood glucose (SMBG) is a useful method for assessing real time blood glucose levels.

Author (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of Effect*	*Relevance Rating*
	Level	*Study Type*			
Blonde et al., 2002	III-2	Prospective cohort	High	High^{+}	High
Chen et al., 2003	IV	Cross-sectional	High	High^{+}	High
Davis et al., 2006	III-2	Prospective cohort	High	Low^{-}	High
Davis et al., 2007	III-2	Prospective cohort	High	Medium^{+}	High
Estey et al., 1990	II	RCT	Low	Low^{-}	Medium
Evans et al., 1999	III-2	Prospective cohort	Medium	High^{+}	High
Faas et al., 1997	I	Systematic review	High	Low^{-}	High
Farmer et al., 2007	II	RCT	High	Low^{+}	High
Harris, 2001	IV	Cross-sectional	High	Low^{-}	High
Jaber et al., 1996	II	RCT	Low	High^{+}	Low
Jansen, 2006	I	Systematic review	High	High^{+}	High
Karter et al., 2001	III-2	Prospective cohort	High	High^{+}	High
Karter et al., 2000	IV	Cross-sectional	Medium	Medium^{+}	Low
Kwon et al., 2004	II	RCT	Low	High^{+}	High
Martin et al., 2006	III-2	Prospective cohort	High	High^{+}	High
McAndrew et al., 2007	I	Systematic review	High	Low^{-}	High
McGeoch et al., 2007	I	Systematic review	High	Medium^{+}	High
O'Kane et al., 2008	II	RCT	High	Low^{-}	High
Sarol et al., 2005	I	Systematic review	High	High^{+}	High
Towfigh et al., 2008	I	Systematic review	High	High^{+}	High
Welschen et al., 2005	I	Systematic review	High	High^{+}	High

$^{+}$ Self measurement of blood glucose (SMBG) is a useful method for assessing real time blood glucose levels.

Clinical importance rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

Evidence Table: There are limited data on the frequency and timing of SMBG testing.

Author (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of Effect*	*Relevance Rating*
	Level	*Study Type*			
Avignon et al., 1997 (France)	IV	Cross-sectional	High	Medium[+]	High
Bjorsness et al., 2003 (USA)	IV	Cross-sectional	High	Medium[+]	Medium
Bonora et al., 2001 (Italy)	III-2	Prospective cohort	High	High[+]	High
Guillausseau, 1997 (France)	III-2	Prospective cohort	High	High[+]	High
Hoffman, 2002	III-2	Prospective cohort	High	High[+]	High
Monnier et al., 2003 (France)	III-2	Prospective cohort	High	High[+]	High
Rohlfing et al., 2002 (USA)	III-2	Prospective cohort	High	High[+]	High
Soonthornpun et al., 1999 (Thailand)	IV	Cross-sectional	Medium	High[+]	Medium

[+] There are limited data on the frequency and timing of SMBG testing.

Clinical importance rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

Section 4: Blood Glucose Control

Question

What are the targets for blood glucose control?

Recommendations

The general HbA1c target in people with type 2 diabetes is ≤ 7%. Adjustment to diabetes treatment should be considered when HbA1c is above this level. (Grade A)

Targets for self-monitored blood glucose levels are 6–8 mmol/L fasting and preprandial, and 6–10 mmol/L 2 h postprandial. (Grade C)

Practice Point

An HbA1c target above 7% may be appropriate in people with type 2 diabetes who have a history of severe hypoglycaemia, a limited life expectancy, co-morbidities or who are elderly.

Evidence Statements

- There is a continuous relationship between HbA1c and complications in people with type 2 diabetes without evidence of a threshold
  Level of Evidence II

- Blood glucose control intervention studies inform decisions on HbA1c targets
  Level of Evidence II

- Intervention and epidemiological studies inform self-monitored blood glucose targets
  Level of Evidence II

Background – Target for Blood Glucose Control

As reviewed in previous Sections of this guideline, there is a well established association between blood glucose control (assessed by HbA1c) and microvascular and macrovascular complications. Lowering of HbA1c is associated with reduced risk of development or progression of microvascular complications and neuropathy, but a beneficial effect on macrovascular complications has not yet been established.

Routine GHb testing is recommended in all people with type 2 diabetes to document blood glucose control and as a measure of risk for the development of diabetes microvascular complications. Most major international diabetes organisations recommend HbA1c targets to guide treatment. These targets are considered to be an HbA1c level at or below which there is a low absolute risk of developing long term microvascular complications of diabetes, and a level above which treatment changes are required to improve blood glucose control. This may involve changing to a different medication, increasing the dosage or frequency of the current medications and intensified health professional surveillance (ADA, 2008).

If there were no adverse effects from lowering blood glucose with available therapies, then the target of therapy would logically be the level found in the population without diabetes. However, available therapies are associated with adverse effects as well as being less than optimal in terms of efficacy. Therefore setting both general and individual targets for blood glucose control will require some compromise between benefits and potential adverse effects.

The setting of targets is designed to provide a guide for both assessment of blood glucose control as a predictor of risk of diabetes complications, and to act as a trigger to consider and initiate changes in therapy in individuals above target.

This Section reviews the evidence in relation to targets for both HbA1c and SMBG results.

Evidence – Target for Diabetes Control

There is a continuous relationship between HbA1c and complications in people with type 2 diabetes without evidence of a threshold

The relationship between blood glucose control and complications in people with type 2 diabetes has been examined in both intervention and cohort studies.

Stratton et al (2000) analysed the UKPDS data and showed a curvilinear relationship between complications and blood glucose control assessed by mean updated HbA1c (see Table 1 and Figure 1). Each 1% reduction in updated mean HbA1c was associated with risk reductions in the following:

- 21% for any end point related to diabetes (CI 17% to 24%, $p < 0.0001$)
- 21% for deaths related to diabetes (CI 15% to 27%, $p < 0.0001$)
- 14% for myocardial infarction (CI 8% to 21%, $p < 0.0001$)
- 37% for microvascular complications (CI 33% to 41%, $p < 0.0001$).

No threshold of glycaemia was observed for any diabetes complication. Any reduction in HbA1c was associated with a reduced risk of complications, with the lowest risk being in those with HbA1c values in the normal range (< 6.0%). In people in the lowest category of mean HbA1c the risk of myocardial infarction was higher than that of microvascular complications.

The Kumamoto study examined the relationship between retinopathy and microalbuminuria after 6 and 8 years follow up (Ohkubo et al., 1995; Shichiri et al., 2000). Blood glucose was assessed by periodic one day hospitalisation during which 11 blood glucose levels were measured – fasting, 1 and 2 h post-prandial, bedtime and fasting the following morning. Overall there was a curvilinear relationship between HbA1c and microvascular complications but there was no development or progression of retinopathy and nephropathy in subjects whose HbAlc, fasting blood glucose and 2-h post-prandial blood glucose concentration were below 6.5%, 6.1 mmol/L, and 10 mmol/L, respectively.

Molyneaux et al (1998) analysed data collected prospectively in an Australian cohort of 963 people with type 2 diabetes (mean age 57.5 y) who were followed up for a median 28 months in order to construct dose response curves relating their blood glucose control to the development of retinopathy and microalbuminuria. A continuous smooth curve relationship between the development of retinopathy and increasing hyperglycaemia was found. For every 10% decrease in HbA1c, there was a significant 24% (CI 16–32) reduction in relative risk. The relationship between microalbuminuria and HbA1c was more linear and less steep with a non-significant relative risk reduction of 9% (CI −2–19) for any 10% fall in HbA1c. No threshold of HbA1c was found for the relative risk of developing complications.

Blood glucose control intervention studies inform decisions on HbA1c targets

Intervention studies have established the important role of glucose control in prevention or progression of microvascular complications in people with type 2 diabetes. However the relationship between blood glucose control and complications is continuous, without evidence of a specific threshold which could be used to set a specific evidence-based target. Consequently, evidence from levels achieved in intervention studies and extrapolations from epidemiological analyses is used to set blood glucose control targets.

Table 2. Mean HbA1c levels achieved in intervention studies of intensive blood glucose control and improved microvascular outcomes.

Study	HbA1c Intensive group	HbA1c Conventional group
Kumamoto	7.1%	9.4%
UKPDS	7.0%	7.9%
VACSDM	7.1%	9.2%
ADVANCE	6.5%	7.2%

In the Kumamoto study, there was no development or progression of microvascular complications below an HbA1c of 6.5% (Ohkubo et al., 1995; Shichiri et al., 2000). Extrapolations from the UKPDS data indicate that a low incidence of microvascular complications (e.g. a rate of < 10/1000 person y) is observed at an HbA1c of < 7.0% whereas for myocardial infarction this incidence rate is not observed even at HbA1c levels below 6.0% (Stratton et al., 2000).

In the ADVANCE study (ADVANCE Collaborative Group, 2008), an intensive glucose-control strategy where mean glycated haemoglobin values were maintained at 6.5% was associated with a 21% relative reduction in the risk of new or worsening nephropathy compared with less intensive glucose-control which achieved a mean HbA1c of 7.2%.

It is important to agree on an HbA1c target with the person with diabetes and to use this target to guide management. The targets recommended in this guideline are designed not only to assess blood glucose control but also as a level at which therapeutic changes should be considered if the target is not being achieved.

Intervention and epidemiological studies inform self-monitored blood glucose targets

There are few data to guide targets for self monitored glucose levels.

The Kumamoto study reported a curvilinear relationship between retinopathy and microalbuminuria and fasting, and 2h post-prandial blood glucose levels. There was no development or progression of retinopathy and nephropathy with fasting blood glucose below 6.1 mmol/L and 2h post-prandial blood glucose below 10 mmol/L (Ohkubo et al., 1995; Shichiri et al., 2000).

In the UKPDS, there was a similar relationship between fasting plasma glucose and complications as was observed for HbA1c (UKPDS Study Group, 1998). The mean fasting blood glucose corresponding to an HbA1c of 7.0% was approximately 7.8 mmol/L. However, detailed blood glucose information similar to that for mean updated HbA1c has not been published.

In the Diabetes Control and Complications Trial (DCCT), subjects in the intensively treated group aimed to achieve target fasting and pre-prandial capillary blood glucose levels of 3.9 to 6.7 mmol/L, and were able to achieve an average of 7.7 mmol/L (DCCT Study Group, 1993). This was associated with a mean HbA1c of 7.1% and significantly less diabetes complications.

Some extrapolation is possible from the numerous clinical trials on pharmacotherapies for type 2 diabetes which are reviewed in Section 5. Overall an HbA1c of approximately 7% is associated with a pre-breakfast glucose concentration of approximately 6.5 mmol/L and a 2h post- prandial glucose concentration of approximately 8.5 mmol/L.

From the above data, fasting blood glucose levels of 6–8 mmol/L and 2h post-prandial levels of 6–10 mmol/L are associated with an HbA1c $\leq$ 7.0%.

Table 1: Incidence of complications in people with Type 2 diabetes by category of updated mean HbA1c (%). Rates per 1000- person-yr follow up adjusted in Poisson regression model to white men age 50 to 54 yr at diagnosis of diabetes and followed up for 7.5 to <12.5 yr, termed "10 yr" (n=4585)

Aggregate end points	**<6.0%**	**6.0 to <7.0%**	**7.0 to <8.0%**	**8.0 to <9.0%**	**9.0 to <10.0%**	**>10.0%**
Complications related to diabetes:						
Adjusted rate	35.9	48.7	65.5	74.5	103.2	124.9
(95% CI)	(29.9 to 43.1)	(41.3 to 57.3)	(55.5 to 77.2)	(62.6 to 88.8)	(84.2 to 126.5)	(97.3 to 160.3)
Deaths related to diabetes:						
Adjusted rate	8.9	12.0	19.9	23.5	29.5	33.0
(95% CI)	(6.3 to 12.7)	(8.9 to 16.3)	(14.8 to 26.7)	(17.2 to 32.0)	(20.4 to 42.6)	(19.8 to 55.1)
Fatal or non-fatal myocardial infarction:						
Adjusted rate	16.0	20.8	29.2	30.0	39.6	38.6
(95% CI)	(12.1 to 21.2)	(16.2 to 26.7)	(22.8 to 37.4)	(22.9 to 39.4)	(28.8 to 54.5)	(24.4 to 61.0)
Fatal or non-fatal stroke:						
Adjusted rate	4.3	6.6	8.3	7.4	6.7	12.0
(95% CI)	(2.6 to 7.0)	(4.4 to 10.1)	(5.4 to 12.7)	(4.5 to 11.9)	(3.5 to 12.7)	(5.7 to 25.3)
Amputation or death from peripheral vascular disease:						
Adjusted rate	1.2	1.2	2.6	4.0	10.9	12.2
(95% CI)	(0.4 to 3.2)	(0.5 to 3.1)	(1.1 to 5.8)	(1.8 to 9.0)	(5.0 to 23.7)	(4.6 to 32.4)
Fatal or non-fatal microvascular disease:						
Adjusted rate	6.1	9.3	14.2	22.8	40.4	57.8
(95% CI)	(4.1 to 9.0)	(6.7 to 12.9)	(10.3 to 19.5)	(16.7 to 31.3)	(28.9 to 56.5)	(39.3 to 85.1)

Median HbA1c for each category: <6.0%, 5.6%; 6.0 to <7.0, 6.5%; 7.0 to 8.0%, 7.5%; 8.0 to <9.0%, 8.4%; 9.0 to <10.0%, 9.4%; >10.0%, 10.6%. (adapted from Stratton et al., 2000).

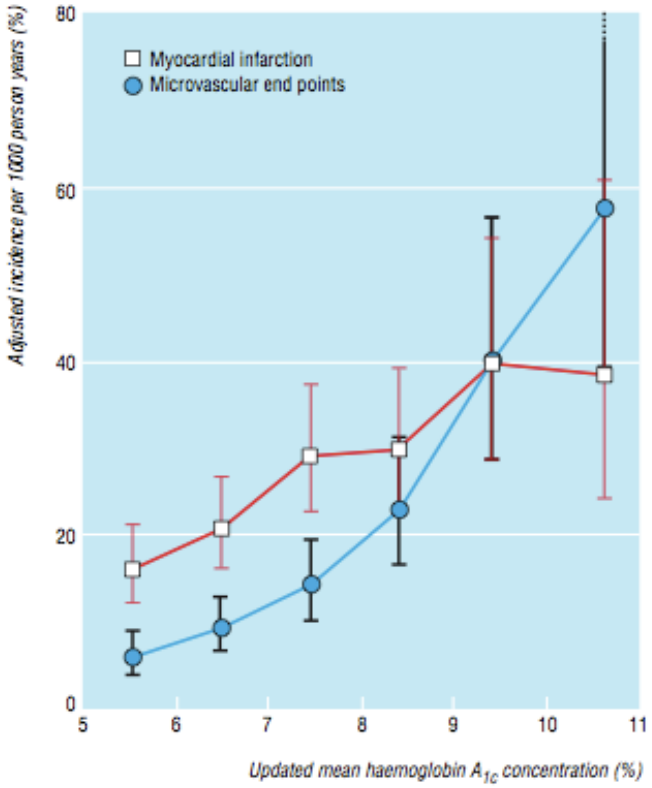


Figure 1
Incidence rates and 95% confidence intervals for myocardial infarction and microvascular complications by category of updated mean haemoglobin HbA1c concentration, adjusted for age, sex, and ethnic group, expressed for white men aged 50-54 years at diagnosis and with mean duration of diabetes of 10 years. (adapted from Stratton et al., 2000).

Evidence Table: There is a continuous relationship between HbA1c and complications in people with type 2 diabetes without evidence of a threshold

Author (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of Effect*	*Relevance Rating*
	Level	*Study Type*			
Molyneaux et al., 1998 (Australia)	III-2	Prospective cohort	High	High[+]	High
Ohkubo et al., 1995 (Japan)	II	RCT	High	High[+]	High
Shichiri et al., 2000 (Japan)	II	RCT	High	High[+]	High
Stratton et al., 2000 (UK)	II	RCT	High	High[+]	High

[+] There is a continuous relationship between HbA1c and complications in people with type 2 diabetes without evidence of a threshold.

Clinical importance rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

Evidence Table: Blood glucose control intervention studies inform decisions on HbA1c targets

Author (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of Effect*	*Relevance Rating*
	Level	*Study Type*			
ADVANCE Collabortive Group, 2008 (Australia)	II	RCT	High	High[+]	High
Ohkubo et al., 1995 (Japan)	II	RCT	High	High[+]	High
Shichiri et al., 2000 (Japan)	II	RCT	High	High[+]	High
Stratton et al., 2000 (UK)	II	RCT	High	High[+]	High

[+] Blood glucose control intervention studies inform decisions on HbA1c targets.

Clinical importance rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

Evidence Table: Intervention and epidemiological studies inform self-monitored blood glucose targets

Author (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of Effect*	*Relevance Rating*
	Level	*Study Type*			
DCCT Study Group, 1993	II	RCT	High	High[+]	High
Ohkubo et al., 1995 (Japan)	II	RCT	High	High[+]	High
Shichiri et al., 2000 (Japan)	II	RCT	High	High[+]	High
UKPDS Study Group 33, 1998	II	RCT	High	Medium[+]	High

[+] Intervention and epidemiological studies inform self-monitored blood glucose targets.

Clinical importance rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

Section 5: Blood Glucose Control

Question

What lifestyle modification and therapeutic interventions can be used to improve blood glucose control in people with type 2 diabetes?

Recommendation

Interventions to achieve target glycated haemoglobin should begin with lifestyle modification followed by therapeutic options selected on the basis of individual clinical circumstances, side effects and contraindications. (Grade A)

Practice Points

People with newly diagnosed type 2 diabetes should routinely be offered a trial of lifestyle modification. However, pharmacotherapy may also be required in people presenting with significant hyperglycaemia.

Treatment should be intensified if diabetes control is not at target and is not improving or is worsening after 3-6 months of a specific treatment strategy. However, this time interval should be shortened in the presence of significant hyperglycaemia.

It is preferable to add a second oral anti-diabetic medication rather than using a maximum dose of one medication alone.

Metformin is contraindicated in people with an eGFR < 30 mL/min/1.73m^2 and should be used with caution in people with an eGFR of 30-45 mL/min/1.73m^2.

People who are not responding to usual diabetes management should be assessed for other conditions (e.g. Latent Autoimmune Diabetes of Adults [LADA], malignancy).

Evidence Statements

- Lifestyle modification (diet and physical activity) is an integral component of diabetes care.
  Level of Evidence I

- Weight control is an important component of diabetes care.
  Level of Evidence 1

- Metformin is a widely used, safe and effective therapy for type 2 diabetes.
  Level of Evidence I

- Lactic acidosis is rare in people with type 2 diabetes treated with metformin.
  Level of Evidence I

- Sulphonlyureas, used as monotherapy or combination therapy, are safe and effective for type 2 diabetes.
  Level of Evidence I

- Thiazolidinediones are a useful agent for improving glycaemic control when used as add-on therapy to other anti-diabetic medications.
  Level of Evidence I

- Thiazolidinediones are associated with increased risk of heart failure, oedema and fractures.
  Level of Evidence I

- Some reports suggest an increased risk of cardiovascular events and death with some anti-diabetic medications and combinations.
  Level of Evidence I

- Acarbose is an option for improving glycaemic control in people with type 2 diabetes.
  Level of Evidence I

- DPP-4 inhibitors are a new option for improving glycaemic control in people with type 2 diabetes as an add-on therapy.
  Level of Evidence I

- Insulin is frequently required for glycaemic control in people with type 2 diabetes and can be initiated as basal therapy or as premixed insulins, usually in combination with oral anti-diabetic medications.
  Level of Evidence I

- Repaglinide is an option for improving glycaemic control in people with type 2 diabetes.
  Level of Evidence I

- Exenatide is a new option for improving glycaemic control in people with type 2 diabetes as an add-on therapy.
  Level of Evidence I

Background – interventions to improve blood glucose control

Improving diabetes control in people with type 2 diabetes is associated with reduced development and progression of microvascular complications. A number of treatment options exist for improving diabetes control in people with type 2 diabetes including diet, physical activity, a variety of oral medications, and insulin.

The UKPDS provides information on the natural history of therapy for type 2 diabetes and demonstrates a pattern of increasing requirements for blood glucose lowering therapies. The UKPDS included people with newly diagnosed type 2 diabetes. All subjects were initially treated with diet alone for 3 months with subsequent randomisation to continuing diet alone, sulphonylurea (chlorpropamide or glyburide), metformin, or insulin therapy. If target FPG was not achieved, dose of therapies was increased or new therapies added. Turner et al (1999) assessed how well each therapy was able to achieve glycaemic control targets (FPG < 7.8 mmol/L or HbA1c < 7.0%) at 3, 6 and 9 years after randomisation. After 3 years, < 55% of subjects randomised to any single medication maintained FPG concentrations below 7.8 mmol/L or HbA1c < 7.0%. After 9 years of diet, insulin, or sulphonylurea monotherapy, 8%, 42%, and 24%, respectively, achieved FPG < 7.8 mmol/L and 9%, 28%, and 24% achieved HbA1c levels < 7%. With the progressive deterioration of glycaemic control, by 9 years only 25% were able to achieve glycaemic targets indicating a need for multiple therapies to achieve long-term glycaemic control.

The efficacy of the various therapeutic options for people with type 2 diabetes is reviewed in this Section.

An overview management algorithm for improving blood glucose control in people with type 2 diabetes is shown in Figure 2.

Many studies have been published on interventions to improve blood glucose control in people with type 2 diabetes. The following criteria have been used for including studies of therapeutic interventions in this review:

1. Therapeutic intervention
   - Available in Australia through the Pharmaceutical Benefits Scheme (PBS), or approved by the TGA for marketing in Australia
   - Used in accordance with approved prescribing criteria in Australia
2. Study characteristics
   - Intervention studies comparing the therapeutic agent with placebo or another agent
   - Included at least 100 subjects with type 2 diabetes
   - Duration of study of at least 24 weeks
   - Included data on glycated haemoglobin.

The occasional exception to the study characteristic for number of subjects and duration was included when there were no studies fulfilling these criteria addressing a particular intervention.

Evidence – interventions to improve blood glucose control

Lifestyle modification (diet and physical activity) is an integral component of diabetes care

Lifestyle modification is recommended for people with type 2 diabetes not only to achieve weight loss in overweight individuals but to also independently lower blood glucose levels. A number of different diets have been recommended for people with diabetes.

Commonly used diets for blood glucose control include low fat, high unrefined carbohydrate (approximately 25-30% of energy from fat and 50% of total energy from unrefined carbohydrate), or low glycaemic index diets usually both in combination with weight reducing advice. Because of study limitations, it is not possible to make firm conclusions about recommending a specific diet in the management of people with type 2 diabetes. However, several approaches can be used and are reviewed below.

Diet

A systematic review by Nield et al (2007) assessed 36 articles reporting 18 randomised controlled trials of dietary advice studying a total of 1,467 participants with type 2 diabetes. Dietary approaches assessed in this review included low-fat/high-carbohydrate diets, high-fat/low-carbohydrate diets, low-calorie (1,000 kcal per day) and very-low-calorie (500 kcal per day) diets and modified fat diets. In Comparison 1, nine studies assessed two types of diabetic dietary advice that did not differ in intent to lose weight. There were a total of 378 participants in this comparison grouping. HbA1c values ranged from a reduction of –0.7% in a low fat diet to + 0.4% in a monounsaturated diet at 6 months for both. No conclusions could be drawn from the comparison. In Comparison 2, two studies assessed very-low-calorie dietary advice versus a low-calorie diet in a total of 129 subjects. In this comparison, mean HbA1c values ranged from a reduction of –1.7% in one low calorie diet group to an increase of 1.4% in a different study with a low calorie diet group, at 6 and 12 months respectively. No firm conclusions could be drawn from the data. In Comparison 3, six studies compared interventions that examined the effect of dietary advice alone or dietary advice plus exercise. In all, 340 participants took part in these trials. Mean HbA1c levels rose in one study by 0.9% in both a diet only group and a diet plus exercise group at 12 months but was reduced by 1.4% in a different study using diet and exercise over the same time period. The evidence suggested that exercise plus dietary advice had the potential to have an impact on weight and glycaemic control, although there was a high potential for bias. Finally in Comparison 4, three studies assessed dietary advice versus dietary advice plus behavioural approaches. There was a total of 499 participants in these three trials. HbA1c data were not reported in a number of studies, however, one study reported a reduction in mean HbA1c of 0.2% at 6 months follow-up with the intervention while another reported an increase of 0.1% over 6 months in a clinic-based intervention group. Firm conclusions could not be drawn from the

comparisons. There were no high quality data on the efficacy of dietary treatment in type 2 diabetes and therefore no firm conclusions could be made.

Van de Laar et al (2007) systematically reviewed results, quality and validity of systematic reviews on diet in people with type 2 diabetes. PUBMED, EMBASE, and the Cochrane Database were used to identify systematic reviews on nutritional interventions in people with type 2 diabetes. Of the six included systematic reviews, two focused on strategies including diet that promote weight loss while one investigated dietary advice in general and has since been updated (reviewed above). The systematic review by Brown et al (1996) included 89 studies of which 40% involved dietary interventions. Dietary interventions (ADA reduced calorie, very-low-calorie, protein sparing modified diets) lowered body weight by approximately 9 kg and reduced HbA1c by 2.7%. Twenty-two studies were included in the meta-analysis by Norris et al (2004), however, pooled results for diet-only studies were sparse. A meta-analysis of two studies in the review compared very-low-calorie diet with low-calorie diets. This resulted in a decrease in body weight of 3 kg (95% CI 0.5–6.4) in favour of the very-low-calorie diet. In an additional meta-analyses, the effects of treatment in individual study arms (i.e. pre-test value considered control, post-test value intervention), the effect of 'usual care' was a decrease of 2 kg in body weight (95% CI 0.6–3.5) and the low-calorie diet resulted in a decrease of 3.7 kg (95% CI 2.3–5.1). Overall most systematic reviews resulted in inconclusive findings, and where a statistically significant finding was reported, interpretation was difficult because data necessary to assess external validity were mostly lacking.

A meta-analysis was performed by Kirk et al (2008) to evaluate the effects of dietary carbohydrate restriction in people with type 2 diabetes. Primary endpoints included blood glucose control (HbA1c), weight and blood lipid concentrations. Searches were conducted using MEDLINE, CINAHL, Combined Health Information Database, Cochrane Library and Web of Science from 1980 to April 2006. Thirteen published studies fulfilled the inclusion criteria. The mean age of the study subjects was 57 ± 6 years (range: 48-66 years). Seven studies were isocaloric by design and compliance to the diets was evaluated by food records, diet recall and interview. Subjects were using insulin in five of the studies. Although activity modification was not specifically addressed, subjects were instructed to continue their regular physical activities. No significant relationship was found between weight loss and carbohydrate content of the diet. In seven studies, changes in mean HbA1c in subjects on the low carbohydrate diets ranged from a reduction of 2.2% to an increase of 0.3% over 5 and 4 weeks, respectively. On the high carbohydrate diets, mean HbA1c ranged from a reduction of 2.2% to an increase of 0.9% over 5 and 12 weeks, respectively. In a statistical regression model, carbohydrate intake predicted percent change in blood glucose with a 10% increase in carbohydrate consumption equating to a 3.2% ± 1.2% increase in glucose change ($p = 0.047$). Inclusion of weight change attenuated the relationship between carbohydrate intake and percent change in glucose and HbA1c and removed the significance of carbohydrate intake predicting percent change in blood glucose.

Daly et al (2006) randomised 102 obese subjects with poorly controlled type 2 diabetes and examined the effects of carbohydrate restriction compared with a reduced-portion low fat (LF) diet over a three month period. Although the low carbohydrate (LC) diet achieved a lower mean energy intake compared with the LF diet, the differences were not significant. Greater weight loss was achieved with the LC diet compared with the LF diet (LC = 3.6 kg vs LF = 0.9 kg), however, there were no significant changes in HbA1c levels. The lack of effect on HbA1c may have been due to an 85% reduction in the amount of insulin subjects used in the LC group.

Brand-Miller et al (2003) conducted a literature search from 1981 to 2001 and identified 14 randomised crossover parallel experimental studies with a mean of 10 weeks duration (12 days to 12 months) which compared the effects of low-GI diets with conventional or high-GI diets on glycaemic control. The average GI of the high- and low-GI diets was 83 and 65, respectively. Of 356 study participants, 203 had type 1 and 153 had type 2 diabetes. The mean difference in end point HbA1c between the low-GI and high-GI diets was -0.43% (CI -0.72, -0.13). Low GI diets have a small but clinically useful effect on medium-term glycaemic control in people with diabetes.

In a controlled trial Barnard et al (2006) investigated the effects of a low-fat vegan diet on glycaemic control and cardiovascular risk factors in 99 people with type 2 diabetes who were randomly assigned to the vegan diet (n = 49) or to a diet based on the American Diabetes Association (ADA) guidelines (n = 50). The vegan diet consisted of vegetables, fruits, grains and legumes with approximately 10% of total energy from fat, 15% from protein and 75% from carbohydrate. Subjects avoided animal products, were told to favour low glycaemic index carbohydrate, and were not restricted to any portion sizes or energy intake. Both groups reduced energy intake (vegan 1,759 ± 468 to 1,425 ± 427 kcal/day, $p < 0.0001$; ADA 1,846 ± 597 to 1,391 ± 382 kcal/ day, $p < 0.0001$ [between-group $p = 0.22$]) and protein intake (vegan 77 ± 27 to 51 ± 16 g/day, $p < 0.0001$; ADA 85 ± 27 to 73 ± 23 g day, $p = 0.002$ [between group $p = 0.01$]). Carbohydrate intake increased in the vegan group from 205 ± 69 to 251 ± 70 g/day ($p < 0.0001$) but fell in the ADA diet group from 213 ± 70 to 165 ± 51 g/day ($p < 0.0001$ [between-group p ± 0.001]). HbA1c fell 1.0% ($p < 0.0001$) in the vegan group and 0.6% ($p = 0.0009$) in the ADA diet group (between-group $p = 0.089$, baseline-adjusted $p = 0.091$). Among participants whose diabetes medications remained unchanged throughout (n = 24 vegan and n = 33 ADA), HbA1c fell 1.2% in the vegan group and 0.4% in the ADA diet group ($p = 0.01$; baseline-adjusted $p = 0.007$). Weight change was significantly associated with HbA1c change and likely responsible for a substantial portion of its effect on HbA1c with each kg weight loss associated with a 0.1% drop in HbA1c.

In an Australian study, Parker et al (2002) evaluated the effects of high protein (HP) intake compared with a lower-protein (LP) diet on insulin sensitivity and glycaemic control in 54 obese men and women with type 2 diabetes during 8 weeks of energy restriction (1,600 kcal) and 4 weeks of energy balance. Subjects were matched for BMI, age, sex, FPG and

medication. The HP diet consisted of 30% energy from protein and 40% energy from CHO, and the LP diet consisted of 15% energy from protein and 60% energy from CHO. Diets were matched for fatty acid profile (8% saturated fatty acids, 12% monounsaturated fatty acids, 5% polyunsaturated fatty acids). Diets were prescriptive fixed menu plans, and subjects were supplied with key foods, which amounted to 60% of energy intake, to assist with dietary compliance. Both men and women lost weight on both diets (LP: 5.8 vs 4.7 kg, HP: 6.0 vs 4.2 kg; respectively). Fasting and postprandial glucose concentrations were reduced by both interventions ($p < 0.001$); however there were no significant difference between diets. HbA1c decreased between baseline and week 12 - LP: 6.3 ± 0.8 to 5.8 ± 0.6%, HP: 6.4 ± 0.8 to 5.9 ± 0.8%, $p < 0.001$) with no significant difference between diets.

In another Australian study, Brinkworth et al (2004) compared long-term weight loss and health outcomes at 1-year follow-up after a 12 week intensive intervention with two low fat, weight loss diets, differing in protein content. Overweight or obese adults (n = 66, BMI: 27–40 kg/m^2) were randomised to either a low protein (LP, 15% protein, 55% CHO) or high protein (HP, 30% protein, 40% CHO) diet for 8 weeks of energy restriction (6.7 MJ/day) and 4 weeks of energy balance. For a further 12 months, subjects were asked to maintain the dietary patterns. There were equal dropouts in each group with a total of 38 subjects reaching study completion. Both groups lost weight after 12 weeks (mean weight loss: 5.3 kg), however, there was a significant weight regain during follow-up. Body weight remained significantly lower at week 64 compared with baseline (LP: –2.2 ± 1.1 kg; HP: –3.7 ± 1.0 kg, $p < 0.01$). HbA1c, fasting glucose, insulin and HOMA values were significantly reduced at 12 weeks but increased during follow-up to the point where no significant difference existed compared with baseline levels (HbA1c LP – baseline: 6.2 ± 0.2, week 12: 5.7 ± 0.1, week 64: 6.6 ± 0.3%; HbA1c HP – baseline: 6.5 ± 0.2, week 12: 6.0 ± 0.2, week 64: 6.6 ± 0.4%).

Hartweg et al (2008) performed a systematic review to assess the effects of omega-3 PUFA supplementation on death and cardiovascular outcomes, cholesterol levels and glycaemic control in people with type 2 diabetes. The literature was searched until December 2006 for randomised controlled trials in which omega-3 PUFA supplementation or dietary intake was randomly allocated in people with type 2 diabetes. In all, 23 randomised controlled trials (1,075 participants) with a mean treatment duration of approximately 9 weeks met the inclusion criteria. The effect of omega-3 PUFA on glycaemic control and lipid levels was the focus in 20 trials; 2 trials assessed omega-3 PUFA on vascular outcomes but also reported glycaemic and lipid endpoints. The mean dose of omega-3 PUFA used in the trials was 3.5 g/d. No trials with vascular events or mortality endpoints were identified. Among those taking omega-3 PUFA, triglyceride levels were significantly lowered by 0.5 mmol/L (95% CI -0.6 to -0.3, $p < 0.00001$) and VLDL cholesterol lowered by -0.07 mmol/L (95% CI -0.13 to 0.00, $p = 0.04$). LDL cholesterol levels were raised by 0.1 mmol/L (95% CI 0.00 to 0.2, $p = 0.05$). No significant change in total or HDL cholesterol, HbA1c, fasting glucose, fasting insulin or body weight was observed.

An Australian study (Dunstan et al., 1997) used a randomised controlled 8-week intervention, to test the effects of moderate exercise and daily fish intake on lipid and lipoprotein levels in people with type 2 diabetes (4 groups of 11 to 14 subjects). Moderate exercise training consisted of 30 min stationary cycling at 50-55% VO2max for the first week and then 55-65% VO2max for 7 weeks. Relative to control subjects who participated in a light exercise program, moderate exercise alone reduced triglycerides by 0.7 mmol/L ($p = 0.03$), but had no effect in combination with fish, compared with fish alone. The rise of 0.06 mmol/L in HDL cholesterol with exercise alone was not significant ($p = 0.06$) and again there was no effect of exercise and fish compared with fish alone. Mean weight loss was 2.1kg in the moderate exercise group and 0.6kg in the light exercise group. An HbA1c reduction of 0.3% was associated with moderate exercise.

Few studies have examined the effects of alcohol on glycaemic control in people with type 2 diabetes. One 3-year study examined the effects of chronic alcohol intake on carbohydrate and lipid metabolism in people with type 2 diabetes (Ben et al., 1991). The study included 46 alcohol-consuming (45 g/day) people (31 females and 15 males) with type 2 diabetes, 35 non-alcohol-consuming people with type 2 diabetes, and 40 non-diabetic controls. Chronic alcohol intake was associated with higher fasting blood glucose levels (9.1 vs 7.8 mmol/L; $p < 0.05$) and HbA1c (6.8 vs 6.1%; $p < 0.05$). However, no significant differences were found in total cholesterol (both 5.7 mmol/L), triglycerides (1.6 vs 1.5 mmol/L) or HDL cholesterol (both 1.3 mmol/L) levels between the drinkers and the control group. Chronic alcohol intake was associated with worse diabetes control in people with type 2 diabetes.

Physical Activity

Physical activity may include moderate or vigorous exercise, resistance exercise and flexibility training practised with varying frequency, intensity and duration. Physical activity is one of the key modifiable risk factors for glycaemic control and used alone or in combination with diet, oral anti-diabetic medications, or insulin, is a key component of therapy for type 2 diabetes.

Thomas et al (2006) performed a meta-analysis of fourteen randomised controlled trials comparing exercise against no exercise in 377 people with type 2 diabetes. Using the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE and manual searches, they searched from January 1966 to March 2005. Trials ranged from 8 weeks to 12 months duration. Compared with controls, the exercise intervention significantly improved glycaemic control with a decrease in glycated haemoglobin levels of 0.6% (-0.6% HbA1c, 95% confidence interval (CI) -0.9 to -0.3; $p < 0.05$). There was no significant difference between groups in whole body mass, probably due to an increase in fat free mass (muscle) with exercise but there was a reduction in visceral adipose tissue with exercise (-45.5 cm^2, 95% CI -63.8 to -27.3), and subcutaneous adipose tissue also decreased. No study reported adverse effects in the exercise group or on diabetes complications. The exercise intervention significantly decreased plasma triglycerides (-0.3 mmol/L, 95% CI -0.5 to -0.02). No

significant difference was found in quality of life (one trial), plasma cholesterol or blood pressure. The meta-analysis showed that exercise significantly improved glycaemic control and reduced visceral adipose tissue and plasma triglycerides, but not plasma cholesterol, in people with type 2 diabetes, even without weight loss.

In a meta-analysis of 27 reports, Snowling and Hopkins (2006) examined the effects of aerobic training, resistance training and combined training in a total of 1,003 people with type 2 diabetes. Mean age was 55 years and study duration ranged from 5 to 104 weeks. With all three exercise modes there was a clear but small reduction in HbA1c, however, the differences between aerobic, resistance, and combined training on HbA1c were trivial. Training for periods longer than 12 weeks produced a reduction of HbA1c of 0.8 ± 0.3% (mean ± 90% confidence interval). Benefits were small to moderate in magnitude for other measures of glucose control including fasting glucose, postprandial glucose, insulin sensitivity, and fasting insulin. There was a large effect on insulin sensitivity when exercise modes were combined.

Di Loreto et al (2005) examined the impact of different amounts of increased energy expenditure on health outcomes in people with type 2 diabetes. Different amounts of increased energy expenditure (metabolic equivalents (Klein et al.) per hour per week) through voluntary aerobic physical activity was performed in 179 people with type 2 diabetes (mean age 62 years) randomised to a physical activity counselling intervention. Subjects were followed for 2 years and divided into six groups based on their increments in METs per hour per week: group 0 (no activity, n = 28), group 1-10 METs (6.8 ± 0.3 METs, n = 27), group 11-20 METs (17.1 ± 0.4 METs, n = 31), group 21-30 METs (27.0 ± 0.5 METs, n = 27), group 31-40 METs (37.5 ± 0.5 METs, n = 32), and group > 40 METs (58.3 ± 1.8 METs, n = 34). At baseline, the six groups did not differ for energy expenditure, age, sex, diabetes duration, and all parameters measured. After 2 years, in group 0 and in group 1-10, no parameter changed; in groups 11-20, 21-30, 31-40, and > 40, HbA1c, blood pressure, total cholesterol, triglycerides, and estimated 10-year coronary heart disease risk improved ($p < 0.05$). Percent HbA1c (± SE) values changed across groups as follows: group 0, 0.03 ± 0.01; group 1–10, –0.06 ± 0.09; group 11–20, –0.4 ± 0.1; group 21–30, –0.9 ± 0.07; group 31–40, –1.1 ± 0.1; group > 40, –1.0 ± 0.1% ($p = 0.001$, between group comparisons). In group 21-30, 31-40, and > 40, body weight, waist circumference, heart rate, fasting plasma glucose, LDL and HDL cholesterol also improved ($p < 0.05$). METs per hour per week correlated positively with changes in HDL cholesterol and negatively with those of other parameters ($p < 0.001$). Energy expenditure > 10 METs per hour per week obtained through aerobic leisure time physical activity was sufficient to achieve health advantages, but full benefits were only achieved with energy expenditure of > 20 METs per hour per week.

Kavookjian et al (2007) conducted a systematic review to assess and summarise evidence regarding interventions for being active (exercise) among individuals with diabetes. Twelve electronic databases were searched; publications eligible for inclusion specifically studied

learning, behavioural, clinical, and humanistic outcomes for exercise interventions in adults with type 1 and type 2 diabetes. Seven reviews (2 systematic reviews, 3 meta-analyses, 2 technical reviews) and 34 individual, non-review studies (18 randomised controlled trials, 16 non-randomised trials) from 1994 – 2006 met the inclusion criteria. An included meta-analysis of 7 studies, presenting data for 9 randomised trials comparing exercise and control groups, quantified the effects of exercise on cardiorespiratory fitness in people with type 2 diabetes (Boule et al., 2003). An analysis across study samples showed an 11.8% increase in VO2max in the exercise group and a 1.0% decrease in the control group (post-intervention standardised mean difference = 0.53, $p < 0.003$). Higher exercise intensity was associated with larger improvements in VO2max and predicted post-intervention weighted mean differences in HbA1c ($r = –0.91$, $p = 0.002$) to a larger degree than did exercise volume ($r = –0.46$, $p = 0.26$) (Boule et al., 2001). The authors noted that high-intensity exercise might prove too difficult or even hazardous for many individuals who had previously been sedentary and that the results would not be sufficient to advocate high-intensity exercise for all people with diabetes. But for people already exercising at a moderate level of intensity, an increase in their level of exercise intensity may provide additional benefits on both metabolic control and cardiorespiratory fitness. For type 2 diabetes, exercise had an overall positive effect on glycaemic control and decreased cardiovascular risk, but the impact of exercise on behavioural and humanistic outcomes was unclear; long-term outcomes and adherence to exercise interventions was unknown because most of the studies were of short duration. Physical activity is better than no exercise at all; intensive regimens, if tolerated by patients, achieved better clinical outcomes than less intensive regimens. Structured exercise regimens exhibited a more significant impact on outcomes.

Gordon et al (2008) systematically reviewed the effect of resistance training (RT) on glycaemic control and insulin sensitivity in adults with type 2 diabetes. MEDLINE (1950 to November 2007), pre MEDLINE (January 2008), OLD MEDLINE (1950 to 1965) and CINAHL (1982 to December 2007) electronic databases were searched. Studies included adults aged above 18 years with type 2 diabetes. In all, 32 studies met the inclusion criteria. In general, there were no baseline differences between intervention and control groups except where studies were intentionally designed to compare different cohorts. The duration of studies varied from a single session of resistance training to 12 months of training. Compliance levels ranged from 83–88% in 17 studies and was reported at 100% in 3 of the studies. Most training took place under supervision. People with diabetes were able to complete resistance training with very little risk to health or injury, while improving glycaemic control, insulin sensitivity and strength. In all, 27 studies reported HbA1c data, with three studies reporting a reduction in HbA1c of up to 1.2% from initial values of $\geq 8.0\%$ after 12, 16 and 24 weeks of training. Home or community-gym maintenance programs reported glycaemic control returning to baseline after 6 months or worse after one year reflecting a likely decrease in compliance. Combined training also resulted in significant HbA1c improvements of up to 1.2% after moderate, moderate-high, and high intensity

training of varying durations up to 12 months. The greatest improvement in glycaemic control occurred when initial baseline values were poor (> 8.0%).

To determine the effects of aerobic training alone, resistance training alone, and combined exercise training on HbA1c in people with type 2 diabetes, Sigal et al (2007) conducted a randomised controlled trial which included 251 adults aged 39–70 years from 8 community-based facilities. A sedentary group was also included. A negative result on a stress test or clearance by a cardiologist, and adherence to exercise during a 4-week run-in period, were required before randomisation. Thereafter, exercise training was performed 3 times weekly for 22 weeks. The median exercise training attendance was 86% in the combined exercise training group, 80% in the aerobic training group, and 85% in the resistance training group. Compared with the control group, the absolute change in HbA1c in the aerobic training group was -0.5% (95% CI, -0.9 to -0.1) and in the resistance training group -0.4% (CI, -0.7 to -0.2). The greatest reduction in HbA1c was observed in the combined exercise training which resulted in an additional change in the HbA1c of -0.5% (CI, -0.8 to -0.1) compared with aerobic training alone and -0.6% (CI, -1.0 to -0.2) compared with resistance training alone. Changes in blood pressure and lipid values were not statistically significantly different among groups. Adverse events were more common in the exercise groups. Exercise-induced improvements in glycaemic control were greater among persons with higher baseline HbA1c values. Among persons with lower baseline HbA1c values, only combined aerobic and resistance training improved values while aerobic or resistance training alone did not. However it should be noted that execise volume differed between the groups.

Weight control is an important component of diabetes care

Overweight is defined as a BMI of 25 to 29.9 kg/m^2, and obesity as a BMI of ≥ 30 kg/m^2 (National Heart Lung and Blood Institute, 1998). Both overweight and obesity are significant risk factors for type 2 diabetes (Pi-Sunyer, 2000) with every 1kg increase in average weight being associated with a 9% relative increase in diabetes prevalence (Mokdad et al., 2000). Approximately 80–90% of people with type 2 diabetes are overweight or obese which exacerbates the metabolic abnormalities of hyperglycaemia, hyperlipidaemia, and hypertension. Weight control is therefore one of the cornerstones of diabetes therapy in obese people. Direct benefits of weight loss include an increase in insulin sensitivity, improvement in glycaemic control, improved lipid profiles, decreased triglycerides and LDL cholesterol and improved blood pressure, mental health and quality of life (Wing et al., 1991; Maggio and Pi-Sunyer, 1997; Pi-Sunyer, 2000). Weight loss can be achieved through dietary and behavioural therapy over 3–12 months, however the majority of obese people regain lost weight within 2 to 5 years (Wadden and Sarwer, 1999). Furthermore, studies suggest that people with diabetes lose less weight than those without diabetes and regain their weight more rapidly (Hensrud, 2001). Greenway (1999) suggests that because obesity is a chronic problem it may require long-term pharmacotherapy, particularly in people where behavioural therapy has failed. Medications targetting obesity work through a variety of mechanisms, including appetite suppression, increased energy expenditure, and nutrient partitioning by decreasing food absorption in the gut.

Non-pharmacological interventions

Norris et al (2005a) conducted a meta-analysis of 22 randomised controlled trials involving 4,659 participants with a follow-up period of 1 to 5 years. People were aged ≥ 18 years with type 2 diabetes and were of any weight or BMI at baseline. Due to heterogeneity of interventions and comparisons, estimates were pooled for only three groups of studies: any intervention versus usual care, very low calorie diet versus low calorie diet, and physical activity versus no or less intensive physical activity. In the first group (7 studies including 585 subjects), the pooled effect for interventions with a follow-up between 1 and 2 years was a reduction in weight of 1.7 kg (95% CI, 0.3 to 3.2). In 2 studies with 126 subjects that compared very low calorie diets with low calorie diets the pooled effect was a nonsignificant reduction of 3.0 kg (95% CI, -0.5 to 6.4) after 104 weeks of follow-up. In two studies reported in a single paper, in which a combination of dietary, physical activity, and behavioural interventions was compared with identical interventions with either no or less physical activity, the pooled effect among 53 subjects was not significant. Between-group changes in HbA1c ranged from –2.6% to 1% and generally corresponded to changes in weight and were not significant when between-group differences were examined although several included studies did have a significant decrease in HbA1c.

Redmon et al (2005) evaluated the effects of a weight loss program combining several weight loss strategies on weight loss and diabetes control in overweight subjects with type 2 diabetes.

A total of 59 overweight or obese individuals with type 2 diabetes were randomly assigned to either a combination therapy weight loss program for 2 years (C therapy) or a standard therapy weight loss program for 1 year followed by a combination therapy weight loss program in the 2nd year (S/C therapy). C therapy combined the use of meal replacement products, repetitive intermittent low-calorie-diet weeks, and pharmacological therapy with sibutramine. Outcome measures included changes in weight, glycaemic control, plasma lipids, blood pressure, and body composition over 2 years. A total of 48 participants (23 in the C therapy group and 25 in the S/C therapy group) completed 2 years of study. After 2 years, the C therapy group had weight loss of 4.6 ± 1.2 kg ($p < 0.001$) and a decrease in HbA1c of 0.5 ± 0.3% ($p = 0.08$) from baseline. At 2 years, the C therapy group had significant reductions in BMI, fat mass, lean body mass, and systolic blood pressure. The S/C therapy group showed changes in weight and HbA1c in year 2 of the study that were similar to those demonstrated by the C therapy group in year 1.

The Look AHEAD Research Group (2007) conducted a study to investigate the one-year changes in CVD risk factors in a trial designed to examine the long-term effects of an intensive lifestyle intervention on the incidence of major CVD events. The study consisted of a multi-centred, randomised, controlled trial of 5,145 individuals with type 2 diabetes, aged 45-74 years, with BMI >25 kg/m^2 (>27 kg/m^2 if taking insulin). An intensive lifestyle intervention (ILI) involving group and individual meetings to achieve and maintain weight loss through decreased caloric intake and increased physical activity was compared with a diabetes support and education (DSE) condition. Participants assigned to ILI lost an average 8.6% of their initial weight vs 0.7% in the DSE group ($p < 0.001$). Mean fitness increased in ILI by 20.9 vs 5.8% in the DSE ($p < 0.001$). A greater proportion of ILI participants had reductions in diabetes, hypertension, and lipid-lowering medications. During the 1st year, use of glucose-lowering medications among ILI participants decreased from 86.5 to 78.6%, whereas it increased from 86.5 to 88.7% among DSE participants ($p < 0.001$). Despite this difference, mean fasting glucose declined more among ILI participants compared with DSE participants ($p < 0.001$), as did mean HbA1c which decreased from 7.3 to 6.6% in the ILI group ($p < 0.001$) vs from 7.3 to 7.2% in the DSE group.

Pedersen et al (2007) evaluated the efficacy of portion control tools to induce weight loss in a randomised controlled trial in people with type 2 diabetes. One hundred and thirty obese people with type 2 diabetes (including 55 taking insulin) were randomised to the daily use of a commercially available portion control plate for 6 months (intervention group) or to usual care in the form of dietary teaching (usual care control group). Follow-up was 93.8%. Subjects in the intervention group lost significantly more weight than control subjects (mean ± SD, 1.8% ± 3.9% vs 0.1% ± 3.0%, $p = 0.006$). HbA1c did not differ between the group at baseline or at follow-up ($p = 0.34$); however, more patients in the intervention group had a decrease in their diabetes medications at 6 months (26.2% vs 10.8%, $p = 0.04$).

Pharmacological Interventions

A meta-analysis conducted by Norris et al (2005b) assessed the efficacy of pharmacotherapy for weight loss in adults with type 2 diabetes. Systematic searches using MEDLINE, EMBASE and Web of Science between 1974 and May 2004 produced 22 randomised controlled trials with a total of 2,036 subjects for orlistat, and 1,047 subjects for sibutramine. Pharmacotherapy produced modest reductions in weight for orlistat 2.0 kg (CI, 1.3 – 2.8) at 12 to 57 weeks follow-up, and sibutramine 5.1 kg (CI, 3.2 – 7.0) at 12 to 52 weeks follow-up. The pooled reduction for HbA1c was 0.5% (95% CI, 0.3 to 0.6) for orlistat (follow-up between 24 and 57 weeks); and 0.5% (95% CI, -0.2 to 1.3) for sibutramine (follow-up 12 to 52 weeks). Main adverse events were gastrointestinal with orlistat and palpitations with sibutramine.

In a German meta-analysis, Ruof et al (2005) examined seven randomised controlled trials of orlistat in overweight and obese people with type 2 diabetes. There was a total of 1,249 people treated with orlistat and 1,230 with placebo. The treatment duration was one year in four trials, and 6 months in the other three. A subgroup analysis involving people who achieved a response (defined as a weight loss of ≥ 5% after 12 weeks of treatment) was conducted. Mean age was 54.5 ± 8.9 y (mean ± SD) in both groups, and BMI 34.8 ± 4.9 kg/m^2. After 12 weeks, 23% in the orlistat group achieved a weight loss of ≥ 5%, and 49% achieved a loss of ≥ 3%. At the same time point, 59% exhibited a ≥ 0.6% reduction in HbA1c. People who achieved a weight reduction of ≥ 3% showed a decrease in HbA1c of 1.0% at study end; those whose HbA1c decreased by ≥ 0.6% at week 12 achieved a reduction in HbA1c of 1.1% at study end. The most commonly reported adverse events in the orlistat group were gastrointestinal which were mild to moderate in severity.

In a UK study, Rowe et al (2005) characterised the effect and concomitant diabetes medication use in people with diabetes treated with orlistat. Of the 100 subjects recruited, 91 had type 2 diabetes. At baseline, mean BMI was 39.5 kg/m^2 (SD 6.5) and mean HbA1c (n = 93) was 7.6% (SD 1.5). Fifty-one were treated with insulin, with a mean daily dose of 130 units (SD 135.4); 57 with oral anti-diabetic medications (45 metformin, 15 with sulphonylureas, and 2 with rosiglitazone). Follow-up was at 1–3 month intervals, with a maximum treatment period of 24 months. At 6 months follow-up, mean weight loss was 7.1 kg ($p < 0.001$). There was a significant average absolute HbA1c reduction of 0.6% ($p < 0.001$) with the largest decrease in those with the highest baseline HbA1c values – a mean relative reduction of 20% for those above the 75th percentile. The mean dose of all medications was reduced at 6 months although the findings were significant for insulin only.

In a Swedish study, Lindegarde (2000) assessed the effect of orlistat on body weight and cardiovascular risk amongst 376 obese people with type 2 diabetes (mean age 53 years, mean BMI 33 kg/m^2) who were at high coronary risk. Subjects were randomised to orlistat 120 mg/d or placebo three times daily in conjunction with dietary intervention for one year. Orlistat-treated people achieved greater weight reduction than placebo-treated people after

52 weeks (5.6 ± 5.2 vs 4.3 ± 5.9 kg, $p < 0.05$), and significantly more people had weight loss of ≥ 5% (54.2 vs 40.9%, $p < 0.001$). Treatment with orlistat was associated with reduction in HbA1c (-2.7% vs -0.5%, $p < 0.05$), and total and LDL cholesterol (-3.3% vs -0.5%, $p < 0.05$; -7.0% vs -1.1%, $p < 0.05$). The overall incidence of adverse events was similar in the orlistat and placebo group. Orlistat treatment in conjunction with diet promoted significant weight loss and reduced cardiovascular risk factors over diet alone amongst obese people with type 2 diabetes.

Vettor et al (2005) examined 8 placebo-controlled, double blind, randomised trials in a meta-analysis of 1,093 obese people with type 2 diabetes. The literature search included results from the Cochrane Library, MEDLINE and EMBASE. In all, 552 people were treated with sibutramine over times ranging from 3 to 12 months. There was a significant decrease in body weight and waist circumference with sibutramine when compared with placebo. Body weight and waist circumference decreased from baseline on average 5.5 ± 0.2 kg and 5.3 ± 0.3 cm in the sibutramine group compared with –0.9 ± 0.2 kg and –1.1 ± 0.2 cm in the placebo group ($p = 0.0000$ for both). HbA1c significantly decreased after sibutramine treatment with an overall effect size compared with placebo of –0.3% (–0.1 to –0.4; $p = 0.0002$) with some heterogeneity ($p = 0.0104$) among the studies.

Anti-diabetic medications (general)

In a literature search of MEDLINE, EMBASE, and The Cochrane Library through to January 2006, Bolen et al (2007), summarised the benefits and harms of oral agents (second-generation sulphonylureas, biguanides, thiazolidinediones, meglitinides, and alpha-glucosidase inhibitors) in the treatment of adults with type 2 diabetes. Because the evidence from clinical trials was inconclusive on major clinical end points, such as cardiovascular mortality the review was limited mainly to studies of intermediate end points. Most of the oral agents (thiazolidinediones, metformin, and repaglinide) improved glycaemic control to the same degree as sulphonylureas (absolute decrease in HbA1c level of about 1%). Nateglinide and alpha-glucosidase inhibitors had slightly weaker effects, on the basis of indirect comparisons of placebo-controlled trials. Thiazolidinediones were the only class that had a beneficial effect on HDL cholesterol levels (mean relative increase, 0.08 to 0.13 mmol/L) but a deleterious effect on LDL cholesterol levels (mean relative increase, 0.26 mmol/L) compared with other oral agents. Metformin decreased LDL cholesterol levels by about 0.26 mmol/L, whereas other oral agents had no obvious effects. Most agents other than metformin increased body weight by 1 to 5 kg. Sulphonylureas and repaglinide were associated with greater risk for hypoglycaemia, thiazolidinediones with greater risk for heart failure, and metformin with greater risk for gastrointestinal problems compared with other oral agents. Lactic acidosis was no more common in metformin recipients without comorbid conditions than in recipients of other oral diabetes agents.

Metformin is a widely used, safe and effective therapy for type 2 diabetes

Used in the treatment of type 2 diabetes for approximately 50 years, metformin is a biguanide derivative and commonly used as first-line therapy in overweight and obese people with type 2 diabetes not controlled by lifestyle modification. Metformin is an insulin-sensitising agent which improves peripheral and liver sensitivity to insulin, as well as decreasing basal hepatic glucose output. Metformin lowers both fasting and postprandial blood glucose levels and is associated with weight stabilisation or weight loss. Gastrointestinal effects are the most commonly reported adverse effects.

A meta-analysis including 29 trials with 37 arms (5,259 participants), compared metformin monotherapy with sulphonylureas, placebo, diet, thiazolidinediones, insulin, meglitinides, and alpha-glucosidase inhibitors (Saenz et al., 2005). With regard to outcomes, in the UKPDS, obese people allocated to intensive blood glucose control with metformin showed a greater benefit than intensive treatment with chlorpropamide, glibenclamide, or insulin for any diabetes-related outcomes ($p = 0.009$) and for all-cause mortality ($p = 0.03$). Also obese participants assigned to intensive blood glucose control with metformin showed a greater benefit than overweight people on conventional treatment for any diabetes-related outcomes ($p = 0.004$), diabetes-related death ($p = 0.03$), all-cause mortality ($p = 0.01$), and myocardial

infarction (p = 0.02). Four additional trials reported data on ischaemic heart disease events (Teupe and Bergis, 1991; DeFronzo and Goodman, 1995; Horton et al., 2000; Hallsten et al., 2002). Events were reported as myocardial infarction, ischaemic heart disease, death due to hypertensive heart disease, and myocardial infarction, respectively. There were no significant differences among comparisons from these four trials for all-cause mortality (p = 0.35), or for ischaemic heart disease (p = 0.17) when the data were pooled. In the general meta-analysis, people assigned to metformin monotherapy showed a significant benefit in glycaemic control, weight, dyslipidaemia, and diastolic blood pressure. Metformin showed strong benefits for HbA1c compared with placebo and diet and a slight benefit in HbA1c (0.14%) and BMI (0.45) compared with sulphonylureas.

Johansen (1999) conducted a meta-analysis by searching the Current List of Medical Literature, Cumulated Index Medicus, Medline, and EMBASE to evaluate the efficacy of metformin in the treatment of type 2 diabetes. A total of 19 randomised controlled trials including 9 comparing metformin with placebo and 10 comparing metformin with sulphonylureas were identified. The outcome measures were fasting blood glucose, HbA1c, and body weight. The duration of treatment ranged from one month to two years. The dose of metformin varied between 1500 and 3000 mg/d and the duration of treatment from one to 36 months. Sulphonylurea agents included tolbutamide, glibenclamide, gliclazide and glipizide. In the metformin-placebo comparison, blood glucose decreased on average 2.6 mmol/L, HbA1c 1.3% and body weight 0.8 kg after metformin treatment. The weighted mean difference (WMD) of fasting blood glucose after treatment between metformin and placebo was -2.0 mmol/L (95% CI -2.4 to -1.7), and for HbA1c was -0.9% (95% CI -1.1 to -0.7). Body weight was not significantly changed after treatment. In the metformin-sulphonylurea comparison, the WMD for HbA1c and FPG were not significant, meaning that both treatments resulted in equivalent glycaemic control. However, body weight decreased 1.2 kg after metformin and increased 1.7 kg after sulphonylurea treatment; the WMD for body weight between two treatments was -2.9 kg (95% CI -4.4 to -1.1). No data for hypoglycaemia were reported.

Campbell and Howlett (1995) performed a meta-analysis via Medline, Embase, Pascal and Biosis between 1957 and 1994 and identified 11 trials comparing sulphonylureas with metformin which were either crossover or non-crossover, open or blinded. A total of 656 people aged 36 to 94 years with type 2 diabetes were involved and study duration ranged from 6 to 52 weeks. Both the metformin and sulphonylurea treatments resulted in a similar fall in HbA1c (12.5%). There was a 14%, and a 19% reduction in FPG with metformin and sulphonylureas treatment, respectively, and a 44.5% reduction in postprandial glucose concentration with both treatments. In 7 of 9 trials with weight data, significant weight loss was reported with metformin treatment, whereas there was no significant weight change with sulphonylurea treatment in any of the 9 trials. The difference between the groups was significant (p < 0.01-0.001). Less than 1% of people on sulphonylurea withdrew due to

hypoglycaemic symptoms, while 3% on metformin withdrew because of gastrointestinal symptoms.

The effect of metformin was evaluated in 1,704 newly diagnosed diet-treated overweight people with type 2 diabetes (UKPDS Study Group, 1998). Of these, 753 were included in a randomised controlled trial, median duration 10.7 years, of conventional policy, primarily with diet alone (n = 411) versus intensive blood glucose control with metformin, aiming for FPG below 6 mmol/L (n = 342). A secondary analysis compared the 342 people allocated metformin with 951 overweight people allocated intensive blood glucose control with chlorpropamide (n = 265), glibenclamide (n = 277), or insulin (n = 409). The median HbA1c during the 10 years of follow-up was 7.4% in the metformin group and 8.0% in the conventional treatment group (difference not significant). Subjects assigned intensive blood glucose control with metformin had a 32% lower risk (p=0·0023) of developing any diabetes-related endpoint than those allocated conventional blood-glucose control. The risk reduction was greater than in those groups assigned intensive therapy with sulphonylurea or insulin (p=0·021). The metformin group had a 39% lower risk (p=0·010) of myocardial infarction than the conventional treatment group, but did not differ from the other intensive treatment group. There was no difference in microvascular outcomes.

Schwartz et al (2006) determined the efficacy and safety of a novel extended-release metformin in 750 people with type 2 diabetes during a 24-week double-blind treatment. Subjects (newly diagnosed, treated with diet and exercise only, or previously treated with oral anti-diabetic medications) were randomly assigned to receive one of three extended-release metformin treatment regimens (1,500 mg/day once daily, 1,500 mg/day twice daily, or 2,000 mg/day once daily) or immediate-release metformin (1,500 mg/day twice daily). Significant decreases ($p < 0.001$) in mean HbA1c levels were observed by week 12 in all treatment groups. The mean changes from baseline to study end in the two groups given 1,500 mg extended-release metformin (-0.73 and -0.74%) were not significantly different from the change in the immediate-release metformin group (-0.70%), whereas the 2,000-mg extended-release metformin group showed a greater decrease in HbA1c levels (-1.06%; mean difference [2,000 mg extended-release metformin - immediate-release metformin]). The overall incidence of adverse events was similar for all treatment groups, but fewer people in the extended-release metformin groups discontinued treatment due to nausea during the initial dosing period than in the immediate-release metformin group.

Wulffele et al (2004) conducted a systematic review to examine the effect of metformin on blood pressure and lipid profiles in people with type 2 diabetes. By searching Medline and Embase, a total of 41 RCTs (metformin compared with sulphonylurea, or insulin, or placebo, or acarbose) were obtained. Seventeen trials compared metformin with sulphonylurea derivatives, 13 with diet or placebo, 7 with insulin, 2 with thiazolidinediones, 1 with acarbose and 1 with guar. Compared with control treatment, HbA1c was better with metformin (0.7%, CI -0.8 to -0.7, $p < 0.00001$) and metformin slightly decreased systolic and diastolic blood

pressure (-1.1 mm Hg, CI -3.0 to 0.8, p = 0.3; -1.0 mm Hg, CI -2.2 to 0.2, p = 0.11, respectively). Metformin significantly reduced plasma triglycerides, total and LDL cholesterol (-0.13 mmol/L, CI -0.21 to -0.04, p = 0.0003; -0.26 mmol/L, CI -0.34 to -0.18, p < 0.0001; -0.22 mmol/L, CI -0.31 to -0.13, p < 0.00001, respectively); while slightly increasing HDL cholesterol by 0.01 mmol/L (CI -0.02 to 0.03, p = 0.5). When studies were divided into tertiles according to the dose of metformin, the effect on triglycerides was significant only in the higher dose metformin studies: 1700 to 2550 mg/d (-0.18 mmol/L, CI -0.32 to -0.04, p = 0.01) and 2550 to 3000 mg/d (-0.13 mmol/L, CI -0.25 to 0.01, p = 0.03). The effects on total and LDL cholesterol were not affected by the dosage of metformin.

Monami et al (2008) performed a meta-analysis of 16 randomised clinical trials to determine the efficacy on HbA1c of different anti-diabetic medications when used in combination with metformin, in subjects failing metformin monotherapy, or other oral monotherapies. Follow up ranged from 16–36 months. Medications studied included sulphonylureas (5 trials), alpha-glucosidase inhibitors (5 trials), thiazolidinediones (3 trials), glinides (2 trials) and GLP-1 agonists (1 trial). No studies on DPP-IV inhibitors fulfiling the inclusion criteria were identified. In direct comparisons, sulphonylureas were significantly superior to thiazolidinediones in reducing HbA1c (p < 0.05), with a difference between the two treatments of 0.2% [CI 0.16; 0.18]. No significant difference in HbA1c reduction was observed in studies which compared adding sulphonylurea or insulin. Insulin regimens based on biphasic insulin analogues were more effective than insulin glargine once a day (HbA1c difference 0.3% [CI 0.2; 0.3]; p < 0.01). Combining the results of different placebo-controlled trials, sulphonylureas, alpha-glucosidase inhibitors and thiazolidinediones induced a reduction of HbA1c of 0.9% [CI 0.8; 0.9], 0.6% [CI 0.6; 0.7], and 0.4% [CI 0.4; 0.4], respectively. In direct comparisons, sulphonylureas induced a greater reduction of HbA1c (0.2% [0.16; 0.18]) than thiazolidinediones, and had a similar effect as insulin.

Hermann et al (1994) conducted a study to compare the effects of metformin and the sulphonylurea glyburide, alone or in various combinations on glycaemic control in 144 people (mean age 60 years) with type 2 diabetes who were previously treated with diet alone. Subjects were randomised to treatments with metformin, glyburide or combination therapy during a 6-month period. The doses were adjusted with FPG < 6.7 mmol/L as target. Mean HbA1c levels were significantly reduced in all groups (HbA1c metformin: 6.9 ± 0.3 to 5.8 ± 0.2, glyburide: 6.7 ± 0.3 to 5.3 ± 0.1, metformin/glyburide lowdose: 6.8 ± 0.1 to 5.6 ± 0.1; metformin + glyburide: 7.8 ± 0.3 to 5.4 ± 0.3, glyburide + metformin: 7.8 ± 0.4 to 5.7 ± 0.3, metformin/glyburide highdose: 8.4 ± 0.4 to 6.2 ± 0.3; p = 0.001 for all). Body weight did not change following treatment with metformin or combination therapy but increased by 2.8 ± 0.7 kg following glyburide alone. There were some changes in lipids with high-dose combination, but no significant differences between groups. Hypoglycaemia was more frequent with glyburide and combination therapy, but the different from metformin therapy was not significant.

The efficacy of metformin was assessed among people inadequately controlled by diet alone or diet plus glyburide in a randomised controlled trial (DeFronzo and Goodman, 1995). Subjects (n = 289) were randomised to the metformin or placebo group in Protocol 1, and 632 subjects to the metformin plus glyburide or to metformin or to glyburide group in Protocol 2. In Protocol 1, subjects in the metformin group had a lower HbA1c and FPG levels compared with the placebo group at 29 weeks (7.1 ± 0.1 vs 8.6 ± 0.2%, $p < 0.001$; 10.6 ± 0.3 vs 13.7 ± 0.3 mmol/L, $p < 0.001$, respectively) and lost 0.6 ± 0.3 kg compared with 1.1 ± 0.2 kg in the placebo group ($p = 0.21$). No hypoglycaemia was reported. Diarrhoea and nausea were more common with metformin. In Protocol 2, the combination of metformin and glyburide resulted in a significant reduction in HbA1c and FPG compared with glyburide alone (7.1 ± 0.1 vs 8.7 ± 0.1%, $p < 0.001$; 10.5 ± 0.2 vs 14.6 ± 0.2 mmol/L, $p < 0.001$, respectively). The effect of metformin alone was similar to that of glyburide alone. Mean weight decreased by 3.8 ± 0.2 kg in the metformin group, increased by 0.4 ± 0.2 kg in the combination group, while it did not change significantly in the glyburide group (-0.3 ± 0.2 kg). Hypoglycaemic symptoms occurred during the study in 18% on combined therapy, 3% with glyburide and 2% with metformin. In both protocols, those receiving metformin had significant decreases in total and LDL cholesterol and triglycerides levels ($p = 0.01$ to 0.001).

Umpierrez et al (2006) conducted a randomised, parallel-group, open-label, forced titration study to compare the effect of add-on glimepiride or pioglitazone in 203 subjects with type 2 diabetes (HbA1c 7.5-10%) inadequately controlled on metformin monotherapy. Both treatment groups achieved similar and significant mean decreases from baseline to week 26 in HbA1c ($p = 0.0001$) and FPG ($p < 0.05$). Glimepiride therapy, however, resulted in a more rapid decline in HbA1c levels at weeks 6, 12, and 20 vs pioglitazone ($p < 0.05$). A mean HbA1c ≤ 7% was reached faster in the glimepiride group (median, 80-90 days vs 140-150 days [$p = 0.02$]). Total and LDL cholesterol were significantly higher with pioglitazone treatment than with glimepiride at endpoint ($p < 0.05$). Glimepiride treatment was associated with an increased risk of hypoglycaemia and pioglitazone with higher rate of peripheral oedema. Add-on glimepiride or pioglitazone result in similar overall improvements in glycaemic control in people inadequately controlled on metformin monotherapy.

Garber et al (2006) evaluated the efficacy and safety of fixed combined metformin-glibenclamide vs metformin plus rosiglitazone therapy in 318 people with type 2 diabetes inadequately controlled on metformin monotherapy. After an open-label, metformin lead-in phase, subjects were randomly assigned to treatment with metformin-glibenclamide 500/2.5 mg tablets (initial daily dose 1000/5 mg) or metformin 500 mg plus rosiglitazone 4 mg (initial daily dose 1000-2000 mg + 4 mg, depending on previous treatment) for 24 weeks. Doses were titrated to achieve the therapeutic glycaemic target. At week 24, metformin-glibenclamide resulted in significantly greater reductions in HbA1c (-1.5%) and fasting plasma glucose [-2.6 mmol/L] than metformin plus rosiglitazone [-1.1%, $p < 0.001$; -2 mmol/L, $p = 0.03$]. More subjects receiving metformin-glibenclamide attained HbA1c < 7% than did those in the metformin plus rosiglitazone group (60 vs 47%) and had fasting

plasma glucose levels < 7 mmol/L by week 24 (34 vs 25%). Both treatments were well tolerated. Four percent receiving metformin-glibenclamide withdrew because of symptomatic hypoglycaemia compared with 3% receiving metformin plus rosiglitazone. Hypoglycaemic events were generally mild or moderate in intensity and were easily self-managed.

In a 52-week, randomized, double-blind study, Matthews and Charbonnel (2005) compared the efficacy and safety of metformin plus pioglitazone with combination metformin plus gliclazide in 630 people with type 2 diabetes. People with poorly controlled type 2 diabetes (HbA1c ≥ 7.5% to ≤ 11.0%) on metformin were randomised to receive either pioglitazone 15 mg daily (titrated up to 45 mg; n = 317) or gliclazide 80 mg daily (titrated up to 320 mg; n = 313). The primary efficacy measure was change in HbA1c from baseline to week 52. There were no significant differences in HbA1c (1% decrease in both groups) and FPG between groups. There were significantly greater improvements in triglycerides and HDL-cholesterol in the metformin plus pioglitazone group compared with the metformin plus gliclazide group ($p < 0.001$). Mean LDL-cholesterol decreased with metformin plus gliclazide and increased with metformin plus pioglitazone ($p < 0.001$).

Comaschi et al (2007) compared the effectiveness of co-administration of pioglitazone with metformin or a sulphonylurea (SU), with a fixed-dose combination of metformin and glibenclamide on glycaemic control and beta-cell function in 250 people with type 2 diabetes. Subjects treated with metformin (≤ 3 g/day) or an SU as monotherapy for > 3 months and with HbA1c between 7.5% and 11% inclusive were randomised to receive either pioglitazone (15-30 mg/day) as add-on therapy to metformin or an SU or a fixed-dose combination of metformin (500 mg) and glibenclamide (2.5 mg) (up to three tablets per day) for 6 months. HbA1c and fasting plasma glucose (FPG) were measured at baseline and 2, 4, and 6 months. After 6 months, pioglitazone-based and fixed-dose metformin + glibenclamide resulted in similar reductions in HbA1c (-1.1% vs -1.3%, respectively; $p = 0.2$) and FPG (-2.1 vs -1.8 mmol/L, respectively; $p = 0.4$).

Charbonnel et al (2005) examined the long-term effects of pioglitazone or gliclazide addition to failing metformin monotherapy and pioglitazone or metformin addition to failing sulphonylurea monotherapy over 2 years in people with type 2 diabetes. This randomised, multicentre trial was performed in people with inadequately controlled type 2 diabetes (HbA1c 7.5-11% inclusive), who were receiving either metformin or a sulphonylurea at ≥ 50% of the maximum recommended dose or at the maximum tolerated dose. Subjects on metformin received add-on therapy with pioglitazone (15-45 mg/day, n = 317) or gliclazide (80-320 mg/day, n = 313) in the first study. In study 2, people on sulphonylurea therapy were randomised to receive add-on therapy with either pioglitazone (15-45 mg/day, n = 319) or metformin (850-2,550 mg/day, n = 320). At week 104, the mean reduction from baseline in HbA1c was 0.9% for pioglitazone and 0.8% for gliclazide addition to metformin ($p = 0.2$). There was a statistically significant between-group difference for the change in mean fasting plasma glucose at week 104 (-1.8 mmol/L for pioglitazone vs -1.1 mmol/L for gliclazide,

$p < 0.001$). There were no significant differences in changes from baseline in glycaemic parameters for pioglitazone compared with metformin addition to sulphonylurea therapy. Whether added to metformin or sulphonylurea, pioglitazone caused significantly greater decreases in triglycerides and significantly greater increases in HDL cholesterol than the comparator regimens ($p \leq 0.001$). There were decreases in LDL cholesterol in the comparator groups and these were significantly different from the small changes observed with pioglitazone ($p < 0.001$). All treatment regimens were well tolerated. However, there were weight increases of 2.5 kg and 3.7 kg in the pioglitazone and 1.2 kg in the gliclazide add-on groups, and there was a mean decrease of 1.7 kg in the metformin add-on group.

In addition to combining metformin and sulphonyurea monotherapy, fixed combinations of metformin and sulphonylurea are also available. These have been shown to be as efficacious and may promote increased adherence compared with combined monotherapy. On the other hand the fixed dose combination reduces flexibility in individually adjusting the dose of metformin or sulphonylurea. Garber et al (2003) evaluated the efficacy and incidence of hypoglycaemic symptoms associated with fixed combinations of metformin and glibenclamide formulated within a single tablet (tablet strengths 250 mg/1.25 mg, 500 mg/2.5 mg and 500 mg/5 mg), in comparison with metformin 500 mg and glibenclamide 2.5–5 mg monotherapy, in clinically important subgroups within a population of people with type 2 diabetes. In all, 1,856 subjects from three randomised, double-blind, multicentre trials were stratified at baseline according to HbA1c (< 8% or ≥ 8%), age (< 65 years or ≥ 65 years) and body mass index (BMI < 28 kg/m^2 or ≥ 28 kg/m^2). Studies ranged from 16 to 20 weeks duration. Single-tablet metformin-glibenclamide combination treatment was more effective than either monotherapy irrespective of baseline HbA1c, age or BMI in each trial (Δ HbA1c from baseline: –1.2 to –1.5%, $p < 0.001$ to $p < 0.05$ within each study). Antihyperglycaemic effects were greater in people with HbA1c ≥ 8% at baseline, especially with the combinations. In all three studies, the majority of hypoglycaemic symptoms with glibenclamide-containing treatments occurred in people who were less severely hyperglycaemic at baseline. Subjects with HbA1c < 8% at baseline who received either combination tablet or glibenclamide were 1.8-fold and 4.6-fold more likely to report hypoglycaemic symptoms, respectively, compared with subjects with HbA1c ≥ 8% at baseline. Neither age nor BMI had a marked effect on the efficacy of the combination treatments, and there was no increase in hypoglycaemic symptoms in older subjects.

Davidson et al (2004) reviewed the tolerability profile of metformin/glyburide combination tablets from four double-blind, randomised clinical trials in a total of 2,342 people with type 2 diabetes with hyperglycaemia despite treatment with diet and exercise, a sulphonylurea or metformin. Trials ranged from 16–20 weeks duration. All trials compared one or two dose strengths of the combination tablets with metformin and glyburide monotherapies, and one of the post-diet trials was also placebo controlled. Only 15 randomised participants from all four studies discontinued. The combination tablets were significantly more effective in reducing HbA1c levels than metformin or glyburide alone in all of the four trials at lower doses of

metformin and glyburide, compared with monotherapies. The proportions of subjects achieving HbA1c levels of < 7% after treatment with the various combination tablet strengths (250/1.25 mg, 500/2.5 mg, 500/5 mg metformin/glibenclamide) were 66%, 50% and 60%, respectively, for study 1 (diet-failed subjects); 79%, 62% and 68% for study 2 (diet-failed subjects); 25%, 3% and 3% for study 3 (post-sulphonylurea); and 75%, 38% and 42% for study 4 (post-metformin). Corresponding figures for the higher strength combination tablet evaluated in studies 1, 3 and 4 were 72%, 25% and 64%, respectively. Most hypoglycaemic symptoms were mild or moderate in severity, and the incidence of severe hypoglycaemia was low and similar among the treatment groups.

A number of recent randomised controlled trials have examined the use of the dipeptidyl peptidase-4 inhibitor sitagliptin added to metformin monotherapy or in place of a sulphonylurea add-on where metformin alone or metformin plus a sulphonylurea did not provide adequate glycaemic control. Charbonnel et al (2006), recruited 701 people aged 19-78 years with mild to moderate hyperglycaemia (mean HbA1c 8.0%) receiving metformin (≥ 1500 mg/day) and randomised the group to either sitagliptin 100 mg once-daily or placebo over 24 weeks. Sitagliptin treatment led to significant reductions from baseline in HbA1c (– 0.65%, $p < 0.001$), fasting plasma glucose ($p < 0.001$), and 2-h postprandial glycaemia ($p < 0.001$).

Raz et al (2008) examined the addition of sitagliptin to metformin monotherapy in people type 2 diabetes and HbA1c ≥ 8.0% and ≤ 11.0%. In this multinational trial, 190 people aged 18-78 years were randomised to the addition of 100 mg once daily of sitagliptin or maintained on metformin monotherapy (≥ 1500 mg/day) for 30 weeks. HbA1c (– 1.0% at 18 and 30 weeks), fasting plasma glucose, and 2-h postprandial glycaemia were significantly reduced compared with placebo ($p < 0.001$ for all). A significantly greater proportion of subjects treated with sitagliptin achieved HbA1c levels <7.0% at 30 weeks (22.1% vs 3.3%, $p < 0.001$).

Nauck et al (2007) compared sitagliptin vs glipizide as an adjunct to metformin monotherapy over 52 weeks in 1,172 randomised people where metformin alone gave inadequate glycaemic control. The mean dose of glipizide was 10.3 mg/day and sitagliptin was 100 mg. HbA1c was reduced in both groups – 0.7% from a mean baseline of 7.5%. The proportion achieving an HbA1c < 7% was 63% (sitagliptin) and 59% (glipizide). The proportion experiencing hypoglycaemia episodes was significantly higher with glipizide (32%, $p < 0.001$) than with sitagliptin (5%).

Lactic acidosis is rare in people with type 2 diabetes treated with metformin

Salpeter et al (2006) assessed the incidence of fatal and nonfatal lactic acidosis with metformin compared with placebo and other glucose-lowering treatments in people with type 2 diabetes. A secondary objective was to compare blood lactate levels. The Cochrane Library, MEDLINE, EMBASE, and REACTIONS were searched to identify all studies of metformin treatment from 1966 to August 2005. Prospective trials lasting longer than one month were included if they evaluated metformin alone or in combination with other treatments, compared with placebo or any other glucose-lowering therapy. Observational cohort studies of metformin treatment lasting greater than one month were also included. Pooled data from 206 comparative trials and cohort studies revealed no cases of fatal or nonfatal lactic acidosis in 47,846 person-years of metformin use or in 38,221 person-years in the non-metformin group. Using Poisson statistics with 95% confidence intervals the upper limit for the true incidence of metformin-associated lactic acidosis was 6.3 cases per 100,000 person-years, and the upper limit for the true incidence of lactic acidosis in the non-metformin group was 7.8 cases per 100,000 person-years. There was no difference in lactate levels, either as mean treatment levels or as a net change from baseline, for metformin compared with placebo or other non-biguanide therapies. No evidence from prospective comparative trials or from observational cohort studies indicates that metformin is associated with an increased risk of lactic acidosis, or with increased levels of lactate, compared with other anti-diabetic treatments.

To determine the incidence of lactic acidosis, with special reference to metformin therapy, in community-based people with type 2 diabetes, Kamber et al (2008) conducted this Australian sub-study within a longitudinal observational study. The Fremantle Diabetes Study included 1,279 people from a postcode-defined population of 120,097 people in Western Australia. The main outcome measures were confirmed hospitalisation with lactic acidosis identified through the WA Data Linkage System during two periods: (1) from study entry, between 1993 and 1996, and study close in November 2001; and (2) from study entry to 30 June 2006. At entry, 33.3% of people were metformin-treated, and 23.1% of these had one or more contraindications to metformin (55.1% and 38.0%, respectively, after 5 years follow-up). Five confirmed cases of lactic acidosis were identified during 12,466 person-years of observation; all had at least one other potential cause, such as cardiogenic shock or renal failure. Between study entry and 30 June 2006, incidence of lactic acidosis was 57/100,000 person-years (95% CI, 12-168) in metformin-treated subjects and 28/100,000 person-years (95% CI, 3-100) in the non-metformin-treated group, a non significant difference ($p = 0.4$). The incidence of lactic acidosis in people with type 2 diabetes was low but increased with age and duration of diabetes as cardiovascular and renal causes became more prevalent. Metformin did not increase the risk of lactic acidosis, even when other recognised precipitants were present.

An increasing body of evidence suggests that metformin treatment alone will not result in lactic acidosis unless other contributing factors coexist. Tahrani et al (2007) reviewed the evidence for the use of metformin in the presence of contraindications, particularly in people with heart failure. Medline and the Cochrane Library were searched. Evidence was gathered from case reports and epidemiological data. Metformin treatment alone did not result in lactic acidosis unless other contributing factors coexisted. More importantly, treatment with metformin is not absolutely contraindicated in people who have isolated heart failure, and it may be beneficial. The risk of lactic acidosis due to metformin is negligible in these people and is unrelated to the plasma concentration of metformin. The decision to stop or continue metformin in the presence of heart failure should be individualised to the particular person until further evidence is available.

Metformin and Renal Function

There are currently no clear guidelines on reducing the dose of metformin as kidney function declines and current prescribing information in Australia varies. For example prescribing information for metformin variously contraindicates its use if serum creatinine levels are >135 μmol/L in males and >110 μmol/L in females or where creatinine clearance is < 60 ml/min or < 90 ml/min. Using an eGFR < 60 mL/min/1.73m^2 as a contraindication to its use would result in a significant proportion of people currently using metformin having to discontinue treatment.

The rationale for considering contraindicating the use of metformin with renal impairment is two-fold: metformin is almost exclusively eliminated by the kidney and therefore decreased renal clearance may lead to metformin accumulation and consequently lactic acidosis, and kidney disease can independently lead to lactate accumulation when kidney capacity for oxidative removal of lactate is compromised.

Sirtori et al (1978) demonstrated that the renal clearance of metformin was significantly reduced in people with a creatinine clearance of 20-48 ml/min compared with controls with normal kidney function. While the half-life of metformin was 1½ hours in the control group, it increased to approximately 5 hours in the people with kidney disease. Similarly, Sambol et al (1995) compared the renal clearance of metformin in people with normal, mild (creatinine clearance 61-90 ml/min), moderate (31-60ml/min) and severe (10-30 ml/min) kidney disease. Compared with people with normal kidney function, renal clearance of metformin was significantly reduced by 78% in people with moderate or severe kidney disease. People with mild kidney disease also demonstrated reduced renal clearance of metformin which was 31% below that of the normal kidney function group. What these studies did not demonstrate is whether the reduced renal clearance of metformin is associated with increased blood lactate levels, and consequently, an increased risk of lactic acidosis.

Kidney dysfunction is common in people with type 2 diabetes. Data from the recent Nefron study demonstrated that almost 50% of people with type 2 diabetes who consult their doctor have either microalbuminuria or an eGFR < 60 mL/min/1.73m^2.

The Salpeter review article (detailed above) was unable to conclusively determine if there is an increased risk of lactic acidosis in people with metformin-treated type 2 diabetes and chronic kidney disease. The cases reviewed by Stades and Lalau and Race demonstrated no increased risk of lactic acidosis for people with chronic kidney disease with metformin therapy for type 2 diabetes. While the majority of metformin-associated lactic acidosis cases summarised by Sirtori and Pasik had a reported history of kidney disease, there were insufficient data to determine the levels of kidney function associated with lactic acidosis.

In summary, studies do not demonstrate any consistent association between an increased risk of lactic acidosis for people with metformin-treated type 2 diabetes and chronic kidney disease.

The studies included in this review provided insufficient evidence to answer the question of what level of kidney function should metformin be contraindicated to avoid an increased risk of lactic acidosis. However from the studies reviewed, a contraindication based on an eGFR of < 60 mL/min/1.73m^2 seems overly conservative and would have significant ramifications for many current users of metformin. A more rational approach is to avoid its use with an eGFR of < 30 mL/min/1.73m^2 and to exercise caution in its use with an eGFR between 30 and 45 mL/min/1.73m^2.

Sulphonylureas, used as monotherapy or combination therapy, are safe and effective for type 2 diabetes

Sulphonylureas are oral anti-diabetic agents which improve glycaemic control by increasing insulin release from the pancreatic beta cells. Sulphonylureas bind ATP-dependent K+ channels on cell membranes of the pancreatic beta cells which, through a rise in intracellular calcium lead to increased insulin secretion. Potential side effects include hypoglycaemia and hypersensitivity.

The meta-analysis by Campbell and Howlett (1995) of 11 trials comparing sulphonylureas and metformin was reviewed in the Metformin Monotherapy section. Both metformin and sulphonylurea treatments resulted in a similar reduction in HbA1c.

Schade et al (1998) evaluated the efficacy of glimepiride therapy in people with type 2 diabetes who were unsuccessfully controlled by diet alone (FPG 8.4-16.7 mmol/L). Subjects (n = 249) were randomly assigned to receive glimepiride or placebo for a total of 22 weeks. The dose of glimepiride was titrated up to 8 mg once a day to achieve optimal glycaemic control (FPG 5.0-8.4 mmol/L). At baseline, the median HbA1c, FPG and 2h PPG were similar between the glimepiride and placebo groups (9.1 vs 8.9%, 11.8 vs 11.4 mmol/L, and 16.2 vs 14.8 mmol, respectively). At 22 weeks, the difference in the median HbA1c between the two groups was 1.2% (6.7 vs 7.9%, $p < 0.001$). Optimal glycaemic control (HbA1c $\leq$ 7.2%) was achieved in 69% receiving glimepiride compared with 32% on placebo. Similarly, glimepiride resulted in a greater reduction in FPG and 2h PPG than placebo (8.4 vs 10.7 mmol/L, $p < 0.001$; 9.7 vs 13.2 mmol/L, $p < 0.001$, respectively). No hypoglycaemia with blood glucose < 3.3 mmol/L) was reported during the study. People receiving glimepiride gained an average of 1.8 kg, compared with an average weight loss of 0.7 kg in those treated with placebo.

The efficacy and safety of Diamicron MR was assessed in a double-blind 10-month study (Diamicron MR Study Group, 2000). People (n = 800) with type 2 diabetes who were previously treated with diet for 3 months with or without oral anti-diabetic medications (OADs) were randomised to either Diamicron MR (n= 401) or Diamicron (80-320 mg/d) (n= 399). In 310 elderly people ($\geq$ 65 years), 45% had impaired renal function (creatinine clearance 20-80 mL/min). During the first 4 months of titration, dosages were adjusted to achieve FPG 4.4-6.6 mmol/L in subjects aged under 65 years, and 5.5-7.7 mmol/L for those aged 65 years and above. After 10 months of treatment, glycaemic control was improved in both groups; the difference between groups was small: -0.08 ± 0.08% (95% CI -0.22 to 0.06) for HbA1c and 0.14 ± 0.18 mmol/L (95% CI -0.15 to 0.44) for FPG. Diamicron MR was as effective as Diamicron in reducing HbA1c ($p < 0.001$) and FPG ($p < 0.001$). Few people experienced hypoglycaemic symptoms with no difference between groups (5.2% in the Diamicron MR group and 4.0% in the Diamicron group). In elderly people, the rate was

1.4%, and 1.2%, respectively. No subject experienced nocturnal hypoglycaemia in either group and no other serious side effects were reported.

Weitgasser et al (2003) examined the efficacy and safety of glimepiride (0.5 to 4 mg) administered once daily in a 4-month open, uncontrolled study of 1,770 people with type 2 diabetes who had been treated by diet or physical activity alone or with OADs. There were a total of 284 subjects (mean age 65 years) who completed follow-up (to 1.5 years). The mean HbA1c decreased from 8.4% at baseline to 7.1% at 4 months (-1.4%), and 6.9% after 1 (-1.5%) and 1.5 years (-1.7%) ($p < 0.0001$ for each time point). Treatment with glimepiride resulted in reductions in body weight from 79.8 kg at baseline to 77.9 kg at 4 months (-1.9 kg, $p < 0.0001$), 77.2 kg after 1 year (-2.9 kg, $p < 0.05$) and 76.9 kg after 1.5 years (-3.0 kg, $p < 0.005$). Greater body weight decreases were observed with higher BMI: -12.3% in people with BMI >30 kg/m^2 compared with -3.5% in those with a BMI of 25-30 kg/m^2 ($p < 0.001$).

Gregorio et al (1999) performed an open clinical trial on sulphonylurea-treated people over 70 years of age with poorly controlled type 2 diabetes (FGP $\geq$ 11.1 mmol/L and HbA1c $\geq$ 9.5%). Subjects (n = 198) were randomly assigned to sulphonylurea increased to its maximum dosage (S - glibenclamide up to 15 mg/d, or gliclazide 240 mg/d) or to the addition of metformin (M - metformin 1700 mg/d) for 18 months. Similar improvement in glycaemic control was observed in both groups; HbA1c decreased from 10.3 ± 0.1 to 8.6 ± 0.1% in the S group ($p < 0.0005$) and from 10.4 ± 0.2 to 8.5 ± 0.1% in the M group ($p < 0.0005$). Plasma lipid levels did not change in the S group, whereas a reduction in LDL-cholesterol level (4.5 ± 1.4 to 4.1 ± 0.1 mmol/L, $p < 0.05$) and an increase in HDL-cholesterol level (0.98 ± 0.04 to 1.10 ± 0.03 mmol/L, $p < 0.02$) were observed in the M group. BMI did not change in either group. However, when overweight metformin-treated subjects were analysed separately from normal weight people, a significant decrease in weight occurred from 82.4 ± 1.4 to 80.3 ± 1.3 kg ($p < 0.03$). More hypoglycaemic episodes were reported in the S group ($p < 0.03$ v the M group).

Schernthaner et al (2004) randomised 845 people (mean age 60 years) with HbA1c 6.9-11.5% to either gliclazide MR 30-120 mg daily, or glimepiride 1-6 mg daily in combination with their current treatment of metformin or an α-glucosidase inhibitor in a 27-week study. Mean HbA1c decreased significantly with both gliclazide MR (8.4 to 7.2%, $p < 0.001$) and glimepiride (8.2 to 7.2%, $p < 0.001$). Approximately 50% achieved HbA1c of < 7.0% and 25% < 6.5%. Hypoglycaemia with a blood glucose level < 3.0 mmol/L occurred significantly less with gliclazide MR than with glimepiride (3.7 vs 8.9%, $p = 0.003$). No hypoglycaemic events required external assistance. Body weight remained stable during the study with mean changes from 83.1 to 83.6 kg and 83.7 to 84.3 kg, respectively.

In a multicentre study (Hanefeld et al., 2004), 639 people aged 35-75 years who were inadequately controlled with sulphonylurea alone were randomised to receive pioglitazone

15mg (up to 45 mg/d, n = 319) or metformin 850 mg (up to 2550 mg/d, n = 320) for one year. Glibenclamide (42%), gliclazide (31%) and glimepiride (19%) were the most commonly used SUs in both groups. There were no differences in glycaemic control between the two treatment groups. The mean HbA1c level was reduced by 1.2% in the SU plus pioglitazone group and 1.4% in the SU plus metformin group. The reduction in FPG from baseline to week 52 was similar in both groups: -2.2 mmol/L and -2.3 mmol/L, respectively. Pioglitazone addition to SU significantly reduced triglycerides (-16 vs -9%, $p = 0.008$) and increased HDL cholesterol (14 vs 8%, $p < 0.001$) compared with metformin addition, while the metformin group decreased LDL cholesterol more than the pioglitazone group (–5% vs +2%, $p < 0.001$). A mean weight gain of 2.8 kg was observed in the pioglitazone group compared with a reduction of 1.0 kg in the metformin group over the 52 weeks. Overall, the incidence of adverse events was similar in both groups.

Roberts et al (2005) evaluated the efficacy and tolerability of glimepiride in people with type 2 diabetes inadequately controlled with a combination of immediate- or extended-release metformin and a thiazolidinedione. The study was a multicentre, randomised controlled trial consisting of a 4-week stabilisation and eligibility period and a 26-week treatment period. Subjects received glimepiride (titrated sequentially from 2 to 4 to 8 mg/d over 6 weeks, followed by 20 weeks of maintenance therapy) or placebo. The study included 159 subjects in the efficacy analysis and 168 in the safety analysis. Baseline characteristics were similar between the glimepiride and placebo groups (mean age, 56.5 and 56.4 years, respectively; weight, 100.9 and 96.3 kg). HbA1c was significantly improved at end point with glimepiride combination therapy compared with placebo (mean [SE], -1.3% [0.1] vs -0.3% [0.1], respectively; $p < 0.001$). The majority (62.2%) receiving glimepiride achieved an HbA1c value of ≤ 7%, compared with 26.0% receiving placebo ($p < 0.001$ between groups). The mean change in weight was greater with glimepiride than with placebo (3.76 [0.54] vs 0.45 [0.52] kg; $p < 0.001$). Clinically significant adverse events, laboratory abnormalities, and rates of severe hypoglycaemia were similar between treatment groups. Incidence of milder hypoglycaemia, however, was 51.2% in the glimepiride group and 8.3% in the placebo group ($p < 0.001$).

Davidson et al (2007) examined the efficacy and tolerability of the addition of rosiglitazone to glyburide once daily in a randomised controlled trial in African American and Hispanic American people with type 2 diabetes previously inadequately controlled with sulphonylurea monotherapy. Eligible subjects were aged ≥ 21 years, had type 2 diabetes, a fasting plasma glucose (FPG) level > 7.8 mmol/L, and an HbA1c ≥ 7.5%, and had been treated with sulphonylurea monotherapy for at least 2 months before screening. Subjects were assigned to receive glyburide 10 or 20 mg/d plus rosiglitazone 8 mg (GLY+RSG) or placebo (GLY+PBO) for 24 weeks. A total of 245 people (101 African American and 144 Hispanic American) were enrolled. Demographic characteristics were comparable between the GLY+RSG and GLY+PBO groups: mean (SD) age (52 [11.9] vs 53 [10.4] years), HbA1c (9.2% [1.3%] vs 9.4% [1.4%]), and mean (SD) weight (86.3 [18.8] vs 88.3 [19.4] kg). In the

overall study population, treatment with GLY+RSG was associated with a significantly greater mean (CI) reduction from baseline in HbA1c compared with GLY+PBO (between-group delta, -1.4% [-1.7% to -1.1%]; $p < 0.001$). The most frequently reported adverse events with GLY+RSG were oedema and weight increase and with GLY+PBO were upper respiratory tract infection.

In a 12-month multicentre study (Derosa et al., 2005), 91 people who were previously treated with diet and metformin or a sulphonylurea received glimepiride 4 mg/d were randomised to take pioglitazone 15 mg/d (G+P, n = 45) or rosiglitazone 4 mg/d (G+R, n = 42). At 12 months, HbA1c was significantly lower in both groups compared with baseline (6.8 vs 8.2% in G+P, $p < 0.01$; 6.7 vs 8.0% in G+R, $p < 0.01$). FPG and PPG were also improved at 12 months in both groups ($p < 0.01$ for both groups). Both groups experienced similar significant increases in mean BMI (24.4 ± 0.8 vs 25.6 ± 0.9 kg/m^2 in G+P, $p < 0.05$; 24.3 ± 0.7 vs 25.8 ± 0.9 kg/m^2 in G+R, $p < 0.05$). The G+R group experienced a significant increase from the baseline value in mainly lipid risk factors for CVD (total cholesterol 14.9%; LDL cholesterol 16.5%; TG 17.9%, all $p < 0.05$), while lipid profiles improved in the G+P group ($p < 0.05$).

In a 26-week study, Baksi et al (2004) randomised 471 people (mean age 61 years) with inadequate glycaemic control on gliclazide 160 mg/d to add rosiglitazone (4 mg bid) or to maximum doses of gliclazide 320 mg/d. Mean HbA1c value was 8.5 ± 1.5% in the combination group and 8.6 ± 1.5% in the gliclazide group at baseline. At endpoint the reduction in mean HbA1c was 1.3% lower in the combination group compared with the gliclazide group ($p < 0.0001$), and more achieved an HbA1c < 7.0% (48 vs 22%). FPG was also significantly lower with combination therapy (-3.0 mmol/L, $p = 0.0001$). Increases in total (8.8%, CI 5.4-11.8), HDL (6.8%, CI 2.5-10.3) and LDL cholesterol (10.9%, CI 7.7-14.0) and triglyceride (7.7, CI 0-12.7) were observed at week 26 in the combination group, while little changes were observed in the gliclazide group. Subjects in the combination group gained an average of 3.4 kg compared with the gliclazide group ($p = 0.0001$).

In a 26-week study of 348 people (Vongthavaravat et al., 2002), 175 were randomised to receive rosiglitazone 2 mg twice daily in conjunction with existing sulphonylurea therapy (RSG+SU), while 173 continued their SU therapy. The addition of RSG was associated with a significant reduction in mean HbA1c and FPG from baseline (9.7 to 7.9%; 11.1 to 8.9 mmol/L, respectively) compared with a non-significant increase in the SU group (8.9 to 9.0%; 10.8 to 11.1 mmol/L) (both $p = 0.0001$). Adverse events were similar in both groups. More subjects in the RSG+SU group reported hypoglycaemia (19 vs 2 cases, $p < 0.001$), but none was associated with a blood glucose < 2.8 mmol/L.

In a 26-week study, Kerenyi et al (2004) randomised 340 subjects (mean age 60 years) with inadequate glycaemic control ($7.0 \leq FPG \leq 15.0$ mmo/L) to a combination therapy of rosiglitazone 8 mg/d and glibenclamide 7.5 mg/d (R+G) or to glibenclamide monotherapy

(G, up to a maximum dose of 15 mg/d). A total of 268 people completed the study. There was a significant reduction at week 26 from baseline in mean HbA1c and FPG levels in the R+G group compared with the G group (-0.81%, $p < 0.0001$; -2.4 mmol/L, $p < 0.0001$, respectively). A greater proportion achieved HbA1c < 7.0% with combination versus monotherapy (75% vs 25%). Both treatments increased HDL cholesterol levels (15.8%, CI 14.6-17.1%; 14.6%, CI 12.9-16.3%, respectively). However, the combination therapy increased total cholesterol by 7.7% (CI 6.3-9.2%) and LDL cholesterol by 7.0% (CI 5.2-8.9%). Moderate hypoglycaemia was reported in 18.5% in the R+G group and 4.1% in the G group; oedema was a common adverse event reported by 9.5% in the R+G group. Overall both treatments were well tolerated.

Rosenstock et al (2006) compared the efficacy, safety and tolerability of adding rosiglitazone (RSG) versus sulphonylurea (SU) dose escalation in older people with type 2 diabetes inadequately controlled on SU therapy alone. In all, 227 people ≥ 60 years were randomised to receive RSG (4 mg) or placebo once daily in combination with glipizide 10 mg twice daily for 2 years in a double-blind, parallel-group study. Disease progression (time to reach confirmed FPG ≥ 10 mmol/L while on maximum doses of both glipizide and study medication or placebo) was reported in 29% of people up-titrating SU plus placebo compared with only 2% taking RSG and SU combination ($p < 0.0001$). RSG + SU significantly decreased HbA1c by a mean of 0.7% from a baseline of 7.7% over 104 weeks ($p < 0.0001$), whereas uptitrated SU alone produced no significant improvement from baseline (increase 0.1% from a baseline of 7.7%, $p = 0.19$). The HbA1c reduction with RSG + SU was significantly different from uptitrated SU alone (–0.8%, $p < 0.0001$). RSG + SU produced maximal improvements in HbA1c by 24 weeks that were sustained over the 2 years of the study, with a mean HbA1c of < 7% at study end. Specifically, 50 and 32% of people in the RSG + SU group achieved target HbA1c < 7% and ≤ 6.5%, respectively, compared with only 22 and 9% with uptitrated SU alone.

Thiazolidinediones are a useful agent in improving glycaemic control when used as add-on therapy to other anti-diabetic medications

Glitazones (thiazolidinediones [TZD]) are a newer class of oral hypoglycaemic agents which improve glycaemic control primarily by decreasing insulin resistance. Glitazones improve insulin sensitivity of the liver and peripheral tissues, and may also slow the decline in pancreatic beta-cell function. They are generally well tolerated. However, they increase subcutaneous fat mass and increase weight.

In Australia, both TZDs (rosiglitazone and pioglitazone) have been PBS authorised as second or third line therapy in combination with other oral anti-diabetic medications or insulin. However since August 21, 2008, rosiglitazone is no longer PBS reimbursed for commencement as third line therapy or in combination with insulin.

To assess the effects of rosiglitazone treatment in type 2 diabetes Richter et al (2007) performed a meta-analysis of 18 randomised controlled trials and a total of 3,888 participants. The mean age of subjects randomised to rosiglitazone treatment ranged from 47 to 61 years. Most participants were overweight or obese with the mean BMI of subjects randomised to rosiglitazone ranging from 23.3 to 33.6 kg/m^2 (mean BMI 29 kg/m^2). The longest duration of therapy was 4 years with a median of 26 weeks. Baseline HbA1c in the rosiglitazone arms ranged from 6.8% and 9.5%, with a mean of 8.8%. HbA1c did not demonstrate clinically relevant differences when rosiglitazone was compared with other oral anti-diabetic drugs. The following comparisons were acceptable for evaluation: 1) rosiglitazone versus placebo, 2) rosiglitazone versus another oral anti-diabetic medication (meglitinide analogues, metformin, pioglitazone, sulphonylureas), 3) rosiglitazone in combination with an oral anti-diabetic medication or insulin versus a combination of an oral anti-diabetic medication or insulin (agents and treatment schemes had to be identical). The percentage of overall adverse events was comparable between the intervention and control groups, however serious adverse events were somewhat more often after rosiglitazone treatment (median of 6% versus 4% in the control groups). Median discontinuation rate following rosiglitazone administration was also higher than after control therapy (median of 7% versus 4%). Occurrence of oedema was significantly increased with rosiglitazone (OR 2.27, 95% confidence interval (CI) 1.83 to 2.81). Eleven studies evaluated body weight and observed an increase of up to 5.0 kg after rosiglitazone treatment, 4 studies described changes in BMI with an increase up to 1.5 kg/m^2. Seven of the 18 included studies reported data on hypoglycaemia. Compared with active monotherapy, rosiglitazone treatment resulted in somewhat lower rates of hypoglycaemia, especially when compared with sulphonylureas. Severe hypoglycaemic events were rarely reported. New data reported increased fracture rates in women.

In a meta-analysis, Richter et al (2006) assessed the effects of pioglitazone in the treatment of type 2 diabetes by evaluating randomised controlled trials in adults where trial duration was at least 24 weeks. Studies were obtained from MEDLINE, EMBASE, and the Cochrane

Library; the last search was conducted in August 2006. The types of interventions included in the analysis were pioglitazone versus placebo; pioglitazone versus any other oral anti-diabetic medication (e.g. rosiglitazone, metformin, sulphonylureas and acarbose); pioglitazone in combination with any other oral anti-diabetic medication or insulin versus any other combination of oral anti-diabetic medication or insulin. Primary outcome measures included mortality, morbidity, and adverse events. In all, 22 trials were included with a total of 6,200 subjects randomised to pioglitazone treatment. The longest duration of therapy was 34.5 months. Pioglitazone treatment did not provide convincing evidence that patient-oriented outcomes such as mortality, morbidity, adverse effects, costs and health-related quality of life were positively influenced by the medication. Studies did not demonstrate clinically relevant differences compared with other oral anti-diabetic agents. Metabolic control as measured by HbA1c varied in the pioglitazone arms between 7.4% and 10.3%, with most participants ranged between 8% and 9%. The occurrence of oedema was evaluated in 18 or 22 studies. Overall, 11,565 people provided data on the occurrence of oedema. The total number of events was 842 in the pioglitazone and 430 in the control groups. After pooling the data, the relative risk of oedema was 2.86 (CI 2.14 to 3.18, $p < 0.00001$).

Noble et al (2005) reviewed RCTs on the use of TZDs in the management of type 2 diabetes. RCTs showed TZDs lower HbAIc levels by 1.0% to 1.5% with effects being seen in as little as 4 weeks, but full lowering taking 6 to 12 weeks. Several RCTs were found but there were no systematic reviews. One study examined pioglitazone 30 and 45 mg in nearly 300 people with type 2 diabetes. HbA1c decreased by 0.8 and 0.9% respectively at 16 weeks. In another trial examining the effect of 4 and 8 mg doses of rosiglitazone in 959 people for 26 weeks, HbA1c levels were reduced by 0.8% and 1.5%, respectively. One third of subjects achieved HbA1c levels of < 7% by the end of the study. When compared head-to-head with metformin in 205 subjects, pioglitazone and metformin were both equally effective for blood glucose control. When used in combination with other anti-diabetic agents, such as sulphonylureas and biguanides, TZDs' hypoglycaemic effects were complementary. In one 16 week study, people receiving a pioglitazone-metformin combination had lower HbA1c levels (0.8% decline) compared with a placebo plus metformin group. Overall, there was no evidence that TZDs were superior to other anti-diabetic agents.

An analysis by Belcher et al (2005), compared the safety and tolerability of pioglitazone, metformin, and gliclazide. Data collected from four 1-year, double-blind studies comparing treatment of over 3,700 people with type 2 diabetes with pioglitazone, metformin, or gliclazide were combined to provide comparative tolerability and safety profiles. All treatments were well tolerated with approximately 6% withdrawing from treatment because of side-effects. Side-effect profiles varied between treatments, with pioglitazone being associated with oedema, metformin with gastrointestinal side-effects, and gliclazide with hypoglycaemia. Cardiovascular outcome was similar with all treatments, with no excess reports of cardiac failure with pioglitazone treatment. Both pioglitazone and gliclazide resulted in mean weight gain, whilst with metformin there was mean weight loss. Mean liver

enzyme values decreased with pioglitazone and to a lesser extent with metformin. With gliclazide, mean liver enzyme values increased. The expected small decreases in mean haemoglobin and haematocrit seen with pioglitazone also occurred with metformin and to a lesser degree with gliclazide. All three drugs were safe, but tolerability profiles vary. Each treatment provides an alternative therapy for type 2 diabetes, dependent on the particular needs of individual subjects.

In a 24-week, double-blind study, 630 individuals with type 2 diabetes inadequately controlled with insulin therapy alone were randomised to treatment with rosiglitazone (2 or 4 mg/d) or placebo in combination with ongoing insulin therapy (Hollander et al., 2007). The primary efficacy end point was change in HbA1c concentrations from baseline to week 24. The dosage of insulin therapy could be adjusted at the investigator's discretion if required for hypoglycemia or additional glycemic control. The addition of rosiglitazone (2 or 4 mg/d) to insulin therapy significantly decreased mean HbA1c compared with placebo plus insulin (-0.3% [$p = 0.02$] and -0.4% [$p < 0.001$]) and compared with baseline (-0.6% and -0.8% [both $p < 0.001$]) after 24 weeks. The adverse event profile, including incidence of hypoglycaemia and oedema, was similar between treatment groups, and most adverse events were mild to moderate in intensity. The addition of low-dose rosiglitazone to insulin therapy was an effective and well-tolerated treatment option for people with type 2 diabetes who continued to have poor glycaemic control despite administration of exogenous insulin as monotherapy.

Mattoo et al (2005) examined the effect of pioglitazone 30 mg plus insulin (PIO + INS) versus placebo plus insulin (PLB + INS) on glycaemic control, lipid profile, and selected cardiovascular risk factors in people with type 2 diabetes inadequately controlled with insulin therapy alone. This 6-month, randomised controlled trial included 263 people with type 2 diabetes and an HbA1c value $\geq 7.5\%$ who were using insulin (with or without OADs) and who entered a 3-month insulin intensification phase to achieve blood glucose targets with insulin monotherapy. After insulin intensification, those subjects with HbA1c values $\geq 7.0\%$ were randomised to PIO + INS or PLB + INS. Of the 289 subjects randomised to treatment (mean [SD] age, 58.9 [7.1] years; 164 women, 125 men), 142 received PIO + INS and 147 received PLB + INS. After 6 months, PIO + INS reduced mean HbA1c (-0.7%; $p < 0.002$) and mean fasting plasma glucose ([FPG] -1.5 mmol/L; $p < 0.002$) from baseline. PLB + INS produced no significant changes in HbA1c or FPG. The between-treatment differences for HbA1c (-0.6%; $p < 0.002$) and FPG (-1.8 mmol/L; $p < 0.002$) occurred despite a reduction of insulin dose in the PIO + INS group from baseline (-0.16 U/d . kg; $p < 0.002$). Significant between-group differences were observed for high-density lipoprotein cholesterol (0.13 mM; $p < 0.002$) and triglycerides (ratio of geometric mean [PIO/PLB], 0.871; $p < 0.01$). The use of PIO + INS was generally well tolerated. The rate of clinical and biochemical hypoglycaemia (blood glucose < 2.8 mmol/L) did not differ statistically between treatment groups, but reported incidences of subjective hypoglycaemia occurred more often with PIO + INS than with PLB + INS (90 vs 75; $p < 0.05$). Oedema was more common with PIO + INS than with

PLB + INS (20 vs 5 instances, respectively), as was gain (mean [SEM]) in body weight (4.05 [4.03] vs 0.20 [2.92] kg, respectively).

Jones et al (2003) analysed data from two 6-month RCTs to evaluate the efficacy of rosiglitazone (RSG) added to a maximum dose of metformin (MET) (2.5 g/day) in people with type 2 diabetes. Among a total of 550 subjects, 57 were not overweight (BMI < 25 kg/m^2), 223 overweight (BMI 25-30 kg/m^2) and 283 obese (BMI > 30 kg/m^2). Addition of RSG 8 mg/d to MET produced a significant reduction in HbA1c in all subgroups, and this effect was most profound in obese subjects (-0.9% vs +0.2% MET alone, p = 0.025).

Dailey et al (2004) assessed the efficacy and safety of rosiglitazone add-on therapy by randomising 365 people (mean age 57 years) with type 2 diabetes previously treated with metformin/glyburide and who had not achieved adequate glycaemic control (HbA1c levels > 7.0% and ≤ 10.0%) to rosiglitazone 4 mg once daily (n=181) or to placebo (n=184) for 24 weeks. The dose of rosiglitazone was titrated to 8 mg daily if HbA1c levels remained ≥ 7.0%. The baseline characteristics were similar between the treatment groups. After 24 weeks, people in the rosiglitazone group achieved better glycaemic control than people in the placebo group (HbA1c -0.9% vs +1.0%, p < 0.001), and more had HbA1c levels < 7.0% in the rosiglitazone group at 24 weeks (42% vs 14%). The adverse event profile in the rosiglitazone-treated group included mild-to-moderate oedema (8%), hypoglycaemia (22%), and weight gain of 3 kg. More people in the rosiglitazone group experienced symptoms of hypoglycaemia, but did not require third-party assistance.

Seufert et al (2008) examined the effectiveness of pioglitazone as add-on therapy to metformin or sulphonylurea in reducing post-load serum glucose levels, assessed by 3-h oral glucose tolerance test (OGTT), in 1,269 subjects with type 2 diabetes who participated in 2 clinical trials. One study compared pioglitazone as add-on to failing metformin therapy (N=317) with add-on gliclazide to metformin (N=313). The other study compared combination therapy with pioglitazone added to failing sulphonylurea therapy (N=319) with metformin treatment in addition to sulphonylurea (N=320). Mean HbA1c reduction from baseline to week 104 was 0.9% for pioglitazone and 0.8% for gliclazide added to metformin (p = 0.2) and 1.0% with pioglitazone and 1.2% with metformin added to sulphonylurea (p = 0.173). In the 299 subjects who underwent OGTT, 2 years of treatment with pioglitazone, whether added to existing metformin or sulphonylurea medication, resulted in decreases in glucose excursions without increasing post-load serum insulin. In contrast, gliclazide in combination with metformin therapy increased both post-load serum glucose and insulin, whereas metformin add-on to sulphonylurea did not have a significant effect on post-load serum glucose and increased insulin levels. HbA1c did not differ significantly between the groups.

Stewart and Cirkel (2006) investigated the effect of metformin plus rosiglitazone (RSGMET), compared with metformin alone (MET) on glycaemic control in well-controlled type 2

diabetes. Subjects were randomized (n = 526), following a 4-week placebo run-in period, to RSGMET [4 mg rosiglitazone (RSG)/500 mg MET] or MET 500 mg. From weeks 2–18, medication was escalated every 4 weeks (based on gastrointestinal tolerability), then remained at RSGMET 8 mg/2 g or MET 3 g for 14 weeks. RSGMET reduced HbA1c from 7.2 ± 0.6 to 6.7 ± 0.8% at week 32, compared with a reduction from 7.2 ± 0.6 to 6.8 ± 0.9% with MET (treatment difference -0.13%; p = 0.04). More subjects achieved an HbA1c ≤ 6.5% at week 32 with RSGMET (51.6 vs 43.7%), but the treatment difference was not significant (odds ratio 1.37, p = 0.0949). RSGMET produced larger reductions from baseline in mean fasting plasma glucose (adjusted difference -0.62 mmol/L, p < 0.0001), with the odds ratio of achieving a target of < 7.0 mmol/L being 2.33 (p < 0.0001). Overall rates of gastrointestinal adverse events (relevant to the known profile of MET) were comparable, but with a lower incidence of diarrhoea (8 vs 18%) with RSGMET. Hypoglycaemia was reported in ≤ 7% subjects per group.

Bailey et al (2005) conducted a 24-week, multicentre, randomised, double-blind, study investigating a fixed-dose combination rosiglitazone and metformin (RSG/MET) compared with high-dose metformin (MET) monotherapy in 568 people with type 2 diabetes. People previously treated with MET entered a 4-week, single-blind, run-in period with MET 2 g/d and were then randomized to RSG/MET 4 mg/2 g per day or MET 2.5 g/d. At week 8, medication was titrated up to RSG/MET 8 mg/2 g per day or MET 3 g/d. The primary efficacy end point was change in glycated hemoglobin (HbA1c) at week 24. Altogether there were 280 people in the MET group and 288 people in the RSG-MET group. Baseline characteristics were comparable in the 2 groups; BMI (mean [SD]) was 32.2 (4.8) kg/m^2 and 32.1 (4.9) kg/m^2 in the RSG/MET and MET groups, respectively. RSG/MET reduced HbA1c (mean [SD]) from 7.4% (1.0%) to 7.1% (1.1%) at week 24, compared with a reduction from 7.5% (1.0%) to 7.4% (1.1%) with MET (treatment difference, -0.22%; p = 0.001). Fasting plasma glucose (mean [SD]) was reduced from 9.2 (1.6) to 8.0 (1.8) mmol/L with RSG/MET and from 9.4 (1.8) to 9.1 (2.1) mmol/L with MET (treatment difference, -1.0 mmol/L; p < 0.001). In addition, 54% of subjects treated with RSG/MET achieved HbA1c levels < 7.0% compared with 36% with MET (odds ratio, 2.42; p < 0.001). RSG/MET was generally well tolerated, with the majority of adverse effects (AE) being mild to moderate in nature. Serious AEs were reported in 3% of subjects receiving RSG/MET and 2% with MET. Overall rates of gastrointestinal AEs were 23% with RSG/MET and 26% with MET; however, there was an increased incidence of diarrhoea (14% vs 6%) and abdominal pain (9% vs 6%) with MET. There was a mean (SE) increase in weight with RSG/MET (1.3 [0.22] kg) and a mean decrease (-0.9 [0.26] kg) with MET.

To determine the effects of pioglitazone combined with insulin on glucose and lipid metabolism in people with type 2 diabetes, Davidson et al (2006) recruited 690 people [BMI 33.2 ± 5.5 kg/m^2; HbA1c 9.8 ± 1.5%; mean duration, 12.9 years] with diabetes poorly controlled with a stable insulin dose (> 30 U/day for ≥ 30 days) and randomly allocated them to pioglitazone 30 or 45 mg once daily in an RCT for 24 weeks. In the pioglitazone 30- and

45-mg groups, respectively, 71 and 70% completed the study. At 24 weeks, statistically significant, dose-dependent mean decreases from baseline were seen in the pioglitazone 30- and 45-mg groups for HbA1c (-1.2 and -1.5%, respectively). Insulin dosage also decreased significantly (-4.5 and -7.3 U, respectively; $p \leq 0.05$) from baseline. Decreases in triglycerides [pioglitazone 45 mg: -5.9% ($p \leq 0.05$)] and increases in HDL cholesterol (9.7 and 13.0%, respectively; $p < 0.0001$) were observed. Small but significant increases in total and LDL cholesterol ($p < 0.01$) were also observed. Mean weight gain was 2.9 and 3.4 kg in the respective groups; lower limb oedema was reported in 13 and 12%, respectively.

In a 24-week double-blind study, Home et al (2007) compared the efficacy and safety of either continuing or discontinuing rosiglitazone + metformin fixed-dose combination when starting insulin therapy in 324 people with type 2 diabetes inadequately controlled on oral therapy. Subjects were randomly assigned to twice-daily premixed insulin therapy (target pre-breakfast and pre-evening meal glucose ≤ 6.5 mmol/L) in addition to either rosiglitazone + metformin (8/2000 mg) or placebo. Insulin dose at week 24 was significantly lower with rosiglitazone + metformin (33.5 ± 1.5 U/day, mean ± se) compared with placebo [59.0 ± 3.0 U/day; model-adjusted difference -26.6 (95% CI -37.7, -15,5) U/day, $p < 0.001$]. Despite this, there was greater improvement in glycaemic control [HbA1c rosiglitazone + metformin vs placebo 6.8 ± 0.1 vs 7.5 ± 0.1%; difference -0.7 (-0.8, -0.5)%, $p < 0.001$] and more individuals achieved glycaemic targets (HbA1c < 7.0% 70 vs 34%, $p < 0.001$). The proportion of individuals reporting at least one hypoglycaemic event during the last 12 weeks of treatment was similar in the two groups (rosiglitazone + metformin vs placebo 25 vs 27%). People receiving rosiglitazone + metformin in addition to insulin reported greater treatment satisfaction than those receiving insulin alone. Both treatment regimens were well tolerated but more participants had oedema [12 (7%) vs 4 (3%)] and there was more weight gain [3.7 vs 2.6 kg; difference 1.1 (0.2, 2.1) kg, $p = 0.02$] with rosiglitazone + metformin.

Thiazolidinediones are associated with increased risk of heart failure, oedema and fractures

In a meta-analysis of 7 reports, Lago et al (2007) examined the risk of congestive heart failure in people with type 2 diabetes taking thiazolidinediones. In all, 360 of 20,191 subjects with either prediabetes or type 2 diabetes had congestive heart failure events (214 with TZDs and 146 with comparators). There was no heterogeneity of effects across studies (I^2 = 22.8%; p for interaction = 0.26), which indicated a class effect for TZDs. Compared with controls, the risk of congestive heart failure was higher in people given TZDs (RR 1.72, CI 1.21-2.42, p = 0.002). However, despite the higher incidence of congestive heart failure in people, this was not associated with higher rate of cardiovascular death (0.93, 0.67-1.29, p = 0.68).

Singh et al (2007) conducted a teleo-analysis to evaluate the magnitude of the risk of heart failure in people with type 2 diabetes. A random-effects meta-analysis of three randomised controlled trials showed an odds ratio (OR) of 2.1 (95% CI 1.08–4.08; p = 0.03) for the risk of heart failure in subjects randomised to TZDs compared with placebo. Four observational studies revealed an OR of 1.55 (1.33–1.80; p < 0.00001) for heart failure with TZDs. A dose-time-susceptibility analysis of 28 published reports and 214 spontaneous reports from the CADRMP database showed that heart failure was more likely to occur after several months (with median treatment duration of 24 weeks after initiation of therapy). Heart failure equally occurred at high and low doses. The adverse reaction was not limited to the elderly, with 42 of 162 (26%) of the reported cases occurring in people aged <60 years. Taken together, the teleo-analysis confirmed an increased magnitude of heart failure risk with thiazolidinedione use.

In the A Diabetes Outcome Progression Trial (ADOPT) study, Kahn et al (2006) evaluated metformin, rosiglitazone, and glyburide as initial treatment for recently diagnosed type 2 diabetes in a double-blind, randomised, controlled clinical trial involving 4,360 people treated for a mean of 4 years. Congestive heart failure events occurred in 22 people in the rosiglitazone group (1.5%), 19 in the metformin group (1.3%), and 9 in the glyburide group (0.6%). The hazard ratio for congestive heart failure in the rosiglitazone group, compared with the metformin group, was 1.22 (CI, 0.66 to 2.26; p = 0.52) and 2.20 (CI, 1.01 to 4.79; p = 0.05) compared with glyburide. Episodes of CHF classified as serious adverse events occurred in 12 people in the rosiglitazone group, 12 in the metformin group, and 3 in the glyburide group.

Eurich et al (2007) conducted a meta-analysis of controlled studies on the association between anti-diabetic medications and morbidity and mortality in people with heart failure and diabetes. Electronic databases, manual reference search, and contact with investigators were utilised. Eight studies were included in the final analysis. Three of four studies found that insulin use was associated with increased risk for all cause mortality (OR 1.25 [CI 1.03-

1.51] and 3.42 [CI 1.40-8.37] in studies that did not adjust for diet and anti-diabetic medications; HR 1.66 [CI 1.20-2.31] and 0.96 [CI 0.88-1.05] in the studies that did). Metformin was associated with significantly reduced all cause mortality in 2 studies (HR 0.86, CI 0.78 to 0.97) compared with other oral anti-diabetic medications. Metformin was not associated with increased hospital admission for any cause or for heart failure. In four studies, use of thiazolidinediones was associated with increased risk of hospital admission for heart failure (pooled OR 1.13 CI 1.04 to 1.22, $p = 0.004$). The two studies of sulphonylureas had conflicting results, probably because of differences in comparator treatments. Important limitations were noted in all studies.

A meta-analysis by Berlie et al (2007) assessed the risk of TZD induced oedema. A systematic literature search was conducted using five electronic databases. All prospective, randomised, either placebo-controlled or comparative studies reporting the incidence of oedema with TZD therapy were included. The analysis included 26 studies consisting of 15,332 people with type 2 diabetes. Statistical heterogeneity was not present ($p = 0.14$) in the primary analysis. The analysis revealed a two-fold increase in the relative risk of oedema associated with TZD therapy compared with placebo, oral anti-diabetic medications, or insulin. The pooled odds ratio for TZD induced oedema was 2.26 (CI: 2.02–2.53; $p < 0.00001$). A secondary analysis explored differences in risk for developing oedema between pioglitazone and rosiglitazone. Rosiglitazone was associated with a significantly increased risk of oedema compared with pioglitazone (2.74 [CI 2.33–3.14]).

Meier et al (2008), conducted a nested case-controlled analysis using the UK General Practice Research Database of case subjects with fracture aged 30 to 89 years with an incident fracture diagnosis between January 1994 and December 2005. Subjects were matched with controls for age, sex, calendar time, and general practice attendance. The odds ratios of having a fracture associated with the use of rosiglitazone, pioglitazone, other oral anti-diabetic medication or insulin was assessed. In all, there were 1,020 case subjects with an incident low-trauma fracture and 3,728 matched controls. After adjustment for age, BMI, other anti-diabetic medication, co-medication, and comorbidities, the ORs for users of 8 or more thiazolidinedione prescriptions (corresponding to approximately 12-18 months of therapy) compared with non-use was 2.43 (CI 1.49-3.95). Rosiglitazone (OR 2.38; CI 1.39-4.09) and pioglitazone (OR 2.59; CI, 0.96-7.01) were used more frequently by case subjects with fracture (predominantly hip and wrist fractures) than by controls. The association was independent of age and sex and tended to increase with thiazolidinedione dose. No materially altered relative fracture risk was found in association with the use of other oral anti-diabetic medications.

Kahn et al (2008) examined possible factors associated with the increased risk of fractures observed with rosiglitazone in the ADOPT study. Data from the 1,840 women and 2,511 men randomly assigned in ADOPT to rosiglitazone, metformin, or glyburide for a median of 4.0 years were examined with respect to time to first fracture, rates of occurrence, and sites of

fractures. In men, fracture rates did not differ between treatment groups. In women, at least one fracture was reported with rosiglitazone in 60 subjects (9.3%, 2.74 per 100 person-years), metformin in 30 subjects (5.1%, 1.54 per 100 person-years), and glyburide in 21 subjects (3.5%, 1.29 per 100 person-years). The cumulative incidence of fractures in women at 5 years was 15.1% (CI 11.2-19.1) with rosiglitazone, 7.3% (CI 4.4-10.1) with metformin, and 7.7% (CI 3.7-11.7) with glyburide, representing hazard ratios of 1.81 (CI 1.17-2.80) and 2.13 (CI 1.30-3.51) for rosiglitazone compared with metformin and glyburide, respectively. The increase in fractures with rosiglitazone occurred in pre- and postmenopausal women, and fractures were seen predominantly in the lower and upper limbs. No particular risk factor underlying the increased fractures in females who received rosiglitazone therapy was identified.

The final results of the RECORD study (Home et al, 2009) which included 4,447 people with type 2 diabetes followed for a mean 5.5 years, showed that heart failure causing admission to hospital or death occurred in 61 people in the rosiglitazone group and 29 in the active control group (HR 2.10, 1.35–3.27, risk difference per 1000 person-years 2.6 (1.1–4.1). Upper and distal lower limb fracture rates were increased mainly in women randomly assigned to rosiglitazone.

Some reports suggest an increased risk of cardiovascular events and death with some oral anti-diabetic medications and combinations

The ADVANCE study (ADVANCE Collaborative Group, 2008) examined the effects of intensive glucose control on vascular outcomes in 11,140 people with type 2 diabetes. The intensive glucose control arm was based on use of gliclazide MR plus other medications as required to achieve an HbA1c of 6.5% or less. After 5 years of follow-up, the mean HbA1c was 6.5% in the intensive-control group and 7.3% in the standard-control group. There were non significant reductions in major macrovascular events (HR 0.94; CI, 0.84 to 1.06; p = NS), death from cardiovascular causes (HR 0.88; CI, 0.74 to 1.04; p = NS), or death from any cause (HR 0.93; CI, 0.83 to 1.06; p = NS) in the gliclazide-based intensive treatment group.

In the A Diabetes Outcome Progression Trial (ADOPT) study, Kahn et al (2006) evaluated metformin, rosiglitazone, and glyburide as initial treatment for recently diagnosed type 2 diabetes in a double-blind, randomised, controlled clinical trial involving 4,360 people treated for a mean of 4 years. Glyburide was associated with a lower risk of cardiovascular events (including congestive heart failure) than was rosiglitazone ($p < 0.05$), and the risk associated with metformin was similar to that with rosiglitazone.

This retrospective cohort study examined risk of death with level of exposure to sulphonylureas (Simpson et al., 2006). In all, 5,795 subjects were grouped according to their use of oral anti-diabetic agents during follow-up. Subjects using insulin or combination therapy were excluded. Exposure level was defined by daily dose and degree of adherence. Primary outcome measures were all-cause mortality and death from an acute ischaemic event. The mean age of the subjects was 66.3 (SD 13.4) years; 43.4% were female; and mean duration of follow-up was 4.6 (SD 2.1) years. First-generation sulphonylureas were used exclusively by 120 subjects, glyburide by 4,138, and metformin by 1,537. A greater risk of death was associated with higher daily doses of the first-generation sulphonylureas (adjusted HR 2.1, CI 1.0-4.7) and glyburide (HR 1.3, CI 1.2-1.4), but not metformin (HR 0.8, CI 0.7-1.1). Similar associations were observed for death caused by an acute ischaemic event.

There have been conflicting data with respect to combination therapy with sulphonylurea and metformin. The UKPDS compared intensive blood-glucose control with either sulphonylurea or insulin and conventional treatment on the risk of microvascular and macrovascular complications in 3,867 people with newly diagnosed type 2 diabetes (median age 54 years) (UKPDS Study Group, 1998). Within the trial, there were 268 people who received metformin as an add-on therapy when a sulphonylurea alone was not adequate for blood glucose control. Adding metformin to sulphonylurea was associated with a 96% increased risk of diabetes-related death ($p = 0.039$) and increased the risk of death from any cause (60%

increase, p = 0.041). There was no significant difference between people allocated metformin in addition to chlorpropamide or glibenclamide in a subgroup analysis.

Rao et al (2008) performed a meta-analysis of observational studies retrieved from a search of MEDLINE (January 1966–July 2007) that examined the association between combination therapy of sulfonylureas and metformin on risk of CVD or all-cause mortality. From 299 relevant reports, 9 were included in the meta-analysis. The pooled RRs of outcomes for individuals with type 2 diabetes prescribed combination therapy of sulfonylureas and metformin were 1.19 (CI 0.88–1.62) for all-cause mortality, 1.29 (CI 0.73–2.27) for CVD mortality, and 1.43 (CI 1.10–1.85) for a composite end point of CVD hospitalizations or mortality (fatal or nonfatal events). The combination therapy of metformin and sulfonylurea significantly increased the RR of the composite end point of cardiovascular hospitalization or mortality (fatal and nonfatal events) irrespective of the reference group (diet therapy, metformin monotherapy, or sulfonylurea monotherapy); however, there were no significant effects of this combination therapy on either CVD mortality or all-cause mortality alone. The authors highlighted the limitations of this meta-analysis and emphasized that it should not be used as a basis for clinical decisions.

Several recent reports have examined risk of cardiovascular events and death with glitazones. Lincoff et al (2007) systematically reviewed the effect of pioglitazone on ischaemic cardiovascular events in a meta-analysis of 19 reports which included 16,390 people with type 2 diabetes. Drug treatment duration ranged from 4 months to 3.5 years. Death, myocardial infarction, or stroke occurred in 375 of 8,554 people (4.4%) receiving pioglitazone and 450 of 7,836 people (5.7%) receiving control therapy (HR, 0.82; CI, 0.72-0.94; p = 0.005). Progressive separation of time-to-event curves became apparent after approximately 1 year of therapy. Individual components of the primary end point were all reduced by a similar magnitude with pioglitazone treatment, with HRs ranging from 0.80 to 0.92. Serious heart failure was reported in 200 (2.3%) of the pioglitazone-treated people and 139 (1.8%) of the controls (HR, 1.41; CI, 1.14-1.76; p = 0.002). The magnitude and direction of the favourable effect of pioglitazone on ischaemic events and unfavourable effect on heart failure was homogeneous across trials of different duration, for different comparators, and for subjects with or without established vascular disease. Pioglitazone was associated with a significantly lower risk of death, myocardial infarction, or stroke among a diverse population of people with diabetes. Serious heart failure is increased by pioglitazone, although without an associated increase in mortality.

To systematically review the long-term cardiovascular risks of rosiglitazone, Singh et al (2007) searched randomised controlled trials, systematic reviews and meta-analyses through to May 2007. Studies selected for inclusion were randomised controlled trials of rosiglitazone for the prevention or treatment of type 2 diabetes with at least 12 months of follow-up, and numerical documentation of cardiovascular events. Four studies were included in the meta-analysis which included 14,291 individuals with 6,421 receiving treatment with rosiglitazone

with a 1-4 year follow-up. Rosiglitazone significantly increased the risk of myocardial infarction (n = 94/6421 vs 83/7870; RR, 1.42; CI, 1.06-1.91; p = 0.02) and heart failure (n = 102/6421 vs 62/7870; RR, 2.09; CI, 1.52-2.88; p < 0.001) without a significant increase in risk of cardiovascular mortality (n = 59/6421 vs 72/7870; RR, 0.90; CI, 0.63-1.26; p = 0.53). There was no evidence of substantial heterogeneity among the trials for these end points. The use of rosiglitazone for at least 12 months in the treatment of type 2 diabetes significantly increases the risk of myocardial infarction and heart failure, without a significantly increased risk in cardiovascular mortality.

Nissen et al (2007) performed a meta-analysis of 42 randomised controlled trials with 27,847 subjects which used rosiglitazone for more than 24 weeks duration and which included outcome data for myocardial infarction and death from cardiovascular causes. Mean age of subjects was 57 years, there was an overall predominance of men, and overall diabetes control was poor throughout with mean baseline HbA1c of approximately 8.2%. In the rosiglitazone group, compared with the control group, the odds ratio for myocardial infarction was 1.43 (CI, 1.03 to 1.98; p = 0.03), and for death from cardiovascular causes was 1.64 (CI, 0.98 to 2.74; p = 0.06). Although the study had some limitations including a lack of access to original source data, rosiglitazone was associated with a significant increase in the risk of myocardial infarction.

Recently, the final results of the RECORD study were published (Home et al, 2009). Data were available for 4,447 people with type 2 diabetes. In the rosiglitazone group 321 people and in the active control group 323 people experienced the primary outcome during a mean 5.5-year follow-up (HR 0.99, 95% CI 0.85–1.16). HR was 0.84 (0.59–1.18) for cardiovascular death, 1.14 (0.80–1.63) for myocardial infarction, and 0.72 (0.49–1.06) for stroke. Addition of rosiglitazone to glucose-lowering therapy in people with type 2 diabetes did not increase the risk of overall cardiovascular morbidity or mortality compared with standard glucose-lowering medications.

The ACCORD study (2008) which found an increased risk of death in the intensively treated group, did not find that this increased risk was association with any particular diabetes treatment and noted that 91% of the intensively treated group was taking rosiglitazone. Similarly in the VADT study, which found no effect of intensified treatment on cardiovascular events, rosiglitazone was used by the majority of the intensively treated group (Duckworth, 2009) – see Sections 1 and 2.

Hanefeld et al (2004) assessed the effect of acarbose on cardiovascular events in people with type 2 diabetes in a meta-analysis of 7 reports. The meta-analysis included subjects randomised to either acarbose (n = 1248) or placebo (n = 932) with a minimum treatment duration of 52 weeks. The primary outcome measure was time to develop a cardiovascular event. There were favourable trends in risk reduction for all cardiovascular event categories with acarbose treatment. Myocardial infarction and ‘any cardiovascular event’ were

significantly reduced (MI HR 0.36 CI 0.16–0.80], p = 0.012; Any CV event: 0.65 [CI 0.48–0.88], p = 0.0061).

Acarbose is an option for improving glycaemic control in people with type 2 diabetes

Acarbose is a reversible inhibitor of alpha-glucosidase, an enzyme present in the brush border of the small intestine. Acarbose delays absorption of carbohydrate and reduces postprandial glucose peaks. Gastrointestinal side effects such as flatulence and diarrhoea are frequently reported.

In a meta-analysis of 41 randomised controlled trials, Van de Laar et al (2005) assessed alpha-glucosidase inhibitors in people with type 2 diabetes. The trials were of at least 12 weeks duration and compared alpha-glucosidase inhibitor monotherapy with any other intervention that included at least one of the following outcomes: mortality, morbidity, quality of life, glycaemic control, lipids, insulin levels, body weight, and adverse events. Data were obtained electronically from The Cochrane Library, MEDLINE, EMBASE, Current Contents, LILACS, databases of ongoing trials, and reference lists of reviews. Thirty trials investigated acarbose, 7 miglitol, 1 voglibose and 3 compared different alpha-glucosidase inhibitors. Study duration was 24 weeks in most cases and only 2 studies were longer than one year. The meta-analysis showed that, compared with placebo, alpha-glucosidase inhibitor lowered HbA1c by -0.8% (CI -0.9 to -0.6, 28 comparisons) for acarbose and -0.7% (CI -0.9 to -0.4, seven comparisons) for miglitol. In the one voglibose study, HbA1c was reduced by -0.5% (CI -0.6 to -0.3). There was no clear dose dependency effect on HbA1c for acarbose. Acarbose also had positive effects on fasting blood glucose -1.1 mmol/L (CI -1.4 to -0.9) and post-load blood glucose -2.3 mmol/L (CI -2.7 to -1.9). There was no clinically relevant effect on lipids or body weight. Adverse effects were mostly of gastro-intestinal origin and dose dependent.

Feinbock et al (2003) compared acarbose with glimepiride in people with diabetes not controlled by diet alone. Subjects (n = 219) were randomised to receive either glimepiride (1-6 mg daily, n = 111) or acarbose (50-200 mg TID, n = 108) to achieve the target FPG of $\leq$ 7.8 mmol/L during a period of 20 weeks. At the study end, glimepiride showed a significantly greater reduction in HbA1c (-2.5 ± 2.2 vs -1.8 ± 2.2%, p = 0.014) and FPG (-2.6 ± 2.6 vs -1.4 ± 2.8 mmol/L, p = 0.004). A mean weight loss of 0.4 ± 5.2 kg (p = 0.8) and 1.9 ± 3.9 kg (p = 0.001) was observed with glimepiride and acarbose therapy, respectively.

Neuser et al (2005) assessed the safety profile of acarbose in doses ranging from 50–300 mg three times daily in people with diabetes. A total of 359 subjects (acarbose 240, placebo 119) were recruited for this 56-week, double blind, parallel-group, multi-centre comparison. The study included 190 people with type 2 diabetes in the acarbose group and 95 in the placebo group. Most subjects were also receiving sulphonylurea or insulin treatment. HbA1c improved significantly with a mean change of –0.24% compared with placebo. Abdominal pain, diarrhoea and flatulence occurred more frequently in the acarbose treated group (p < 0.005). Study withdrawal was 35% for acarbose and 24% for placebo recipients.

A randomised controlled trial investigated the effect of acarbose in 163 people with type 2 diabetes and with newly initiated insulin treatment who were previously inadequately controlled with oral anti-diabetic medications (Schnell et al., 2007) over a 20 week period. Inclusion criteria were type 2 diabetes, age > 40 years, HbA1c ≥ 8%, BMI ≥ 26 kg/m^2 and newly initiated on insulin. The primary outcomes were changes in HbA1c and daily insulin dose. Acarbose plus insulin significantly reduced HbA1c compared with placebo (2.31 vs 1.81%, p = 0.03). Insulin dose was comparable at the end of treatment (p = 0.85). BMI decreased with acarbose (30.36 ± 3.99 kg/m^2 to 29.78 ± 5.22 kg/m^2) and increased with placebo (29.89 ± 4.57 kg/m^2 to 34.99 ± 4.36 kg/m^2). Apart from gastrointestinal complaints associated with acarbose (48 adverse events reported vs 34 placebo), the treatment was well tolerated.

Bachmann et al (2003) randomised 373 subjects (aged 50 to 75 years) taking maximum dose of sulphonylurea (glibenclamide 15 mg/d or gliclazide 240 mg/d) and poor glycaemic control (HbA1c > 9.0%, FPG > 11.1 and 1-h PPG > 16.7 mmol/L) to either acarbose 300 mg/d or matching placebo. The dose of sulphonylurea remained unchanged during the study period. The two groups were well matched for all characteristics at baseline. After 18 months, the difference in mean HbA1c between acarbose and placebo was -0.5% (CI -0.9 to -0.2, p = 0.001). Acarbose significantly reduced both mean FPG and 1-h PPG compared with placebo (12.4 vs 13.2 mmol/L, p = 0.02; 16.3 vs 18.2 mmol/L, p < 0.0001, respectively). A number of subjects discontinued the study because of commencement of insulin (14.2% in the acarbose group vs 24.5% in the placebo group). Acarbose had a good safety profile and was generally well tolerated.

DPP-4 inhibitors are a new option for improving glycaemic control in people with type 2 diabetes

Dipeptidyl peptidase-4 (DPP-4) inhibitors competitively and reversibly inhibit the DPP-IV enzyme which breaks down the incretins GLP-1 and GIP, gastrointestinal hormones that are released in response to a meal. By preventing their breakdown, the incretin hormones are increased and glucose-induced insulin release from the pancreas is increased and the release of glucagon is suppressed.

In Australia the DPP-4 inhibitor sitagliptin is available through the PBS. It is indicated for use as dual therapy in people with type 2 diabetes, in combination with metformin or a sulphonyurea, where a combination of metformin and sulphonylurea is contraindicated or not tolerated.

The safety and efficacy of incretin-based therapy in adults with type 2 diabetes was examined in a meta-analysis of RCTs by Amori et al (2007). MEDLINE (1966–May 20, 2007) and the Cochrane Central Register of Controlled Trials was searched for randomised controlled trials involving an incretin mimetic (glucagon-like peptide 1 [GLP-1] analogue) or enhancer (dipeptidyl peptidase 4 [DPP4] inhibitor). Selected trials ranged from 12 to 52 weeks duration, compared incretin therapy with placebo or other anti-diabetic medication, and reported HbA1c data in non-pregnant adults with type 2 diabetes. In all, 29 reports met the inclusion criteria. Incretins lowered HbA1c compared with placebo (weighted mean difference, −1.0% [CI, −1.1% to −0.8%] for GLP-1 analogues and −0.7% [CI, −0.9% to −0.6%] for DPP-4 inhibitors and were non-inferior to other anti-diabetic medications. In contrast with nearly all available anti-diabetic medications that cause weight gain, GLP-1 analogues resulted in moderate and continuous weight loss (1.4 kg and 4.8 kg vs placebo and insulin, respectively) while DPP-4 inhibitors were weight neutral. GLP-1 analogues had more gastrointestinal side effects (RR 2.9 [CI, 2.0-4.2] for nausea and 3.2 [CI, 2.5-4.4] for vomiting). DPP-4 inhibitors had an increased risk of infection (RR 1.2 [CI, 1.0-1.4] for nasopharyngitis and 1.5 [CI, 1.0-2.2] for urinary tract infection) and headache (RR 1.4 [CI, 1.1-1.7]). All but 3 trials had a 30-week or shorter duration and therefore long-term efficacy and safety could not be evaluated.

Goldstein et al (2007) examined the efficacy and safety of initial combination therapy with sitagliptin and metformin in people with type 2 diabetes over 24 weeks. A total of 1,091 subjects with inadequate glycaemic control on diet and exercise were included. Baseline HbA1c values ranged from 7.5 to 11%. Subjects were randomised to one of six treatments: sitagliptin 100 mg/metformin 1,000 mg; sitagliptin 100 mg/metformin 2,000 mg; metformin 1,000 mg; metformin 2,000 mg (all as divided doses administered twice daily), sitagliptin 100 mg, or placebo. The placebo-subtracted HbA1c change from baseline ranged from – 2.1% in the sitagliptin 100 mg/metformin 2,000 mg group to – 0.8% in the sitagliptin 100 mg group ($p < 0.001$ for multiple comparisons). The incidence of serious adverse experiences was

generally similar across treatment groups, with slightly higher incidences in the placebo and sitagliptin monotherapy groups.

Sitagliptin was assessed in 441 people where glimepiride alone or metformin in combination with glimepiride produced unsatisfactory glycaemic control (Hermansen et al., 2007). Mean baseline HbA1c was 8.3% in the sitagliptin and placebo groups. Compared with placebo, sitagliptin reduced HbA1c by 0.7% ($p < 0.001$) after 24 weeks. In the subset on glimepiride plus metformin, sitagliptin reduced HbA1c by 0.9% compared with placebo, compared with a reduction of 0.6% in the subset on glimepiride alone. Sitagliptin also reduced fasting blood glucose concentrations (– 1.1 mmol/L, $p < 0.001$) and 2-h postprandial glucose (2.0 mmol/L, $p < 0.001$) compared with placebo. The addition of sitagliptin produced a moderate increase in adverse events (15% vs 7%) compared with placebo largely because of a higher incidence of hypoglycaemia.

In a multinational, randomised, placebo-controlled, parallel group, double-blind trial, Raz et al (2008) examined the addition of sitagliptin to metformin monotherapy in people with type 2 diabetes and HbA1c ≥ 8.0% and ≤ 11.0%. One hundred and ninety people aged 18-78 years were randomised to the addition of 100 mg once daily sitagliptin or maintained on metformin monotherapy (≥ 1500 mg/day) for 30 weeks. HbA1c (– 1.0% at 18 and 30 weeks), fasting plasma glucose, and 2-h postprandial glucose were significantly reduced with addition of sitagliptin ($p < 0.001$ for all). A significantly greater proportion of subjects treated with sitagliptin achieved HbA1c levels < 7.0% at 30 weeks (22.1% vs 3.3%, $p < 0.001$).

Insulin is frequently required for glycaemic control in people with type 2 diabetes and can be initiated as basal therapy or as premixed insulins, usually in combination with oral anti-diabetic medications

Insulin is an essential protein hormone with extensive effects on metabolism and is necessary for the uptake of glucose into most of the body's cells where it is stored as glycogen in skeletal muscle and the liver. Insulin is generally withheld until people with type 2 diabetes are unresponsive to other therapies. Treatment for type 2 diabetes often begins with oral monotherapy, but after 3 years of treatment, more than half will require more than one pharmacological agent, and eventually most will require insulin (Nelson and Palumbo, 2006).

A number of insulin therapies are available and include rapid-acting insulin analogues such as aspart or lispro, short-acting insulins such as actrapid or humulin, intermediate-acting insulins such as NPH and long-acting insulins such as glargine and detemir. In addition there are a number of pre-mixed preparations of rapid-acting/short-acting and intermediate-acting insulins.

Insulin added to oral anti-diabetic medications

Goudswaard et al (2004) assessed the effects of insulin monotherapy versus insulin and anti-diabetic medication (OAD) combination therapy in 1,811 participants. MEDLINE, EMBASE, and The Cochrane Library were searched for eligible studies upto May 2004 and included RCTs with 2 months minimum follow-up. Twenty RCTs (mean trial duration 10 months), with mean subject age 59.8 years and mean known duration of diabetes 9.6 years were included. No studies assessed diabetes-related morbidity, mortality or total mortality. From 13 studies (21 comparisons), sufficient data were extracted to calculate pooled effects on glycemic control and showed the following:

- Insulin-OAD combination therapy had statistically significant benefits on glycaemic control over insulin monotherapy only when the latter was used as a once-daily injection of NPH insulin.
- Twice-daily insulin monotherapy (NPH or premixed insulin) provided superior glycaemic control to insulin-OAD combination therapy regimens where insulin was administered as a single morning injection.
- Regimens utilising OADs with bedtime NPH insulin provided comparable glycaemic control to insulin monotherapy (administered as twice daily, or multiple daily injections).
- Overall, insulin-OAD combination therapy was associated with a 43% relative reduction in total daily insulin requirement compared with insulin monotherapy.
- Compared with insulin-sulphonylurea, insulin-metformin combination therapy resulted in a significantly greater improvement in glycaemic control.
- There was no significant difference in the frequency of symptomatic or biochemical hypoglycaemia between insulin and combination therapy regimens.

- Combination therapy which included metformin resulted in less weight gain compared with insulin monotherapy.

Rosenstock et al (2006) evaluated the efficacy and safety of add-on insulin glargine versus rosiglitazone in 217 insulin-naïve people with type 2 diabetes inadequately controlled on dual oral anti-diabetic therapy with sulphonylurea plus metformin in a 24-week multicentre, randomised controlled trial. Subjects (HbA1c 7.5-11%, BMI >25 kg/m^2) on ≥ 50% of maximal-dose sulphonylurea and metformin received add-on insulin glargine 10 units/day or rosiglitazone 4 mg/day. Insulin glargine was forced-titrated to target FPG 5.5-6.7 mmol/L, and rosiglitazone was increased to 8 mg/day any time after 6 weeks if FPG was > 5.5 mmol/L. HbA1c improvements from baseline were similar in both groups (-1.7 vs -1.5% for insulin glargine vs rosiglitazone, respectively); however, when baseline HbA1c was > 9.5%, the reduction of HbA1c with insulin glargine was greater than with rosiglitazone ($p < 0.05$). Insulin glargine yielded better FPG values than rosiglitazone (-3.6 ±0.23 vs -2.6 ± 0.22 mmol/l; $p = 0.001$). Insulin glargine final dose per day was 38 ±26 IU vs 7.1 ± 2 mg for rosiglitazone. Confirmed hypoglycaemic events at plasma glucose < 3.9 mmol/l were slightly greater for the insulin glargine group (n = 57) than for the rosiglitazone group (n = 47) ($p = 0.05$). The calculated average rate per patient-year of a confirmed hypoglycaemic event (< 3.9 mmol/L), after adjusting for BMI, was 7.7 (95% CI 5.4-10.8) and 3.4 (2.3-5.0) for the insulin glargine and rosiglitazone groups, respectively ($p = 0.007$). More subjects in the insulin glargine group had confirmed nocturnal hypoglycaemia of < 3.9 mmol/L ($p = 0.02$) and < 2.8 mmol/L ($p < 0.05$) than in the rosiglitazone group. Insulin glargine had less weight gain than rosiglitazone (1.6 ± 0.4 vs 3.0 ±0.4 kg; $p = 0.02$), fewer adverse events (7 vs 29%; $p = 0.0001$), and no peripheral oedema (0 vs 12.5%).

Schwartz et al (2003) randomised 188 people with type 2 diabetes and inadequate response to two OADs (HbA1c > 8.0%) to either a third OAD (n = 98) or an insulin 30/70 mix twice daily plus metformin (n = 90) for 24 weeks in an open-label, parallel group trial. Both groups were comparable at baseline. At the end of the study, improvement in glycaemic control was similar in both groups (HbA1c: 9.6 ± 1.3 to 7.7 ± 1.4% for triple OADs vs 9.7 ± 1.6 to 7.7 ± 1.3% for insulin plus metformin, $p = 0.96$; FPG: -3.1 vs -3.6 mmol/L, $p = 0.29$). Insulin plus metformin reduced total cholesterol and triglyceride significantly compared to triple OADs ($p = 0.04$, $p = 0.03$, respectively). Mean body weight increased similarly in both groups (2.9 ± 4.2 vs 3.5 ± 3.8 kg).

Gerstein et al (2006) tested the hypothesis that adding insulin earlier to achieve glycemic goals would be advantageous. People (n = 405) aged 18-80 years with type 2 diabetes for at least 6 months, HbA1c of 7.5-11%, and on 0, 1 or 2 oral agents, were randomised to one of two therapeutic approaches for 24 weeks: evening insulin glargine plus self-titration by 1 unit/day if the fasting plasma glucose (FPG) was > 5.5 mmol/L, or conventional therapy with physician adjustment of oral glucose-lowering agents if capillary FPG levels were > 5.5 mmol/L. Two consecutive HbA1c levels of ≤ 6.5% were the primary outcome measures.

Participants were allocated to glargine (n = 206) and to oral anti-diabetic agents (n = 199). Compared with OAD treated subjects, participants receiving glargine were 1.68 times more likely to achieve two consecutive HbA1c levels ≤ 6.5% (95% CI 1.00-2.83; p = 0.049) and HbA1c decreased by 1.6 vs 1.3% (p = 0.005) achieving an adjusted mean of 7.0 (vs 7.2% p = 0.0007). They also had greater increases in treatment satisfaction (p = 0.045) but a 1.9 kg greater increase in weight (p < 0.0001). No differences in hypoglycaemia were noted.

Yki-Jarvinen et al (1999) compared combination therapy with OADs plus insulin with other insulin regimens on glycaemic control in 96 people (mean age 58 years) with type 2 diabetes who were poorly controlled on sulphonylurea therapy alone. Subjects were randomised to one of the following treatments: bedtime NPH insulin plus glyburide (10.5 mg) and placebo, bedtime NPH insulin and metformin (2.0 g) and placebo, glyburide and metformin, or bedtime NPH and a second NPH injection in the morning. Subjects in the insulin plus metformin group showed a progressive decrease in HbA1c over time (from 9.7 ± 0.4 to 7.2 ± 0.2%, p < 0.001), and at 12 months, the difference between this group and all other three groups was significant (p < 0.05). Subjects in the insulin plus metformin group gained less weight (0.9 ± 1.2 kg, p < 0.001), while subjects gained more weight in the insulin plus glyburide, insulin plus both OADs, and twice daily insulin injection group (3.9 ± 0.7 kg, 3.6 ± 1.2 kg, and 4.6 ± 1.0 kg, respectively). In addition, fewer hypoglycaemic episodes were reported in the insulin plus metformin group than in all other groups (1.8 ± 0.4 per person, vs 3.4 ± 1.0, 3.3 ± 1.6, and 3.9 ± 1.6 per person, respectively, p < 0.05).

Philis-Tsimikas (2006) compared the effectiveness and tolerability of detemir versus NPH administered with 1 or more OAD in a 20-week, multicentre, randomised, open-label, 3-arm, parallel-group trial of 504 poorly controlled people with type 2 diabetes, and to compare different administration times of detemir. Eligibility include age ≥ 18 years, BMI ≤ 40 kg/m^2, type 2 diabetes for at least 12 months, being insulin naïve, and HbA1c between 7.5% to 11.0% following at least 3 months' treatment with ≥ 1 OAD. Subjects were randomised to an evening injection of detemir (n=170), or a pre-breakfast injection of detemir (n=168), or an evening injection of NPH insulin (n=166). Morning and evening detemir were associated with reductions in HbA1c similar to those with evening NPH (-1.6%, -1.5%, and -1.7%, respectively). Compared with evening NPH, 24-hour and nocturnal hypoglycaemia were reduced by 53% (p = 0.019) and 65% (p = 0.031), respectively, with evening detemir. Incidences of hypoglycaemia did not differ significantly between groups that received morning and evening detemir, but nocturnal hypoglycaemia was reduced further, by 87%, with morning detemir compared with evening NPH (p < 0.001). Weight gain was 1.2, 0.7, and 1.6 kg with morning detemir, evening detemir, and NPH, respectively (p = 0.005 for evening detemir vs NPH). No between-treatment differences were seen in other tolerability end points.

Stehouwer et al (2003) compared glycemic control and incidence rate of hypoglycaemic events among 3 treatment regimens (glimepiride plus NPH at bedtime; NPH BID and 30/70 premixed insulin BID) in 261 overweight people with secondary failure to sulphonylurea and metformin (aged 40-70 years, mean BMI 29 kg/m^2) in a multicentre study. After 9 months, mean HbA1c was significantly higher in the glimepiride group (9.4 ± 1.4 to 8.9 ± 1.2%) compared with the two insulin groups (NPH BID: 9.4±1.4 to 8.3 ± 1.0%; premixed insulin BID: 9.4 ± 1.3 to 8.3 ± 1.2%) ($p < 0.001$). Only 1.2%, 3.4% and 5.7% of people achieved the target HbA1c of ≤ 6.5%, respectively. The incidence of hypoglycaemic events was similar, 0.36 versus 0.48 versus 0.53 events per person month, respectively. The mean weight gain and insulin dose were comparable in all three groups.

A randomised trial of 12 months duration compared the effects of combined therapy with OHA and insulin or insulin alone on glycaemic control in 100 insulin-treated subjects (Yki-Jarvinen et al., 1997). Glycaemic control was significantly improved for the whole study group; the mean HbA1c decreased from 9.7 ± 0.2% at baseline to 8.0 ± 0.1%, 8.0 ± 0.1%, 8.2 ± 0.1%, and 8.5 ± 0.2% at 3, 6, 9, and 12 months, respectively (all $p < 0.001$). However, glycemic control at 12 months was significantly worse than that at 3 ($p < 0.001$), 6 ($p < 0.001$), and 9 months ($p < 0.02$). HbA1c decreased significantly in non-obese participants by –2.0 ± 0.2% ($p < 0.001$, 3 vs 0 months) during the first 3 months of insulin therapy and was maintained throughout the 12-month treatment period. The decrease in HbA1c was similar in the combination and insulin therapy groups. In obese participants, HbA1c decreased during the first 3 months by –1.4 ± 0.2% ($p < 0.001$ vs 0 months). Thereafter, glycaemic control deteriorated gradually between 3 and 12 months. At 12 months, HbA1c was not significantly lower than that at baseline (change, –0.5 ± 0.4%). The worsening of glycaemic control was similar in the combination and insulin therapy groups. The decrease in HbA1c at 6, 9, and 12, but not that at 3 months, was significantly greater in the non-obese than in the obese group ($p < 0.05$ or less at all time points). This was true for both the combination and the insulin therapy groups. The worst glycaemic control was associated with weight gain ($p < 0.02$) and initial weight ($p < 0.02$). The non-obese people gained less weight with combined therapy than with insulin alone ($p < 0.05$), while the obese people had similar weight gain with both therapies. There was no difference in hypoglycaemic episodes.

Janka et al (2007) compared initiation of insulin therapy in a 24-week randomised controlled trial by adding once-daily insulin glargine to OADs with switching subjects to premixed 30/70 regular human insulin without OADs. In all, 364 poorly controlled people with type 2 diabetes were treated with once-daily morning insulin glargine with continued OADs (glimepiride+metformin) (glargine+OAD) or twice-daily 30/70 premixed insulin alone. Subjects aged 65 years and older with type 2 diabetes who had been treated with a stable dose of sulphonylurea or metformin for at least one month were enrolled. Inclusion criteria included BMI ≤ 35 kg/m^2, HbA1c levels between 7.5% and 10.5%, and FBG ≥ 6.7 mmol/L. Insulin dosage in each group was titrated to target FBG of ≤ 5.6 mmol/L using a weekly

titration algorithm. HbA1c decreased from baseline to endpoint for both glargine+OAD (from 8.8% to 7.0%) and 30/70 (from 8.9% to 7.4%); adjusted mean HbA1c decrease for glargine+OAD and 30/70 was -1.9% and -1.4%, respectively ($p = 0.003$). More subjects reached HbA1c $\leq$ 7.0% without confirmed nocturnal hypoglycaemia with glargine+OAD (n = 37, 55.2%) than with 30/70 (n = 19, 30.2%) ($p = 0.006$). FBG decreased significantly more with glargine+OAD (-3.2 mmol/L) than with 30/70 (-2.2 mmol/L) ($p = 0.002$). Subjects treated with glargine+OAD experienced fewer episodes of any hypoglycaemia (3.68/patient-year) than did those treated with 30/70 (9.09/patient year) ($p = 0.008$).

In a 24-week, multinational, multicentre, open, parallel group clinical trial, Janka et al (2005) compared the efficacy and safety of adding once-daily basal insulin with switching to twice-daily premixed insulin in 371 insulin-naive people with type 2 diabetes insufficiently controlled (fasting blood glucose [FBG] $\geq$ 6.7 mmol/L, HbA1c 7.5-10.5%) by OADs (sulphonylurea plus metformin). Subjects were randomised to once-daily morning insulin glargine plus glimepiride and metformin (glargine plus OAD) or to 30/70 premixed insulin twice daily without OADs. Insulin dosage was titrated to target FBG $\leq$ 5.6 mmol/L (both insulins) and pre-dinner blood glucose $\leq$ 5.6 mmol/L (30/70 only) using a weekly forced-titration algorithm. Mean HbA1c decrease from baseline was significantly more pronounced (-1.6 vs -1.3%, $p = 0.0003$), and more subjects reached HbA1c $\leq$ 7.0% without confirmed nocturnal hypoglycaemia (45.5 vs 28.6%, $p = 0.001$) with glargine plus OAD than with 30/70 alone. Similarly, FBG decrease was greater with glargine plus OAD (adjusted mean difference -0.9 mmol/L, $p < 0.0001$), and more subjects reached target FBG $\leq$ 5.6 mmol/L with glargine plus OAD than with 30/70 alone (31.6 vs 15.0%, $p = 0.0001$). Glargine plus OAD subjects had fewer confirmed hypoglycaemic episodes than 30/70 subjects (mean 4.07 vs 9.87/person-year, $p < 0.0001$).

Roach et al (2001) randomised 172 people (mean age 59.5 years) with type 2 diabetes who were not optimally controlled with glyburide (GB) alone to receive either insulin lispro Mix25 injection twice daily (n = 85) or GB 15 mg daily (n = 87) for 4 months. The recommended initial Mix25 dose was 0.3-0.5 U/kg, and dose was adjusted to achieve target FPG < 7.0 mmol/L and 2h PPG 10.0 mmol/L. At baseline, there were no differences in HbA1c values (Mix25 vs GB, 10.1 ± 1.4% vs 9.9 ± 1.2%) and self-monitored blood glucose values between two treatment groups. The mean HbA1c value was significantly lower in the Mix25 group than in the GB group (8.5 ± 1.3% vs 9.4 ± 1.8%, $p = 0.001$), with a greater reduction in the Mix25 group (-1.4 ± 1.4% vs -0.7 ± 1.6%, $p = 0.004$). With regard to self-monitored blood glucose values, FPG and both 2h PPG after the morning and evening meals were significantly lower in the Mix25 group than in the GB group at 4 months ($p < 0.05$ for FPG, $p < 0.001$ for both 2h PPGs), with a greater reduction from baseline to the end point in the Mix25 group for the 4-point glucose profile ($p < 0.001$–0.05). The incidence of hypoglycaemic episode, which was defined as any symptoms or blood glucose value of < 3.0 mmol/L, was significantly higher in the Mix25 group than in the GB group (44.7% vs 10.3%, $p = 0.001$). The mean hypoglycaemia rate (events per person per 30 days) was also higher in

the Mix25 group (0.30 ± 0.53 vs 0.5 ± 0.20, $p < 0.001$). Mean body weight increased from baseline by 1.32 ± 2.4 kg in the Mix25 group and decreased by 0.70 ± 2.6 kg in the GB group ($p < 0.001$).

Johnson et al (1996) conducted a search using the Medline database from January 1980 to March 1992 to assess the efficacy of combination therapy with insulin and sulphonylurea in people with type 2 diabetes. Sixteen randomised, placebo-controlled trials (sulphonylurea plus insulin vs placebo plus insulin) with a total population of 351 subjects, and study duration ranging from 8 to 52 weeks, were identified. Combination therapy resulted in a significant decrease in HbA1c ($p < 0.025$) and FPG ($p < 0.01$). Moreover, improved metabolic control was achieved with a lower daily insulin dose ($p < 0.01$) and without a significant increase in body weight. The combination therapy also enhanced endogenous insulin secretion expressed by an increase in fasting serum C-peptide concentration ($p < 0.05$).

Pugh et al (1992) assessed the efficacy of combination therapy with insulin and sulphonylurea in the treatment of type 2 diabetes by performing a Medline search from 1966 to 1991. Seventeen randomised controlled trials were identified with a total of 354 subjects (mean age 60.8 years) with type 2 diabetes and a minimum treatment duration of 8 weeks. Overall, glycaemic control was better in the combinated treatment than in the control group. For HbA1c, the treatment group decreased concentrations from 11.0 to 10.2% compared with 11.0 to 11.2% in the control group ($p < 0.0001$).

An earlier systematic review reported that combination therapy with insulin and a sulphonylurea slightly improved glycaemic control in people with type 2 diabetes (Peters and Davidson, 1991). A total of 22 RCTs which included 8 parallel and 14 crossover studies were identified through a Medline search from 1979 to 1990. In parallel studies which lasted from 6 to 52 weeks and where 184 subjects were studied, the mean pre- and post-treatment HbA1c values were 10.8% and 11.1%, respectively in the insulin plus placebo group, and 10.7% and 10.0%, respectively, in the insulin plus sulphonylurea group. At the end of the studies, overall insulin doses were lower in the insulin plus sulphonylurea group. Weighted mean pre- and post-treatment HbA1c values were 10.8% and 11%, respectively, in the insulin plus placebo group and 10.7% and 10.0%, respectively, in the insulin plus sulphonylurea group. In crossover studies with an average duration of 10.6 weeks for each treatment and with 191 subjects, the mean HbA1c values were 10.6% and 9.8% after the placebo and sulphonylurea treatment respectively. Similarly, insulin doses were lower in the insulin plus sulphonylurea phase than with insulin plus placebo. No data on weight changes and hypoglycemic events were reported.

A study of 175 subjects compared combination therapy of insulin and sulphonylurea to insulin monotherapy on glycaemic control (Landstedt-Hallin et al., 1999). Subjects who failed treatment with sulphonylurea alone were started on premixed insulin (25% regular

insulin and 75% NPH insulin) combined with glibenclamide 10.5 mg/day, and insulin doses were adjusted to achieve optimal glycaemic control with FPG < 8.0 mmol/L and postprandial glucose < 10.0 mmol/L during the first 4 months (Phase I). Subjects were then randomly assigned to the SU withdrawal group (placebo plus insulin, n = 112) or to the control group (glibenclamide plus insulin, n = 39) for a further 1–4 months (Phase II). HbA1c improved from 9.7% to 7.2% ($p < 0.0001$) during Phase I. At the end of Phase II, HbA1c remained unchanged in the control group, whereas HbA1c was significantly increased in the SU withdrawal group, with the difference between groups being significant ($p < 0.0001$).

Wright et al (2002) evaluated the efficacy of the addition of insulin to sulphonylurea on glycaemic control in the UKPDS. Subjects (n = 826) with newly diagnosed type 2 diabetes were randomised to conventional therapy, primarily with diet or intensive therapy with insulin alone (I) or sulphonylurea (chlorpropamide or glipizide). Insulin was added if FPG was > 6.0 mmol/L on maximum dose of sulphonylureas (SI). Over 6 years, 53% of subjects in the sulphonylurea group were commenced on insulin. The mean HbA1c was significantly lower in the SI group than in the I group (6.6% [6.0-7.6] vs 7.1% [6.2-8.0], $p = 0.007$) and more subjects achieved an HbA1c < 7.0% (47 vs 35%, $p = 0.01$). Median insulin doses at 6 years were greater in the I group (0.30 U/kg [0.24-0.40]) than in the SI group (0.24 U/kg [0.16-0.40], $p = 0.005$). Weight gain was similar. Overall, hypoglycaemia occurred less frequently in the SI group compared with the I group (1.6 vs 3.2% per year, $p = 0.003$). Early addition of insulin when maximal sulphonylurea therapy is inadequate can significantly improve glycaemic control without promoting increased hypoglycaemia or weight gain.

Basal insulin therapy

In a meta-analysis of 12 randomised controlled trials, Bazzano et al (2008) examined the safety and efficacy of neutral protamine Hagedorn (NPH) insulin and glargine in 4,385 people with type 2 diabetes. Medline (1966-March 2007), EMBASE (1974-2007), the American Diabetes Association abstract database and the Cochrane Central Register of Controlled Trials were searched. In all, 54.1% of the participants were male, mean age was 58.3 years, mean BMI was 28.4 kg/m^2, and mean duration of diabetes was 10.5 years. Average study length was 27.8 weeks, with a range of 4 to 52 weeks, and average study size was 366 participants with a range of 24 to 756 participants. Data were pooled using a random-effects model. The mean net change (95% CI) for FPG, HbA1c and body weight for subjects treated with NPH insulin compared with glargine was 0.21 mmol/L (–0.02 to 0.45), 0.08% (–0.04 to 0.21) and –0.33 kg (–0.61 to –0.06), respectively, with negative values favouring NPH and positive values favouring glargine. Final mean (SD) HbA1c was 7.6% (0.9) and 7.7% (0.9) for glargine and NPH insulin, respectively. Mean percentages of participants reporting any (59.0 vs 53.0%, $p < 0.001$), symptomatic (51.4 vs 42.9%, $p < 0.001$), and nocturnal hypoglycaemia (33.3 vs 19.1%, $p < 0.001$) were significantly greater among people using NPH insulin compared with those taking glargine, respectively. There was no significant difference in confirmed or severe episodes. There was no difference

in glycaemic control between insulin glargine and NPH insulin, but less patient-reported hypoglycaemia with glargine and slightly less weight gain with NPH.

A meta-analysis of 14 RCTs examined long-acting insulin analogues compared with NPH insulin in people with type 2 diabetes (Monami et al., 2008). Data on HbA1c and BMI at endpoint, and incidence of any, symptomatic, nocturnal, and severe hypoglycaemia, were extracted and meta-analysed. Study duration ranged from 12 to 52 weeks (mean 28.7 weeks) and compared either the insulin analogues detemir or glargine with human NPH, either combined with an oral hypoglycaemic agent or with a prandial insulin. The Medline search collected all RCTs up to February 2008. Overall, HbA1c improvement with long-acting insulin analogue did not differ significantly to NPH, however, NPH showed a significant superiority (by 0.1%) over detemir, but not glargine. Detemir, but not glargine, was associated with a significantly smaller weight gain than NPH. Both analogues were associated with a reduced risk for nocturnal and symptomatic hypoglycaemia (OR: 0.46[CI 0.38-0.55] and 0.69[CI 0.60-0.80]; all $p < 0.01$).

Duckworth et al (2007) conducted a systematic review to compare insulin glargine and NPH insulin. English language articles were identified from 1996 to 2005 through searches of the National Center for Biotechnology Information PubMed database. Six original multi-centre, randomised, open-label, parallel-group trials conducted in Europe or the United States, ranging in duration from 4 to 52 weeks, met the inclusion criteria. Two additional analyses represented a sub-analysis and a study extension. All of the studies compared insulin glargine with NPH insulin given once or twice dail0y as monotherapy or in conjunction with oral anti-diabetic agents in people with type 2 diabetes. Insulin glargine showed equal clinical efficacy to that of NPH insulin and similar reductions in HbA1c. Reductions in HbA1c for glargine ranged from –0.4% to – 0.5% and –0.1% to –0.6% for NPH. Less frequent nocturnal hypoglycaemia was found with insulin glargine compared with NPH insulin.

In a 26-week randomised controlled trial (PREFER Study), Liebl et al (2008) compared two insulin analogue regimens in 719 people with type 2 diabetes previously uncontrolled by oral antidiabetic agents (OADs) with or without basal insulin. OADs were discontinued and participants were randomised to analogue basal-bolus therapy (insulin detemir once daily and insulin aspart mealtimes) or biphasic insulin aspart 30 (30% rapid-acting insulin aspart), twice daily. Insulin was titrated to targets for fasting, predinner and postprandial plasma glucose, as appropriate. In all, 92% of the 719 subjects completed the study and 58% achieved HbA1c levels of $\leq 7.0\%$, with reductions of 1.56% (to 6.96%) with basal-bolus therapy and 1.23% (to 7.17%) with biphasic insulin aspart. Reduction with basal-bolus therapy was superior in the overall population by 0.23% ($p = 0.005$), with no difference between regimens in insulin-naive participants. Major hypoglycaemia occurred in five basal-bolus subjects (0.9%) and in no subjects with biphasic insulin aspart. Incidence of minor hypoglycaemia was similar in both groups. All insulin doses increased during titration, with

increase in lunchtime insulin aspart dose and equal distribution of breakfast and dinner biphasic insulin aspart doses. Insulin detemir remained once daily in 87% of subjects.

Rosenstock et al (2005) assessed the risk of hypoglycaemia in a meta-analysis of controlled trials for insulin glargine versus once- or twice-daily NPH insulin in adults with type 2 diabetes. The meta-analysis included four open-labeled, randomised, parallel-group studies conducted in Europe and North America of at least a 24–28 weeks duration. Subject demographics were similar between the insulin glargine (n = 1,142) and NPH insulin (n = 1,162) groups. The proportion of subjects achieving target HbA1c (≤ 7.0%) was similar in the insulin glargine– and NPH insulin–treated subjects (30.8 and 32.1%, respectively). There was a consistent significant reduction of hypoglycaemia risk associated with insulin glargine, compared with NPH insulin, in terms of overall symptomatic (11%; $p < 0.0006$) and nocturnal (26%; $p < 0.0001$) hypoglycaemia. The risk of severe hypoglycaemia and severe nocturnal hypoglycaemia were reduced with insulin glargine by 46% ($p = 0.0442$) and 59% ($p = 0.0231$), respectively.

Mullins et al (2007) analysed the interaction between hypoglycaemia and HbA1c comparing insulin glargine (glargine) with NPH in people with type 1 or type 2 diabetes. A model was then used to compare rates of hypoglycaemia associated with use of these insulins. Patient-level data from randomised Phase III/IV clinical trials sponsored by the manufacturer which was made available in May 2004 were included in the model. MEDLINE, EMBASE, and BIOSIS were also searched for comparative RCTs of glargine and NPH. Unadjusted rates of symptomatic, confirmed, and severe hypoglycaemia were compared with those derived from negative binomial regression analysis, which stratified the results by HbA1c at end point (with last observation carried forward), treatment, and duration of diabetes. Eleven RCTs were included in the model (n = 5,074 subjects). Rates of hypoglycaemia had a curvilinear relationship with HbA1c, increasing at lower end-point HbAlc values. In combined analyses of the studies of type 1 and type 2 diabetes, unadjusted rates of hypoglycaemia were lower for glargine than NPH: 6.1% lower for all symptomatic hypoglycaemia, 21.6% lower for confirmed hypoglycaemia, and 23.9% lower for severe hypoglycaemia (all, $p < 0.05$). When modelled using the negative binomial distribution with end-point HbA1c as a covariate, the corresponding results were 9.1% ($p < 0.05$), 26.6% ($p < 0.001$), and 30.0% ($p = 0.08$), respectively. When only Phase IV trials were analysed, the relative reductions with glargine were 16.2% ($p < 0.01$), 40.8% ($p < 0.01$), and 46.8% ($p < 0.05$). The results of the separate analyses of studies of type 1 and type 2 diabetes were comparable.

Standl et al (2006) compared the incidence of nocturnal hypoglycaemia and glycaemic control following bedtime or morning insulin glargine plus glimepiride in a 24-week, multinational, open, randomised study. Subjects (n = 624) with type 2 diabetes poorly controlled on oral anti-diabetic medications received morning or bedtime glargine plus morning glimepiride (2, 3 or 4 mg) and were titrated to a target fasting blood glucose level ≤ 5.5 mmol/l. The incidence of nocturnal hypoglycaemia was equivalent between the two

groups, with morning glargine non-inferior to bedtime (13.0 vs 14.9 % of subjects). At study endpoint, similar improvements in glycaemic control were observed with morning compared with bedtime glargine: HbA1c: -1.7 ± 1.2 vs -1.6 ± 1.2%; p = 0.42; fasting blood glucose: -4.25 ± 2.82 vs -4.48 ± 2.75 mmol/L; p = 0.08. The endpoint mean daily glargine dose was comparable (34.7 ± 17.4 vs 32.4 ± 17.0 IU; p = 0.15), and there was no significant between-treatment difference in the change in body weight (2.1 vs 1.8 kg; p = 0.39). Once-daily glargine can be administered in a morning or bedtime regimen (plus morning glimepiride) without any difference in hypoglycemia.

Davies et al (2005) conducted a prospective, multicentre (n = 611), multinational (n = 59), open-label, 24-week randomised trial in 4,961 suboptimally controlled people with type 2 diabetes. The study compared two treatment algorithms for insulin glargine initiation and titration: algorithm 1 (investigator led) versus algorithm 2 (performed by study subjects). At baseline, mean diabetes duration was 12.3 ± 7.2 years, and 72% of subjects were pretreated with insulin. At end point, there was no significant difference in the incidence of severe hypoglycaemia between algorithms 1 and 2 (0.9 vs 1.1%). There was a significant reduction in HbA1c from 8.9 ± 1.3 to 7.8 ± 1.2% (p < 0.001), with a greater decrease with algorithm 2 (-1.2%) versus algorithm 1 (-1.1%). The reduction in fasting blood glucose was greater (p < 0.001) with algorithm 2 (9.4 to 6.1 mmol/L) than with algorithm 1 (9.4 to 6.3 mmol/L). Mean basal insulin dose increased from 22.9 ± 15.5 to 43.0 ± 25.5 IU, with a significant difference (p < 0.003) between algorithm 2 (21.6 IU) and algorithm 1 (18.7 IU). Self adjustment of glargine was safe and effective in improving glycaemic control with a lower incidence of severe hypoglycaemia compared with physician-managed titration.

Campbell et al (2001) conducted a systematic review through a search of Medline (1966-2001), the Institute for Scientific Information Web of Science (1995-2001) and proceedings of the ADA scientific meetings to identify relevant information about the efficacy and risk of hypoglycaemia of insulin glargine. Two Phase II trials comparing insulin glargine with human NPH insulin in 361 people with type 2 diabetes showed significant reduction in FPG in all treatment groups. There were no significant differences between treatment groups in hypoglycaemic episodes in one study (n = 157) and insulin glargine groups had a lower incidence of nocturnal hypoglycaemia compared with the NPH group in the other study (n = 204). Among 6 large Phase III trials, two were conducted in people with type 2 diabetes. In a 52-week study, 289 were randomly allocated to insulin glargine and 281 received NPH insulin once daily at bedtime plus OADs. There were no significant differences between groups in the mean changes from baseline in FPG (insulin glargine vs NPH insulin -2.7 vs -2.6 mmol/L) and in HbA1c (-0.5 vs -0.4%). People receiving insulin glargine had fewer episodes of symptomatic hypoglycaemia (35% vs 41%, p = NS) and nocturnal hypoglycemia (12% vs 24%, p = 0.002). In the other study, 259 people received insulin glargine once daily at bedtime and 259 received NPH insulin once or twice daily for up to 28 weeks. The two treatments produced similar reductions from baseline in FPG (insulin glargine vs NPH insulin: -1.7 vs -1.2 mmol/L) and HbA1c (-0.4% vs -0.6%). The overall incidence of

symptomatic hypoglycaemia was similar in both groups (61.4% vs 66.8%), however, the incidence of nocturnal hypoglycaemia was significantly lower with insulin glargine, compared with NPH insulin (31.3% vs 40.2%, $p < 0.02$).

To compare the safety and efficacy of insulin detemir with that of NPH insulin in 416 older (aged ≥ 65) and 880 younger (aged 18-64) people with type 2 diabetes, Garber et al (2007) analysed pooled, post hoc data from three open-label, randomised studies. Subjects were treated for 22 to 26 weeks with basal insulin plus mealtime insulin or oral anti-diabetic agents. Mean treatment difference for HbA1c (insulin detemir-NPH insulin) indicated that insulin detemir was not inferior to NPH insulin for both age groups (0.04%, CI -0.11-0.18 and 0.1%, CI -0.02-0.22, for older and younger persons, respectively). Relative risk of all hypoglycaemic episodes (insulin detemir/NPH insulin) was 0.59 (CI, 0.42-0.83) for older persons and 0.75 (CI, 0.59-0.96) for younger persons. Adverse events were similar between treatments. Fasting plasma glucose was similar between treatments (mean treatment difference 0.05 mmol/L (CI, 8.01-9.95) and 0.26 mmol/L (CI, 2.30-11.67), for older and younger persons, respectively). Mean treatment difference for weight was -1.02 kg (CI -1.61 to -0.42) and -1.13 (CI -1.58 to -0.69) for older and younger persons, respectively.

In a pooled analysis, Raslová et al (2007) investigated whether insulin detemir had a weight-sparing effect compared with other basal insulins and when used as the basal component of basal-bolus therapy. Data were pooled from two randomised, parallel group trials of 22 and 24 weeks' duration, in which 900 insulin-treated people with type 2 diabetes had their treatment intensified to basal-bolus therapy. Subjects received once- or twice-daily insulin detemir or NPH insulin in conjunction with insulin aspart or human soluble insulin at meal times. Subjects treated with insulin detemir had minimal weight gain (mean < 1 kg), regardless of their BMI at entry (estimated slope -0.032), whereas, in people treated with NPH insulin, weight gain increased as baseline BMI increased (estimated slope 0.075, $p = 0.025$). NPH insulin-treated subjects with the largest BMI (> 35 kg/m^2) gained the most weight (mean of ~2.4 kg). In contrast, insulin detemir-treated subjects with a BMI > 35 kg/m^2 lost weight (mean of approximately -0.5 kg). Glycaemic control was similar with the two treatments.

Premixed insulin therapy

In a systematic review, Qayyum et al (2008) examined the effectiveness and safety of premixed insulin analogues compared with other antidiabetic agents in 14,603 people with type 2 diabetes. Medline, EMBASE, CINAHL, and the Cochrane Library were searched from inception to February 2008. The median duration of follow-up in the trials was 16 weeks (range: 1 day to 2 years), the median numbers of participants 93 (8 to 8,166), the median age 59 years (51 to 68 years), and 52% were male. The study population had a median HbA1c of 8.7% (7.3 to 10.7%), median BMI 29.4 kg/m^2 (24 to 37 kg/m^2), and a median diabetes

duration of 11 years (4 to 16 years). Because the evidence from clinical trials was inconclusive for clinical outcomes, the review focused on intermediate outcomes. Premixed insulin analogues were similar to premixed human insulin in decreasing fasting glucose levels, HbA1c, and the incidence of hypoglycemia but were more effective in decreasing postprandial glucose levels (mean difference, -1.1 mmol/L; 95% CI, -1.4 to -0.7 mmol/L). Compared with long-acting insulin analogues, premixed insulin analogues were superior in decreasing postprandial glucose levels (mean difference, -1.5 mmol/L; CI, -1.9 to -1.2 mmol/L) and HbA1c (mean difference, -0.39% [CI, -0.50% to -0.28%]) but were inferior in decreasing fasting glucose levels (mean difference, 0.7 mmol/L; CI, 0.3 to 1.0 mmol/L) and were associated with a higher incidence of hypoglycaemia. Compared with noninsulin antidiabetic agents, premixed insulin analogues were more effective in decreasing fasting glucose levels (mean difference, -1.1 mmol/L; CI, -1.7 to -0.6 mmol/L), postprandial glucose levels (mean difference, -2.1 mmol/L; CI, -3.4 to -0.8 mmol/L), and HbA1c (mean difference, -0.49% [CI, -0.86% to -0.12%]) but were associated with a higher incidence of hypoglycaemia.

Ilag et al (2007) conducted a systematic review (Ovid, MEDLINE, and EMBASE (1995-2007)) of prandial premixed insulin analogues (insulin aspart and insulin lispro) compared with basal insulin analogues (insulin glargine, insulin detemir, and insulin lispro), with or without a prandial insulin analogue in the management of type 2 diabetes. Studies ranged from 12 to 28 weeks. Of the identified randomised controlled trials, 3 studies compared premixed insulin analogues containing 70% or 75% basal and 30% or 25% rapid acting insulin analogue with basal insulin analogues only, and 3 studies evaluated premixed insulin analogues containing 50% basal and 50% rapid-acting insulin analogue with basal insulin analogues only. Use of prandial premixed insulin analogues was associated with better overall and postprandial glycaemic control. In studies that compared twice-daily premixed insulin analogues with a basal insulin analogue, changes in HbA1c ranged from -1.0% to -2.8% and from -0.4% to -2.4%, respectively ($p < 0.01$). In the studies that compared thrice-daily premixed insulin analogues with a basal insulin analogue, changes in HbA1c ranged from -0.7% to -1.2% and from -0.3% to -0.8%, respectively ($p < 0.01$). Greater HbAlc lowering from baseline to end point was seen with intensive basal-bolus (IBB) therapy (8.5% to 7.0%) compared with twice-daily insulin aspart 70/30 (8.4% to 7.2%), with a treatment difference of 0.2% ($p < 0.006$). Fifty percent of people treated with insulin aspart 70/30 and 60% of those treated with IBB achieved an HbA1c value ≤ 7.0%. People previously treated with insulin had a greater HbA1c reduction with IBB therapy than with twice-daily insulin aspart 70/30 (1.2% vs 0.8%, respectively; $P < 0.013$), whereas the HbA1c reductions were similar in insulin-naive people treated with twice-daily insulin aspart 70/30 and those treated with IBB (1.7% and 1.4%). These results were achieved with some increase in overall hypoglycaemia, but not in nocturnal or severe hypoglycaemia.

This 6-month RCT (Wolffenbuttel et al., 1996) of 95 elderly people (mean age 68 years) with type 2 diabetes compared the effects of three different insulin regimens on glycaemic control

- two insulin injections before breakfast and dinner (Mixtard 30/70, regimen A); combination of glibenclamide with one NPH insulin injection at bedtime (regimen B); combination of glibenclamide with one NPH insulin injection before breakfast (regimen C). At baseline, the mean HbA1c was 11.2 ± 1.3% in group A, 10.5 ± 1.2% in group B, and 11.1±1.3% in group C. After 6 months of treatment, a significant reduction of 25-30% in HbA1c ($p < 0.001$) was observed in all treatment groups, with a mean final HbA1c of 8.3%. Subjects treated with twice-daily insulin were more likely to achieve an HbA1c of < 8.0% but insulin dose was also the highest in this group. There was no difference in weight gain between the three groups (all $p < 0.05$ v baseline value). Improvement of lipid and lipoproteins were also observed in three groups (all $p < 0.05$ v baseline value).

Boehm et al (2004) compared the long-term safety and efficacy of biphasic insulin aspart 30 (BIAsp30) with that of biphasic human insulin 30 (BHI30) over a period of 24 months in 125 people with type 2 diabetes. Participants were assigned to twice-daily BIAsp30 (n = 58) or BHI30 (n = 67) and took part in both a 3-month initial period and a 21-month extension of a randomised, controlled, multinational trial. Both groups were comparable in terms of age (BIAsp30, 62.8 ± 8.0 years; BHI30, 62.6 ± 8.6 years), duration of diabetes (BIAsp30, 15.5 ± 9.7 years; BHI30, 12.9 ± 6.6 years), BMI (BIAsp30, 29.1 ± 3.3 kg/m^2; BHI30, 27.2 ± 3.8 kg/m^2) and HbA1c (BIAsp30, 8.11 ± 1.22%; BHI30, 8.21 ± 1.22%; all data mean ± SD). In the BIAsp30 group, 55% were male, and in the BHI30 group 51%. No significant difference was found in mean HbA1c after 24 months [BIAsp30, 8.35 ± 0.20%; BHI30 8.13 ± 0.16%; adjusted mean difference (BIAsp30-BHI30) 0.03 (90% CI -0.29 to 0.34)%, $p = 0.89$]. The proportion of subjects experiencing major hypoglycaemia was also similar during the first year (BIAsp30, 5%; BHI30, 8%; $p = 0.72$), but it was significantly lower with BIAsp30 than with BHI30 during the second year (BIAsp30, 0%; BHI30, 10%; $p = 0.04$). There was no difference in the proportion experiencing minor hypoglycaemia. Body weight change was 0.05 ± 0.81 kg in the BIAsp30 group and 2.00 ± 0.69 kg in the BHI30 group ($p = 0.07$).

Halimi et al (2005) reviewed data on the efficacy of BIAsp 30 in comparison with other treatment strategies in type 2 diabetes, including oral antidiabetic medications (e.g. metformin, sulphonylureas, meglitinides, thiazolidinediones), conventional insulins (e.g. BHI 30, NPH insulin), and other analogue insulins (e.g. insulin glargine, biphasic insulin lispro 25 [Mix 25, 25% biphasic insulin lispro and 75% protaminated lispro]). Clinical studies published until February 2005 involving BIAsp 30 in people with type 2 diabetes were identified via a MEDLINE search with a total of 21 relevant studies retrieved. One study with 219 people with type 1 and type 2 diabetes reported a non significant difference in HbA1c reduction (HbA1c (mean [SEM]) -0.8% [0.1%] vs -0.6% [0.1%] for BHI 30 and BIAsp 30, p = NS). In another study with a subset of 73 people with type 2 diabetes, HbAlc at baseline, 24 months, and 48 months were 8.0%, 8.1%, and 8.0%, respectively, in the BIAsp 30 group and 7.9%, 8.0%, and 8.3% in the BHI 30 group (no statistical differences from baseline). BIAsp 30 was compared with NPH monotherapy in a 16-week, parallel-group, double-blind trial involving 403 people with type 2 diabetes. The magnitude of the

reduction from baseline HbA1c of 8.8% in both groups was 0.7% for BIAsp 30 and 0.6% for NPH insulin (not significant). BIAsp 30 was not associated with an increased risk of major hypoglycaemia compared with other insulin regimens. The incidence of minor hypoglycaemic events with BIAsp 30 varied across studies but the risk similar to BHI 30, Mix 25, or NPH.

Davidson et al (2005) evaluated the safety profile of BIAsp 30 in people with type 1 or type 2 diabetes compared with other insulins, including BHI 30 and biphasic insulin lispro 25 (Mix 25 [25% biphasic insulin lispro and 75% protaminated lispro], Humalog Mix 75/25), together with the basal insulins, including NPH insulin and insulin glargine. Articles were searched for using Medline up to February 2005 and collected from peer-reviewed journals. In all, 17 publications were analysed and included > 2,600 people with type 2 diabetes (mean [range] age, 58 [36-70] years; duration of diabetes, 11.8 [9-17] years; and baseline HbA1c, 8.6% [7.5%-9.9%]). Hypoglycaemia occurred in 43% to 57% of subjects receiving BIAsp 30 versus 32% to 57% receiving BHI 30 and 28% receiving NPH insulin. Major hypoglycaemic events were uncommon in most studies but when they did occur, they were reported less frequently in subjects receiving BIAsp 30 (2%-8% of subjects) than in those receiving BHI 30 (2%-14% of subjects). Furthermore, subjects treated with BIAsp 30 were at lower risk of experiencing minor nocturnal hypoglycaemia than those receiving comparator insulin. The adverse event profile, weight gain during treatment, and formation of antibodies were not different between BIAsp 30 and BHI 30.

Malone et al (2005) compared the glycaemic control of an insulin lispro mixture (25% insulin lispro and 75% NPL) twice daily in combination with metformin to that of once-daily insulin glargine plus metformin in 97 people with type 2 diabetes inadequately controlled with intermediate insulin, or insulin plus oral agent(s) combination therapy. Subjects were randomised in a multicentre, open-label, 32-week crossover study. HbA1c was lower with the insulin lispro mixture plus metformin compared with glargine plus metformin (7.5% ± 0.9% vs 8.1% ± 1.0%, $p < 0.001$). Change in HbA1c from baseline to endpoint was greater with the insulin lispro mixture plus metformin (-1.0% vs -0.4%; $p < 0.001$). Two-hour post-prandial BG was lower after morning, midday, and evening meals ($p < 0.001$) during treatment with the insulin lispro mixture plus metformin. The fasting BG values were lower with glargine plus metformin ($p = 0.007$). Despite lower BG at 03:00 hours ($p < 0.01$), subjects treated with the insulin lispro mixture plus metformin had a lower rate of nocturnal hypoglycaemia (0.14 ± 0.49 vs 0.34 ± 0.85 episodes/person/30 days; $p = 0.002$), although the overall hypoglycaemia rate was not different between treatments (0.61 ± 1.41 vs 0.44 ± 1.07 episodes/person/30 days; $p = 0.47$).

Ligthelm et al (2006) compared three times daily meal-time biphasic insulin aspart (BIAsp) with a four times daily basal-bolus regimen with human isophane insulin (NPH) and insulin aspart (IAsp) in a multinational, randomised, open-label parallel-group trial in 394 people with type 2 diabetes who were on a once or twice daily insulin regimen. Subjects were

randomised to BIAsp or IAsp+NPH for 16 weeks. Subjects with BMI ≤ 30 kg/m^2 administered BIAsp 30 and those with BMI > 30 kg/m^2 used BIAsp 50 with breakfast and lunch and all used BIAsp 30 with dinner. The IAsp+NPH group injected IAsp at meals and NPH at bedtime as basal insulin. Mean HbA1c (± SD) decreased from 9.1± 0.7% to 7.8 ± 1.0% with both treatments. Similar improvements in glycaemic control in both groups were confirmed by self-measured 8-point plasma glucose (PG) profiles, average and fasting PG concentrations, and average prandial PG increments.

Garber et al (2006) conducted a study in 100 people with type 2 diabetes who were failing oral agent therapy with or without basal insulin to assess whether the addition of biphasic insulin aspart 70/30 (BIAsp 30) could achieve AACE and ADA HbA1c targets of ≤ 6.5% and < 7%, respectively. Subjects were ≥ 18 years of age, had diabetes ≥ 12 months, and had HbA1c levels ≥ 7.5% and ≤ 10%. Subjects discontinued prior basal insulin and added one injection of BIAsp 30 within 15 min of dinner initiation. Subjects self-titrated their BIAsp 30 dose with investigator guidance every 3 or 4 days to achieve pre-breakfast fasting blood glucose (FBG) of 4.4–6.1 mmol/L. At 16 weeks, a pre-breakfast injection of BIAsp 30 was added if week 15 HbA1c exceeded 6.5%; the added dose was titrated to achieve pre-dinner BG of 4.4 -6.1 mmol/L. After an additional 16 weeks, pre-lunch BIAsp 30 was added if HbA1c exceeded 6.5%. This added dose was adjusted based on 2-h post-lunch BG to achieve postprandial glucose of 5.6 -7.8 mmol/L. Subjects achieving an HbA1c 6.5% at 15 and 31 weeks completed the study at weeks 16 and 32 respectively. Addition of once-daily BIAsp 30 before dinner enabled 21% to achieve AACE targets (HbA1c ≤ 6.5%) and 41% to achieve ADA targets (HbA1c < 7%). With two daily injections of BIAsp 30, these glycaemic goals were achieved by 52 and 70% of subjects. With three daily BIAsp 30 injections, 60% achieved HbA ≤ 6.5%, and 77% achieved HbA< 7.0%. Minor hypoglycaemic events were reported by most (84%) of the subjects during the study at a rate of 15.4, 22.4 and 12.0 events per patient year during once-daily, twice-daily and thrice-daily dosing respectively. Seven subjects reported major hypoglycaemic events (three during both once-daily and twice-daily dosing and one during thrice-daily dosing).

Multiple daily insulin injections and continuous subcutaneous insulin infusion

Herman et al (2005) compared the efficacy and safety of continuous subcutaneous insulin infusion (CSII) and multiple daily injection (MDI) in 107 adults (mean age 66 years, BMI 32 kg/m^2, HbA1c 8.2%) with insulin-treated type 2 diabetes. Subjects were randomised to CSII (using insulin lispro) or multiple daily injections (MDI) using insulin lispro and insulin glargine in a 12-month, prospective, randomised controlled trial. Forty-eight CSII subjects (91%) and 50 MDI subjects (93%) completed the study. Mean HbA1c fell by 1.7 ± 1.0% in the CSII group to 6.6% and by 1.6 ± 1.2% in the MDI group to 6.4% (p = 0.20). Eighty-one percent of CSII subjects and 90% of MDI subjects experienced at least one episode of minor (self-treated) hypoglycaemia (p = 0.17), and three CSII and six MDI subjects experienced severe hypoglycaemia (p = 0.5). Severe hypoglycaemic events were similarly low in the two groups (CSII 0.08 and MDI 0.23 events per person-year, p = 0.6). Weight gain did not differ

between groups ($p = 0.7$). Treatment satisfaction improved significantly with both CSII and MDI ($p < 0.0001$), and the difference between groups was not statistically significant ($p = 0.6$).

In a multicentre, open-label, randomised study, Raskin et al (2003) compared the efficacy, safety and patient satisfaction of continuous subcutaneous insulin infusion (CSII, using insulin aspart) with MDI (bolus insulin aspart and basal NPH insulin). The study included 132 people aged ≥ 35 years with type 2 diabetes, who were treated with insulin for at least 6 months, with or without an OAD. After 24 weeks of treatment, mean HbA1c decreased similarly in both groups (CSII: 8.2 ± 1.4 to 7.6 ± 1.2%; MDI: 8.0 ± 1.1 to 7.5 ± 1.2%). The eight-point blood glucose profiles were lower at most time points in the CSII group, but only significant 90 min after breakfast ($p = 0.02$). Mean weight increased slightly in both groups (CSII 96.4 ± 17.0 to 98.1 ± 18.1 kg; MDI 96.9 ± 17.9 to 97.6 ± 19.2 kg, p = NS). Hypoglycaemic episodes were reported during the study by a similar percentage (CSII 54% vs MDI 59%). The CSII group reported significantly greater improvement from baseline to endpoint in general satisfaction ($p < 0.001$), convenience ($p < 0.001$), flexibility ($p < 0.001$), and less life interference ($p < 0.001$).

Repaglinide is an option for improving glycaemic control in people with type 2 diabetes

Repaglinide is a novel short-acting oral hypoglycaemic agent structurally unrelated to the sulphonylurea drugs. It lowers blood glucose levels acutely by stimulating the release of insulin from the pancreas. Repaglinide closes ATP-dependent potassium channels in the β-cell membrane by binding to sites which are pharmacologically distinguishable from the sulphonylurea binding sites. In Australia repaglinide can be used alone or in combination with metformin or insulin.

Black and Donnelly (2007) assessed the effects of meglitinide analogues in a systematic review of people with type 2 diabetes. Searched databases included The Cochrane Library, MEDLINE and EMBASE. Randomised controlled, parallel or cross-over trials comparing at least 10 weeks of treatment with meglitinide analogues to placebo, head-to-head, metformin or in combination with insulin were included. In all, 15 trials involving 3,781 participants were included. In the 11 studies comparing repaglinide with placebo, repaglinide resulted in reductions in HbA1c of 0.1% to 2.1%. Repaglinide (248 participants in 3) had a similar HbA1c lowering as metformin. One study examined repaglinide in combination with metformin and monotherapy of each medication. In subjects receiving combined therapy, HbA1c was reduced by 1.4 ± 0.2%, from 8.3 to 6.9% ($p = 0.002$) and fasting plasma glucose by 2.2 mmol/L ($p = 0.0003$). No significant changes were observed in subjects treated with either repaglinide or metformin monotherapy in HbA1c (0.4 and 0.3% decrease, respectively) or fasting plasma glucose (0.5 mmol/L increase and 0.3 mmol/L decrease respectively). An increase in body weight occurred in the repaglinide and combined therapy groups (2.4 ± 0.5 and 3.0 ± 0.5 kg, respectively; $p < 0.05$). Another study compared repaglinide with metformin in combination with insulin. Only people taking metformin plus insulin achieved a reduction in HbA1c over the 13 week trial period (0.4% reduction). In the repaglinide plus insulin group, the mean HbA1c increased by 0.4%.

Exenatide is a new option for improving glycaemic control in people with type 2 diabetes

Exenatide is a glucagon-like peptide-1 (GLP-1) analogue which possesses similar activity naturally-occurring GLP-1, and is the first in this new class of compounds for the treatment of type 2 diabetes. Exenatide mirrors many of the effects of GLP-1 and improves glycaemic control via a number of mechanisms including glucose-dependent stimulation of insulin secretion, suppression of glucagon secretion, slowing of gastric emptying and reduced appetite. Exenatide is generally well-tolerated with nausea being the most commonly reported adverse effect, which is usually transient.

In Australia, exenatide is indicated as adjunctive therapy to improve glycaemic control in people with type 2 diabetes who are taking metformin, a sulphonylurea, or a combination of metformin and a sulphonylurea but are not achieving adequate glycaemic control.

The safety and efficacy of incretin-based therapy in adults with type 2 diabetes was examined in a meta-analysis of RCTs by Amori et al (2007). MEDLINE (1966–May 20, 2007) and the Cochrane Central Register of Controlled Trials was searched for randomised controlled trials involving an incretin mimetic (glucagon-like peptide 1 [GLP-1] analogue) or enhancer (dipeptidyl peptidase 4 [DPP4] inhibitor). Selected trials ranged from 12 to 52 weeks duration, compared incretin therapy with placebo or other diabetes medication, and reported HbA1c data in non-pregnant adults with type 2 diabetes. In all, 29 reports met the inclusion criteria. Incretins lowered HbA1c compared with placebo (weighted mean difference, −1.0% [CI, −1.1% to −0.8%] for GLP-1 analogues and −0.7% [CI, −0.9% to −0.6%] for DPP-4 inhibitors) and were non-inferior to other hypoglycaemic agents. In contrast with nearly all available hypoglycaemic agents that cause weight gain, glucagon-like peptide 1 analogues resulted in moderate and continuous weight loss (1.4 kg and 4.8 kg vs placebo and insulin, respectively) while DPP4 inhibitors were weight neutral. Glucagon-like peptide 1 analogues had more gastrointestinal side effects (risk ratio, 2.9 [CI, 2.0-4.2] for nausea and 3.2 [CI, 2.5-4.4] for vomiting). In three of the studies, exenatide significantly improved a number of cardiovascular risk factors. In those who lost the most weight, the greatest improvements were achieved in triglycerides, HDL-C, and blood pressure. All but 3 trials had a 30-week or shorter duration; thus, long-term efficacy and safety could not be evaluated.

Ratner et al (2006) conducted an interim 82 week analysis (total cohort = 150) of an eligible population of 183 who opted to continue exenatide treatment in an open-label extension of a previous 30-week RCT (DeFronzo et al., 2005). In all, 92 subjects achieved 82 weeks of exenatide therapy while continuing metformin throughout the study. Reductions in HbA1c were sustained after 82 weeks with changes from baseline of -1.3 ± 0.1%. The percent who achieved HbA1c ≤ 7% at weeks 30 and 82 was 46 and 59% respectively. Exenatide caused a reduction in weight from baseline of -3.0 ± 0.6 kg at 30 weeks, with a progressive reduction in weight of -5.3 ± 0.8 kg after 82 weeks. In addition, exenatide treatment produced clinically

significant improvements in cardiovascular risk factors after 82 weeks. The most frequent adverse event after 30 and 82 weeks of exenatide was nausea, which was generally of mild-or-moderate intensity. Hypoglycaemia was rare, with no severe events.

Riddle et al (2006) and Blonde et al (2006) followed up two initial 30 week RCTs (Buse et al., 2004; Kendall et al., 2005) in the context of exenatide with sulphonylurea or sulphonylurea plus metformin as background treatment in a 52-week open-label, uncontrolled extension study in which all subjects received 10 μg exenatide twice daily and prior oral therapies. Reduction in HbA1c from baseline were sustained up to week 82 (-1.0 ± 0.1%). Of 207 subjects with baseline HbA1c > 7%, 44% achieved HbA1c ≤ 7% at week 82. Reduction of body weight was progressive up to week 82 (-4.0 ± 0.3 kg). The most frequent adverse events were nausea and hypoglycaemia, both generally mild to moderate in intensity. Blonde et al (2006) also followed up the same previous two studies to examine the effect of exenatide on glycaemic control cardiovascular risk factors over an 82-week period. Reduction in HbA1c from baseline to week 30 [–0.9 ± 0.1% (mean ± SE)] was sustained to week 82 (–1.1 ± 0.1%), with 48% of subjects achieving HbA1c ≤ 7% at week 82. At week 30, exenatide reduced body weight from baseline (–2.1 ± 0.2 kg), with progressive reduction at week 82 (–4.4 ± 0.3 kg). Similar results were observed for the intent-to-treat population (n = 551), with reductions in HbA1c and weight at week 82 of –0.8 ± 0.1% and –3.5 ± 0.2 kg respectively.

In a follow-up study to examine the effects of exenatide use of ≥ 3 years, Klonoff et al (2008) evaluated people from three previous placebo-controlled trials (Buse et al., 2004; DeFronzo et al., 2005; Kendall et al., 2005). Subjects from the studies were enrolled into one open-ended, open-label clinical trial and were randomised to twice daily (BID) placebo, 5 μg exenatide, or 10 μg exenatide for 30 weeks, followed by 5 μg exenatide BID for 4 weeks, then 10 μg exenatide BID for ≥ 3 years. Participants also continued metformin and/or sulphonylureas. In all, 217 people (64% male, age 58 ± 10 years, BMI 34 ± 5 kg/m^2, HbA1c 8.2 ± 1.0% [mean ± SD] completed 3 years of exenatide exposure. HbA1c levels from baseline to week 12 (-1.1 ± 0.1% [mean ± SEM]) were sustained to 3 years (-1.1 ± 0.1%, $p < 0.0001$) with 46% achieving HbA1c ≤ 7%. In addition, exenatide reduced body weight from baseline (-5.3 ± 0.4 kg at 3 years, $p < 0.0001$). A subset achieved 3.5 years of exenatide exposure and had serum lipids available for analysis (n = 151). Triglycerides decreased 12% ($p = 0.0003$), total cholesterol decreased 5% ($p = 0.0007$), LDL-C decreased 6% ($p < 0.0001$), and HDL-C increased 24% ($p < 0.0001$). Exenatide was generally well-tolerated. The most frequent adverse event was mild-to-moderate nausea.

Barnett et al (2007) conducted a multinational, randomised, open-label, crossover non-inferiority study comparing the safety and efficacy of exenatide 10 pg twice daily and insulin glargine once daily (titrated targeting a fasting serum glucose (FSG) level ≤ 5.6 mmol/L) in people with type 2 diabetes who had not achieved glucose control with metformin or sulphonylurea monotherapy. The study included two 16-week treatment periods. Subjects

were randomised (n = 138) to study treatment (mean [SEM] age: 54.9 [0.8] years; duration of diabetes, 7.4 [0.4] years; body mass index, 31.1 [0.4] kg/m^2; weight, 84.8 [1.4] kg) while continuing to receive metformin (55.1%) or a sulphonylurea (44.9%). Mean HbA1c was 9%. Both exenatide and insulin glargine therapy were associated with similar significant changes from baseline in HbA1c (both, -1.4% [0.1%]; $p < 0.001$). The difference between groups was not statistically significant. Mean HbA1c at end point was above the ADA target with both treatments (exenatide: 7.6%; insulin glargine: 7.6%). Similar proportions of subjects achieved an HbA1c $\leq$ 7% (37.5% and 39.8%, respectively) or $\leq$ 6.5% (21.5% and 13.6%). Subjects lost weight during exenatide treatment, whereas they gained weight during insulin glargine treatment; the between-group difference in weight change was statistically significant (mean difference, -2.2 kg; CI, -2.8 to -1.7; $p < 0.001$). Both exenatide and insulin glargine were associated with significant reductions from baseline in fasting glucose (-2.9 [0.2] and -4.1 [0.2] mmol/L, respectively; both, $p < 0.001$), although the reduction was significantly greater with insulin glargine compared with exenatide. Compared with insulin glargine, exenatide was associated with significantly lower 2-hour postprandial glucose (PPG) excursions ($p < 0.016$) and total daily mean glucose excursion ($p < 0.001$). The proportions of subjects reporting nausea during exenatide and insulin glargine treatment were 42.6% and 3.1%, respectively; the proportions reporting vomiting were 9.6% and 3.1%. The incidence of hypoglycaemia in the 2 groups was 14.7% and 25.2%.

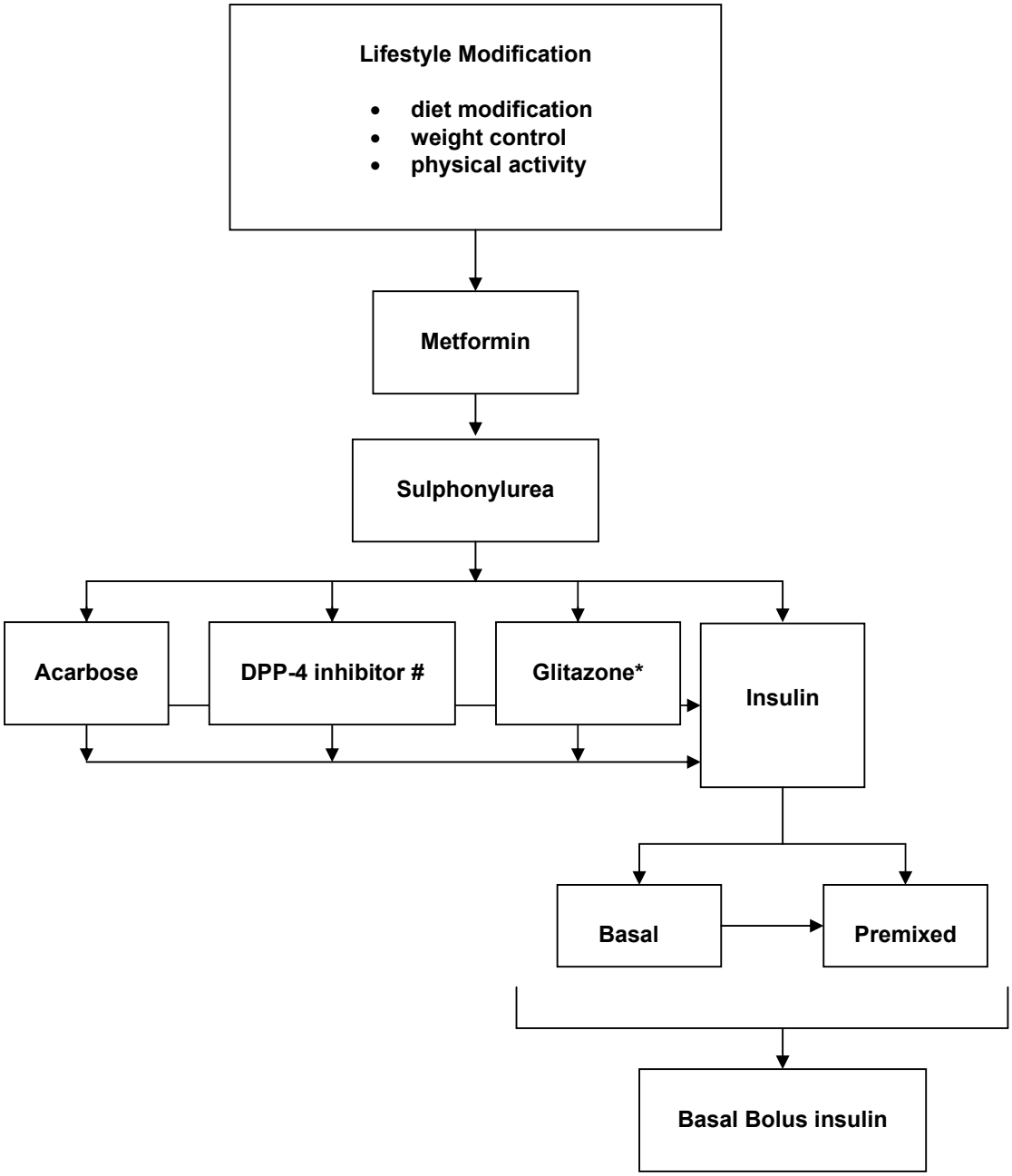
Management Algorithm for Blood Glucose Control in Type 2 Diabetes

The following flow chart summarises the management algorithm for people with type 2 diabetes using only therapeutic agents available through the PBS. If HbA1c remains above 7% after a 3-month period, intensification of treatment should be considered provided hypoglycaemia is not a concern.

This algorithm commences with a trial of lifestyle intervention (diet modification and increased physical activity) before considering metformin therapy. This recommendation is in agreement with the recommendation of the UK NICE type 2 diabetes guidelines (NICE, 2008), the Canadian diabetes guidelines (Canadian Diabetes Association, 2008) and the International Diabetes Federation Global Guideline for Type 2 Diabetes (IDF, 2005). The recent consensus statement of the ADA and EASD (Nathan et al, 2009) acknowledged that lifestyle interventions should be initiated as the first step in treating new-onset type 2 diabetes. However, the authors were of the view that most individuals with type 2 diabetes failed to achieve or maintain metabolic goals on lifestyle interventions, and therefore reached a consensus that metformin therapy should be initiated concurrently with lifestyle intervention at diagnosis. The Expert Advisory Group which oversaw the preparation of this Australian guideline considered this information and was of the opinion that a period of lifestyle modification was justified before initiating pharmacotherapy.

In people with type 2 diabetes, if glycaemic targets are not achieved using lifestyle management within 2 to 3 months, antihyperglycaemic agents should be initiated.

Management algorithm for blood glucose control in type 2 diabetes



- The algorithm includes only therapeutic agents available through the PBS.
- If HbA1c >7% consider intensifying treatment provided hypoglycaemia is not a problem.

Authorised only as dual therapy with metformin or sulphonylurea where combination metformin and sulphonylurea is contraindicated or not tolerated.

* Rosiglitazone is not authorised for triple therapy or for use with insulin (from February 1, 2009) but is approved only as dual therapy with metformin or sulphonylurea where combination metformin and sulphonylurea is contraindicated or not tolerated.

Evidence Table: Lifestyle modification (diet and physical activity) is an integral component of diabetes care

Author (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of Effect*	*Relevance Rating*
	Level	*Study Type*			
Barnard et al., 2006	II	RCT	High	High^{+}	High
Belcher et al., 2005	I	Systematic review	High	Medium^{+}	High
Ben et al., 1991 (Italy)	II	RCT	Medium	High^{+}	High
Bolen et al., 2007	I	Systematic review	High	Medium^{+}	High
Boule et al., 2001	I	Systematic review	High	High^{+}	High
Boule et al., 2003	I	Systematic review	High	High^{+}	High
Brand-Miller et al., 2003	I	Systematic review	High	High^{+}	High
Brinkworth et al., 2004 (Australia)	II	RCT	High	High^{+}	High
Brown et al., 1996	I	Systematic review	High	High^{+}	High
Daly et al., 2006 (UK)	II	RCT	High	High^{+}	High
DiLoreto et al., 2005	II	RCT	High	High^{+}	High
Dunstan et al., 1997	II	RCT	High	High^{+}	High
Gordon et al., 2008	I	Systematic review	High	High^{+}	High
Hartweg et al., 2008	I	Systematic review	High	Low^{-}	High
Kavookjian et al., 2007	I	Systematic review	High	High^{+}	High
Kirk et al., 2008	I	Systematic review	High	High^{+}	High
Lindgarde, 2000 (Sweden)	II	RCT	High	High^{+}	High
Look AHEAD Research Group, 2007	II	RCT	High	High^{+}	High
Mokdad et al., 2000	IV	Cross-sectional	Medium	High^{+}	Low
Nield et al., 2007	I	Systematic review	High	Medium^{+}	High
Norris et al., 2004	I	Systematic review	High	Medium^{+}	High
Parker et al., 2002 (Australia)	II	RCT	High	High^{+}	High
Pedersen et al., 2007	II	RCT	High	Low^{-}	High
Redmon et al., 2005	II	RCT	High	High^{+}	High

Rowe et al., 2005	III-2	Prospective cohort	High	High[+]	High
Ruof et al., 2005	I	Systematic review	High	High[+]	High
Sigal et al., 2007 (Canada)	II	RCT	High	High[+]	High
Snowling and Hopkins, 2006	I	Systematic review	High	Low[+]	High
Thomas et al., 2006	I	Systematic review	High	High[+]	High
van de Laar et al., 2007	I	Systematic review	High	High[+]	High
Vettor et al., 2005	I	Systematic review	High	High[+]	High

[+] Lifestyle modification is an integral component of diabetes care.

Clinical importance rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

Evidence Table: Weight control is an important component of diabetes care

Author (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of Effect*	*Relevance Rating*
	Level	*Study Type*			
Bolen et al., 2007	I	Systematic review	High	Medium^{+}	High
Lindgarde, 2000 (Sweden)	II	RCT	High	High^{+}	High
Look AHEAD Research Group, 2007	II	RCT	High	High^{+}	High
Mokdad et al., 2000	IV	Cross-sectional	Medium	High^{+}	Low
Norris et al., 2005a	I	Systematic review	High	Medium^{+}	High
Norris et al., 2005b	I	Systematic review	High	High^{+}	High
Pedersen et al., 2007	II	RCT	High	Low^{-}	High
Redmon et al., 2005	II	RCT	High	High^{+}	High
Rowe et al., 2005	III-2	Prospective cohort	High	High^{+}	High
Ruof et al., 2005	I	Systematic review	High	High^{+}	High
Vettor et al., 2005	I	Systematic review	High	High^{+}	High
Wing et al., 1991 (USA)	II	RCT	Low	Medium^{+}	Medium

$^{+}$ Weight control is an important component of diabetes care.
Clinical importance rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

Evidence Table: Metformin is a widely used, safe and effective therapy for type 2 diabetes

Author (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of Effect*	*Relevance Rating*
	Level	*Study Type*			
Campbell and Howlett, 1995	I	Systematic review	High	Low[+]	High
Charbonel et al., 2006	II	RCT	High	High[+]	High
Charbonel et al., 2005	II	RCT	Medium	Low[+]	Medium
Comaschi et al., 2007	II	RCT	High	Low[+]	High
DeFronzo and Goodman, 1995	II	RCT	High	High[+]	High
Garber et al., 2006	II	RCT	High	High[+]	High
Hallsten et al., 2002	II	RCT	Low	High[+]	Medium
Hermann et al., 1994	II	RCT	High	High[+]	High
Horton et al., 2000	II	RCT	High	High[+]	High
Johansen, 1999	I	Systematic review	High	Medium[+]	High
Matthews et al., 2005	II	RCT	High	Low[+]	High
Monami et al., 2008	I	Systematic review	High	Medium[+]	High
Nauck et al., 2007 (Germany)	II	RCT	High	Low[+]	High
Raz et al., 2008 (Israeal)	II	RCT	High	High[+]	High
Saenz et al., 2005	I	Systematic review	High	High[+]	High
Schwartz et al., 2006	II	RCT	High	High[+]	High
Teupe and Bergis, 1991	III-2	Prospective cohort	Low	Low[+]	Medium
UKPDS Study Group 34, 1998	II	RCT	High	Low[+]	High
Umpierrez et al., 2006	II	RCT	High	High[+]	High
Wulffele et al., 2004	I	Systematic review	High	High[+]	High

[+] Metformin is a widely used, safe and effective therapy for type 2 diabetes.

Clinical importance rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

Evidence Table: Lactic acidosis is rare in people with type 2 diabetes treated with metformin

Author (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of Effect*	*Relevance Rating*
	Level	*Study Type*			
Kamber et al., 2008	III-2	Prospective cohort	High	Medium^{-}	High
Salpeter et al., 2006	I	Systematic review	High	High^{+}	High
Sambol et al., 1995	III-2	Prospective cohort	Medium	High^{+}	High
Sirtori et al., 1978	III-2	Prospective cohort	Medium	High^{+}	High
Tahrani et al., 2007	I	Systematic review	High	High^{+}	High

$^{+}$ Lactic acidosis is rare in people with type 2 diabetes treated with metformin.

Clinical importance rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

Evidence Table: Sulphonlyureas, used as monotherapy or combination therapy, are safe and effective for type 2 diabetes

Author (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of Effect*	*Relevance Rating*
	Level	*Study Type*			
ADVANCE Collaborative Group, 2008	II	RCT	High	High[+]	High
Baksi et al., 2004 (UK)	II	RCT	High	High[+]	High
Campbell and Howlett, 1995	I	Systematic review	High	High[+]	High
Davidson et al., 2007	II	RCT	High	High[+]	Medium
Derosa et al., 2005	II	RCT	High	Low[+]	High
Diamicron MR Study Group, 2000	II	RCT	High	High[+]	High
Hanefeld et al., 2004	II	RCT	High	Low[+]	High
Kerenyi et al., 2004	II	RCT	High	High[+]	High
Roberts et al., 2005	II	RCT	High	High[+]	High
Rosenstock et al., 2006	II	RCT	High	High[+]	High
Schade et al., 1998	II	RCT	High	High[+]	High
Schernthaner et al., 2004	II	RCT	High	Low[+]	High
Vongthavaravat et al., 2002	II	RCT	High	High[+]	High
Weitgasser et al., 2003	III-2	Prospective cohort	High	High[+]	High

[+] Sulphonlyureas, used as monotherapy or combination therapy, are safe and effective for type 2 diabetes.

Clinical importance rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

Evidence Table: Thiazolidinediones are a useful agent for improving glycaemic control when used as add-on therapy to other anti-diabetic medications

Author (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of Effect*	*Relevance Rating*
	Level	*Study Type*			
Bailey et al., 2005 (UK)	II	RCT	High	High[+]	High
Belcher et al., 2005	I	Systematic review	High	Medium[+]	High
Dailey et al., 2004 (USA)	II	RCT	High	High[+]	High
Davidson et al., 2006	II	RCT	High	High[+]	High
Hollander et al., 2007	II	RCT	High	High[+]	High
Home et al., 2007 (Home)	II	RCT	High	High[+]	High
Jones et al., 2003	I	Systematic review	High	High[+]	High
Mattoo et al., 2005	II	RCT	High	High[+]	High
Noble et al., 2005	I	Systematic review	High	High[+]	High
Richter et al., 2006	I	Systematic review	High	High[+]	High
Richter et al., 2007	I	Systematic review	High	High[+]	High
Seufert and Urquart, 2008	II	RCT	High	Low[+]	High
Stewart et al., 2006	II	RCT	High	High[+]	High

[+] Thiazolidinediones are a useful agent for improving glycaemic control when used as add-on therapy to other anti-diabetic agents.

Clinical importance rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

Evidence Table: Thiazolidinediones are associated with increased risk of heart failure, oedema and fractures

Author (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of Effect*	*Relevance Rating*
	Level	*Study Type*			
Berlie et al., 2007	I	Systematic review	High	High^{+}	High
Eurich et al., 2007	I	Systematic review	High	Medium$^{+/-}$	High
Holman et al., 2009 (UK)	II	RCT	High	High^{+}	High
Kahn et al., 2008	IV	Cross-sectional	High	Medium^{-}	High
Lago et al., 2007	I	Systematic review	High	High^{+}	High
Meier et al., 2008	III-2	Case-control	High	High^{+}	High
Singh et al., 2007	I	Systematic review	High	High^{+}	High

$^{+}$ Thiazolidinediones are associated with increased risk of heart failure, oedema and fractures.

Clinical importance rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect
0

Evidence Table: Some reports suggest an increased risk of cardiovascular events and death with some anti-diabetic medications and combinations

Author (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of Effect*	*Relevance Rating*
	Level	*Study Type*			
ACCORD Study Group, 2008 (USA)	II	RCT	High	High^{-}	High
ADVANCE Collaborative Group, 2008	II	RCT	High	High^{-}	High
Hanefeld et al., 2004	I	Systematic review	High	High^{-}	High
Holman et al., 2009 (UK)	II	RCT	High	High^{-}	High
Kahn et al., 2006 (USA)	II	RCT	High	High^{-}	High
Lincoff et al., 2007	I	Systematic review	High	High^{+}	High
Nissen et al., 2007	I	Systematic review	High	High^{+}	High
Rao et al., 2008	I	Systematic review	High	Low^{+}	High
Simpson et al., 2006	III-2	Retrospective cohort	High	High^{-}	High
Singh et al., 2007	I	Systematic review	High	High^{+}	High
UKPDS Study Group 34, 1998	II	RCT	High	High^{+}	High

$^{+}$ Cardiovascular events and death with some anti-diabetic medications.

Clinical importance rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

0Evidence Table: Acarbose is an option for improving glycaemic control in people with type 2 diabetes

Author (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of Effect*	*Relevance Rating*
	Level	*Study Type*			
Bachmann et al., 2003	II	RCT	High	High^{+}	High
Feinbock et al., 2003	II	RCT	High	High^{-}	High
Neuser et al., 2005	II	RCT	High	High^{+}	High
Schnell et al., 2007	II	RCT	High	High^{+}	High
van de Laar., 2005	I	Systematic review	High	High^{+}	High

$^{+}$ Acarbose is an option for improving glycaemic control in people with type 2 diabetes.

Clinical importance rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

Evidence Table: DPP-4 inhibitors are a new option for improving glycaemic control in people with type 2 diabetes as an add-on therapy

Author (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of Effect*	*Relevance Rating*
	Level	*Study Type*			
Amori et al., 2007	I	Systematic review	High	High[+]	High
Goldstein et al., 2007	II	RCT	High	High[+]	High
Hermansen et al., 2007	II	RCT	High	High[+]	High
Raz et al., 2008 (Israel)	II	RCT	High	High[+]	High

[+] DPP-4 inhibitors are a new option for improving glycaemic control in people with type 2 diabetes as an add-on therapy

Clinical importance rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

Evidence Table: Insulin is frequently required for glycaemic control in people with type 2 diabetes and can be initiated as basal therapy or as premixed insulins, usually in combination with oral anti-diabetic medications

Author (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of Effect*	*Relevance Rating*
	Level	*Study Type*			
Bazzano et al., 2008	I	Systematic review	High	High^{+}	High
Boehm et al., 2004	II	RCT	High	High^{+}	High
Campbell et al., 2001	I	Systematic review	High	Low^{+}	High
Davidson et al., 2005	I	Systematic review	High	Medium^{+}	High
Davies et al., 2005	II	RCT	High	High^{+}	High
Douek et al., 2005	II	RCT	High	High^{+}	High
Duckworth et al., 2007	I	Systematic review	High	Low^{+}	High
Garber et al., 2007	II	RCT	High	Medium^{+}	High
Garber et al., 2006	II	RCT	High	Medium^{+}	High
Gerstein et al., 2006	II	RCT	High	High^{+}	High
Goudswaard et al., 2004	I	Systematic review	High	High^{+}	High
Halimi et al., 2005	I	Systematic review	High	High^{+}	High
Herman et al., 2005	II	RCT	High	Low^{+}	High
Ilag et al., 2007	I	Systematic review	High	High^{+}	High
Janka et al., 2005	II	RCT	High	High^{+}	High
Janka et al., 2007	II	RCT	High	High^{+}	High
Johnson et al., 1996	I	Systematic review	High	High^{+}	High
Landstedt-Hallin et al., 1999	II	RCT	High	High^{+}	High
Liebl et al., 2008	II	RCT	High	High^{+}	High
Ligthelm et al., 2006	II	RCT	High	Low^{+}	High
Malone et al., 2005	II	RCT	High	High^{+}	High
Monami et al., 2008	I	Systematic review	High	Medium^{+}	High
Mullins et al., 2007	IV	Cross-sectional	High	Medium^{+}	Medium
Nelson and Palumbo, 2006	I	Systematic review	High	High^{+}	High

Peters and Davidson, 1991	I	Systematic review	High	High[+]	High
Philis-Tsimikas., 2006	II	RCT	High	Medium[+]	High
Pugh et al., 1992	I	Systematic review	High	High[+]	High
Qayyum et al., 2008	I	Systematic review	High	High[+]	High
Raskin et al., 2003	II	RCT	High	Low[+]	High
Raslova et al., 2007	II	RCT	High	High[+]	High
Roach et al., 2001	II	RCT	High	High[+]	High
Rosenstock et al., 2005	I	Systematic review	High	High[+]	High
Rosenstock et al., 2006	II	RCT	High	Medium[+]	High
Schwartz et al., 2003	II	RCT	High	Low[+]	High
Standl et al., 2006	II	RCT	High	Low[+]	High
Stehouwer et al., 2003	II	RCT	High	High[+]	High
Wolffenbuttel et al., 1996	II	RCT	High	Low[+]	High
Wright et al., 2002	II	RCT	High	High[+]	High
Yki-Jarvinen et al., 1997	II	RCT	High	High[+]	High
Yki-Jarvinen et al., 1999	II	RCT	High	High[+]	High

[+] Insulin is frequently required for glycaemic control in people with type 2 diabetes and can be initiated as basal therapy or as premixed insulins, usually in combination with oral anti-diabetic medications.

Clinical importance rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

Evidence Table: Repaglinide is an option for improving glycaemic control in people with type 2 diabetes

Author (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of Effect*	*Relevance Rating*
	Level	*Study Type*			
Black and Donnelly, 2007	I	Systematic review	High	High[+]	High

[+] Repaglinide is an option for improving glycaemic control in people with type 2 diabetes

Clinical importance rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

Evidence Table: Exenatide is a new option for improving glycaemic control in people with type 2 diabetes as an add-on therapy

Author (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of Effect*	*Relevance Rating*
	Level	*Study Type*			
Amori et al., 2007	I	Systematic review	High	High[+]	High
Barnett et al., 2007	II	RCT	High	Low[+]	High
Blonde et al., 2006	II	RCT	High	High[+]	High
Buse et al., 2004	II	RCT	High	High[+]	High
DeFronzo et al., 2005	II	RCT	High	High[+]	High
Kendall et al., 2005	II	RCT	High	High[+]	High
Klonoff et al., 2005	II	RCT	High	High[+]	High
Ratner et al., 2006	II	RCT	High	High[+]	High
Riddle et al., 2006	II	RCT	High	High[+]	High

[+] Exenatide is a new option for improving glycaemic control in people with type 2 diabetes as an add-on therapy.

Clinical importance rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

Section 6: Blood Glucose Control

Question

What are the economic consequences of and socio-economic influences on blood glucose control?

Recommendation

Routine care of people with type 2 diabetes should address disparities associated with socioeconomic status and ethnicity. (Grade C)

Practice Point

Disparities in diabetes control may require additional efforts to improve accessibility of services.

Evidence Statements

- Type 2 diabetes is a costly condition
  Level of Evidence III

- Improving blood glucose control in type 2 diabetes is cost-effective
  Level of Evidence II

- There are disparities in diabetes care and control, especially between advantaged and disadvantaged groups
  Level of Evidence I

Background – Economic and socioeconomic influences on blood glucose control

Evidence about economic and socioeconomic influences on diabetes are important for improving care and organising appropriate health services for people with diabetes. About 1 million Australians have diabetes, and although complications can be avoided, delayed or improved, if diabetes is poorly controlled, the resultant complications (micro and macrovascular disease) can be devastating to the person with diabetes and their families and costly to the community. In Australia, the DiabCo$t study found the average annual costs for each person with type 2 diabetes to be $5,360 which translated into an annual cost of $2.2 billion, and $3.1 billion if carers costs are included. An additional Commonwealth benefit of approximately $5,540 is also paid to people with type 2 diabetes which further increases costs to $6 billion a year (Colagiuri et al, 2003).

In addition quality of life is affected in people with type 2 diabetes, especially those with complications. Also disparities in the quality of diabetes care and outcomes are well documented in disadvantaged groups who are less likely to receive the recommended standards of diabetes care.

Cost-effectiveness ratios which are considered to represent value for money to a health system vary according to country resources and willingness to pay. In the US, consensus indicates that interventions having cost-effectiveness ratios of less than US$20,000 per quality adjusted life year (QALY) gained should be readily adopted, those having ratios between US$20,000 and US$100,000 per QALY are usually provided, and those with ratios than US$100,000 per QALY have weak evidence for adoption (Engelgau et al, 2000). Since its inception in 1999, the National Institute for Health and Clinical Excellence (NICE) has adopted a cost effectiveness threshold range of £20,000 to £30,000 per QALY gained. Recently, Australian published cost-effectiveness ratios were analysed via a comprehensive literature review of 245 reports (Dalziel et al., 2008). The median cost-effectiveness ratio was A$18,100 per QALY/DALY/LY (quality adjusted life year gained or, disability adjusted life year, averted or life year gained). Some modalities tended to perform worse, such as diagnostics (median cost/QALY $68,000), than others such as allied health, lifestyle, and in-patient interventions (median cost/QALY/DALY/LY all at ~A$9,000). Interventions addressing diabetes and impaired glucose tolerance tended to perform well (median cost/QALY/DALY/LY < A$3,700).

This section reviews the costs, cost-effectiveness and socio-economic aspects of blood glucose control in people with type 2 diabetes. With respect to economic considerations, only general comparisons are reviewed and not studies which have reported on specific therapeutic medications.

Evidence – economic consequences

Type 2 diabetes is a costly condition

Diabetes and its related complications incur considerable health care costs placing a large burden on health care systems in terms of hospital expense, aged care, medication, diagnostic services, and other out-of-hospital diagnostic and medical services. People with diabetes are more likely to use health services and for longer periods of time than those without diabetes, particularly when complications are present (Ramsey et al., 2002). There are four broad categories of diabetes-related costs:

- Direct health care costs including hospital treatment, mediction, GP visits, allied health and specialist care, diagnostic services and medical research
- Direct non-health care costs including transport to and from medical services, child care, and home care
- Indirect costs including lost productivity, lost income, disability, and lost years of life
- Intangible costs such as the impact on quality of life

Recurrent health expenditure data from the AIHW Disease Expenditure Database showed that between 2004 and 2005, the direct health-care expenditure on diabetes was $907 million (of which type 2 diabetes accounted for 81% at $733 million), accounting for 1.7% of the total allocatable recurrent health expenditure for that year (Australian Institute of Health and Welfare, 2008). The costs were broken down as follows: hospital services $379 million (42%), diabetes-related pharmaceuticals $273 million (30%), out-of-hospital medical services $200 million (22%), and research $55 million (6%). These figures almost certainly underestimate the true cost of diabetes to society in Australia. The DiabCo$t study reported that the average total (direct plus indirect) health costs for an individual with type 2 diabetes was $5360 per year and demonstrated clearly that complications accounted for the majority of costs associated with diabetes (Colagiuri et al., 2003). The costs per year for individuals with both macrovascular and microvascular complications was on average 2.4 times higher than for those with no complications ($9625 vs $4020). Based on a diabetes prevalence of 7.4%, the total annual cost for people with type 2 diabetes in Australia was estimated to be $2.2 billion, and if the cost of carers is included this figure rises to $3.1 billion. In addition, people with type 2 diabetes receive $5,540 per year on average in Commonwealth benefits, increasing the total annual cost of diabetes to $6 billion.

The direct medical costs associated with type 2 diabetes, as well as its treatments, complications, and co-morbidities, were described in a random sample of 1,364 subjects with

type 2 diabetes who were members of a Michigan health maintenance organisation (Brandle et al., 2003). Demographic characteristics, duration of diabetes, diabetes treatments, glycaemic control, complications, and co-morbidities were assessed by surveys and medical chart reviews. Annual resource utilisation and costs were assessed using health insurance claims. The median annual direct medical costs for subjects with diet-controlled type 2 diabetes, BMI 30 kg/m^2, and no microvascular, neuropathic, or cardiovascular complications were US$1,700 for white men and US$2,100 for white women. A 10 kg/m^2 increase in BMI, treatment with oral anti-diabetic or antihypertensive agents, diabetic kidney disease, cerebrovascular disease, and peripheral vascular disease were each associated with a 10–30% increase in cost. Insulin treatment, angina, and myocardial infarction were each associated with 60-90% increase in cost while dialysis was associated with an 11-fold increase in cost.

In an American study (Brown et al., 1999) incremental costs (costs caused by the diagnosis of diabetes) were isolated by subtracting the costs of individually matched health maintenance organisation (HMO) members without diabetes from costs of members with diabetes. The economic burden of diabetes was immediately apparent from the time of diagnosis. In year 1, total medical costs were 2.1 times higher for people with diabetes compared with those without diabetes. Diabetes-associated incremental costs (type 2 diabetes costs minus matched costs for people without diabetes) averaged US$2,257 per person with type 2 diabetes per year during the first 8 post-diagnostic years. People with type 2 diabetes incurred substantially higher costs than matched non-diabetic people for the first 8 years following diabetes diagnosis, but those high costs remained largely flat.

Oglesby et al (2006) quantified the association between direct medical costs attributable to type 2 diabetes and level of glycaemic control in a longitudinal analysis using a large health plan administrative database. In all, 10,780 individuals were included in the analyses. People were stratified into groups of good (n = 6,069), fair (n = 3,586) and poor (n = 1,125) glycaemic control based on mean HbA1c values across the study period. Suboptimal control (defined as fair or poor) was found in those treated with oral anti-diaetic agents (42.1%), with oral anti-diabetic agents and insulin (66.1%), and those treated with insulin alone (57.2%) throughout the study period (average duration of follow-up was 2.95 years). Results show that direct medical costs attributable to type 2 diabetes were 16% lower for individuals with good glycaemic control than for those with fair control (US$1,505 vs US$1,801, $p < 0.05$), and 20% lower for those with good glycaemic control than for those with poor control (US$1,505 vs US$1,871, $p < 0.05$). Prescription drug costs were also significantly lower for individuals with good glycaemic control compared with those with fair (US$377 vs US$465, $p < 0.05$) or poor control (US$377 vs US$423, $p < 0.05$).

To estimate Australian health care costs in the first year of occurrence and in subsequent years for major diabetes-related complications, Clarke et al (2008) used administrative information on hospital services and primary health care services financed through Medicare. There were data available for 70,340 people with diabetes in Western Australia (mean

duration = 4.5 years follow-up). For a male aged 60 years, the event costs in the year of the first occurrence ranged from $8,126 (CI 5,678–11,829) for blindness to $27,820 (CI 22,136–33,283) for renal failure. Other costs included amputation $20,416 (CI 18,670–22,411); nonfatal myocardial infarction (MI) $11,660 (CI 10,931–12,450); nonfatal stroke $14,012 (CI 12,849–15,183); ischaemic heart disease $12,577 (CI 12,026–13,123); heart failure $15,530 (CI 13,965–17,009); renal failure $28,661 (CI 22,989–34,202); and chronic leg ulcer $15,413 (CI 13,089–18,123). The costs in subsequent years for a man aged 60 years ranged from 14% for nonfatal MI to 106% for renal failure, of event costs.

Using data from 5,102 people in the UKPDS, Clarke et al (2003) developed a model for estimating immediate and long-term health care costs associated with seven diabetes-related complications. Using a multiple linear regression analysis, in-patient and out-patient costs were estimated based on costs calculated from the length of admission multiplied by the average specialty cost and a survey of 3,488 UKPDS subjects' health care usage conducted from 1996–1997. The estimate of the cost of first complications according to the model were as follows: amputation £8459 (CI £5295, £13 200); non-fatal myocardial infarction £4070 (CI £3580, £4722); fatal myocardial infarction £1152 (CI £941, £1396); fatal stroke £3383 (CI £1935, £5431); non-fatal stroke £2367 (CI £1599, £3274); ischaemic heart disease £1959 (CI £1467, £2541); heart failure £2221 (CI £1690, £2896); cataract extraction £1553 (CI £1320, £1855); and blindness in one eye £872 (CI £526, £1299). The annual average in-patient cost of events in subsequent years ranged from £631 (CI £403, £896) for heart failure to £105 (CI £80, £142) for cataract extraction. Non-in-patient costs for macrovascular complications were £315 (CI £247, £394) and for microvascular complications were £273 (CI £215, £343) in the year of the event. In each subsequent year the costs were, respectively, £258 (CI £228, £297) and £204 (CI £181, £255).

Stephens et al (2006) conducted a systematic literature review (January 2000-November 2005) focused on the economic and resource utilisation burden on the impact of anti-diabetic medications and glycaemic control on the overall costs of care for people with type 1 and type 2 diabetes in US managed care organisations (MCOs). The pharmacy component accounts for approximately 20% to 30% (full range, 10%–65%) of overall costs for MCO people with diabetes. About 30% of pharmacy expenses are directly related to glycaemic control, while the balance is spent on the management of macrovascular and microvascular complications related to diabetes and other common comorbidities such as hypertension and hyperlipidaemia. Cost offsets and/or cost savings have been shown with the initiation of insulin therapy, including the use of newer short-acting insulins. Increasing medication possession ratios for anti-diabetic medications (including insulins) are correlated with reduced overall health care costs, particularly reductions in hospitalisation rates. Subjects with diagnosed diabetes not receiving medications have significantly increased health care resource utilisation. The literature (eight studies) suggested that improving glycaemic control and anti-diabetic medication persistence reduced overall medical costs for people with diabetes in managed care plans. Appropriate use of anti-diabetic medications, including

medication compliance, is an important component in a strategy to achieve glycaemic control which may improve outcomes for people with diabetes.

A retrospective database analysis using eligibility data, medical and pharmacy claims data, and laboratory data from a large US health care organisation determined whether people with type 2 diabetes at or below the target HbA1c level of 7% had lower diabetes-related costs compared with people above an HbA1c level of 7% (Shetty et al., 2005). Subjects were included in the study if they had 2 or more claims for type 2 diabetes and at least one HbA1c value during the 12-month period from January 1, 2002, through December 31, 2002. Subjects with 2 or more medical claims for type 1 diabetes were excluded. Demographic, clinical, and cost variables were extracted from the administrative database. Multiple linear regression analysis was used to compare treatment costs between subjects at target HbA1c and those above target. A total of 3,121 people (46.0%) were identified as being at the target HbA1c, and 3,659 (54%) were identified as being above the target during the study period. The total diabetes-related cost for the above-target group (after controlling for confounding factors) during the 1-year follow-up period was $US1,540 per person, 32% higher than the total diabetes-related cost ($US1,171) for the at-target group ($p < 0.001$).

In a French randomised controlled study, Varroud-Vial et al (2004) enrolled 340 people with type 2 diabetes by 57 GPs. GPs in the intervention group were educated in the Staged Diabetes Management (SDM) program, and GPs in the control group were asked to provide usual care. People in the intervention group (n = 198) were managed more adequately in accordance with the guidelines ($p < 0.05$ for 9 out of 10). There was a larger utilisation of metformin when people had a BMI > 28 kg/m^2 (77.4 vs 2.5%, $p < 0.05$) and a much higher proportion of people performing SMBG (90.1 vs 38.7%, $p < 0.001$) in the intervention group. At study end, mean HbA1c was significantly different between the two groups (-0.3% vs +0.6%, $p < 0.001$) resulting in a difference of 0.9%. Blood pressure and lipid profiles did not differ between the groups. Costs were available for 253 subjects (141 in the intervention group, 112 in the control group). Before the study, healthcare costs per person per month were slightly lower in the intervention group: €178.5 ± 233 vs €240.5 ± 373 in the control group ($p = 0.05$). The incremental cost during the study in the intervention group was €35 per person per month, but this difference was not significant ($p = 0.09$) and did not result in different costs between groups: €213.5 ± 272 in the intervention group vs €231.9 ± 277 in the control group ($p = 0.76$). The proportion of costs attributable to hospitalisation was 31.5% in the intervention group and 31.8% in the control group.

A randomised trial was conducted to evaluate integrated care for diabetes in clinical, psychosocial, and economic terms in 274 adult people with diabetes attending a hospital clinic and registered with one of three general practices (Anonymous, 1994). Subjects were stratified by treatment (insulin or other) and randomly allocated to conventional clinic care or integrated care. Integrated care subjects were seen in general practice every three or four

months and in the hospital clinic annually; general practitioners were given written guidelines for integrated care. The primary outcome measures included metabolic control, psychosocial status, knowledge of diabetes, beliefs about control of diabetes, satisfaction with treatment, disruption of normal activities, numbers of consultations and admissions, frequency of metabolic monitoring, costs to subjects and to the NHS. A higher proportion of subjects defaulted from conventional care (14 [10%]) than from integrated care (4 [3%], CI of difference 2% to 13%). After two years no significant differences were found between the groups in metabolic control, psychosocial status, knowledge, beliefs about control, satisfaction with treatment, unscheduled admissions, or disruption of normal activities. Integrated care was as effective for insulin dependent as non-insulin dependent subjects. People in integrated care had more visits and higher frequencies of examination. In conventional care, the mean annual cost per person year was £55.00; in integrated care the mean annual cost per person year was estimated at £78.00 in one practice and £101.00 in the second. The discrepancy between the two practices was partly explained by differences in organisation of care. Costs to person were lower in integrated care (mean £1.70) than in conventional care (£8.00).

Criveria et al (2006) estimated the incremental medication cost of providing optimal therapy to reach recommended goals versus actual therapy in 601 people with type 2 diabetes. Subjects' charts were randomly selected who were receiving care from the outpatient clinics of Massachusetts General Hospital March 1, 1996-August 31, 1997 and clinical and medication data were abstracted. Treatment algorithms were applied based on 2004 clinical practice guidelines for hyperglycaemia, hyperlipidaemia, and hypertension to subjects' current medication therapy to determine how current medication regimens could be improved to attain recommended treatment goals. Four clinicians and three pharmacists independently applied the algorithms and reached consensus on recommended therapies. Mean incremental medication costs, the cost differences between current and recommended therapies, per person (expressed in 2004 dollars) were calculated with 95% bootstrap confidence intervals (CIs). Mean duration of diabetes was 7.7 years, mean age 65 years, 32% had ideal glucose control, 25% had ideal systolic blood pressure, and 24% had ideal LDL cholesterol. If treatment algorithm recommendations were applied, the average annual medication cost/person increased from US$1,525 to $2,164. Annual incremental costs/person increased by US$168 (CI $133- $206) for antihyperglycaemic medications, US$75 (CI $57- $93) for antihypertensive medications, US$392 (CI $354-$434) for antihyperlipidaemic medications, and US$3 ($3-$4) for aspirin prophylaxis. Yearly incremental cost of recommended laboratory testing ranged from US$77-$189/person. Although baseline data come from the clinics of a single academic institution, collected in 1997, the care of these people with diabetes was remarkably similar to care observed nationally. Average yearly incremental cost of optimising drug regimens to achieve recommended treatment goals for type 2 diabetes was approximately $600/person.

Improving care of people with type 2 diabetes is cost-effective

The UKPDS provided the necessary clinical information on both micro and macrovascular complications to allow the analysis of blood glucose control cost effectiveness in people with type 2 diabetes Gray et al (2000). Subjects (n = 3,867) with newly diagnosed type 2 diabetes (mean age 53 years) were randomly allocated to conventional management or to intensive management with sulphonylureas or insulin. The primary outcome measures were incremental cost per event-free year gained within the trial period. Hospital admissions formed the largest element of complication costs. The mean cost of hospital admissions was £4,266 in the conventional group and £3,494 in the intensive group. The increased costs of anti-diabetes treatment among the intensive group were counterbalanced by reduced costs of complications so that the net trial costs per person did not differ between the groups (conventional group: £9,869; intensive group: £9,608). Intensive glucose control increased trial treatment costs by £695 (CI £555 to £836) per person but reduced the cost of complications by £957 (CI £233 to £1681) compared with conventional management. If standard practice visit patterns were assumed rather than trial conditions, the incremental cost of intensive management was £478 (CI -£275 to £1232) per person. The within trial event-free time gained in the intensive group was 0.60 (CI 0.12 to 1.10) years and the lifetime gain 1.14 (CI 0.69 to 1.61) years. The incremental cost per event-free year gained was £1166 (costs and effects discounted at 6% a year) and £563 (costs discounted at 6% a year and effects not discounted). Intensive blood glucose control in people with type 2 diabetes significantly increased treatment costs but substantially reduced the cost of complications and increased the time free of complications.

Using data from the UKPDS Clarke et al (2001) estimated the cost-effectiveness of intensive blood-glucose control with metformin compared with conventional therapy in 753 overweight people with newly diagnosed type 2 diabetes. Subjects were randomly allocated to an intensive blood glucose control group with metformin (n = 342) or a conventional group primarily with diet (n = 411). The analysis was based on the cost of health care resources associated with metformin and conventional therapy and the estimated effectiveness in terms of life expectancy gained from within-trial effects. The glucose control policy using metformin increased the total cost of therapy used in the intensive group by an average of £1,085 per person compared with the conventional glucose control policy. A greater number of visits to health professionals was largely responsible for the difference in costs. Intensive blood-glucose control with metformin produced a net saving of £258 per person (1997 UK prices) over the trial period (mean = 10.7 years) due to lower complication costs, and increased life expectancy by 0.4 years (costs and benefits discounted at 6%). Metformin was cost-saving and extended life expectancy in the UK as a first line pharmacological therapy in overweight people with type 2 diabetes.

In another study using data from the UKPDS, Clarke et al (Clarke et al., 2005) estimated the economic efficiency of (1) intensive blood glucose control and tight blood pressure control in people with type 2 diabetes who also had hypertension, and (2) of metformin therapy in overweight people with type 2 diabetes. Intensive blood glucose control with sulphonylurea/insulin, intensive blood glucose control with metformin for overweight people, and tight blood pressure control of hypertensive subjects were evaluated. Incremental cost:effectiveness ratios were calculated based on the net cost of healthcare resources associated with these policies and on effectiveness in terms of quality-adjusted life years gained, estimated over a lifetime from within-trial effects using the UKPDS Outcomes Model. The intensive blood glucose control policy increased the anti-diabetic treatment costs by £678 and the incremental costs of visits and self-testing in a standard practice setting by £1,461 when compared with conventional glucose control. Intensive blood glucose control with metformin in overweight subjects increased therapy costs by £1,742 compared with those on conventional therapy, mainly due to the costs associated with implementing the policy in a standard practice setting. The cost of complications was £2,765 less per person in the metformin group, compared with conventional treatment. As the increased cost of metformin therapy (including standard practice costs) was less than the reduction in the cost of complications, there was on average a net cost-saving from the intervention of £1,023 per person. The incremental cost per quality-adjusted life years gained (in year 2004 UK prices) for intensive blood glucose control was £6,028, and for blood pressure control was £369. Metformin therapy was cost-saving and increased quality-adjusted life expectancy. Each of the three policies evaluated had a low cost per quality-adjusted life year gained and the results provide an economic rationale for ensuring that care of people with type 2 diabetes corresponds at least to the levels of these interventions.

Wake et al (2000) assessed the cost and effectiveness of intensive insulin therapy for type 2 diabetes in the Japanese Kumamoto study of 110 people with type 2 diabetes randomly assigned to multiple insulin injection therapy (MIT) group or a conventional insulin injection therapy (CIT) group. The National Health Insurance viewpoint was adopted for estimating costs. Direct medical costs associated with diabetes care during 10 years were calculated and evaluated. In a base case analysis, all costs were discounted to the present value at an annual rate of 3%. MIT prolonged the period in which subjects were free of complications, including 2.0 years for progression of retinopathy ($p < 0.0001$), 0.3 years for photocoagulation ($p < 0.05$), 1.5 years for progression of nephropathy ($p < 0.01$) and 2.2 years for clinical neuropathy ($p < 0.0001$). Treatment costs, such as costs of clinic visits, laboratory tests, and self-monitoring were significantly higher for MIT (by US$475, 631 and 3,834, respectively) compared with those of CIT. Furthermore, the total treatment cost per person for MIT was significantly higher ($p < 0.001$) by US$6,080 compared with the costs for CIT. In terms of complication costs, CIT was associated with increased costs of hospitalisation, drugs, and specific treatment of ophthalmic disorders US$3,239, US$3,419 and US$1,315, respectively, compared with those under MIT. Total complication costs in the CIT group were US$7,974 higher than that in MIT ($p < 0.001$). The total cost (discounted at 3%) per person during the

10-year period for each group was US$30,310 and US$31,525, respectively. MIT was more beneficial than CIT in both cost and effectiveness.

The incremental cost-effectiveness of intensive glycaemic control (relative to conventional control), intensified hypertension control, and reduction in serum cholesterol was estimated for people with newly diagnosed type 2 diabetes in a hypothetical cohort of individuals living in the US, aged 25 years or older (CDC Diabetes Cost-effectiveness Group, 2002). To create a model of disease progression and treatment patterns, results from the UKPDS and other studies were used. Costs were based on those used in community practices in the United States. The interventions used were insulin or sulphonylurea therapy for intensive glycaemic control; angiotensin-converting enzyme inhibitor or beta-blocker for intensified hypertension control; and pravastatin for reduction of cholesterol. The primary outcome measure was cost per QALY gained. Costs (in 1997 US dollars) and QALYs were discounted at a 3% annual rate. The incremental cost-effectiveness ratio for intensive glycaemic control was US$41,384 per QALY; this ratio increased with age at diagnosis from US$9,614 per QALY for people aged 25 to 34 years to US$2.1 million for people aged 85 to 94 years. For intensified hypertension control the cost-effectiveness ratio was -US$1959 per QALY. The cost-effectiveness ratio for reduction in cholesterol was US$51,889 per QALY; this ratio varied by age at diagnosis and was lowest for people diagnosed between the ages of 45 and 84 years. Intensive glycaemic control and reduction in cholesterol increase costs and improve health outcomes, while blood pressure control was cost saving.

In a high-risk remote Indigenous Australian Islander population, McDermott and Segal (2006) conducted a study to estimate the direct costs and downstream savings of improved quality of diabetes services, compared with usual care in a primary care setting. Costs of quality improvement were compared with actual and projected savings in avoidable diabetes-related hospitalisations in a cost impact analysis over 6 years (2000–2005). Costs were estimated from district financial reports and costs of diabetes-related complications requiring hospitalisation using published Diagnosis Related Group costings in Australian dollars (year 2000). The study population and setting consisted of a district health service in remote northern Australia, with 9,600 mainly Indigenous residents, including 1,000 adults with known diabetes served by 21 primary care centres and two hospitals. The primary outcome was the costs of primary level diabetes service and hospitalisations among people with diabetes for acute complications, lower limb amputations, end-stage renal disease and CVD. Hospitalisations for infections, some of which required amputation, declined by 2% between 1999 and 2002 with the intervention. Dialysis and the very high costs of patient transport avoided with improved diabetes care was estimated at $205,000 per year in years 2002 to 2003, and thereafter at least $280,000 for the 2006–10 period. Reductions in CVD events of 10% per year were estimated through better blood pressure management. Over the 6 years, a net present value cost of $570,000 was estimated for the new service, equivalent to $1,800 for each major event avoided. Annual cost savings were projected to exceed annual program delivery costs after 4 years of initiation.

In an Australian study, Taylor et al (2005) conducted an economic evaluation of a pharmacy-delivered disease state management (DSM) service for type 2 diabetes. The study was a parallel design with a control and intervention group. The specialised service included one initial visit with regular follow-up visits, all of which took place over 9 months. The control group was assessed at baseline and again at 9 months. Each of the groups was based in three different settings – rural, metropolitan community pharmacy settings, and a hospital diabetes clinic. There were nine intervention pharmacists and 20 control pharmacists. Subjects were required to have had an HbA1c measurement in the 6 months prior to the study, and one during the study period. In all, 239 people were recruited into the DSM study, of which 128 (54%) were in the intervention group and 111 (46%) in the control group. There were 51 dropouts. HbA1c levels decreased by 0.46% (p =0.02) in the intervention group (baseline value: 7.9 ± 1.4%) compared with a change of 0.03% (p = 0.81) in the control group (baseline value: 7.4 ± 1.1%) at 9 months. A greater proportion (28%) achieved a clinically significant reduction in HbA1c (≥ 1%) in the intervention group compared with the controls (15%) although not significant. The average cost of medications per intervention subject per month was $156.4 and per 9 months was $1,407.4; the average cost of medications per control subject per month was $137.8 and after 9 months was $1,240.3. To obtain the 0.46% (CI 0.34–0.52) HbA1c reduction by the specialised service, the cost to the health care sector was $383 (CI $A46.2–717.5) per person.

Palmer et al (2004) calculated the projected effects on life expectancy (LE), quality-adjusted life expectancy (QALE) and total costs of complications (TC) of 10% improvements in baseline levels of either HbA1c, total cholesterol, HDL cholesterol, systolic blood pressure (SBP), and all four parameters combined. A cohort of newly diagnosed people with type 2 diabetes (baseline mean age 52 years, HbA1c 9.1%) was used. The CORE Diabetes Model was used to simulate LE, QALE, and TC over subjects' lifetimes, assuming no change in risk factors, an isolated 10% improvement in each parameter, or a 10% improvement in all parameters simultaneously. A 10% change in all four risk factors, individually and in combination, improved life expectancy and QALE compared with baseline. The base-case simulation produced a mean life expectancy (± SD) of 14.19 ± 0.22 years and QALE of 9.75 ± 0.15 years. Mean total costs over the base-case subject's lifetime were US$83,666 ± 3,086. The single greatest influence on outcomes was HbA1c; a 10% reduction in HbA1c was associated with improvement in QALE of 0.81 ± 0.20 years and saved US$10,800 ± 4,030 of total lifetime costs compared with the base-case. Reducing the incidence of renal disease via HbA1c improvement had the largest effect on cost saving amounting to $10,758.

A clustered randomised trial reported empirical findings on the cost-effectiveness of two implementation strategies compared with usual hospital outpatient care and also included both patient-related and intervention-related cost (Dijkstra et al., 2006). Thirteen Dutch general hospitals were randomly assigned to a control group, a professional-directed or a patient-centred implementation programme. Analyses were performed on 240 people people with type 2 diabetes in the patient-centred group, 248 in the professional-directed group and

276 in the control group. Professionals received feedback on baseline data, education and reminders. Subjects in the patient-centred group received education and diabetes passports. A validated probabilistic Dutch diabetes model and the UKPDS risk engine were used to compute lifetime disease outcomes and cost in the three groups, including uncertainties. Approximately 46% of subjects were male in all three trial groups; mean age at diagnosis was 50 years. Baseline values were comparable among the three groups, although mean HbA1c levels were higher in controls. HbA1c at one year decreased by 0.2% in the professional-change group and by 0.3% in the patient-centred group, while it increased by 0.2% in the control group. Costs of primary implementation were < €5 per head in both groups, but average lifetime costs of improved care and longer life expectancy rose by €9,389 and €9620, respectively. Life expectancy improved by 0.34 and 0.63 years, and QALYs by 0.29 and 0.59. Accordingly, the incremental cost per QALY was €32,218 for professional-change care and €16,353 for patient-centred care compared with controls, and €881 for patient-centred vs professional-change care. By Dutch standards, both guideline implementation strategies in secondary care were cost-effective compared with current care. Additional annual costs were low for subjects using patient passports.

Collins and Anderson (1995) examined the savings in prescription costs associated with a weight reduction program in 40 obese men and women with type 2 diabetes. Subjects were aged 40-70 years, had a BMI of 30-40 kg/m^2 and type 2 diabetes of more than 1 year duration and were assigned to one of two 800-kcal weight-loss programs for 12 weeks. Thirty-three of the 40 subjects were taking anti-hypertensive medications. The seven subjects who managed their diabetes with diet alone were not included in this medication cost analysis. A cost analysis was done on the 32 subjects who were taking anti-hypertensive and/or anti-diabetes medications. A list of medications and monthly amounts was obtained at the start, upon completion, and 1 year following completion of the diet. The average out-of-pocket cost for a month's supply of each prescription was calculated by polling 16 retail pharmacies in Lexington, Kentucky. Subjects lost an average of 15.3 kg (14.8% of pre-diet body weight) over the 12 weeks. At 1-year follow-up, subjects maintained a mean 9.0 kg weight loss. The average monthly pre-diet out-of-pocket cost for anti-hypertensive and anti-diabetes medications and supplies was US$63.30 per subject. Following completion of the diet, this cost per month decreased to US$20.40 and at 1-year follow-up the average monthly cost per subject was US$32.40. The estimated average savings in prescription costs per subject over the year was US$442.80. The average monthly cost savings associated with the cessation or reduction in use of oral anti-diabetic agents was US$29.2 per subject, or an 88% reduction in the monthly cost of these medications following completion of the very low calorie diet. Significant savings in prescription costs were achieved following a 12-week hypocaloric weight reduction program for obese subjects with type 2 diabetes.

Lee et al (2006) conducted a systematic literature review using a comprehensive list of relevant search terms (1990-2005) to identify studies on adherence among people with type 2 diabetes, and its economic effect. Results of the review were placed into three categories: 1)

quantitative and qualitative information on adherence to diabetes medications (n = 13), 2) the effect of adherence on overall health care costs (n = 7), and 3) the effect of medication co-payment on levels of adherence and overall health care costs (n = 7). A lack of adequate treatment adherence (36%-87%) among people with diabetes was confirmed, primarily measured by medication possession ratio (MPR). Adherence varied among oral anti-diabetic medications-only (36%-87%) versus concomitant or insulin-only (54%-81%) regimens. Seven studies were identified that showed increased health care costs owing to subjects' inability to adhere to prescribed medications for diabetes. Adherence and its effect on overall health care costs were also studied among a low-income population. For example, people receiving thiazolidinedione therapy, who had better treatment adherence calculated using MPR in comparison with people receiving other oral antidiabetic agents (13% increase in MPR, $p < 0.01$), experienced a 16.1% decrease in total annual health care costs ($p < 0.01$) in the year following the start of medication. Economic consequences of adherence were a decrease in health care costs, ranging from 8.6% to 28.9%, with an approximate 10% increase in MPR, mostly in the form of a 4.1% to 31.0% decrease in hospitalisation. Increased cost sharing was associated with a 9% to 23% decline in medication use.

White et al (2004) assessed the relationship between anti-diabetic medication (OAD) adherence, total healthcare costs, and utilisation for people with type 2 diabetes and concomitant diabetes and cardiovascular disease (CVD). The study was a retrospective analysis of pharmacy and medical claims from 1 April 1998 through 31 March 2000 within a managed care organisation's database. Subjects were identified who had received an OAD or had a diagnosis of CVD, were continuously enrolled in the health plan, and were ≥ 30 years of age. The likelihood of an emergency room (ER) or hospital admission and total healthcare costs related to all causes, stratified by anti-diabetic medication adherence cohort within the diabetes only and diabetes + CVD groups, were examined over 360 days from the date the subject was identified. For people with diabetes with ≤ 75, > 75 to ≤ 95, and > 95% adherence, adjusted total healthcare costs (from April 1998 to March 2000) were US$5,706, US$5,314, and US$4,835, respectively ($p < 0.001$). People with ≤ 75 and > 75 to ≤ 95% adherence had a 31% and 19% greater chance of a hospital/ER admission than those in the > 95% cohort, respectively. Adjusted healthcare costs (from April 1998 to March 2000) for those with ≤ 75, > 75 to ≤ 95, and > 95% adherence within the diabetes + CVD cohort was US$37,648, US$31,547, and US$25,354 ($p < 0.001$). People who were ≤ 75 and > 75 to ≤ 95% adherent had a 44% and 51% greater chance of a hospital/ER admission than those with > 95% adherence, respectively.

Di Loreto et al (2005) examined the impact of different amounts of increased energy expenditure on health outcomes and costs in people with type 2 diabetes in a post hoc analysis. Different amounts of increased energy expenditure (metabolic equivalents per hour per week) through voluntary aerobic physical activity was performed in 179 subjects with type 2 diabetes (age 62 ± 1 years [mean ± SE]) randomised to a physical activity counselling intervention. Subjects were followed for 2 years and divided into six groups based on their

increments in METs per hour per week: group 0 (no activity, n = 28), group 1-10 (6.8 ± 0.3, n = 27), group 11-20 (17.1 ± 0.4, n = 31), group 21-30 (27.0 ± 0.5, n = 27), group 31-40 (37.5 ± 0.5, n = 32), and group > 40 (58.3 ± 1.8, n = 34). At baseline, the six groups did not differ for energy expenditure, age, sex, diabetes duration, and all parameters measured. After 2 years, in group 0 and in group 1-10, no parameter changed; in groups 11-20, 21-30, 31-40, and > 40, HbA1c, blood pressure, total serum cholesterol, triglycerides, and estimated percent of 10-year coronary heart disease risk improved ($p < 0.05$). HbA1c (± SE) changed across groups as follows: group 0, 0.03 ± 0.01%; group 1–10, –0.06 ± 0.09%; group 11–20, –0.4 ± 0.1%; group 21–30, –0.9 ± 0.07%; group 31–40, –1.1 ± 0.1%; group > 40, –1.0 ± 0.1% ($p = 0.001$, between group comparisons). After 2 years, per capita yearly costs of medications increased ($p = 0.008$) by US$393 in group 0, did not significantly change in group 1-10 (US$206, $p = 0.09$), and decreased in group 11-20 (US$-196, $p = 0.01$), group 21-30 (US$-593, $p = 0.009$), group 31-40 (US$-660, $p = 0.003$), and group > 40 (US$-579, $p = 0.001$). Energy expenditure > 10 METs/h/week obtained through aerobic leisure time physical activity was sufficient to achieve health and financial advantages, but full benefits were achieved with energy expenditure of > 20 METs/h/week.

Franz et al (1995) conducted a cost analysis and cost-effectiveness study on a sample of 179 subjects with type 2 diabetes between the ages of 38 and 76 years based on a randomised clinical trial of basic nutrition care (BC) and practice guidelines nutrition care (PGC) provided by dietitians in outpatient clinics. People with type 2 diabetes were recruited from three states (Minnesota, Florida, Colorado) and were randomly assigned to receive BC or PGC over a 6-month period. Along with data about medical and clinical outcomes, data about cost resources were collected. The cost-effectiveness of PGC compared with BC was calculated using per-person costs and glycaemic outcomes for the 6 months of the study. A net cost-effectiveness ratio comparing BC and PGC, including the cost savings resulting from changes in medical therapy, was also calculated. Subjects in the PGC group experienced a mean 1.1 ± 2.8 mmol/L decrease in fasting plasma glucose level 6 months after entry to the study, for a total per-person cost of US$112. PGC costs included one HbA1c assay used by the dietitian to evaluate nutrition outcomes. Subjects in the BC group experienced a mean 0.4 ± 2.7 mmol/L decrease, for a total per-person cost of US$42. In the PGC group, 17 persons had changes in therapy, which yielded an average 12-month cost savings pro-rated for all subjects of US$31.5. In contrast, in the BC group, 9 persons had changes in therapy, for an average 12-month pro-rated cost savings of US$3.1. Each unit of change in fasting plasma glucose level from entry to the 6-month follow-up could be achieved with an investment of US$5.8 by implementing BC or of US$5.8 by implementing PGC. If net costs were considered (per-person cost-cost savings due to therapy changes), the cost-effectiveness ratios became US$5.3 for BC and US$4.2 for PGC, assuming the medical changes in therapy were maintained for 12 months.

Rothman et al (2006) examined the labour characteristics and the program costs in a randomised controlled trial of a primary care-based diabetes disease management

intervention. In all, 217 people with type 2 diabetes and poor glycaemic control (HbA1c ≥ 8.0%) were recruited. The intervention group received 12 months of intensive management from clinical pharmacists and a diabetes care co-ordinator who provided education, applied algorithms for medication management, and addressed barriers to care. The control group attended a single session led by pharmacists, followed by usual care from their primary providers. The process outcomes included the number of person -related activities, time spent per subject, and number of drug titrations or additions. The program costs were calculated based on Bureau of Labour Statistics wage data using a sensitivity analysis. The disease management team performed a mean of 4.0 care-related activities for a mean of 38.6 minutes per person per month for intervention subjects and a mean of 1.1 care-related activities for a mean of 10.7 minutes per person per month for control subjects ($p < 0.001$). Intervention subjects had a median of 7 drug titrations or additions during the study. The incremental program cost for the intervention was US$36.9 (sensitivity analysis, $16.2–$88.6) per person per month.

Evidence – Socioeconomic consequences

There are disparities in diabetes care and control, especially in disadvantaged groups

Overland et al (2002) collected information on the number of services for select Medicare item codes using a Health Insurance Commission data file covering 177,280 people with type 2 diabetes within NSW. People with the greatest social disadvantages were significantly less likely to be under the care of a general practitioner (adjusted OR 0.41; 95% CI 0.40–0.41) or consultant physician (adjusted OR 0.50; 95% CI 0.48–0.53), despite this group having the highest prevalence of diabetes. The difference in attendance to other specialists was less marked but nevertheless significant (adjusted OR 0.71; 95% CI 0.68–0.75). When a doctor's care was established, people at most disadvantage were slightly more likely to undergo HbA1c or microalbuminuria estimation (adjusted OR 1.04; 95% CI 1.00–1.10 and adjusted OR 1.22; 95% CI 1.12–1.33, respectively) and received a level of monitoring relatively equal to that provided to less disadvantaged people.

In an Australian study, Georgiou et al (2004) used a cross-sectional comparison of the ratio in the number of Service Incentive Payments (SIP) items claimed between August 2002 and July 2003 to estimate the prevalence of diabetes by divisions of general practice (DGP). In all, 95,486 SIPs were claimed by general practices for completion of an annual cycle of care for people with diabetes, representing a mean of 10.1% of the population estimated to have diabetes. The ratio was higher in DGP with a more disadvantaged population, and more of their GP members in large practices. The provision of IT support in DGP and the proportion of GPs who had patients registered on the division's register were associated with a higher ratio of claims. This exploratory study identified a correlation between socioeconomic status and SIP claims; a regression model with two factors: socioeconomic disadvantage and the proportion of GP members in practices of five or more GPs predicted 41% of the variance.

Differences in glycated haemoglobin were compared between indigenous populations and non-indigenous reference groups (Daniel et al., 1999). Multivariate and stratified analyses were undertaken of cross-sectional data from multi-centre community-based diabetes diagnostic and risk factor screening initiatives in Canada and Australia. Population groups were Australian Aborigines (n = 116), Torres Strait Islanders (n = 156), Native Canadians (n = 155), Greek migrants to Australia (n = 117), and Caucasian Australians (n = 67). Measurements included HbA1c concentration, fasting and 2-h post-load glucose concentrations, body mass index, waist-to-hip ratio, and demographic variables. Statistically significant and biologically important differences in HbA1c between culturally distinct population groups of indigenous people and comparison groups of Greek migrants and Caucasian Australians were found. Mean HbA1c concentrations were highest for the indigenous groups ($p < 0.0001$). The covariate adjusted indigenous versus non-indigenous difference was 0.9 (CI 0.6–1.2)%, 18.2% higher for indigenous people.

Thomas et al (2007) systematically compared diabetes management and outcomes in 144 Indigenous Australians enrolled in the NEFRON study with that in non-Indigenous people presenting consecutively to the same practitioner (n = 449). The mean age of the subjects was 66 years with a median duration of diagnosed diabetes of 6 years. Indigenous Australians came from urban, rural and remote settings throughout Australia. The non-Indigenous control group was predominantly Caucasian (87%). Metabolic control was significantly worse in Indigenous people than other diabetic people in the same practice. While 48% of all NEFRON subjects achieved HbA1c targets of < 7.0%, these targets were achieved in only 24% of Indigenous subjects. Indigenous people were more likely to have an HbA1c ≥ 8.0% (55%) compared with Caucasians or Asians; this excess persisted even after controlling for other risk factors for poor glycaemic control (adjusted OR 2.8; CI 2.0–4.3), and despite the similar frequency use of oral anti-diabetic agents and insulin. Indigenous Australians with diabetes had high rates of micro- and macrovascular disease. Sixty percent of Indigenous subjects had an abnormal albumin to creatinine ratio compared with 33% of non-Indigenous subjects ($p < 0.01$). When compared with non-Indigenous people, Indigenous people were more likely to have established macrovascular disease (adjusted OR 2.7). This excess in complications was associated with poor glycaemic control.

Data collected from Aboriginal people with type 2 diabetes in the Fremantle Diabetes Study were analysed and compared with those from Caucasian participants (Davis et al., 2007). Aboriginal people were significantly younger at diagnosis and recruitment than the Caucasians but had similar diabetes duration. HbA1c levels were markedly higher in the Aboriginal people compared with Caucasians despite similar glycaemic management. There was a trend towards a higher prevalence of retinopathy in the Aboriginal group, but neuropathy and macrovascular complications did not differ significantly. Only half the Aboriginal group had been educated beyond primary level compared with 85% of Caucasians and household income was lower. Aboriginal people had a higher number of general practitioner (GP) visits each year (median (inter-quartile range) 4 (1–8) vs 2 (1–4); $p = 0.08$), but were less likely to have received diabetes education (44 vs 72%; $p = 0.016$), to have been seen by a podiatrist (12 vs 33%; $p = 0.07$) or to self-monitor blood glucose (SMBG; 50 vs 71%; $p = 0.07$). Self-reported treatment adherence also tended to be lower in the Aboriginal group (42 vs 20% occasionally or regularly missing doses; $p = 0.07$). Total annual diabetes-attributable costs were not significantly different, but higher GP costs were offset by lower SMBG and podiatry costs.

Kirk et al (2005) examined ethnic disparities in the quality of diabetes care among adults with diabetes in the US through a systematic qualitative review. Published material was searched from 1993 through to June 2003 using PubMed, Web of Science, Cumulative Index to Nursing and Allied Health, the Cochrane Library, Combined Health Information Database, and Education Resources Information Centre. Eligible studies included people with diabetes

in which at least 50% of study participants were ethnic minorities and studies that made ethnic group comparisons. Research on individuals having prediabetes, those < 18 years of age, or women with gestational diabetes were excluded. A total of 390 studies were reviewed, with 78 meeting inclusion criteria; data on glycaemia, blood pressure, and LDL cholesterol were extracted. Three investigations showed mean HbA1c levels to be ≥ 1% higher among ethnic minorities than among non-Hispanic whites. All but two studies found a statistically significant difference between minority ethnic groups and non-Hispanic whites, with the majority showing poorer glycaemic control among ethnic minorities. Studies among African Americans had HbA1c levels equal to or higher than non-Hispanic whites. Most studies showed blood pressure to be poorly controlled among ethnic minorities.

Quandt et al (2005) analysed data from a cross-sectional survey of randomly selected older (≥ 65 years) adults with type 2 diabetes in rural North Carolina to examine ethnic variation in glycaemic control. The participants (n = 693) were men and women from three ethnic groups: African American, Native American and Caucasian. HbA1c levels (< 7%, 7% – < 8%, and ≥ 8%) were compared across ethnic and gender groups. Multiple regression models were used to evaluate potential predictors of HbA1c ≥ 7%. Overall, 36.4% had an HbA1c ≥ 7%. African Americans and Native American men had the worst glycaemic control (≥ 7%) while African American women and Caucasian men had the best glycaemic control. Bivariate analysis showed that ethnicity, living arrangements, use of medications for diabetes, having a diabetes-related health care visit in the past year, and duration of diabetes were significantly associated with glycaemic control. Model 1 showed that being Native American, having a low income without Medicaid, and being married were associated with the worst glycaemic control, while Model 2 showed that longer diabetes duration and diabetes medication therapy were significant predictors of glycaemic control. Overall, individuals from older ethnic minorities in rural communities were most at risk for diabetes complications.

Dowell et al (2004) aimed to describe economic and clinical relationships associated with selected access, equity, and outcome characteristics of a large population with type 2 diabetes from a standardised national database. There was a secondary analysis of data about 101,944 patients in hospitals in the US, 40 years of age and older with a primary diagnosis of type 2 diabetes from the Health Care Cost and Utilisation Project (HCUP-3) database for 1994–1997. Questions addressed in the study were 1) What are economic and clinical trends related to access characteristics? 2) What are economic and clinical trends related to equity characteristics? 3) What are economic and clinical trends related to outcome characteristics? and 4) What are the relationships between and among selected access, equity and outcome characteristics? People more likely to be admitted to hospital on an emergency basis were blacks Americans (63%) and Hispanics (52%). Significant racial and sex disparities were found in health care access, equity, and outcomes, with equity characteristics showing alarming disparities in types of procedures (amputations and peripheral vascular bypass grafts) performed, lengths of stay, and dispositions. In whites, blacks, and native Americans, men were more likely than were women to have amputations ($p < 0.0001$). A wide disparity

by ethnic group was evident in the total number of people with type 2 diabetes undergoing lower-extremity amputation, with the incidence of amputation for native Americans was a consistently higher for each of the 4 years ($p < 0.0001$).

A cross sectional observational study examined the association between race/ethnicity and cardiovascular disease risk factor control in a cohort of 338 insulin-treated veterans with type 2 diabetes at three Veterans Affairs Medical Centres in the American Southwest (Wendel et al., 2006). Veterans with insulin-treated type 2 diabetes were randomly selected using electronic pharmacy databases. Medical records and patient survey data on diabetes control and management, cardiovascular disease risk factors, co-morbidities, demographics, socio-economic factors, psychological status, and health behaviours were collected. Analysis of variance and multivariate linear regression was used to determine the effect of race/ethnicity on glycaemic control, insulin treatment intensity, lipid levels, and blood pressure control. The study cohort included 72 (21.3%) Hispanic subjects (H), 35 (10.4%) African Americans (AA), and 226 (67%) non-Hispanic whites (NHW). The mean (SD) HbA1c differed significantly by race/ethnicity: NHW 7.9 (1.4)%, H 8.2 (1.6)%, AA 8.8 (2.9)%, $p = 0.05$. The multivariate-adjusted HbA1c was significantly higher for AA (+0.9%, $p = 0.002$) compared with NHW. Insulin doses (unit/day) also differed significantly: NHW 70.6 (48.8), H 58.4 (32.6), and AA 53.1 (36.2), $p < 0.01$. Multivariate-adjusted insulin doses were significantly lower for AA (-17.8 units/day, $p = 0.01$) and H (-10.5 units/day, $p = 0.04$) compared with NHW. Insulin dose differences were even greater among minority subjects with poorly controlled diabetes (HbA1c $\geq$ 8%). The disparities in glycaemic control and insulin treatment intensity could not be explained by differences in age, body mass index, oral hypoglycaemic medications, socioeconomic barriers, attitudes about diabetes care, diabetes knowledge, depression, cognitive dysfunction, or social support. There were no significant racial/ethnic differences in lipid or blood pressure control.

Sequist et al (2008) examined variations in diabetes outcomes by ethnic group at the level of individual physicians. Ninety primary physicians caring for at least 5 white and 5 black adults with diabetes across 13 ambulatory sites were identified; rates of ideal control (HbA1c < 7.0%, LDL-cholesterol < 2.6 mmol/L, and blood pressure <130/80 mm Hg) were calculated. Physician effects modelled the extent to which black subjects achieved lower control rates than white subjects within the same physician's panel ("within-physician" effect) compared with the extent to which black subjects were more likely than white subjects to receive care from physicians achieving lower overall control rates ("between-physician" effect). White subjects (n = 4,556) were significantly more likely than black subjects (n = 2,258) to achieve control of HbA1c (47% vs 39%), LDL-cholesterol (57% vs 45%), and blood pressure (30% vs 24%; $p < 0.001$ for all comparisons). Patient socio-demographic factors explained 13% to 38% of the racial differences in these measures, whereas within-physician effects accounted for 66% to 75% of the differences. Physician-level variation in disparities was not associated with either individual physicians' overall performance or their number of black subjects with diabetes. Racial differences in diabetes outcomes were mainly

related to subjects' characteristics and within-physician effects, wherein individual physicians achieve less favourable outcomes among their black than their white subjects.

Adams et al (2008) examined racial differences in self-management and medication adherence in a retrospective, longitudinal repeated-measures study on disparities in glycaemic control (HbA1c) among black and white people with type 2 diabetes at a large multi-specialty group practice. In all, 1,806 adults (aged ≥ 18 at diagnosis, 467 black and 1,339 white) with newly initiated oral anti-diabetic therapy between 1 December 1994 and 31 December 2000 were identified. Race was identified using an electronic medical record and patient self-report. Baseline was defined as the 13 months preceding and included the month of therapy initiation. Included subjects were required to have at least 12 months of follow-up. Black subjects had higher average HbA1c values at initiation of therapy compared with whites (9.8 vs 8.9%, $p < 0.0001$) and had lower average medication adherence during the first year of therapy (72 vs 78%; $p < 0.0001$). Although more frequent medication refills were associated with lower average HbA1c values, adjustment for adherence did not eliminate the black-white gap. Frequent medication refills and test strip refills were associated with lower average HbA1c values among white and black subjects. An increase in adherence of 25% was associated with a 0.05% lower HbA1c value among blacks and 0.07% lower HbA1c among whites. More frequent physician visits were also associated with lower average HbA1c.

A cross-sectional analysis of 468 subjects with diabetes among a cohort of 3,075 non-disabled black and white people evaluated racial differences and factors associated with worse glycaemic control in well-functioning older individuals with type 2 diabetes (de Rekeneire et al., 2003). Subjects were aged 70-79 years living in the community enrolled in the Health, Aging and Body Composition Study. Of the subjects in the study cohort, 58.5% were black. Racial differences in glycaemic control remained significant, even after adjusting for current insulin therapy, cardiovascular disease, higher total cholesterol, and not receiving a flu shot in the previous year, all of which were associated with higher HbA1c concentrations. Controlling for these factors reduced the association by 27% but race remained an important factor in glycaemic control, even when results were stratified by education or income. Differences in glycaemic control by ethnic group were associated with disease severity, health status, and poorer quality of care, but these factors did not fully explain the higher HbA1c levels in older black subjects.

To address racial disparities in the quality of diabetes care processes, intermediate outcomes, and treatment intensity, Heisler et al (2003) conducted an observational study of 801 white and 115 black people who completed the Diabetes Quality Improvement Project survey (response rate = 72%) in 21 Veterans Affairs (VA) facilities using survey data. Medical record information on receipt of diabetes services (HbA1c, LDL cholesterol, nephropathy screen, and foot and dilated eye examinations), and intermediate outcomes (HbA1c result; cholesterol control measured by LDL; and achieved level of blood pressure); and pharmacy

data on filled prescriptions were acquired. No racial differences in receipt of an HbA1c test or foot examination were found. Black subjects were less likely than white people to have LDL checked in the past 2 years (72% vs 80%, $p < 0.05$) and to have a dilated eye examination (50% vs 63%, $p < 0.01$). Black people remained significantly less likely to have LDL testing than white people who received care within the same facility (68% vs 83%, $P<0.01$). After adjusting for confounding effects, black people were substantially more likely than white people to have poor cholesterol control (LDL $\geq$ 3.4 mmol/L) and blood pressure control (BP $\geq$ 140/90 mm Hg, $p < 0.01$) but intensity of treatment was similar. Disparities in receipt of eye examinations were the result of black people being more likely to receive care at lower-performing facilities, whereas for other quality measures, racial disparities within facilities were substantial.

In a before-after analysis, Rothman et al (2004b) examined the role of literacy in 159 people with poorly controlled type 2 diabetes and poor glycaemic control (HbA1c $\geq$ 8.0%) who were participating in a diabetes management program that included low-literacy-oriented interventions. Clinic-based pharmacists offered one-to-one education and medication management for these subjects using techniques that did not require high literacy. Literacy was measured by the Rapid Estimate of Adult Literacy in Medicine (REALM) test and dichotomised at the 6th-grade level. HbA1c values were collected prior to enrolment, at enrolment, and approximately 6 months after enrolment. In all, 55% of the 111 subjects had literacy levels at the 6th-grade level or below. Lower literacy was more common among African Americans, older subjects, and subjects who required medication assistance. There was no significant relationship between literacy status and HbA1c prior to enrolment or at enrolment. Over the 6-month study period, subjects with low and high literacy had similar improvements in HbA1c. Using individualised teaching with low-literacy techniques, the diabetes care program significantly improved HbA1c values independent of literacy status.

Rothman et al (2004a) examined the role of literacy on the effectiveness of a comprehensive disease management program in 217 people aged 18 years or older with type 2 diabetes and poor glycaemic control (HbA1c levels $\geq$ 8.0%) in an analysis of the influence of literacy on glycaemic control and systolic blood pressure using data from a randomised controlled trial of a comprehensive diabetes management program. All communication to subjects was individualised and delivered to enhance comprehension among subjects with low literacy. Intervention subjects received intensive disease management from a multidisciplinary team. Control subjects received an initial management session and continued with usual care. Primary outcome measures were achievement of goal HbA1c levels and systolic blood pressure at 12-month follow-up for control and intervention subjects stratified by literacy status. Complete 12-month data were available for 193 subjects (89%). Among subjects with low literacy (more than one third), intervention subjects were more likely than control subjects to achieve goal HbA1c levels ($\leq$ 7.0%) (42% vs 15%, respectively; adjusted OR 4.6; CI, 1.3 to 17.2; $p = 0.02$). Subjects with higher literacy had similar odds of achieving goal HbA1c levels regardless of intervention status (24% vs 23%; adjusted OR 1.0; CI, 0.4 to 2.5;

p = 0.98). Improvements in systolic blood pressure were similar by literacy status. A comprehensive diabetes disease management program benefited people with low literacy to a greater degree than subjects with higher literacy.

Because South Asian inhabitants of the Netherlands have a higher diabetes prevalence in combination with a low socio-economic position, an intervention study investigated 1) which subject characteristics were associated with a greater chance of success in the intervention and 2) did subjects with the lowest socio-economic position benefit most from the intervention (Middelkoop and van der Wal, 2004). Subjects' (n = 101) HbA1c was measured before and after the intensive guidance. There were 46 males and 55 females in the study with average age of 53 years. Males were younger, more often had diabetes complications, were thinner and had higher HbA1c levels both before and after the intervention. High initial HbA1c, a low BMI and presence of complications were significantly related to success (defined as a decrease in HbA1c $\geq$ 0.8%). The average improvement in HbA1c was significant only in the group with a higher socio-economic position. Although the subjects with the lowest socio-economic position did not sufficiently benefit from this intervention, an overall improvement was achieved in this poorly educated study population.

Mayer-Davis et al (2004) evaluated lifestyle interventions in 152 people with diabetes living in rural communities in a 12-month randomised clinical trial of "intensive-lifestyle" and "reimbursable-lifestyle" interventions with usual care as a control. All subjects were given a study goal of achieving and maintaining a 10% weight loss over 12 months. Overall, 80% of participants were women, 82% black, average age was 60 years, and average BMI was 36.7 kg/m^2. Modest weight loss occurred by 6 months among intensive-lifestyle participants and was greater than the weight loss among usual-care participants (2.6 kg vs 0.4 kg, $p < 0.01$). At 12 months, a greater proportion of intensive-lifestyle participants had lost 2 kg or more than usual-care participants (49% vs 25%, $p < 0.05$). No differences in weight change were observed between reimbursable-lifestyle and usual-care participants. HbA1c was reduced among all groups (Usual Care: –1.12, $p < 0.0001$; Reimbursable-lifestyle Intervention: –0.843, $p < 0.05$; Intensive-lifestyle Intervention: –1.56, $p < 0.0001$) but was not different between groups. Day-to-day diabetes management among 70 black women were influenced by a number of factors: spirituality, general life stress, feelings of dietary deprivation, physical and emotional tiredness, worry, and fear of diabetes complications were key themes. Among intensive-lifestyle participants, transportation played an important role in achieving the overall retention rate of 81% and an attendance rate of 73%. The study demonstrated that modest weight loss and improved glycaemic control is attainable by culturally appropriate state-of-the-art lifestyle interventions among black and white individuals with type 2 diabetes living in rural medically underserved communities. The same intervention approach, when delivered in the amount of time normally reimbursed by health insurance (i.e. 4–5 hours over 12 months), was not effective in terms of weight loss, however some improvement in glycaemic control was noted.

Evidence Table: Type 2 diabetes is a costly condition

Author (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of Effect*	*Relevance Rating*
	Level	*Study Type*			
Brandle et al., 2003	IV	Cross-sectional	High	High[+]	High
Brown et al., 1999	III-2	Case-control	High	High[+]	High
Clarke et al., 2003	III-2	Prospective cohort	Medium	Medium[+]	Medium
Clarke et al., 2008	III-2	Prospective cohort	High	High[+]	High
Oglesby et al., 2006	IV	Cross-sectional	High	High[+]	Medium
Ramsey et al., 2002	III-2	Cross-sectional	High	High[+]	Medium

[+] Type 2 diabetes is a costly condition.

Clinical importance rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

Evidence Table: Improving blood glucose control in type 2 diabetes is cost-effective

Author (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of Effect*	*Relevance Rating*
	Level	*Study Type*			
Anonymous, 1994	II	RCT	High	Low[+]	High
Clarke et al., 2001	II	RCT	High	High[+]	High
Clarke et al., 2005	II	RCT	High	High[+]	High
Collins and Anderson, 1995	III-2	Prospective cohort	High	Low[+]	Medium
Crivera et al., 2006	IV	Cross-sectional	High	High[+]	Medium
Di Loreto et al., 2005	II	RCT	High	High[+]	Medium
Dijkstra et al., 2006	II	RCT	High	High[+]	Medium
Franz et al., 1995	IV	Cross-sectional	High	Medium[+]	Medium
Gray et al., 2000	II	RCT	High	High[+]	High
Lee et al., 2006	I	Systematic review	High	High[+]	High
McDermott and Segal, 2006	IV	Cross-sectional	High	High[+]	High
Rothman et al., 2006	II	RCT	High	High[+]	Medium
Shetty et al., 2005	III-2	Retrospective cohort	High	High[+]	Medium
Stephens et al., 2006	I	Systematic review	High	High[+]	High
Taylor et al., 2005	III-2	Prospective cohort	High	High[+]	High
Varroud-Vial et al., 2004 (France)	II	RCT	High	High[+]	Medium
Wake et al., 2000	II	RCT	High	High[+]	Medium
White et al., 2004	III-2	Retrospective cohort	High	High[+]	Medium

[+] Improving blood glucose control in type 2 diabetes is cost-effective.

Clinical importance rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

Evidence Table: There are disparities in diabetes care and control, especially in disadvantaged groups

Author (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of Effect*	*Relevance Rating*
	Level	*Study Type*			
Adams et al., 2008	III-2	Prospective cohort	High	High^{+}	Medium
Daniel et al., 1999	IV	Cross-sectional	High	High^{+}	High
Davis et al., 2007	IV	Cross-sectional	High	High^{+}	High
de Rekeneire., 2003	IV	Cross-sectional	High	High^{+}	Medium
Dowell et al., 2004	IV	Cross-sectional	High	High^{+}	Low
Georgiou et al, 2004	IV	Cross-sectional	High	High^{+}	Medium
Heisler et al., 2003	IV	Cross-sectional	High	Medium^{+}	Medium
Kirk et al., 2005	I	Systematic review	High	Medium^{+}	Low
Mayer-Davis et al., 2004	II	RCT	High	Low^{+}	Medium
Middlekoop and van der Wal, 2004	III-2	Prospective cohort	High	High^{+}	Medium
Overland et al, 2002	IV	Cross-sectional	High	High^{+}	High
Quandt et al., 2005	IV	Cross-sectional	High	High^{+}	Low
Rothman et al., 2004a	III-2	Prospective cohort	High	Low^{-}	Medium
Rothman et al., 2004b	IV	Cross-sectional	High	High^{+}	High
Sequist et al., 2008	IV	Cross-sectional	High	High^{+}	Medium
Thomas et al., 2007	IV	Cross-sectional	High	High^{+}	High
Wendel et al., 2006	IV	Cross-sectional	High	High^{+}	Low

$^{+}$ There are disparities in diabetes care and control, especially in disadvantaged groups.

Clinical importance rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

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APPENDICES

Appendix 1 - Guideline Search Strategy and Yield

Electronic databases searched:

Medline
Embase.com
Cochrane Library
Cinahl
PsycINFO

Terms used to search the databases:

Detailed in search strategy tables.

Other searching:

Reference lists of relevant articles were hand searched.
Relevant articles were solicited from expert colleagues and organisations.
Local and international practice guidelines were reviewed for relevant references.

Search inclusion criteria:

Where possible searches were limited by the English language, human research, and to the years of publication between January 1990 and 20 March 2008.

Abbreviations and explanation of table headings

Identified = number of articles which matched the mesh terms listed or contained the text terms in each particular database.
Relevant = those articles considered relevant to the questions being asked after viewing titles or abstracts.
Articles identified by other strategies = articles identified by hand searching, other searches for other questions, or from colleagues.
Total for Review = those articles considered relevant to the question after viewing titles and abstracts, contained original data or were systematic reviews of original articles and met the inclusion/exclusion criteria in Appendix 2.
Total no. reviewed and graded = articles used in the evidence section of the guidelines which have been summarised and graded.

Questions		Number articles identified	Number relevant articles	Articles identified by other strategies	Total for review	Total number reviewed and graded	Level I	Level II	Level III	Level IV	Highest level of evidence
1	What is the effect of improving blood glucose control on: a) macrovascular comps b) microvascular comps c) quality of life	5202	367	23	143	46	7	28	8	3	I
2	Are there any potentially harmful effects of improving blood glucose control?	3172	278	29	116	25	5	10	10	0	I
3	How should blood glucose control be assessed?	1803	180	12	164	57	9	9	22	17	I
4	What are the targets for blood glucose control?	2982	339	3	121	7	0	6	1	0	II
5	What lifestyle modification (diet, physical activity, weight loss) and therapeutic interventions can be used to improve blood glucose control in people with type 2 diabetes?	3980	453	61	183	156	53	93	7	3	I
6	What are the economic consequences of and socioeconomic influences on blood glucose control?	1328	197	33	87	39	3	10	11	15	I

Search Strategies

Question 1 − What is the effect of improving blood glucose control on:

a) Microvascular complications (retinopathy, neuropathy, nephropathy)?
b) Macrovascular complications (heart disease, stroke, PVD)?
c) Quality of life?

#	Searches	Results
1	Diabetes Mellitus, Type 2/	51070
2	(type 2 diabetes or type II diabetes).tw.	31308
3	(diabetes type 2 or diabetes type II).tw.	498
4	(diabetes mellitus type 2 or diabetes mellitus type II).tw.	947
5	(non insulin dependent diabetes or noninsulin dependent diabetes or diabetes non insulin dependent or diabetes mellitus non insulin dependent or NIDDM).tw.	11621
6	(newly diagnosed diabetes or diabetes newly diagnosed or diabetes mellitus newly diagnosed).tw.	356
7	(adult onset diabetes or diabetes adult onset or diabetes mellitus adult onset).tw.	338
8	(maturity onset diabetes or diabetes maturity onset or diabetes mellitus maturity onset).tw.	1217
9	(new onset diabetes or diabetes new onset or diabetes mellitus new onset).tw.	482
10	or/1-9	63437
11	(glycemic control or glycaemic control).tw.	9697
12	(glucose control or blood glucose monitoring).tw.	3994
13	metabolic control.tw.	6656
14	diabetes control.tw.	1398
15	(microvascular or macrovascular).tw.	28503
16	diabetic retinopath$/ or retinopath$.tw.	21200
17	diabetic nephropath$.tw. or diabetic nephropathies/	17046
18	cardiovascular diseases/ or coronary diseases/ or diabetic angiopathies/	192572
19	(cardiovascular disease or cardiovascular diseases or coronary disease or coronary diseases or diabetic angiopathy or diabetic angiopathies).tw.	62631
20	vascular diseases/ or peripheral vascular diseases/ or stroke/	59668

21	(vascular disease or vascular diseases or peripheral vascular disease or peripheral vascular diseases or stroke).tw.	107285
22	cerebrovascular disorders/ or cerebrovascular disorders.tw.	42008
23	(diabetic complication or diabetic complications or diabetes complication or diabetes complications).tw.	4086
24	quality of life/ or (quality of life or life quality).tw.	103160
25	or/11-23	442118
26	meta analysis/	19286
27	(meta-anal$ or metaanal$).tw.	22629
28	(systematic$ review$ or systematic$ overview$).tw.	16175
29	(quantitativ$review$ or quantitativ$ overview$).tw.	63
30	(methodologic$ review$ or methodologic$ overview$).tw.	196
31	review.pt. and (medline or pubmed).tw.	22209
32	or/27-31	50513
33	randomized controlled trial/	263468
34	controlled clinical trial.tw.	5472
35	random allocation.tw.	764
36	double-blind studies/	99912
37	single-blind studies/	12433
38	or/33-37	294177
39	animals/ not (animals/ and humans/)	3247594
40	38 not 39	289276
41	clinical trial.pt.	457363
42	exp clinical trial/	560480
43	(clinic$ adj25 trial$).ti,ab.	150625
44	(crossover or cross-over or cross over).tw.	41720
45	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.	99433
46	placebos/	28018
47	placebo$.ti,ab.	113108
48	random$.ti,ab.	422854
49	research design/	54086
50	or/41-49	941792
51	50 not 39	871495
52	40 or 51	877301
53	and/10,25,32	433
54	limit 53 to (english and yr="2005 - 2008")	221
55	and/10,25,52	5506
56	limit 55 to (english and yr="2005 - 2008")	2041
57	and/10,25	22470
58	limit 57 to (english and yr="2005 - 2008")	6958

Question 2 − Are there any potentially harmful effects of improving blood glucose control?

#	Searches	Results
1	diabetes mellitus, type 2/	51070
2	(type 2 diabetes or type II diabetes).tw.	31308
3	(diabetes type 2 or diabetes type II).tw.	498
4	(diabetes mellitus type 2 or diabetes mellitus type II).tw.	947
5	(non insulin dependent diabetes or noninsulin dependent diabetes or diabetes non insulin dependent or diabetes mellitus non insulin dependent or NIDDM).tw.	11621
6	(newly diagnosed diabetes or diabetes newly diagnosed or diabetes mellitus newly diagnosed).tw.	356
7	(adult onset diabetes or diabetes adult onset or diabetes mellitus adult onset).tw.	338
8	(maturity onset diabetes or diabetes maturity onset or diabetes mellitus maturity onset).tw.	1217
9	(new onset diabetes or diabetes new onset or diabetes mellitus new onset).tw.	482
10	or/1-9	63437
11	(glycemic control or glycaemic control).tw.	9697
12	(glucose control or blood glucose monitoring).tw.	3994
13	metabolic control.tw.	6656
14	diabetes control.tw.	1398
15	hypoglycemia/ or (hypoglycemia or hypoglycaemia).tw.	26895
16	weight gain/ or (weight gain or gain weight).tw.	35318
17	harmful effects.tw.	3493
18	(adverse effect or adverse effects).tw.	62426
19	(side effect or side effects).tw.	124665
20	or/11-19	259817
21	meta-analysis.pt.	19286
22	(meta-anal$ or metaanal$).tw.	22629
23	(systematic$ review$ or systematic$ overview$).tw.	16175
24	(quantitativ$review$ or quantitativ$ overview$).tw.	63
25	(methodologic$ review$ or methodologic$ overview$).tw.	196
26	review.pt. and (medline or pubmed).tw.	22209

27	or/21-26	55584
28	randomized controlled trial.pt.	263468
29	controlled clinical trial.pt.	79901
30	randomized controlled trials as topic/	56584
31	random allocation/	62530
32	double blind method/	99912
33	single blind method/	12433
34	or/28-33	444721
35	animals/ not (animals/ and humans/)	3247594
36	34 not 35	416392
37	clinical trial.pt.	457363
38	exp clinical trials as topic/	210725
39	(clinic$ adj25 trial$).ti,ab.	150625
40	cross-over studies/	22777
41	(crossover or cross-over or cross over).tw.	41720
42	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.	99433
43	placebos/	28018
44	placebo$.ti,ab.	113108
45	random$.ti,ab.	422854
46	research design/	54086
47	or/37-46	951763
48	47 not 35	882427
49	36 or 48	906279
50	and/10,20,27	330
51	limit 50 to (english language and humans and yr="2005 - 2008")	165
52	and/10,20,49	3753
53	limit 52 to (english language and humans and yr="2005 - 2008")	1277
54	and/10,20	10582
55	limit 54 to (english language and humans and yr="2005 - 2008")	2985

Question 3 − How should blood glucose control be assessed?

#	Searches	Results
1	diabetes mellitus, type 2/	51070
2	(type 2 diabetes or type II diabetes).tw.	31308
3	(diabetes type 2 or diabetes type II).tw.	498
4	(diabetes mellitus type 2 or diabetes mellitus type II).tw.	947
5	(non insulin dependent diabetes or noninsulin dependent diabetes or diabetes non insulin dependent or diabetes mellitus non insulin dependent or NIDDM).tw.	11621
6	(newly diagnosed diabetes or diabetes newly diagnosed or diabetes mellitus newly diagnosed).tw.	356
7	(adult onset diabetes or diabetes adult onset or diabetes mellitus adult onset).tw.	338
8	(maturity onset diabetes or diabetes maturity onset or diabetes mellitus maturity onset).tw.	1217
9	(new onset diabetes or diabetes new onset or diabetes mellitus new onset).tw.	482
10	or/1-9	63437
11	(glycemic control or glycaemic control).tw.	9697
12	(glucose control or blood glucose monitoring).tw.	3994
13	metabolic control.tw.	6656
14	diabetes control.tw.	1398
15	or/11-14	19617
16	hemoglobin A, glycosylated/ or (glycosylated hemoglobin or glycosylated haemoglobin or glycated hemoglobin or glycated haemoglobin or hba1c or a1c).tw.	20620
17	fructosamine.tw.	1430
18	blood glucose self-monitoring/ or (blood glucose self-monitoring or blood glucose monitoring or blood sugar self monitoring or self monitoring blood sugar or self monitoring blood glucose).tw.	3252
19	(assessment or measurement).tw.	551115
20	(monitor or frequency).tw.	441685
21	or/16-20	981270
22	meta analysis.pt.	19286
23	(meta-anal$ or metaanal$).tw.	22629
24	(systematic$ review$ or systematic$ overview$).tw.	16175
25	(quantitativ$review$ or quantitativ$ overview$).tw.	63
26	(methodologic$ review$ or methodologic$ overview$).tw.	196

27	review.pt. and (medline or pubmed).tw.	22209
28	or/22-27	55584
29	randomized controlled trial.pt.	263468
30	controlled clinical trial.pt.	79901
31	randomized controlled trials as topic/	56584
32	random allocation/	62530
33	double blind method/	99912
34	single blind method/	12433
35	or/29-34	444721
36	animals/ not (animals/ and humans/)	3247594
37	35 not 36	416392
38	clinical trial.pt.	457363
39	exp clinical trials as topic/	210725
40	(clinic$ adj25 trial$).ti,ab.	150625
41	cross-over studies/	22777
42	(crossover or cross-over or cross over).tw.	41720
43	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.	99433
44	placebos/	28018
45	placebo$.ti,ab.	113108
46	random$.ti,ab.	422854
47	research design/	54086
48	or/38-47	951763
49	48 not 36	882427
50	37 or 49	906279
51	and/10,15,21,28	123
52	limit 51 to (english language and humans and yr="2005 - 2008")	60
53	and/10,15,21,50	1867
54	limit 53 to (english language and humans and yr="2005 - 2008")	654
55	and/10,15,21	4197
56	limit 55 to (english language and humans and yr="2005 - 2008")	1297

Question 4 − What are the targets for blood glucose control?

#	Searches	Results
1	diabetes mellitus, type 2/	51070
2	(type 2 diabetes or type II diabetes).tw.	31308
3	(diabetes type 2 or diabetes type II).tw.	498
4	(diabetes mellitus type 2 or diabetes mellitus type II).tw.	947
5	(non insulin dependent diabetes or noninsulin dependent diabetes or diabetes non insulin dependent or diabetes mellitus non insulin dependent or NIDDM).tw.	11621
6	(newly diagnosed diabetes or diabetes newly diagnosed or diabetes mellitus newly diagnosed).tw.	356
7	(adult onset diabetes or diabetes adult onset or diabetes mellitus adult onset).tw.	338
8	(maturity onset diabetes or diabetes maturity onset or diabetes mellitus maturity onset).tw.	1217
9	(new onset diabetes or diabetes new onset or diabetes mellitus new onset).tw.	482
10	or/1-9	63437
11	(glycemic control or glycaemic control).tw.	9697
12	(glucose control or blood glucose monitoring).tw.	3994
13	metabolic control.tw.	6656
14	diabetes control.tw.	1398
15	hemoglobin A, glycosylated/ or (glycosylated hemoglobin or glycosylated haemoglobin or glycated hemoglobin or glycated haemoglobin or hba1c or a1c).tw.	20620
16	or/11-15	32880
17	therapeutics/ or therapeutic$.tw.	401634
18	(therapy or therapies).tw.	895794
19	(treatment or treatments).tw.	2061331
20	(goal or goals).tw.	112536
21	(target or targets).tw.	328334
22	or/17-21	3072477
23	meta analysis.pt.	19286
24	(meta-anal$ or metaanal$).tw.	22629
25	(systematic$ review$ or systematic$ overview$).tw.	16175
26	(quantitativ$review$ or quantitativ$ overview$).tw.	63
27	(methodologic$ review$ or methodologic$ overview$).tw.	196

28	review.pt. and (medline or pubmed).tw.	22209
29	or/23-28	55584
30	randomized controlled trial.pt.	263468
31	controlled clinical trial.pt.	79901
32	randomized controlled trials as topic/	56584
33	random allocation/	62530
34	double blind method/	99912
35	single blind method/	12433
36	or/30-35	444721
37	animals/ not (animals/ and humans/)	3247594
38	36 not 37	416392
39	clinical trial.pt.	457363
40	exp clinical trials as topic/	210725
41	(clinic$ adj25 trial$).ti,ab.	150625
42	cross-over studies/	22777
43	(crossover or cross-over or cross over).tw.	41720
44	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.	99433
45	placebos/	28018
46	placebo$.ti,ab.	113108
47	random$.ti,ab.	422854
48	research design/	54086
49	or/39-48	951763
50	49 not 37	882427
51	38 or 50	906279
52	and/10,16,22,29	236
53	limit 52 to (english language and humans and yr="2005 - 2008")	123
54	and/10,16,22,51	3179
55	limit 54 to (english language and humans and yr="2005 - 2008")	1108
56	and/10,16,22	6799
57	limit 56 to (english language and humans and yr="2005 - 2008")	2052

Question 5 − What lifestyle modification and therapeutic interventions can be used to improve blood glucose control in people with type 2 diabetes?

#	Searches	Results
1	Diabetes Mellitus, Type 2/	51070
2	(type 2 diabetes or type II diabetes).tw.	31308
3	(diabetes type 2 or diabetes type II).tw.	498
4	(diabetes mellitus type 2 or diabetes mellitus type II).tw.	947
5	(non insulin dependent diabetes or noninsulin dependent diabetes or diabetes non insulin dependent or diabetes mellitus non insulin dependent or NIDDM).tw.	11621
6	(newly diagnosed diabetes or diabetes newly diagnosed or diabetes mellitus newly diagnosed).tw.	356
7	(adult onset diabetes or diabetes adult onset or diabetes mellitus adult onset).tw.	338
8	(maturity onset diabetes or diabetes maturity onset or diabetes mellitus maturity onset).tw.	1217
9	(new onset diabetes or diabetes new onset or diabetes mellitus new onset).tw.	482
10	or/1-9	63437
11	(glycemic control or glycaemic control).tw.	9697
12	(glucose control or blood glucose monitoring).tw.	3994
13	metabolic control.tw.	6656
14	diabetes control.tw.	1398
15	exp Hyperglycemia/ or (hyperglycemia or hyperglycaemia).ti,ab.	31351
16	exp Hyperglycemia/ or (hyperglycemia or hyperglycaemia).tw.	31351
17	hypoglycemic agents/ or (hypoglycemic agent$ or hypoglycaemic agent$).tw.	26137
18	hemoglobin A, glycosylated/ or (glycosylated hemoglobin or glycosylated haemoglobin or glycated hemoglobin or glycated haemoglobin or hba1c).tw.	19481
19	or/11-18	78111
20	exp insulin/ or insulin.tw.	224413
21	metformin/ or metformin.tw.	4711
22	acarbose/ or acarbose.tw.	1215
23	thiazolidinediones/ or thiazolidinediones.tw.	6083
24	exp sulfonylurea compounds/ or sulfonylurea compounds.tw.	14146

25	20 and 21	2629
26	20 and 24	5689
27	20 and 22	520
28	21 and 24	860
29	22 and 17	665
30	exp diet therapy/ or diabetic diet/ or (diet therapy or diabetic diet or diet restriction).tw.	34032
31	glycemic index/ or (glycemic index or glycaemic index).tw.	1267
32	(weight loss/ and medication.tw.) or (weight loss and medication).tw.	682
33	exercise/ or exercise therapy/	61590
34	exercise/ or exercise therapy/ or (exercise or physical activity).tw.	162063
35	or/20-34	419359
36	meta analysis.pt.	19286
37	(meta-anal$ or metaanal$).tw.	22629
38	(systematic$ review$ or systematic$ overview$).tw.	16175
39	(quantitativ$review$ or quantitativ$ overview$).tw.	63
40	(methodologic$ review$ or methodologic$ overview$).tw.	196
41	review.pt. and (medline or pubmed).tw.	22209
42	or/36-41	55584
43	randomized controlled trial.ti,ab,kw.	14386
44	randomized controlled trial.pt.	263468
45	controlled clinical trial.pt.	79901
46	randomized controlled trials as topic/	56584
47	random allocation/	62530
48	double blind method/	99912
49	single blind method/	12433
50	or/43-49	446348
51	animals/ not (animals/ and humans/)	3247594
52	50 not 51	417956
53	clinical trial.ti,ab,kw.	46147
54	exp clinical trials as topic/	210725
55	(clinic$ adj25 trial$).ti,ab.	150625
56	cross-over studies/	22777
57	(crossover or cross-over or cross over).tw.	41720
58	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.	99433
59	placebos/	28018
60	placebo$.ti,ab.	113108
61	random$.ti,ab.	422854
62	research design/	54086
63	or/53-62	761432
64	63 not 51	694818
65	52 or 64	792951
66	and/10,19,35,42	329
67	limit 66 to (english language and humans and yr="2005 - 2008")	187
68	and/10,19,35,64	3918
69	limit 68 to (english language and humans and yr="2005 - 2008")	1339
70	and/10,19,35	16284
71	limit 70 to (english language and humans and yr="2005 - 2008")	3908

Question 6 − What are the economic consequences of and socioeconomic influences on blood glucose control?

#	Searches	Results
1	Diabetes Mellitus, Type 2/	51070
2	(type 2 diabetes or type II diabetes).tw.	31308
3	(diabetes type 2 or diabetes type II).tw.	498
4	(diabetes mellitus type 2 or diabetes mellitus type II).tw.	947
5	(non insulin dependent diabetes or noninsulin dependent diabetes or diabetes non insulin dependent or diabetes mellitus non insulin dependent or NIDDM).tw.	11621
6	(newly diagnosed diabetes or diabetes newly diagnosed or diabetes mellitus newly diagnosed).tw.	356
7	(adult onset diabetes or diabetes adult onset or diabetes mellitus adult onset).tw.	338
8	(maturity onset diabetes or diabetes maturity onset or diabetes mellitus maturity onset).tw.	1217
9	(new onset diabetes or diabetes new onset or diabetes mellitus new onset).tw.	482
10	or/1-9	63437
11	(glycemic control or glycaemic control).tw.	9697
12	(glucose control or blood glucose monitoring).tw.	3994
13	metabolic control.tw.	6656
14	diabetes control.tw.	1398
15	exp Hyperglycemia/ or (hyperglycemia or hyperglycaemia).ti,ab.	31351
16	exp Hyperglycemia/ or (hyperglycemia or hyperglycaemia).tw.	31351
17	hypoglycemic agents/ or (hypoglycemic agent$ or hypoglycaemic agent$).tw.	26137
18	hemoglobin A, glycosylated/ or (glycosylated hemoglobin or glycosylated haemoglobin or glycated hemoglobin or glycated haemoglobin or hba1c).tw.	19481
19	or/11-18	78111
20	exp "Costs and Cost Analysis"/ or costs.tw.	179503
21	"cost of illness"/ or "cost benefit analysis"/	53873
22	exp Health Care Costs/ or health care cost.tw.	32434
23	cost effectiveness analysis/de or cost analysis.tw. or cost analyses.tw.	2818

24	(cost effect or cost effective or cost effectiveness or cost benefit or cost benefits).tw.	48187
25	(cost of illness or cost of illnesses or illness cost or illness costs).tw.	592
26	(burden of disease or disease burden or disease burdens or burden of illness or illness burden or illness burdens).tw.	4032
27	(disease cost or disease costs or cost of sickness or costs of sickness or sickness cost or sickness costs).tw.	179
28	(health care cost or health care costs or medical care cost or medical care costs or treatment cost or treatment costs).tw.	8824
29	(health expenditure or health expenditures or economic impact or economic impacts or economic consideration or economic considerations).tw.	4718
30	economic evaluation/ or (health impact or health impacts).tw.	2546
31	socioeconomics/ or (socioeconomic or socioeconomic cost or socioeconomic costs or socioeconomic influence or socioeconomic influences).tw.	27641
32	(economic or economic cost or economic costs or economic influence or economic influences or health economics).tw.	66762
33	or/20-32	279591
34	meta analysis.pt.	19286
35	(meta-anal$ or metaanal$).tw.	22629
36	(systematic$ review$ or systematic$ overview$).tw.	16175
37	(quantitativ$review$ or quantitativ$ overview$).tw.	63
38	(methodologic$ review$ or methodologic$ overview$).tw.	196
39	review.pt. and (medline or pubmed).tw.	22209
40	or/34-39	55584
41	randomized controlled trial.ti,ab,kw.	14386
42	randomized controlled trial.pt.	263468
43	controlled clinical trial.pt.	79901
44	randomized controlled trials as topic/	56584
45	random allocation/	62530
46	double blind method/	99912
47	single blind method/	12433
48	or/41-47	446348
49	animals/ not (animals/ and humans/)	3247594
50	48 not 49	417956
51	clinical trial.ti,ab,kw.	46147
52	exp clinical trials as topic/	210725
53	(clinic$ adj25 trial$).ti,ab.	150625
54	cross-over studies/	22777
55	(crossover or cross-over or cross over).tw.	41720
56	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.	99433
57	placebos/	28018
58	placebo$.ti,ab.	113108
59	random$.ti,ab.	422854
60	research design/	54086
61	or/51-60	761432
62	61 not 49	694818
63	50 or 62	792951
64	and/10,19,33,40	49
65	limit 64 to (english language and humans and yr="1990 - 2008")	46
66	and/10,19,33,63	264
67	limit 66 to (english language and humans and yr="1990 - 2008")	239

Appendix 2

Overview of Guideline Development Process and Methods

Prepared by
The Diabetes Unit
Menzies Centre for Health Policy
The University of Sydney

for the
Diabetes Australia Guideline Development Consortium

Last updated 5 May 2009

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Purpose and Structure of the Document

Purpose

This 2008-9 series of guidelines for type 2 diabetes updates and builds on the original suite of evidence based diabetes guidelines which were initiated in 1999 under funding from the Department of Health and Ageing (DoHA) to the Diabetes Australia (DA) Guideline Development Consortium. Under the initial diabetes guideline project, six evidence based guidelines for type 2 diabetes were endorsed by the NHMRC. The purpose of the initial guidelines and the current guidelines is to provide systematically derived, objective guidance to:

Improve quality and consistency of care and reduce inappropriate variations in practice by assisting clinicians' and consumers' understanding of and decisions about treatment and management options

Inform fund holders and health service planners about the effectiveness and feasibility of the various options

Assist researchers and research authorities to highlight i) areas of diabetes prevention and care for which there is inconclusive evidence and ii) areas of deficiency in the evidence which require further or definitive research.

The specific purpose of this current project which commenced in early 2008 was to update two of the previous guidelines - Primary Prevention, and Case Detection and Diagnosis – and to develop three new guidelines, one for Blood Glucose Control, one for Chronic Kidney Disease and one for Patient Education.

Structure

This *Overview of the Guideline Development Process and Methods* outlines the rationale for the guidelines and the organisational structure, methods and processes adopted for the Type 2 Diabetes Guideline project, including the Blood Glucose Control Guideline. The guidelines are structured to present the recommendations, practice points, evidence statements, documentation of search strategies and search yield and a textual account of the evidence underpinning each recommendation.

Final format and implementation

The contract between the DoHA and the DA Guideline Development Consortium makes provision for locating and synthesising the available evidence on the five index areas into guideline recommendations and describing the objective justification for the recommendations. Thus, the contract covers the development of the guidelines up to and including endorsement by the NHMRC but does not include implementation of the guidelines.

However, following endorsement by the NHMRC there will need to be an independent process of consultation with potential guideline users to determine the final format of the guidelines for wide dissemination to clinicians and consumers. Once this format has been agreed, an implementation strategy to encourage and facilitate the widespread uptake of the guidelines in everyday practice will need to be developed and actioned at national and state

and territory level. It is our understanding that the DoHA has developed an implementation plan and strategies and is currently obtaining internal sign-off on these before enacting them.

1.0 Introduction and Overview

1.1 Diabetes as a health burden

Results of the national diabetes prevalence survey, AusDiab (Dunstan et al, 2002), which was conducted on representative sample of some 11,000 people across Australia, found a prevalence of diabetes of 7.4% in people aged 25 years or older. Another 16.4% of the study population had either impaired glucose tolerance or impaired fasting glucose. AusDiab also confirmed that there is one person with undiagnosed diabetes for every person with diagnosed diabetes. Findings from the second phase of AusDiab, a 5-year follow-up survey of people who participated in the baseline study, have indicated that every year eight out of every 1,000 people in Australia developed diabetes (Barry et al, 2006). This, together with the increasing number of new cases of pre-diabetes, obesity, the metabolic syndrome, and kidney disease, has demonstrated that abnormal glucose metabolism is exerting a major impact on the health of Australians (Magliano et al, 2008).

Diabetes has a demonstrably high health and cost burden (Colagiuri et al, 2003; AIHW, 2008) resulting from its long term complications which include:

- heart disease and stroke
- foot ulceration, gangrene and lower limb amputation
- kidney failure
- visual impairment up to and including blindness
- erectile dysfunction

The health burden of diabetes is described in more detail throughout the guideline series but to put these complications in perspective, it is worth noting here that, in Australia, diabetes is the most common cause of:

- blindness in people under the age of 60 years
- end stage kidney disease
- non-traumatic amputation

Diabetes is heavily implicated in deaths from cardiovascular disease (CVD) but, due to death certificate documentation deficiencies; this link is believed to be substantially under reported. At a global level, diabetes is predicted to increase dramatically in the next decade or two (IDF, 2006). With an ageing and increasingly overweight and physically inactive population, and a cultural mix comprising numerous groups known to be at high risk of type 2 diabetes, Australia is a prime candidate for realising the projected increases.

Due to sheer numbers, the major proportion of the total diabetes burden is attributable to type 2 diabetes which is the most common form of diabetes and accounts for approximately 85% of all diabetes in Australia. Type 2 diabetes occurs predominantly in mature adults with the prevalence increasing in older age groups. However, in high risk populations such as Aboriginal and Torres Strait Islander people it may become manifest much earlier.

These guidelines focus exclusively on type 2 diabetes in non-pregnant adults. Like type 1 diabetes, type 2 diabetes is characterised by high blood glucose levels. However, unlike type 1 diabetes, the key feature of type 2 diabetes is insulin resistance rather than insulin deficiency. Consequently, its treatment does not necessarily require insulin and in many people, particularly in the initial years following diagnosis, type 2 diabetes can be successfully

managed with dietary and general lifestyle modification alone or in combination with oral anti-diabetic medications. Insulin therapy may be required if and when oral medication becomes ineffective in lowering and maintaining the blood glucose within an acceptable range. Assiduous attention to the management of elevated blood pressure, lipid problems and overweight is also required as these common features of type 2 diabetes markedly increase the risk of long term complications.

1.2 Key components and principles of diabetes care

Key components of care
In 1995, the NSW Health Department identified three key components of diabetes care, stating that …. 'there is consensus supported by published literature that diabetes care and outcomes can be improved by providing access for all people with diabetes to:

- information about their condition and self care education
- ongoing clinical care to provide optimal metabolic control
- screening for and appropriate treatment of complications' (Colagiuri R et al, 1995).

These and the principles of care below were included in the initial suite of guidelines for type 2 diabetes and remain as valid now as they were then.

Principles of care
The particular expression of the universally accepted diabetes care principles set out below was abbreviated from those developed by the UK Clinical Advisory Group (CSAG, 1994) and later summarised by the NSW Health Expert Panel on Diabetes (New South Wales (NSW) Department of Health, 1996) and was further adapted for this project:

- People with diabetes should have access to timely and ongoing care from a diabetes team. This should ideally include a doctor, nurse and dietitian with specific training and experience in the management of diabetes. Additional expertise, for example in podiatry, social work, behavioural psychology and counselling, should be available as required as should referral access to specialist services for the management of identified complications

- People with diabetes are entitled to access to opportunities for information, education and skills acquisition to enable them to participate optimally in their diabetes management

- People with diabetes are entitled to access high quality health services regardless of their financial status, cultural background, or place of residence

- For people with diabetes from community groups who may have special needs eg people from Aboriginal, Torres Strait Islander or culturally and linguistically diverse backgrounds and the elderly, diabetes care should be specifically tailored to overcoming access barriers and providing opportunities for optimising diabetes care and outcomes

- Diabetes teams should routinely evaluate the effectiveness of the care they provide

1.3 Rationale for the Guidelines

The magnitude of the impact of diabetes on individuals and society in Australia is manifest in its status as a National Health Priority Area since 1996 and the current attention directed to it by the Council of Australian Governments' National Reform Agenda which seeks to address and avert a greater impact on productivity than already exists as a result of diabetes.

For tangible and lasting benefits, evidence based information is required which synthesises new and existing evidence to guide primary prevention efforts and assist clinicians to identify and treat modifiable primary risk factors, accurately diagnose type 2 diabetes, assess metabolic control, provide effective routine care, and make appropriate and timely referrals.

Since the initial suite of NHMRC diabetes guidelines was released there has been a vast improvement in both the volume and quality of the evidence about preventing type 2 diabetes which is detailed in the Primary Prevention Guideline. Nonetheless, there remain grave concerns that the rapidly increasing prevalence of obesity combined with decreasing levels of physical activity will continue to impact negatively on the incidence and prevalence of diabetes unless addressed as a mater of urgency. Consequently, the Primary Prevention Guideline also cites some of the emerging evidence about environmental influences on food consumption and physical activity.

Type 2 diabetes represents a complex interaction of patho-physiological factors and its prevention and successful management requires clinicians and public health practitioners to maintain a thorough understanding of these interactions especially since there is now irrefutable evidence that both the onset of diabetes and the onset of its complications can be prevented or significantly delayed. Given the typically long pre-clinical phase of type 2 diabetes and that half of all people with diabetes are undiagnosed, the Case Detection and Diagnosis Guideline is an important component of this suite of guidelines.

Integral to the successful management of diabetes is self care knowledge and skills, and the capacity of the person with diabetes to adapt their lifestyle to optimise their physical and psychological well being. The Patient Education Guideline presents evidence addressing these issues.

The care of type 2 diabetes is predominantly carried out by general practitioners, often under 'shared care' arrangements with local Diabetes Centres and/or private endocrinologists. In remote Australia, and even in more densely settled rural regions, the population base is insufficient to support specialist diabetes teams and the general practitioner may not have local access to specialist referral and support. Regardless of geographical factors, standards of diabetes clinical care in Australia are known to be variable. The Chronic Kidney Disease Guideline sets out diagnostic criteria and therapies for achieving the treatment targets to guide the identification, prevention and management of kidney disease in people with diabetes.

Microvascular complications (retinopathy, nephropathy and neuropathy) and the increased risk of macrovascular complications (ischemic heart disease, stroke and peripheral vascular disease) are associated with reduced life expectancy and significant morbidity in type 2 diabetes. Using therapeutic interventions to lower blood glucose and achieve optimal HbA1c levels is critical in preventing diabetes complications and improving the quality of life. The Blood Glucose Control Guideline examines the evidence and the relationships among these issues.

1.4 Funding source

The Type 2 Diabetes Guidelines project is funded by the DoHA under a head contract with DA as convenor of the Guideline Development Consortium. The development of the guidelines is managed in partnership with DA by The Diabetes Unit at the University Sydney under the direction of A/Professor Ruth Colagiuri.

1.5 The Guideline Development Consortium

The Guideline Development Consortium led by DA comprises organisations representing consumers, specialist diabetes practitioners and primary care physicians and includes:

- The Australian Diabetes Society (ADS)
- The Australian Diabetes Educators Association (ADEA)
- The Royal Australian College of General Practitioners (RACGP)
- The Diabetes Unit – Menzies Centre for Health Policy (formerly, the Australian Health Policy Institute), the University of Sydney.

Additionally there are a number of collaborators:

- The NSW Centre for Evidence Based Health Care (University of Western Sydney)
- The Cochrane Renal Review Group (Westmead Children's Hospital)
- The Cochrane Consumer Network
- The Caring for Australians with Renal Impairment Guidelines Group (CARI),
- Kidney Health Australia.

1.6 The scope of the Guidelines

The brief for the Guideline Development Project was to prepare a set of evidence based guidelines for type 2 diabetes to NHMRC standard.

The Type 2 Diabetes Guidelines target public heath practitioners, clinicians (medical, nursing and allied health), diabetes educators and consumers and were designed to be appropriate for use in a wide variety of practice settings. The guidelines focus on care processes and interventions that are primarily undertaken in the non-acute setting ie they do not deal with highly technical procedural interventions such as renal dialysis.

1.7 Use of the Guidelines

Guidelines are systematically generated statements which are designed to assist health care clinicians and consumers to make informed decisions about appropriate treatment in specific circumstances (Field MJ & Lohr, 1990).

Guidelines are not applicable to all people in all circumstances at all times. The recommendations contained in these guidelines are a general guide to appropriate practice and are based on the best information available at the time of their development. The clinical guidelines should be interpreted and applied on an individual basis in the light of the health care practitioner's clinical experience, common sense, and the personal judgments of consumers about what is appropriate for, and acceptable to them.

1.8 Review date

New information on type 2 diabetes is continually and rapidly becoming available. The Project Management Team and Steering Committee recommend that these guidelines are reviewed and revised at least every three years after publication. We anticipate this will be June 2012.

1.9 Economic analysis

Assessment of economic impact i.e., analysing the cost implications of recommendations has become a mandatory component of guideline development.

1.10 Socio-economic impact

The Expert Advisory Groups for each guideline were encouraged to adopt a framework that is recommended by the NHMRC to identify, appraise and collate evidence of the impact of socioeconomic position and other markers of interest eg income, education, occupation, employment, ethnicity, housing, area of residence, lifestyle, gender.

2.0 Organisational structure and staffing

The organisational structure of the Guideline Development Project (Figure 1) comprises:

- A Steering Committee
- Project Management Team
- Expert Advisory Groups
- Guidelines Assessment Register Consultant
- Research Officers
- Research team

The Steering Committee consists of a representation from each of the Consortium members, the Guideline Project Medical Advisor, and the DoHA. Refer to Appendix i for Terms of Reference. The Project Steering Committee provides guidance and directions to the project and to the DoHA via DA. The main role was to oversee the project progress and timeline.

Expert Advisory Groups (EAGs) were established for each of the five guideline areas. They have a core composition of a consumer, a general practitioner, content experts nominated by the Australian Diabetes Society and the Australian Diabetes Educators Association, and other representation as appropriate. Consumers on the expert advisory groups were provided by Diabetes Australia as being representative of people with type 2 diabetes who are experienced in acting as consumer representatives and who had a detailed understanding of issues affecting people with diabetes. Terms of Reference of the EAGs is provided in Appendix ii. Lists of the individual members of each of the EAGs are provided in each guideline.

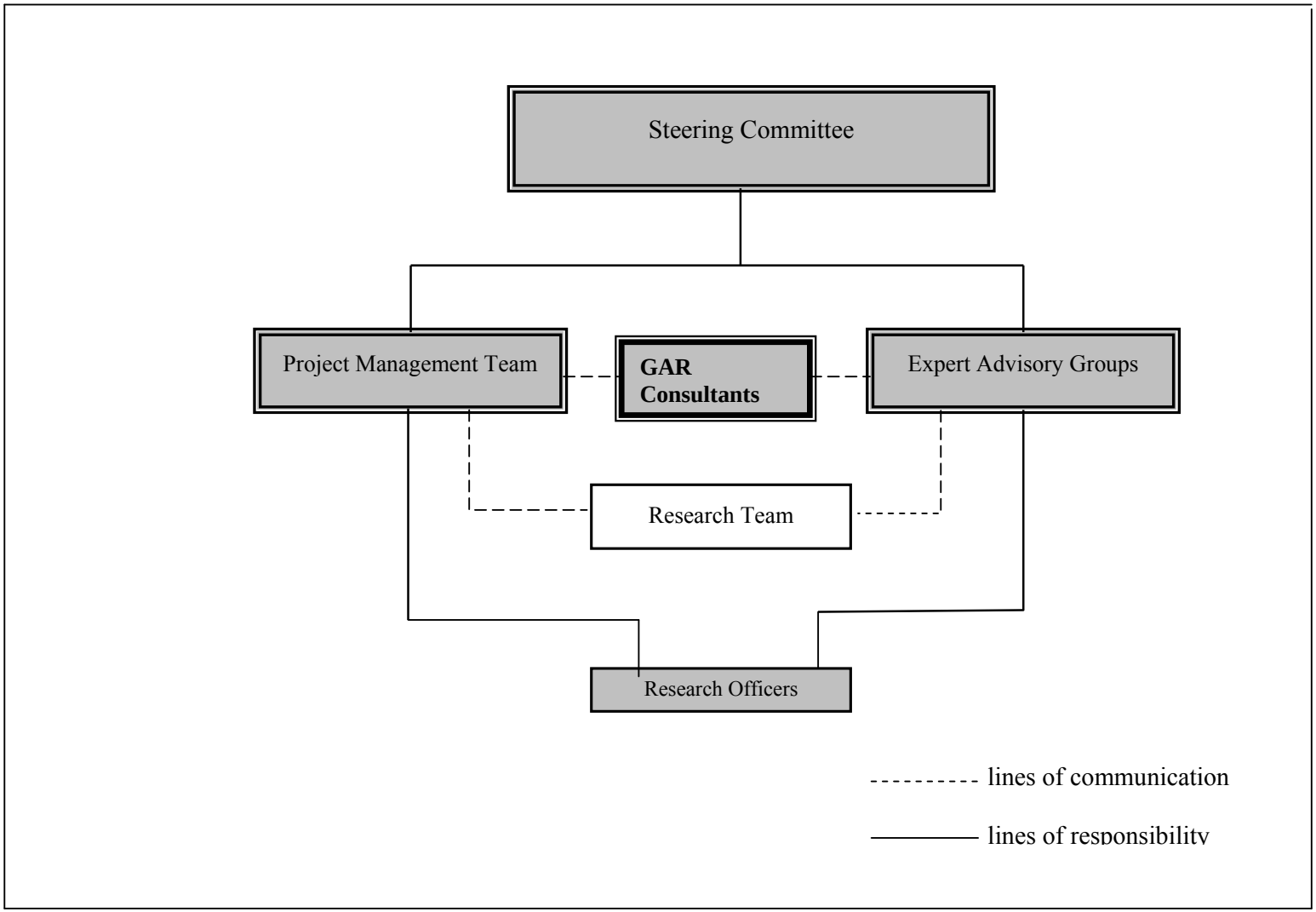
The Project Management Team. The Diabetes Unit, at Menzies Centre for Health Policy (formerly, the Australian Health Policy Institute), University of Sydney was subcontracted by DA to manage the project on behalf of the Consortium. The Diabetes Unit provides guidance on methods, technical support, data management, co-ordinates the input of the EAGs and supervises the project staff on a daily basis. The Project Management Team consists of the Director of the Diabetes Unit, the CEO of Diabetes Australia and the project's Medical Advisor.

Guidelines Assessment Register (GAR) consultans. The NHMRC nominated a GAR consultant for each guideline (except the Blood Glucose Control guideline) to provide guideline developers with support in relation to utilising evidence-based findings and applying the NHMRC criteria. Specifically, the GAR consultants provided advice on evaluating and documenting the scientific evidence and developing evidence-based recommendations based on the scientific literature and NHMRC procedures.

Research Officers were recruited or seconded from a variety of research and health care disciplines and given additional training to conduct the literature searches, and review, grade and synthesise the evidence under the supervision of the Senior Research and Project Manager, Dr Seham Girgis, the Chairs of the EAGs and the Project Management Team.

Research Team refers to the Project Director, Senior Project Manager, Research Officers, and the project's Medical Advisor.

Figure 1: Organisational Structure



3.0 Methods

3.1 Development of Protocols

At the beginning of the project, a Methods Manual was developed for the EAGs and project staff. The Manual was based on the NHMRC *Standards and procedures for externally developed guidelines* (NHMRC, 2007) and the series of handbooks on the development, implementation and evaluation of clinical practice guidelines published by the NHMRC from 2000–03. The NHMRC Standards and procedures document (NHMRC, 2007) introduced an extended set of levels of evidence and an approach to assessing a body of evidence and grading of recommendations. These standards and handbooks have superseded *A guide to the development, implementation and evaluation of clinical practice guidelines* (NHMRC, 1999), which formed the basis of the initial suite of NHMRC guidelines for type 2 diabetes.

The NHMRC has introduced a requirement for guidelines to consider issues related to cost-effectiveness and socioeconomic impact. Two publications in the NHMRC toolkit for developing clinical practice guidelines have been used to address these issues - how to compare the costs and benefits: evaluation of the economic evidence (NHMRC, 2001) and using socioeconomic evidence in clinical practice guidelines (NHMRC, 2003).

The Methods Manual developed for the project contains definitions, procedures and protocols, descriptions of study type classifications, checklists and examples of steps and methods for critical appraisal of the literature. It also includes the revised level of evidence and the minimum requirements for formulating NHMRC evidence based guidelines.

3.2 Guideline Development Process

From the literature and expert opinion the following steps were identified as central to the process of identifying sources of rigorously objective, peer reviewed information and reviewing, grading, and synthesising the literature to generate guideline recommendations:

1. Define specific issues and generate clinically relevant questions to guide the literature searches for each guideline topic.
2. Search the literature systematically using a range of databases and search strategies.
3. Sort the search yield on the basis of relevance to the topic area and scientific rigour.
4. Document the search strategy and the search yield.
5. Critically review, grade and summarise the evidence.
6. Assess the body of evidence according to the published NHMRC standard and formulate guideline statements and recommendation/s in accordance with the evidence.
7. Formulate the evidence statements and recommendations.
8. Conduct quality assurance throughout all these steps.

Step 1: Defining issues and questions to direct the literature searches

Each EAG was asked to define key issues for the guideline and to generate a set of questions focusing on clinically relevant issues to guide the literature searches. These critical clinical issues also formed the focus of the guideline recommendations and accompanying evidence statements. A generic framework was developed and centred on issues such as:

- What are the key treatment/management issues for this area?
- What anthropometric, clinical or behavioural parameters need to be assessed?
- Should everyone be assessed or are there particular risk factors which warrant selective testing or preventative treatment?
- What assessment techniques should be used?
- How often should the assessment be done?
- How should the results be interpreted?
- What action should follow from the results (if abnormal) e.g., management, further investigation, referral?
- What are the overall costs of using the intervention? (particularly in relation to changes in costs if changes to management are recommended)
- What is the impact of socioeconomic position and other markers of interest e.g., income, education, occupation, employment, ethnicity, housing, area of residence, lifestyle, gender.

EAGs were also advised to frame each question using the **'PICO'** elements as follows: **P**opulation **or P**roblem; **I**ntervention (for a treatment intervention question), **or I**ndicator or exposure (for a prognosis or aetiology or question), **or I**ndex test (for a diagnostic accuracy question); **C**omparator; and **O**utcome.

The resulting questions developed by each EAG are presented at the beginning of each guideline and again in the Search Strategy and Yield Table.

Step 2: Searching the literature

NHMRC clinical practice guidelines are required to be based on systematic identification and synthesis of the best available scientific evidence (NHMRC, 2007). A number of systematic strategies were used in this project to identify and assess scientific information from the published literature. The search strategies were designed to reduce bias and ensure that most of the relevant data available on type 2 diabetes were included in the present review and were similar to those detailed in the Cochrane Collaboration Reviewers Handbook (Higgins JPT et al). Several strategies were used to identify potentially relevant studies and reviews from the literature such as:

Electronic Databases

Searches were carried out using the following databases:

- Medline
- Cochrane Library: Databases of Systematic Reviews, DARE, Controlled Trials Register, Central, HTA.
- Additional databases searched where indicated included:
  Embase
  Cinahl
  Psycho Info
  Eric
  Other (where appropriate) such as Internet, Expert sources, Hand searching of reference lists at the end of relevant articles.

Key words

The key words (MeSH terms and some free text terms) used when searching these electronic databases are presented in detail in the Search Strategy and Yield Table at the end of each guideline topic. The EAGs limited their searches through a number of methods including:

- specification of temporal constraints (e.g. 1999-2008 for the updated guideline)
- language constraints (English only)
- where there were overwhelming amounts of literature or if there was a large volume of poor quality research, some groups imposed limits by experimental design to exclude the less rigorous forms of research.

Details of specific inclusion criteria for the EAG are also presented, together with the key words, at the end of each individual guideline.

Consultation with colleagues

The EAGs were encouraged to gather relevant information/articles from other experts and colleagues. The Project Management Team collated the questions developed by each EAG to direct the literature searches and highlight overlapping questions and requested EAGs and Research Officers to send any articles identified as applicable to other guideline topics to the EAG.

Step 3: Sorting the search yield

Two or more members of each EAG were responsible for sorting through the search results by scanning the lists of titles and abstracts generated by the electronic database searches, highlighting potentially relevant articles and requesting printed full articles. Full articles were retrieved and those which were relevant were assessed for quality. Articles were considered relevant if they provided direct or indirect information addressing one or more of the specified 'clinical issues' questions and were applicable to diabetes care or prevention in Australia.

Sorting according to study design

Articles with original data were sorted according to study design. Articles with the most rigorous experimental designs were reviewed in the first instance. Articles conducted to other study designs were included if they added new information not found in the papers of highest levels of evidence. Relevant papers were sorted as follows:

- Meta-analysis, systematic review of randomised controlled trials (interventions)
- Randomised controlled trials (RCT)
- Cohort studies
- Case control studies
- Case series, pre-post or post studies

Exclusion criteria

Articles were not included for review if it was apparent that their relevance to formulating a guideline recommendation was non-existent or negligible. Examples of reasons for non review included criteria such as:

- Studies of inappropriate patient population(s) for the question being addressed (epidemiology, specific diet)
- Hypothesis/mechanism/in vitro study/animal studies
- Genetic studies that are clinically inapplicable
- Non-systematic reviews which presented the author's opinion rather than evidence

Step 4: Documenting the search strategy and its yield

The search strategy (terms and limits) and yield were documented and are available for viewing in a table at the end of each guideline. In brief, the Search Strategy and Yield Table recorded details about the:

1. Questions being investigated
2. Electronic databases searched
3. MeSH terms and key words used to search the database
4. Methods for limiting the searches
5. Number of articles identified by each search
6. Number of articles relevant from that search
7. Number of relevant articles identified through other search processes
8. Number of articles obtained for review
9. Number of relevant articles which were systematic reviews, RCTs or well designed population based studies, quasi-experimental and other (these were documented in the tables according to the updated NHMRC Evidence Levels I –IV).
10. Number of articles reviewed
11. Highest level of evidence found for each question

Step 5. Critically reviewing, grading and summarising the evidence

All relevant articles were reviewed and critically assessed using checklists recommended by the NHMRC (2000) (NHMRC, 2000a; NHMRC, 2000b).The NHMRC checklist sets out an explicit standardised approach to reviewing and incorporating scientific evidence into clinical practice guidelines.

In addition, Research Officers were asked to construct tables to summarise extraction of data and to provide a brief summary of the key results for each article.

Overall assessment of individual studies
At the conclusion of reviewing each article, the reviewers rated the evidence in a summary form as shown in (Table 1) using the following criteria:

- *Levels of evidence*
  The 'interim' NHMRC levels of evidence (NHMRC, 2007) was used in this project to assess levels of evidence for a range of study designs (Appendix iv).
- *Quality rating*
- *Magnitude of effect*
- *Relevance rating*

Criteria for quality of evidence, magnitude of effect, and relevance of evidence were based on those provided by the NHMRC (2000a &b). These criteria are presented in Appendix iv.

Table 1: Example of an Overall Assessment Report

Assessment Category	**Rating**			
	Value	Low	Medium	High
Level of evidence				
Quality rating				
Magnitude of effect				
Relevance rating				

These assessments were then used in the evidence tables which summarises basic information about **Each Study** reviewed, including an overall assessment of the evidence (Table 2).

Table 2: Example of an evidence table with overall study assessment

Author, Year	**Evidence**				
	Level of Evidence		***Quality Rating***	***Magnitude of Effect Rating***	***Relevance Rating***
	Level	***Study Type***			
Author X (1999)	III-2	Cohort	High	Low	High

Step 6. Assessing the body of evidence and formulating guideline evidence statements and recommendations

In addition to considerations of the rigour of the research providing the evidence (Tables 1 and 2), principles for formulating guideline evidence statements and recommendations were derived consistent with the NHMRC recommended standard '*The NHMRC Standards for External Developers of Guidelines* (NHMRC, 2007).

For each identified clinical question, evidence statements are based on an assessment of all included studies for that question (**the Body of Evidence**). The NHMRC considers the following five components in judging the overall body of evidence (NHMRC, 2007) as specified in the '*NHMRC Body of Evidence Matrix'* (Table 3):

- The evidence base, in terms of the number of studies, level of evidence and quality of studies (risk of bias).
- The consistency of the study results.
- The potential clinical impact of the proposed recommendation.
- The generalisability of the body of evidence to the target population for the guideline.
- The applicability of the body of evidence to the Australian healthcare context.

Based on the body of evidence, recommendation/s was formulated to address each of the identified clinical questions for the area. Recommendation/s was written as an action statement.

Principles for formulating the guideline recommendation/s

In the course of the face-to-face meetings of the EAGs, and from published sources, principles were identified re-affirming the need for guideline recommendations to:

- Be developed systematically and objectively by synthesising the best available evidence.
- Have potential to improve health and related outcomes whilst minimising possible harms.
- Be clinically relevant and feasible.
- Take account of ethical considerations, and acceptability to patients.
- Centre on interventions which are accessible to those who need them.
- Propose activities within the scope of the role of those expected to use the guidelines e.g., interventions which could be expected to be conducted in routine general practice.

Grading of recommendation/s

The grading of each recommendation reflects the strength of the recommendation (Table 4) and is based on 'The *NHMRC Standards for External Developers of Guidelines* (NHMRC, 2007).

In face-to-face meetings, the EAG, initially graded each of the five components of the NHMRC Body of Evidence Matrix (Table 3) for each recommendation and then determined the overall grade for the body of evidence by summing the individual component grades (Appendix v).

Cost effectiveness analyses that were based on modelling, could not be evaluated using the NHMRC 'Body of Evidence Matrix'. Hence, cost-effectiveness recommendations were not graded.

Table 3: NHMRC Body of Evidence Matrix

Component	A	B	C	D
	Excellent	**Good**	**Satisfactory**	**Poor**
Evidence base	several level I or II studies with low risk of bias	one or two level II studies with low risk of bias or a SR/multiple level III studies with low risk of bias	level III studies with low risk of bias, or level I or II studies with moderate risk of bias	level IV studies, or level I to III studies with high risk of bias
Consistency	all studies consistent	most studies consistent and inconsistency may be explained	some inconsistency reflecting genuine uncertainty around clinical question	evidence is inconsistent
Clinical impact	very large	substantial	moderate	slight or restricted
Generalisability	population/s studied in body of evidence are the same as the target population for the guideline	population/s studied in the body of evidence are similar to the target population for the guideline	population/s studied in body of evidence different to target population for guideline but it is clinically sensible to apply this evidence to target population	population/s studied in body of evidence different to target population and hard to judge whether it is sensible to generalise to target population
Applicability	directly applicable to Australian healthcare context	applicable to Australian healthcare context with few caveats	probably applicable to Australian healthcare context with some caveats	not applicable to Australian healthcare context

Table 4: Definition of NHMRC grades of recommendation

Grade of recommendation	Description
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution

Step 7. Articulate the guidelines

For each guideline, clinical questions identified by EAGs are addressed in separate sections in a format presenting:

- *Recommendation(s*) - including grading.
- *Practice Point (s)* – including expert consensus in absence of gradable evidence.
- *Evidence Statements* - supporting the recommendations.
- *Background* - to issues for the guideline.
- *Evidence* - detailing and interpreting the key findings.
- *Evidence tables* - summarising the evidence ratings for the articles reviewed.
  At the end of the guideline, references and Search Strategy and Yield Tables documenting the identification of the evidence sources were provided.

To ensure consistency between the guidelines, a template was designed for writers to use when drafting the guidelines.

Step 8. Methods for Quality Assurance across the project

To ensure optimal accuracy and consistency within and between guideline areas, the Project Management Team conducted a range of quality assurance activities throughout the project:

Quality Assurance, Procedures and Protocols

- The provision of a Methods Manual which provides written instructions to the Chairs of the EAGs and research staff identifying the steps and processes to be followed.

- The provision to the EAGs of a selection of key published resource material relevant to the development of the guidelines (NHMRC tool kit 2000-2003; NHMRC, 2007).

- Specification and training of research staff on the search process.

Quality Assurance, Methods

- The appointment of a Senior Research Officer to the Project Management Team to advise on research methods, and provide a resource and support service to the research staff.

- The establishment of a Methods Advisory Group.

- The development of questions based on key clinical issues for each guideline topic to focus and guide the literature searches and the formulation of the guideline recommendations. As previously indicated, these are listed at the beginning of each guideline and the Search Strategy and Yield Table at the end of the guideline.

- The Project Management Team collated and reviewed the questions and undertook a Delphi - like process with the Chairs of EAGs to refine these questions. In addition, all EAGs and the Project Management Team reviewed the combined questions during one of the three face-to-face meetings.

- The design and provision to Chairs of EAGs and Research Officers of standardised forms documenting aspects of the search strategy used, the search yield, and the inclusion and exclusion of articles for review. A completed Search Strategy and Yield Table follows each guideline topic.

- The Senior Research Officer reviewed:
  - all search terms used to ensure that the searches were comprehensive and that the approach was similar across groups.

  - the documentation of the search process.

- The GAR Consultants worked closely with the Senior Research Officer and EAGs. The GAR Consultants provided advice on evaluating and documenting the scientific evidence, developing evidence-based recommendations based on the scientific literature, and NHMRC procedures.

- Double culling of the search yield for each guideline topic by project staff and members of the EAG.

- Double reviewing of a sample of completed reviews for each guideline topic by the Senior Research Officer or an experienced Research Officer, or by a member of the relevant EAG.

- Review of the completed recommendations and written description of the literature review for each guideline area was undertaken to check for:
  - appropriate use of references
  - accurate application of evidence ratings
  - congruence between the recommendations and evidence statements
  - consistency between recommendations
  - clarity of the literature review findings

4.0 Consultation Process

The organisational structure for the Type 2 Diabetes Guidelines Development Project was designed to involve and ensure consultation between the Guideline Development Consortium (DA, ADS, ADEA, RACGP) and the Diabetes Unit. A number of other strategies were employed to ensure wide consultation with a range of stakeholders and interested groups and individuals.

Initial Consultation
Prior to commencement of the project, initial consultation included contacting relevant professional organisations to discuss the guideline development and to seek nomination of content experts.

Internal Consultation
The internal communication and interaction between the Project Management Team and the research officers included fortnightly meetings, email communications, and regular telephone contact. In addition, for each guideline, there was individual informal meetings between the research officers and their project managers.

The Project Steering Committee
The Project Steering Committee comprised representatives from various organisations (who should be consulting with their colleagues in that organisation) include:

- Diabetes Australia (Mr Matt O'Brien)
- Medical Advisor (Professor Stephen Colagiuri)
- Australian Diabetes Society (Dr Maarten Kamp)
- Australian Diabetes Educators Association (Ms Jane Giles)
- Royal Australian Collage of General Practice (Professor Mark Harris)
- Department of Health and Ageing (Ms Suzanne Prosser)
- The Diabetes Unit, Menzies Centre for Health Policy (Associate Professor Ruth Colagiuri)

During the course of the project, DA convened two face-to-face meetings and three teleconferences of the Project Steering Committee members to provide guidance and direction to the project.

Expert Advisory Groups
The EAGs consulted formally through the inclusion of specific interest groups on the individual EAG. Examples include dietitians, clinicians, educators, researches, and consumers.

Communication strategies with EAG members included:

- Face-to-face meetings
  - an initial meeting to scope the coverage of the guideline and view the processes required to develop it, identify and agree on the roles of the EAG.
  - a final meeting to review and grade the recommendations and body of evidence form.

- Email communication seeking advice on research questions and search terms and requesting review of material developed.

- Chairs and individual members of EAGs, consulted with additional content experts regarding approaches and clinical/content issues as required.

Consultation with Guidelines Assessment Register (GAR) Consultants.
The GAR consultant for each guideline provided guideline developers with support in relation to utilising evidence-based findings and applying the NHMRC criteria. GAR consultants attended face-to-face meetings with EAGs. They provided advice on evaluating and documenting the scientific evidence and developing evidence-based recommendations based on the scientific literature and NHMRC procedures.

Consultation with Consumers
Consumer representatives were selected and appointed by Diabetes Australia for each EAG to ensure the consideration of people with type 2 diabetes with respect to their acceptability of the proposed guideline recommendations.

Public Consultation
All guidelines went through a formal public consultation process. This process was as follows:

- The guidelines were released for public consultation by Diabetes Australia through the NHMRC designated public consultation process between August and October 2008.

- The call for submissions was advertised in the national public press and a front page website advertisement was placed on the Diabetes Australia website, which linked to a full website advertisement.

- The NHMRC also advertised the draft guidelines in their 'bulletin'.

- Key stakeholder organisations (Appendix vi) were notified directly by email of the availability of the guidelines for public review and requested to comment. The emailed notice provided a link to the advertisement on the Diabetes Australia website.

- As a result of public consultation, submissions were received and referred to the Project Management Team:
  - six submissions relating to the Primary Prevention Guideline
  - four submissions relating to Case Detection and Diagnosis Guideline
  - two submissions relating to Patient Education
  - two submissions relating to Chronic Kidney Disease
  - five submissions relating to Blood Glucose Control
  - one submission did not relate to any of the guidelines but made comments on the overall process of the guideline development which was subsequently referred to the Diabetes Australia Guideline Consortium Steering Committee.

- The issues raised in these submissions were considered and consulted about internally and externally by the guideline developers and were reviewed by the Project Management and Research Teams, the Medical Advisor, the relevant EAG, and the GAR Consultant.

- Key issues from the submissions for each guideline were summarised into table form and corresponding responses addressing each issue were presented in separate documents entitled *"Response to Public Consultation on … "* and accompanied the guideline drafts presented to independent review by the NHMRC.

- Changes to the guidelines as a result of public consultation and as a result of independent review by the NHMRC were incorporated into the revised final guidelines.

Informal Consultation

Further consultation occurred throughout the project with a wide variety of groups and individuals in response to particular issues and needs. For example, the Chronic Kidney Disease Guideline has been reviewed by the CARI peer reviewers and presented at the Dialysis, Nephrology Transplant 2009 Workshop, Lorne Victoria. Comments from the peer reviewers and from the workshop have been incorporated into the subsequent revision of the draft guideline.

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APPENDICES

Appendix i: Terms of Reference of Steering Committee

Type 2 Diabetes Guidelines Project

1. **Scope**
   The Steering Committee is a composite body which provides guidance and direction to the project and advice in relation to the project to the Department of Health and Ageing via Diabetes Australia.

2. **Function**
   The role of the Steering Committee is to oversight and monitors the project progress and timelines.

3. **Membership**
   The Steering Committee will comprise representatives from the following organisations:
   - Diabetes Australia
   - The Diabetes Unit, Australian Health Policy Institute
   - Australian Diabetes Society
   - Australian Diabetes Educators Association
   - Royal Australian College of General Practitioners
   - Medical Advisor
   - Consumer – person with type 2 diabetes nominated by Diabetes Australia.

The Department of Health and Ageing (the Department) will be represented in an advisory role.

The final composition of the Steering Committee, the operating procedures and the Chair of the Committee will be agreed by the Department.

If a representative is unable to attend a meeting/teleconference they may nominate a proxy representative from their own organisation.

4. **Quorum and Voting**
   The quorum for Steering Committee meetings is to be 50% of membership plus one additional member.

   The Steering Committee shall always attempt to achieve consensus. In the event of decisions requiring a vote, each member of the Committee shall exercise a single vote. Decisions will be by a majority and the Chair shall have a casting vote.

5. **Communication**
   The Steering Committee will communicate directly with Diabetes Australia who in turn will liaise with the Department. Communication between the Steering Group and other teams and groups is essential and will be facilitated by the Chair of the Committee.

6. Frequency of Meetings

The Steering Committee will meet on at least five occasions throughout the contract period. These meetings will comprise two face-to-face meetings and three teleconferences, throughout the contract period.

7. Executive and Operational Support

The Steering Group Secretariat will be provided by Diabetes Australia. The Secretariat will provide support in writing minutes and co-ordinating meetings

8. Funding

The costs of travel, accommodation, meeting location (or teleconference) expenses and other activities proposed by the Steering Committee will be agreed and borne by Diabetes Australia.

Appendix ii: Terms of Reference for Expert Advisory Groups

Type 2 Diabetes Guidelines Project

Purpose

The Expert Advisory Groups (EAGs) for the National Evidence Based Guidelines for Type 2 Diabetes are convened by The Diabetes Unit, Menzies Centre for Health Policy (formerly Australian Health Policy Institute), The University of Sydney under the head agreement between Diabetes Australia and the Department of Health and Ageing to support the development of the guidelines by providing:

1. Overall technical and content advice and critical comment

2. Input into the development or revision of research questions to guide the literature reviews

3. Guidance on search terms and for the literature review

4. Review of drafts of the guidelines and recommendations at critical points along the continuum of their development

5. Perspectives on the feasibility and applicability of the guidelines from the perspective of their own disciplines and their peers and colleagues

Duration

The EAGs are convened for the duration of the project. It is anticipated this will cover approximately 18 months up to end 2008.

Frequency of Meetings

It is anticipated that there will be three meetings of the EAGs mainly by teleconference with one face-to-face meeting at commencement.

The EAG members may also be asked to comment on emailed information from time to time.

Expenses

Reasonable expenses for travel to meeting will be reimbursed on presentation of original receipts

Conflict of Interests

EAG members are asked to declare any/all perceived conflict/s of interest

Appendix iii: NHMRC Evidence Hierarchy, designations of 'levels of evidence' according to type of research question

Level	Intervention	Diagnostic accuracy	Prognosis	Aetiology	Screening Intervention
I	A systematic review of level II Studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive persons with a defined clinical presentation	A prospective cohort study	A prospective cohort study	A randomised controlled trial
III-1	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive persons with a defined clinical presentation	All or none	All or none	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: ▪ Non-randomised, experimental trial ▪ Cohort study ▪ Case-control study ▪ Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: ▪ Non-randomised, experimental trial ▪ Cohort study ▪ Case-control study
III-3	A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single arm study ▪ Interrupted time series without a parallel control group	Diagnostic case-control study	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)	Case series, or cohort study of persons at different stages of disease	A cross-sectional study or case series	Case series

(Source: NHMRC 2007)

Appendix iv: Study Assessment Criteria

I. Study quality criteria

Systematic reviews

1. Were the questions and methods clearly stated?
2. Is the search procedure sufficiently rigorous to identify all relevant studies?
3. Does the review include all the potential benefits and harms of the intervention?
4. Does the review only include randomised controlled trials?
5. Was the methodological quality of primary studies assessed?
6. Are the data summarised to give a point estimate of effect and confidence intervals?
7. Were differences in individual study results adequately explained?
8. Is there an examination of which study population characteristics (disease subtypes, age/sex groups) determine the magnitude of effect of the intervention?
9. Were the reviewers' conclusions supported by data cited?
10. Were sources of heterogeneity explored?

Randomised controlled trials

1. Were the setting and study subjects clearly described?
2. Is the method of allocation to intervention and control groups/sites independent of the decision to enter the individual or group in the study ?
3. Was allocation to study groups adequately concealed from subjects, investigators and recruiters including blind assessment of outcome?
4. Are outcomes measured in a standard, valid and reliable way?
5. Are outcomes measured in the same way for both intervention and control groups?
6. Were all clinically relevant outcomes reported?
7. Are factors other than the intervention e.g. confounding factors, comparable between intervention and control groups and if not comparable, are they adjusted for in the analysis?
8. Were >80% of subjects who entered the study accounted for at its conclusion?%
9. Is the analysis by intention to intervene (treat)?
10. Were both statistical and clinical significance considered?
11. Are results homogeneous between sites? (Multi-centre/multi-site studies only).

Cohort studies

1. Are study participants well-defined in terms of time, place and person?
2. What percentage (%) of individuals or clusters refused to participate?
3. Are outcomes measured in a standard, valid and reliable way?
4. Are outcomes measured in the same way for both intervention and control groups?
5. Was outcome assessment blind to exposure status?
6. Are confounding factors, comparable between the groups and if not comparable, are they adjusted for in the analysis?
7. Were >80% of subjects entered accounted for in results and clinical status described?
8. Was follow-up long enough for the outcome to occur
9. Was follow-up complete and were there exclusions from the analysis?
10. Are results homogeneous between sites? (Multicentre/multisite studies only).

Case-control studies

1. Was the definition of cases adequate?

2. Were the controls randomly selected from the source of population of the cases?
3. Were the non-response rates and reasons for non-response the same in both groups?
4. Is possible that over-matching has occurred in that cases and controls were matched on factors related to exposure?
5. Was ascertainment of exposure to the factor of interest blinded to case/control status?
6. Is exposure to the factor of interest measured in the same way for both case and control groups in a standard, valid and reliable way (avoidance of recall bias)?
7. Are outcomes measured in a standard, valid and reliable way for both case and control groups?
8. Are the two groups comparable on demographic characteristics and important potential confounders? and if not comparable, are they adjusted for in the analysis?
9. Were all selected subjects included in the analysis?
10. Was the appropriate statistical analysis used (matched or unmatched)?
11. Are results homogeneous between sites? (Multicentre/multisite studies only).

Diagnostic accuracy studies

1. Has selection bias been minimised
2. Were patients selected consecutively?
3. Was follow-up for final outcomes adequate?
4. Is the decision to perform the reference standard independent of the test results (ie avoidance of verification bias)?
5. If not, what per cent were not verified?
6. Has measurement bias been minimised?
7. Was there a valid reference standard?
8. Are the test and reference standards measured independently (ie blind to each other)
9. Are tests measured independently of other clinical and test information?
10. If tests are being compared, have they been assessed independently (blind to each other) in the same patients or done in randomly allocated patients?
11. Has confounding been avoided?
12. If the reference standard is a later event that the test aims to predict, is any intervention decision blind to the test result?

(Sources: adapted from NHMRC1999, NHMRC 2000a, NHMRC 2000b, Liddle et al 96; Khan et 2001)

Study quality – Rating

The following was used to rate the quality of each study against the study type criteria listed above.

High: all or all but one of the criteria were met

Medium: 2 or 3 of the criteria were not met

Low: 4 or more of the criteria were not met

II. Classifying magnitude of the effect

Ranking	Statistical significance		Clinical importance of benefit
High	Difference is statistically significant	AND	There is a clinically important benefit for the full range of estimates defined by the confidence interval.
Medium	Difference is statistically significant	AND	The point estimate of effect is clinically important BUT the confidence interval includes some clinically unimportant effects
Low	Difference is statistically significant OR Difference is not statistically significant (no effect) or shows a harmful effect	AND AND	The confidence interval does not include any clinically important effects The range of estimates defined by the confidence interval includes clinically important effects.

(Source: adapted from the NHMRC classification (NHMRC 2000b)

III. Classifying the relevance of the evidence

Ranking	Relevance of the evidence
High	Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival *Or* Evidence of an effect on a surrogate outcome that has been shown to be predictive of patient-relevant outcomes for the same intervention
Medium	Evidence of an effect on proven surrogate outcomes but for a different intervention *Or* Evidence of an effect on proven surrogate outcomes but for a different intervention and population
Low	Evidence confined to unproven surrogate outcomes.

(Source: adapted from the NHMRC classification (NHMRC 2000b)

Appendix v: NHMRC Evidence Statement Form

Key question(s):		Evidence table ref:
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
	A	Several Level I or II studies with low risk of bias
	B	one or two Level II studies with low risk of bias or SR/multiple Level III studies with low risk of bias
	C	Level III studies with low risk of bias or Level I or II studies with moderate risk of bias
	D	Level IV studies or Level I to III studies with high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
	A	Very large
	B	Moderate
	C	Slight
	D	Restricted
4. Generalisability		
	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability		
	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base		
2. Consistency		
3. Clinical impact		
4. Generalisability		
5. Applicability		

Indicate any dissenting opinions

RECOMMENDATION	GRADE OF RECOMMENDATION	
What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.		

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	YES
	NO
Are there any resource implications associated with implementing this recommendation?	YES
	NO
Will the implementation of this recommendation require changes in the way care is currently organised?	YES
	NO
Are the guideline development group aware of any barriers to the implementation of this recommendation?	YES
	NO

Appendix vi: Key stakeholder organisations notified of public consultation

- Diabetes Australia State and Territory member organisations including:
    - Australian Diabetes Society
    - Australian Diabetes Educators Association

- University Schools of Nursing, Medicine, Podiatry, Nutriton/ Dietetics
- Australian Podiatry Association
- Australian Podiatry Council
- Eyes on Diabetes
- Cooperative Centre for Aboriginal Health
- Australian Centre for Diabetes Strategies
- Public and private Diabetes Centres throughout Australia (for which we were able to obtain email addresses)
- State and Federal health departments