

The effectiveness of GLP-1
analogues compared to DPP-4
inhibitors for beta cell function
and diabetes related complications
among adults with type 2 diabetes:
a systematic review and meta-
analysis

Mrs Susan Bellman
Master of Clinical Science
The Joanna Briggs Institute
Faculty of Health Sciences
The University of Adelaide
South Australia

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Declaration

I, Susan Bellman, certify that this work contains no material that has been accepted for the award of any other tertiary institution, and, to the best of my knowledge and belief, contains no material previously published or written by any other person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and, where applicable, any partner institution responsible for the joint award of this degree.

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Susan Marie Bellman

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Abstract

Continued loss of beta cell function is responsible for progressive deterioration of plasma glucose control and complications characteristic of type 2 diabetes. Two classes of incretin-based antihyperglycaemic agents, dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) analogues, have shown favourable effects on beta cell function. The aim of this systematic review was to provide a comprehensive synthesis of randomised clinical studies comparing the effectiveness of GLP-1 analogues to DPP-4 inhibitors in improving beta cell function and managing diabetes related complications.

A search of PubMed, EMBASE and national and international clinical trials databases was conducted for randomised controlled trials that compared GLP-1 analogues to DPP-4 inhibitors, either alone or in combination with metformin, in adults with type 2 diabetes. Methodological quality of included studies was assessed using the Joanna Briggs Institute (JBI) critical appraisal checklist, and research data was extracted using the JBI data extraction tool. Outcomes included beta cell function (measured by homeostasis model assessment-beta [HOMA-beta], plasma connecting peptide [C-peptide] and proinsulin to insulin [PI/I] plasma concentration ratio) glycated haemoglobin (HbA1c), fasting and postprandial plasma glucose levels, diabetes related complications, and adverse drug events.

Seven randomised controlled trials including 2661 participants were included in this review. The overall quality of included studies was good. Treatment duration ranged from 24 to 52 weeks in the included studies and included a number of different dosages. Results of meta-analysis showed that GLP-1 analogues, at different dosages and duration, were associated with statistically significant improvements in beta cell function compared to DPP-4 inhibitors as measured by HOMA-beta; mean difference 23% and 25% for high dose GLP-1 analogues

after 26 and 52 weeks, respectively ($p < 0.00001$); 18.5% and 16.7% for low dose GLP-1 analogues after 26 and 52 weeks, respectively ($p < 0.00001$). Treatment with GLP-1 analogues showed a greater reduction in glycated haemoglobin (HbA1c) compared to treatment with DPP-4 inhibitors: a mean difference of -0.52% and -0.68% (-5.67mmol/mol and -7.41mmol/mol) for high dose GLP-1 analogues after 26 and 52 weeks, respectively ($p < 0.00001$); and -0.38% and -0.45% (-4.14mmol/mol and -4.91mmol/mol) for low dose GLP-1 analogues after 26 and 52 weeks, respectively ($p < 0.00001$). Treatment with GLP-1 analogues resulted in a greater reduction in fasting plasma glucose compared to DPP-4 inhibitors: a mean difference of -1.23 mmol/L and -1.47 mmol/L (-22.16 mg/dL and -26.49 mg/dL) for high dose GLP-1 analogues after 26 and 52 weeks, respectively ($p < 0.00001$); and -1.01mmol/L and -0.84mmol/L (-18.20mg/dL and -15.13 mg/dL) for low dose GLP-1 analogues after 26 and 52 weeks, respectively ($p < 0.00001$). No studies reported outcomes for diabetes related complications. However, DPP-4 inhibitors were associated with fewer gastrointestinal adverse events compared to GLP-1 analogues. There were no differences in other adverse events such as headache and infection.

The findings showed that GLP-1 analogues had greater beneficial effects on pancreatic beta cell function and plasma glucose control than DPP-4 inhibitors, but caused more gastrointestinal adverse events. Longer term safety data is required to better identify the contribution of GLP-1 analogues in reducing diabetes related microvascular complications, and determine their long term pancreatic and cardiac effects.

Chapter 1: Introduction

1.1 Background

Type 2 diabetes is a progressive condition, characterised by a combination of impaired insulin secretion from pancreatic beta cells and increasing insulin resistance arising from diminished tissue sensitivity to the action of insulin.⁽¹⁻⁶⁾ Impaired insulin secretion is a consequence of declining pancreatic beta cell function, and it is well documented that beta cell failure begins early in the course of type 2 diabetes.⁽¹⁻⁵⁾ The landmark United Kingdom Prospective Diabetes Study (UKPDS), which ran from 1977 to 1991, clearly demonstrated progressive beta cell failure amongst individuals with newly diagnosed type 2 diabetes.⁽⁷⁾ The UKPDS showed that not only had individuals with type 2 diabetes lost 50% of their beta cell function at the time of diabetes diagnosis^(1, 2, 8), but extrapolation of this observed rate of decline estimated that beta cell decline had actually begun 10 to 12 years before diagnosis.^(1, 8) With its insidious onset, type 2 diabetes is often unrecognised, and hyperglycaemia may be present for many years before diabetes symptoms develop, or a routine health check reveal elevated plasma glucose levels.⁽⁸⁾ Whilst declining beta cell function is characteristic of type 2 diabetes⁽¹⁻⁵⁾ its pathogenesis is not fully understood.⁽¹⁾ Evidence suggests that exposure of beta cells to chronically elevated plasma glucose levels results in beta cell damage.^(1, 2) However, other factors considered to contribute to beta cell decline include lipotoxicity, islet amyloid polypeptide deposition, inflammation and oxidative stress.⁽¹⁾ Whilst increased insulin resistance also plays a major role in the pathophysiology of type 2 diabetes, research has found that a decline in beta cell function is two to three times greater than the reduction in insulin sensitivity.⁽¹⁾ The continued loss of beta cell function responsible for progressive deterioration of plasma glucose control⁽¹⁾ and persistently elevated levels of plasma glucose over time lead to various cardiovascular and microvascular complications, such as retinopathy, nephropathy and neuropathy.^(9, 10)

Currently, the primary aim of treatment for type 2 diabetes is to stabilise plasma glucose levels to reduce the development of diabetes related complications.⁽¹⁰⁾ However, given the close relationship between disease progression, deterioration of insulin secretion and increased complication risk, preservation of beta cell function should be an important treatment goal for individuals with type 2 diabetes.⁽¹⁾ Instead of diabetes management focusing solely on the management of plasma glucose, treatment should ideally address the underlying diabetes pathology.⁽⁵⁾ Managing type 2 diabetes with new classes of antihyperglycaemic agents that have favourable effects on beta cell function would provide more sustainable glucose lowering effects than the more traditional antihyperglycaemic agents that directly target reduction of plasma glucose.^(1, 11) The traditional pharmacological treatments prescribed for type 2 diabetes, including metformin and sulfonylureas, do not target progressive decline in beta cell function, and therefore despite therapy, individuals continue to advance in their disease state⁽¹²⁾, until insulin replacement therapy is necessary to achieve glycaemic goals.^(13, 14)

Recently, incretin gastrointestinal hormones have been shown to play a crucial role in regulating normal insulin response⁽¹⁵⁾, and have demonstrated positive effects in reducing beta cell function, making the incretin pathway a target for the development of new antihyperglycaemic agents.^(11, 16-18) Incretin hormones are enteric-derived peptides with a variety of glucoregulatory functions.⁽¹⁹⁾ There are two important incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP).^(20, 21) Both *in vitro* and *in vivo* clinical trials have shown that these gastrointestinal incretin hormones have positive effects on the beta cell insulin function.^(2, 11, 16-18) This incretin effect is however reduced or in some cases absent in individuals with type 2 diabetes^(2, 11, 16-18) and it has been postulated that a deficiency in the secretion of one of these hormones, GLP-1,

contributes to the consistent decline in beta cell function that occurs during the course of type 2 diabetes.^(3, 11, 21)

Hence, two new antihyperglycaemic agents that target the incretin hormone GLP-1 have been introduced to the armamentarium of existing pharmacotherapies for diabetes management. GLP-1 analogues (also known as GLP-1 receptor agonists or GLP-1 mimetics) and dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors)^(16, 17, 22) both induce GLP-1 cellular activity.⁽¹⁹⁾ GLP-1 analogues are administered by subcutaneous injection whilst DPP-4 inhibitors are orally ingested agents.^(11, 16) The popularity of both of these antihyperglycaemic agents for use in the management of type 2 diabetes is increasing, and the development of further agents to add to already existing class members is dynamic.⁽¹⁹⁾ Although DPP-4 inhibitors and GLP-1 analogues are now widely used for the control of plasma glucose levels, there is still much debate about their effectiveness on pancreatic beta cell function in adults with type 2 diabetes.⁽²³⁾

One important clinical question that requires further investigation relates to which one of the two classes of incretin-based therapies is the most favourable for the management of type 2 diabetes, in relation to beta cell function and ultimately diabetes related complications.

Numerous clinical trials have compared the efficacy and safety of GLP-1 analogues and DPP-4 inhibitors with other oral antihyperglycaemic agents or placebo⁽²⁴⁻³³⁾; however, few direct comparisons of incretin-based therapies have been published.⁽³⁴⁾

Vilsboll⁽²⁾ concluded that GLP-1 analogues were the first class of type 2 diabetes therapy that had the potential to delay or even reverse disease progression by improving beta cell function. This conclusion has been supported by several other authors.^(13, 35) Results of DPP-4 inhibitors and their impact on beta cell function however have not been as conclusive. Whilst

several studies have shown favourable improvement in beta cell function^(24, 36), a recent Cochrane review of the efficacy of DPP-4 inhibitors stated that no definite conclusions could be drawn from published data on measurements of beta cell function, based on insufficient study data and inconsistency in methods used to measure beta cell function.⁽³⁷⁾

1.2 Aetiology and pathophysiology of diabetes

The disease burden related to diabetes is high and rising in every country.⁽³⁸⁾ The premature morbidity, mortality, reduced life expectancy and financial costs of diabetes make it an important public health concern.⁽³⁸⁾ Worldwide there are 387 million individuals with diabetes, and by the year 2035, this figure is expected to rise to 592 million.⁽³⁹⁾

The aetiological classification of diabetes has been widely accepted.⁽³⁸⁾ Type 1 and type 2 diabetes are the two main diabetes types, with type 2 diabetes accounting for the majority (>85%) of total diabetes prevalence.⁽³⁸⁾ Both forms of diabetes can lead to multisystem complications of microvascular endpoints, including retinopathy, nephropathy and neuropathy, as well as macrovascular endpoints, including ischaemic heart disease, stroke and peripheral vascular disease.⁽³⁸⁾ The overall risk of death among people with diabetes is at least double that of their peers without diabetes, and literature suggests that 50% of people with diabetes die of cardiovascular disease, primarily heart disease and stroke.⁽⁴⁰⁾ One person dies from diabetes every seven seconds⁽³⁹⁾ and the World Health Organization (WHO) projects that globally, diabetes will be the seventh leading cause of death by 2030.⁽⁴⁰⁾

Type 1 diabetes is characterised by absolute deficiency of insulin secretion due to autoimmune mediated destruction of pancreatic beta cells^(14, 37) leading to hyperglycaemia.⁽³⁷⁾

Type 1 diabetes usually develops before the age of 30 years⁽³⁷⁾, but can occur at any age.^(37, 38)

In most populations, the incidence is highest between birth and 14 years of age. Type 1

diabetes has an acute onset, and its rapid presentation for medical treatment allows accurate registering of new cases.⁽³⁸⁾ Daily insulin replacement therapy is required for survival, in the form of subcutaneous insulin injection or insulin pump therapy, also known as continuous subcutaneous insulin infusion (CSII).⁽⁴¹⁾

For type 2 diabetes, the action and secretion of insulin are impaired as opposed to the absolute deficiency of insulin that occurs in type 1 diabetes.⁽³⁷⁾ Table 1.1 outlines the risk factors associated with type 2 diabetes.⁽⁴²⁾

Table 1.1. Aetiological risk factors of type 2 diabetes⁽⁴²⁾

- | |
|---|
| <ul style="list-style-type: none">▪ Family history of diabetes▪ Older age (over 55 years of age)▪ Over 45 years of age and overweight▪ Over 45 years of age with high blood pressure▪ Over 35 years of age and from an Aboriginal or Torres Strait Islander background▪ Over 35 years of age and from Pacific Island, Indian subcontinent or a Chinese cultural background▪ Women who have given birth to large babies (over 4.5kg [9lbs])▪ Women who have a history of gestational diabetes▪ Women with Polycystic Ovarian Syndrome (PCOS) |
|---|

Its slow progression means that the true time of onset is difficult to determine.⁽³⁸⁾ Due to the slow development of symptoms, diagnosis may only be made several years after onset, once complications have already arisen.⁽⁴⁰⁾ Classic symptoms of type 2 diabetes may include frequent urination, fatigue and excessive thirst, while other symptoms of headache and mood swings are less specific.⁽⁴²⁾ A detailed list of symptoms of type 2 diabetes is outlined in Table 1.2.

Table 1.2. Symptoms of type 2 diabetes^(42, 43)

▪ Excessive thirst (polydipsia)	▪ Weight gain
▪ Frequent urination (polyuria)	▪ Mood swings
▪ Lethargy and fatigue	▪ Headaches
▪ Consistent hunger	▪ Dizziness
▪ Poor wound healing	▪ Leg cramps
▪ Frequent fungal or bacterial infections	▪ Loss of sensation (e.g. touch, vibration, cold)
• Blurred vision	

For every person diagnosed with type 2 diabetes, there is another who has undiagnosed diabetes, although the proportion who are undiagnosed varies between countries and ranges from 28% to 80%.⁽⁴⁴⁾ Criteria for the diagnosis of type 2 diabetes have changed over the years as more relevant information regarding its diagnosis becomes available. The WHO has published diagnostic guidelines since 1965 which reflect these changes.⁽⁴⁵⁾ Diagnosis of diabetes is based on measurement of plasma glucose concentrations and Table 1.3 summarises diagnostic criteria currently being used by the WHO for type 2 diabetes, along with the diagnostic criteria as they have changed over the years.⁽⁴⁵⁾

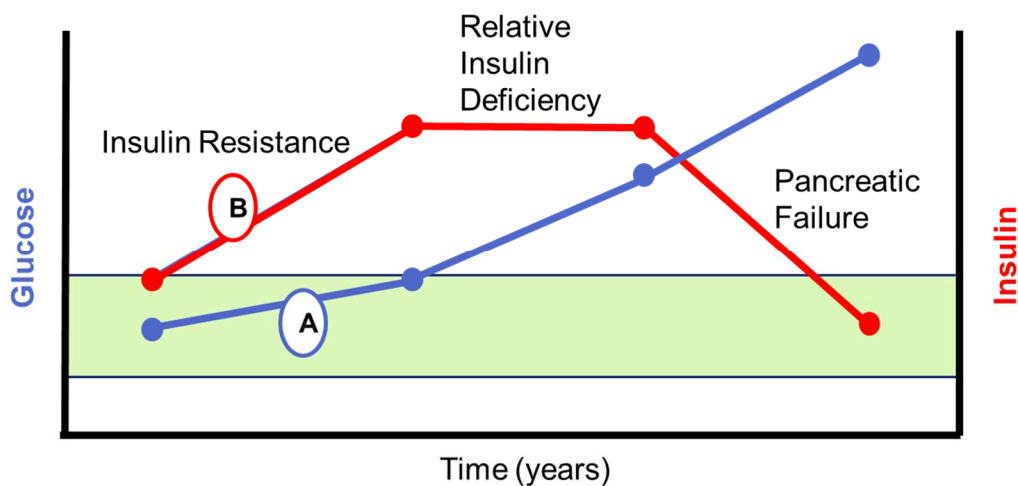
Table 1.3. Summary of WHO diagnostic criteria for type 2 diabetes over time^(45, 46)

Type 2 diabetes	1965	1980	1985	1999	2006	2009
Fasting glucose	Not specified	≥8.0mmol/L (≥144.1 mg/dL) and/or	≥7.8mmol/L (≥140.5mg/dL) or	≥7.0mmol/L (≥126.1mg/dL) or	≥7.0mmol/L (≥126.1mg/dL) or	≥7.0mmol/L (≥126.1mg/dL) or
2-hour glucose	≥7.2mmol/L (≥129.7 mg/dL)	≥11.0mmol/L (≥198.2mg/dL)	≥11.1mmol/L (≥200.0mg/dL)	≥11.1mmol/L (≥200.0mg/dL)	≥11.1mmol/L (≥200.0mg/dL)	≥11.1mmol/L (≥200.0mg/dL)
HbA1c	Not considered	Not considered	Not considered	Not considered	Not suitable	≥ 6.5% (≥48mmol/mol)

Type 2 diabetes is complex in nature, and involves a variety of pathophysiological abnormalities, including insulin resistance, that result in increased hepatic glycogenolysis and/or gluconeogenesis and decreased peripheral glucose uptake and impaired beta cell

function.^(37, 47) Insulin secretion is primarily triggered by increased circulating concentrations of glucose, and in individuals without type 2 diabetes, an immediate response of a short first phase insulin stimulated by glucose is followed by a longer second phase of insulin secretion which continues while hyperglycaemia persists.⁽²³⁾ The first phase of insulin secretion is rapid, and due to mobilisation of a readily releasable pool of insulin granules.⁽²³⁾ The second phase is slow, and due to subsequent supply of new insulin granules for release.⁽²³⁾ In individuals with type 2 diabetes, declining beta cell function is responsible for loss of the first phase insulin response.^(2, 23) The loss of the first phase insulin secretion is considered important due to its primary role not only in insulin's action on target tissues, but also for controlling postprandial glucose excursions.⁽²³⁾

The UKPDS estimates that the rate of decline in pancreatic beta cell function in newly diagnosed type 2 individuals is 4% each year.⁽⁴⁸⁾ Figure 1.1 is a graphical illustration of the natural history of type 2 diabetes. The concept that insulin resistance contributes to the pathogenesis of hyperglycaemia can be explained by the fact that the progressive decline in beta cell function compounds a failure to compensate for decreasing insulin action.⁽⁴⁹⁾



(A) Elevations in blood glucose level over time, (B) progression from compensatory beta cell function to beta cell decline and failure resulting in a decrease in insulin concentration. Shaded area represents normal blood glucose range.

Adapted from Wu T & Overland J. *Initiating and intensifying insulin therapy* ⁽⁵⁰⁾

Figure 1.1. Natural history of type 2 diabetes

VilSBoll⁽²⁾ explained that chronically elevated plasma glucose levels in individuals with type 2 diabetes have a detrimental glucotoxicity effect on beta cells due to increased oxidative stress. Evidence supports the fact that increased exposure of pancreatic beta cells to glucose is associated with not only beta cell desensitisation but also beta cell apoptosis and exhaustion.^(1, 2) This results in a vicious cycle of reduced insulin production, hyperglycaemia and beta cell damage.⁽²⁾

In recent years there has been growing interest around the incretin glucoregulatory hormone's involvement in beta cell function. Research suggests that a defect in the incretin glucoregulatory system plays a role in the pathophysiology of type 2 diabetes^(16, 51, 52) and, notably, it has been postulated that this defect contributes to a consistent decline in beta cell function.⁽¹¹⁾

1.2.1 The incretin effect

Incretin hormones are released in response to the presence of glucose or nutrients in the gastrointestinal tract.^(16, 52) The theory evolved from observations in the 1960s that an oral glucose load elicited a greater insulin secretory response from pancreatic beta cells compared with the same amount of glucose given intravenously.^(11, 16, 17, 52, 53) This effect of insulin secretion mediated by the gut was known as the *intestinal secretion of insulin or incretin effect*. The incretin hormones GLP-1 and GIP have a variety of metabolic effects (refer Table 1.4).^(11, 21, 51, 52, 53) Glucose-dependent insulintrophic polypeptide is a 42-amino acid polypeptide synthesised in duodenal and jejunal K cells in the proximal small bowel, while GLP-1 circulates as two equipotent amino acid polypeptide molecular forms, GLP-1(7-37) and GLP-1(7-36) amide, with the latter GLP-1 amide being more abundant in the circulation after eating.^(11, 52) Most GLP-1 is secreted by L cells in the distal ileum and colon.^(3, 11, 17, 51, 52, 54) Whilst the GIP receptor is predominantly expressed in the pancreatic beta cells, and to a lesser extent in adipose tissue and in the central nervous system, the GLP-1 receptor is expressed in pancreatic alpha and beta cells and in the peripheral tissues, including the central and peripheral nervous systems, heart, kidney, lung and gastrointestinal tract.⁽⁵²⁾

Table 1.4. Comparative actions of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintrophic polypeptide (GIP)^(21, 53)

GLP-1	GIP
Released from L cells in ileum and colon	Released from K cells in duodenum and jejunum
Stimulates all steps of insulin biosynthesis and insulin release from beta cells	Stimulates insulin release from beta cells
Potent inhibition of gastric emptying and promotion of satiety	Modest effects on gastric emptying and no effect on satiety
Potent inhibition of glucagon secretion	No significant inhibition of glucagon secretion
Reduction of body weight	No effect on body weight
Insulintrophic actions preserved in type 2 diabetes	Defective insulintrophic actions in type 2 diabetes

Secretion significantly impaired in type 2 diabetes	Secretion normal or slightly impaired in type 2 diabetes
Significant effects on beta cell growth and survival	No reported effects on beta cell growth and survival

To fully understand the glucoregulatory role of these two incretin hormones, it is important to review glucose homeostasis. The pancreatic hormones, insulin and glucagon have counter-regulatory roles in maintaining glucose homeostasis.⁽⁵¹⁾ Insulin, released from beta cells in the Islet of Langerhans, allows the active transportation of glucose from the bloodstream into muscle and tissues where it is used by the body as an energy source.⁽⁵¹⁾ Insulin also allows the uptake of glucose into fat cells where it is converted to fatty acids for long-term storage.⁽⁵¹⁾ Additionally, insulin facilitates movement of glucose into the liver for conversion into glycogen for short term storage.⁽⁵¹⁾ Glucagon, on the other hand, is released from the pancreatic alpha cells in the Islet of Langerhans, and enables glucose production from hepatic glycogen stores, via glycogenolysis and gluconeogenesis.⁽⁵¹⁾ The resulting glucose is then released into the bloodstream.⁽⁵¹⁾ To maintain glucose homeostasis and prevent hyperglycaemia or hypoglycaemia, hepatic glucose production and insulin-stimulated glucose uptake act in concert, and the process is tightly regulated through a complex system of nutrient, neural and hormonal signals.⁽⁵¹⁾ After food is ingested, endocrine signals, principally GLP-1 and GIP, and also neural signals from adrenergic and cholinergic nerves, reach the pancreas.⁽⁵¹⁾ The pancreas is also directly stimulated by circulating glucose.⁽⁵¹⁾ The net effect is stimulation of beta cells to produce and release insulin in a biphasic fashion, enabling the movement of glucose from the blood supply into muscles and tissues.⁽⁵¹⁾ At the same time, to compensate for the entry of dietary glucose into the blood stream from the gastrointestinal tract, glucagon release from alpha cells is suppressed to decrease hepatic glucose production.⁽⁵¹⁾ In this way, hyperglycaemia is controlled.⁽⁵¹⁾ The shift from hepatic glucose

production to glucose uptake by muscles, fat and liver occurs within 20 minutes after plasma insulin levels begin to rise and glucagon levels fall.⁽⁵¹⁾ The action of incretin hormones relies on the presence of a minimal glucose threshold of between 3.6mmol/L⁽¹⁰⁾ (64.9mg/dL)⁽⁵⁵⁾ and 4.3mmol/L (77.5mg/dL)⁽⁵⁵⁾, ensuring that insulin and glucagon secretion is co-ordinated according to the body's needs.⁽⁵¹⁾ An important component of the finely tuned mechanism to maintain glucose homeostasis is the rapid inactivation of the incretin hormones by DPP-4 enzyme⁽⁵³⁾, an ubiquitous peptidase expressed in a wide variety of tissues.^(3, 11, 51, 54) The incretin hormones' half-life is between one and two minutes, due to their inactivation by DPP-4.^(3, 11, 51, 54)

Research has demonstrated that in individuals with type 2 diabetes, the defective incretin effect contributes significantly to hyperglycaemia.^(11, 12, 17-19, 52, 56) Differing hormonal mechanisms account for the defective incretin effect observed; GLP-1 secretion is reduced whereas cellular activity stimulated by GIP decreases.^(11, 17, 51, 56) Importantly, it has been postulated that reduced GLP-1 secretion is a consequence rather than a cause of diabetes, contributing to the consistent decline in beta cell function.^(11, 21, 57) Animal studies have shown that GLP-1 seems to have multiple positive effects on beta cells⁽²⁾, by promoting beta cell proliferation, inhibiting apoptosis, increasing beta cell neogenesis and increasing beta cell mass in *in vivo* and *in vitro* models of diabetes.^(1-3, 9, 10, 12, 14, 17, 18) Hence, the new focus of type 2 diabetes management has been on restoring GLP-1 physiologic concentrations⁽²¹⁾, with two antihyperglycaemic agents now available that affect glucose homeostasis via GLP-1 pathways. These two classes of incretin-based therapies are classified as GLP-1 analogues and DPP-4 Inhibitors and they join the existing armamentarium against type 2 diabetes.

1.3 Antihyperglycaemic agents

There are a number of different classes of antihyperglycaemic agents available for the management of type 2 diabetes. Metformin is first line therapy, in conjunction with dietary and other lifestyle modifications, including exercise and diet.^(58, 59) Metformin has been used since the second half of the 20th century.⁽²⁰⁾ It is inexpensive and well supported by long-term safety data.⁽⁶⁰⁾ The progressive nature of type 2 diabetes, a consequence of declining beta cell function⁽⁷⁾, usually necessitates addition of other antihyperglycaemic agents to metformin treatment, in order to manage rising plasma glucose levels.^(11, 16, 61) Reports suggest that after three years of treatment, approximately 50% of individuals will require more than one drug to control their blood glucose levels, and after nine years, only 25% can manage their blood glucose levels with one drug.⁽¹¹⁾ An overview of the commonly prescribed antihyperglycaemic agents is described below with a particular emphasis on the two incretin-based therapies, GLP-1 analogues and DPP-4 inhibitors.

1.3.1 Biguanide

Metformin is the sole member of the biguanide class of medication⁽⁶²⁾ and works to reduce plasma glucose levels in three ways: 1) reducing hepatic glucose production and output by inhibiting gluconeogenesis and glycogenolysis^(1, 4, 58); 2) increasing insulin sensitivity, thereby improving peripheral glucose intake and utilisation^(1, 4); and 3) delaying intestinal glucose absorption.⁽⁵⁾ Metformin remains the treatment of choice when initiating therapy for type 2 diabetes⁽⁵⁹⁾ and has been shown to decrease cardiovascular outcomes in type 2 diabetes subjects.⁽⁶³⁾ However, reports suggest that metformin has little or no protective effect on beta cell function.⁽¹⁾ Orally administered, the most common adverse effect is gastrointestinal upset, including nausea, vomiting, diarrhoea and anorexia.^(58, 62) Metformin is unlikely to cause weight gain^(4, 58) and is considered to be one of the oldest and safest oral medications used in the treatment of diabetes.⁽⁶²⁾

1.3.2 Sulfonylureas

Sulfonylureas, also known as insulin secretagogues, reduce plasma glucose levels by stimulating pancreatic beta cells to release insulin.^(4, 64) Orally administered, sulfonylureas bind to the sulfonylurea receptors on the surface of beta cells and inhibit potassium efflux, depolarising the beta cells and facilitating insulin release.⁽⁶²⁾ Not surprisingly, due to their mechanism of action, sulfonylureas exhaust beta cell function^(2, 23) and induce beta cell apoptosis^(37, 65), therefore their clinical usefulness declines over time.⁽⁶⁵⁾ One of the main side effects of sulfonylureas is hypoglycaemia, as they stimulate insulin release independently of plasma glucose levels.⁽⁵⁸⁾ This can be detrimental, particularly in the elderly or those with irregular eating patterns.⁽⁶²⁾ Risk of weight gain is also increased with sulfonylurea use, with some individuals experiencing an increase of ≥ 2 kg.⁽⁶²⁾ Examples of sulfonylureas are glipizide, glibenclamide, gliclazide and glimepiride.⁽⁶⁶⁾

1.3.3 Meglitinides

Oral meglitinides (glinides), like sulfonylureas, stimulate pancreatic beta cells by binding to the sulfonylurea receptor and inducing depolarisation.⁽⁶²⁾ They are used as alternatives to sulfonylureas, have a more rapid effect and shorter half-life than sulfonylureas and therefore require more frequent dosing.⁽⁶²⁾ Glinides have a lower propensity for hypoglycaemia, and therefore may be useful in those individuals at risk of hypoglycaemia, for example, the elderly.⁽⁶²⁾ Weight gain however is still a potential side effect.⁽⁶²⁾ Examples of glinides are repaglinide and nateglinide.^(62, 66)

1.3.4 Thiazolidinediones

The thiazolidinediones, rosiglitazone and pioglitazone, are potent and highly selective agonists for peroxisome proliferator-activated receptors (PPARs).^(58, 62) These receptors are found in such sites as adipose tissue, skeletal muscle and liver.^(1, 4, 58) Orally ingested,

thiazolidinediones act primarily by decreasing insulin resistance and inhibiting hepatic gluconeogenesis.^(1, 4, 58) The ability of thiazolidinediones to improve beta cell function has been the focus of much research with differing reports suggesting either beneficial or neutral effects.^(1, 12, 65, 67) The use of thiazolidinediones is declining in clinical practice due to their adverse effect profile.⁽¹⁾ Thiazolidinedione use is associated with weight gain, increased incidence of oedema, congestive heart failure and bone fractures, particularly in women^(1, 58, 59, 64), and also with bladder cancer, particularly pioglitazone.⁽⁵⁹⁾

1.3.5 Alpha-glucosidase inhibitors

Alpha-glucosidase inhibitors, for example, acarbose, block the action of alpha-glucosidase, an intestinal enzyme responsible for the degradation of ingested carbohydrates.^(58, 62, 66)

Inhibition of alpha-glucosidase leads to a delay in the digestion of carbohydrates, and subsequent reduction in postprandial plasma glucose levels.^(58, 62) The main side effects of this oral preparation are gastrointestinal in nature^(4, 58) and have led to discontinuation of treatment with this medication in up to 25% of people.⁽⁵⁸⁾

1.3.6 Sodium-glucose co-transporter-2 inhibitors

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors block the action of SGLT-2 which is expressed in the proximal tubule of the kidney, and is responsible for the reabsorption of glucose from the glomerular filtrate back into systemic circulation.⁽⁵⁹⁾ Inhibition of SGLT-2 by SGLT-2 inhibitors therefore improves glycaemic control by reducing the amount of glucose that is reabsorbed at the proximal tubule back into systemic circulation, and increases excretion of urinary glucose by up to 80 grams per day.⁽⁵⁹⁾ Urinary glucose loss is the mechanism for weight loss associated with these drugs.⁽⁵⁸⁾ Modest weight loss of approximately 2 kg has been reported.⁽⁵⁹⁾ Adverse effects associated with this oral medication include dehydration, dizziness and increased risk of genitourinary tract infections.⁽⁵⁸⁾

Examples of SGLT-2 inhibitors are dapagliflozin, canagliflozin and empagliflozin.^(58, 68)

1.3.7 Insulin

Discovered in the early 1920s⁽⁶⁹⁾, insulin is the most potent glucose-lowering agent.⁽⁵⁸⁾ Insulin comes in the form of subcutaneous injection preparations which are short-, intermediate- and long-acting, as well as premixed preparations.⁽⁵⁸⁾ Some research suggests that insulin may improve beta cell function initially^(1, 70); however there is lack of evidence that insulin can sustain or further improve beta cell function over longer time periods.⁽⁴⁾ Side effects associated with insulin include weight gain and hypoglycaemia.⁽⁷¹⁻⁷⁴⁾

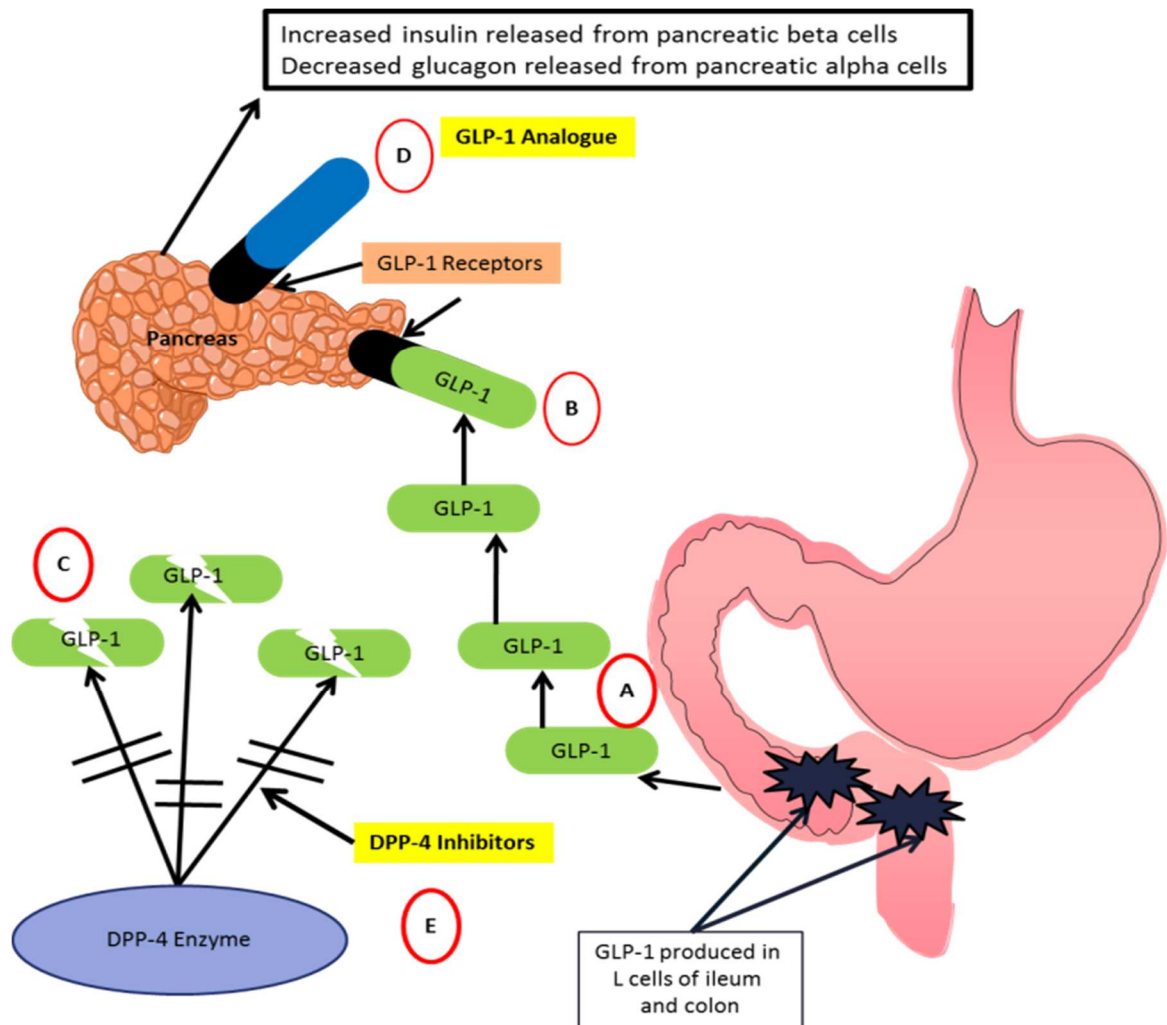
1.3.8 Glucagon-like peptide-1 (GLP) analogues

Glucagon-like peptide-1 (GLP-1) analogues are incretin mimetics^(1, 20) with a structural homology similar to endogenous GLP-1 that are designed to fulfill the role of native GLP-1, but are resistant to degradation by the DPP-4 enzyme.^(9, 20) They improve glycaemic control by increasing beta cell insulin secretion, suppressing glucagon secretion and slowing gastric motility.^(1, 20) Delayed gastric emptying also suppresses appetite, which contributes to weight loss^(1, 58, 75, 76), which contribute to overall glucose lowering potency.⁽⁷⁶⁾ GLP-1 analogues have been associated with reduction in body weight of approximately 3kg.⁽²⁰⁾ Therapeutic doses of GLP-1 analogues can produce supraphysiologic levels of GLP-1 (equivalent to six-10 fold normal GLP-1 levels)⁽⁹⁾ and their lowering of both fasting and postprandial glucose concentrations is dependent on plasma glucose levels, therefore there is minimal hypoglycaemia risk.^(1, 77) GLP-1 analogues are administered by subcutaneous injection.^(1, 58) Results of clinical trials have shown that treatment with GLP-1 analogues can improve beta cell function.^(1, 10, 34, 76, 78) The main adverse effects associated with these agents include nausea, vomiting, diarrhoea and an increased risk of pancreatitis.⁽⁵⁸⁾ An important distinction between GLP-1 analogues currently available on the market is their duration of action⁽⁷⁹⁾,

hence their classification into short and long acting formulations.⁽⁷⁹⁾ Recent research has observed that short acting GLP-1 analogues predominantly affect postprandial plasma glucose, whilst long acting GLP-1 analogues affect fasting plasma glucose.^(79, 80) Examples of short acting GLP-1 analogues are exenatide twice a day and liraglutide and lixisenatide once a day; long acting, extended release GLP-1 analogues which are administered on a weekly basis include dulaglutide, albiglutide⁽⁷⁹⁾ and exenatide, which, unlike the short acting exenatide formulation, is available as biodegradable microspheres that provide a controlled release of exenatide throughout the week.⁽⁸¹⁾

1.3.9 Dipeptidyl peptidase-4 (DPP-4) inhibitors

Dipeptidyl peptidase-4 (DPP-4) inhibitors are incretin enhancers that augment the effects of GLP-1 by competitively inhibiting the DPP-4 enzyme that is responsible for GLP-1 degradation^(1, 9, 76), and thereby increasing the half-life of circulating GLP-1.⁽⁹⁾ Orally administered, DPP-4 inhibitors decrease plasma glucose concentrations by increasing insulin secretion and suppressing glucagon secretion, with a neutral effect on weight.⁽¹⁾ As this effect is glucose dependent, the risk of hypoglycaemia is minimal. There are some reports of improved beta cell function associated with DPP-4 inhibitors^(1, 34, 76); however one review found that, based on published data, no definite conclusion could be drawn on the effects of DPP-4 inhibitors on beta cell function.⁽³⁷⁾ Reported adverse effects include nasopharyngitis, headache and gastrointestinal disturbances.^(9, 64) Occurrences of skin rashes with DPP-4 inhibitors, whilst reportedly rare, are considered potentially serious.⁽⁹⁾ Reports of an association between DPP-4 inhibitors and pancreatitis have also been documented.^(9, 64) Examples of DPP-4 inhibitors are alogliptin, linagliptin, saxagliptin, sitagliptin and vildagliptin.^(11, 82) Figure 1.2 illustrates the physiology of GLP-1 along with the action of GLP-1 analogues and DPP-4 inhibitors at enhancing GLP-1 activity.



(Adapted from: Nauck M, Vilsboll T, Gallwitz B. Incretin-Based Therapies. *Diabetes Care*. 2009;32(Suppl):S223-S231).⁽⁸³⁾

Figure 1.2. Schematic diagram explaining: (A) physiological secretion of GLP-1 from the gut, (B) its binding to GLP-1 receptors on the pancreatic beta cells and (C) its enzymatic degradation by DPP-4. GLP-1 analogue (D) binds to and activates GLP-1 receptor, DPP-4 inhibitors (E) prevent the degradation of biological GLP-1 and thereby enhance its activity on the pancreas

1.4 Measures of beta cell function

In clinical practice, individual management of type 2 diabetes is based on laboratory markers such as glycated haemoglobin (HbA1c), plasma glucose levels, blood pressure and body mass index (BMI).⁽⁸⁴⁾ However, these markers do not provide any information about the underlying pathophysiology and declining beta cell function characteristic of type 2 diabetes. New methods that measure indices of beta cell function are an area of growing interest, where a

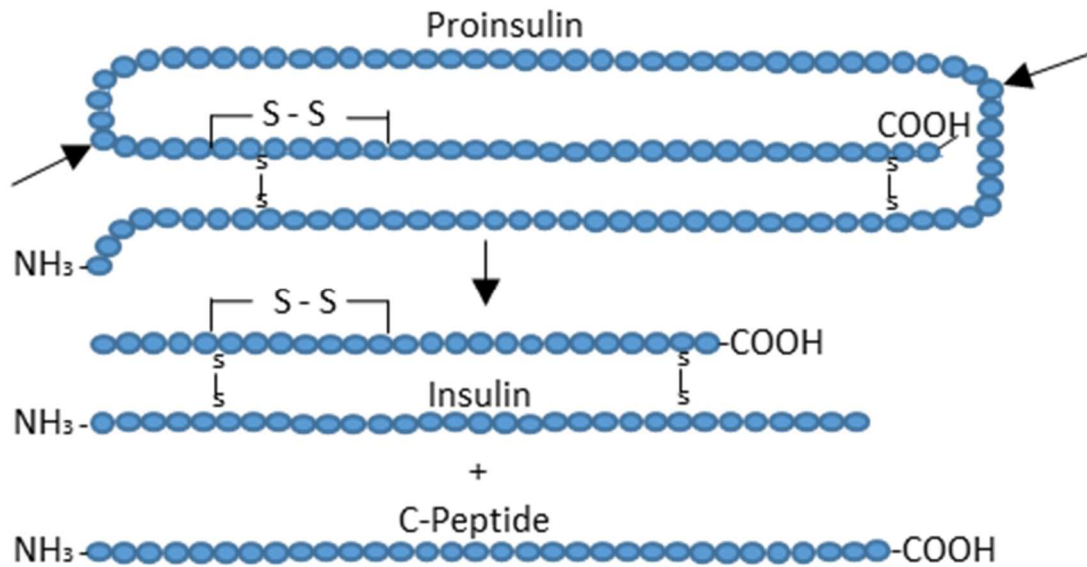
number of different biochemical markers including insulin, proinsulin and connecting peptide (C-peptide) are being utilised.⁽⁸⁴⁾ An overview of the most widely used methods to assess beta cell function is presented in the following section.

1.4.1 Hyperglycaemic clamp technique

The reproducible hyperglycaemic clamp technique measures beta cell function under maximum stimulatory conditions⁽⁵⁾, where the aim is to raise plasma glucose concentration sharply to a set glucose value, and maintain that concentration for two hours.⁽⁸⁵⁾ This involves a two-step intravenous glucose infusion consisting of a 15-minute priming dose, empirically set for all subjects based on body surface area, which raises both the plasma glucose level and glucose in extravascular tissues to the desired hyperglycaemic plateau, and a maintenance dose that is calculated at five-minute intervals throughout the duration of the study.⁽⁸⁵⁾ Computation of the maintenance dosage adjustments is based on a negative feedback system: if the actual glucose concentration is higher than the target, the infusion is decreased and vice versa.⁽⁸⁵⁾ Under steady state plasma glucose concentrations, where the endogenous hepatic production is completely suppressed, the glucose being infused must equal the glucose being metabolised.⁽⁸⁵⁾ Plasma insulin concentrations are measured every two minutes for the first 10 minutes and every 10 minutes thereafter to determine both early and late phase insulin release.⁽⁸⁵⁾ These measures of plasma insulin aim to evaluate beta cell function.⁽⁸⁵⁾ The hyperglycaemic clamp can also be used to evaluate non-glucose insulin secretagogues such as arginine or GLP-1.⁽⁵⁾ The primary strength of the hyperglycaemic clamp is its reproducibility^(5, 85); however as the clamp is technically demanding and difficult to perform, it is costly to implement as it requires advanced skills and trained personnel to operate it.⁽⁵⁾

1.4.2 Measures of plasma connecting peptide (C-peptide)

Connecting peptide (C-peptide) is a 31-amino acid polypeptide that bridges the insulin A and B chains⁽⁸⁶⁾ in the prohormone precursor, proinsulin.⁽⁸⁷⁾ As described in Figure 1.3, C-peptide is enzymatically cleaved from the proinsulin molecule in beta cells by carboxypeptidases⁽⁸⁴⁾ and co-secreted, in equimolar amounts, with insulin^(5, 86) into the portal vein, which perfuses the liver. Insulin, but not C-peptide, is partially hepatically cleared, before it enters the peripheral circulation.⁽⁵⁾ Consequently, insulin concentrations measured in the peripheral circulation varies from the total amount of insulin secreted by the pancreas, and this represents a balance between the insulin secretory rate and the hepatic clearance rate.⁽⁵⁾ Therefore, peripheral plasma insulin levels can only be reliably used to compare insulin secretory rates between individuals and groups with known and comparable hepatic clearance rates.⁽⁵⁾ In contrast, C-peptide prevents degradation by the liver, and is cleared entirely at a relatively constant rate in peripheral tissues.⁽⁵⁾ Therefore, this difference between insulin and C-peptide hepatic clearance has enabled the use of peripheral plasma C-peptide concentrations to more accurately estimate true insulin secretory rates and therefore beta cell function.⁽⁵⁾



Adapted from <http://medical-dictionary.thefreedictionary.com/Insulin+purified+bee>⁽⁸⁸⁾

Figure 1.3. Schematic diagram of proinsulin molecule in beta cells, which yields C-peptide and insulin in equimolar amounts when cleaved by endopeptidases.

1.4.3 Proinsulin to insulin plasma concentration ratio

Proinsulin, a precursor for the insulin molecule, is synthesised by beta cells of the pancreas.⁽⁸⁴⁾ Physiologically, nearly all proinsulin molecules are cleaved intracellularly into insulin and C-peptide by carboxypeptidases, leaving only a small percentage of uncleaved, intact proinsulin to be released into circulation.⁽⁸⁴⁾ Progressive insulin resistance, characteristic of type 2 diabetes, leads to increasing demand for insulin, with eventual exhaustion of the cleavage capacity of the processing enzymes.⁽⁸⁴⁾ As a consequence, intact precursor or partially processed proinsulin is secreted, in addition to insulin and C-peptide.⁽⁸⁴⁾

The focus of this measure is on the defective processing of the proinsulin molecule by the beta cell, where impaired beta cell function results in disproportionately elevated serum proinsulin levels characteristic of type 2 diabetes.⁽⁸⁴⁾ Hence, the ratio of proinsulin to insulin serves as a surrogate measure of inappropriate intracellular processing of the proinsulin into

insulin⁽⁵⁾ and is a marker of beta cell function.^(5, 84) Measures of the proinsulin to insulin ratio are considered simple to obtain from routine clinical plasma or serum fasting samples.⁽⁵⁾ However, reports suggest that the physiological information provided in this measure is limited to steady state conditions, and that sufficient correlations with other beta cell function tests, for example, the hyperglycaemic clamp technique, are lacking under different clinical conditions.⁽⁵⁾ Additionally, it has been documented that when nonspecific assays are used, for example, radioimmunoassay⁽⁸⁹⁾, a high cross reactivity with various fractions of proinsulin-like molecules exist, resulting in only partial and sometimes incorrect conclusions being drawn about the role of proinsulin in the prediction of beta cell function.⁽⁸⁴⁾ The new stable assays (for example, chemiluminescence or enzyme-linked immunosorbent assay [ELISA]) can however distinguish between intact proinsulin and its specific and unspecific cleared products, making this measure a reliable, robust marker of beta cell function.⁽⁸⁴⁾

1.4.4 Homeostasis model assessment (HOMA)

Homeostasis model assessment (HOMA) is a technique for estimating both beta cell function (HOMA-beta) and insulin sensitivity (the reciprocal of insulin resistance) from fasting or steady state plasma glucose and insulin concentrations.⁽⁹⁰⁾ First described by Matthews et al.⁽⁹¹⁾ in 1985, it is a mathematical model which expresses estimates as a percentage of a normal reference population.⁽⁹²⁾ After patient data is inputted, computation of the 'idealised' steady state glucose and insulin concentrations is possible in order to estimate the patients' relative status.⁽⁹⁰⁾ The relationship between glucose and insulin in the fasting state reflects the balance between hepatic glucose output and insulin secretion which is maintained by a feedback loop between the liver and the pancreatic beta cells.⁽⁹⁰⁾ This feedback loop is central to the model^(5, 90), that is, fasting plasma glucose concentration is regulated by insulin-dependent endogenous hepatic glucose output and plasma insulin concentration is dependent upon the beta cell responsiveness to plasma glucose concentrations.⁽⁵⁾ The HOMA

model was updated in 1996, and unlike the earlier model is a computer model^(5, 90) which can be used online.⁽⁵⁾ Figure 1.4 shows the 1985 HOMA model and the 1996 HOMA model.⁽⁹⁰⁾

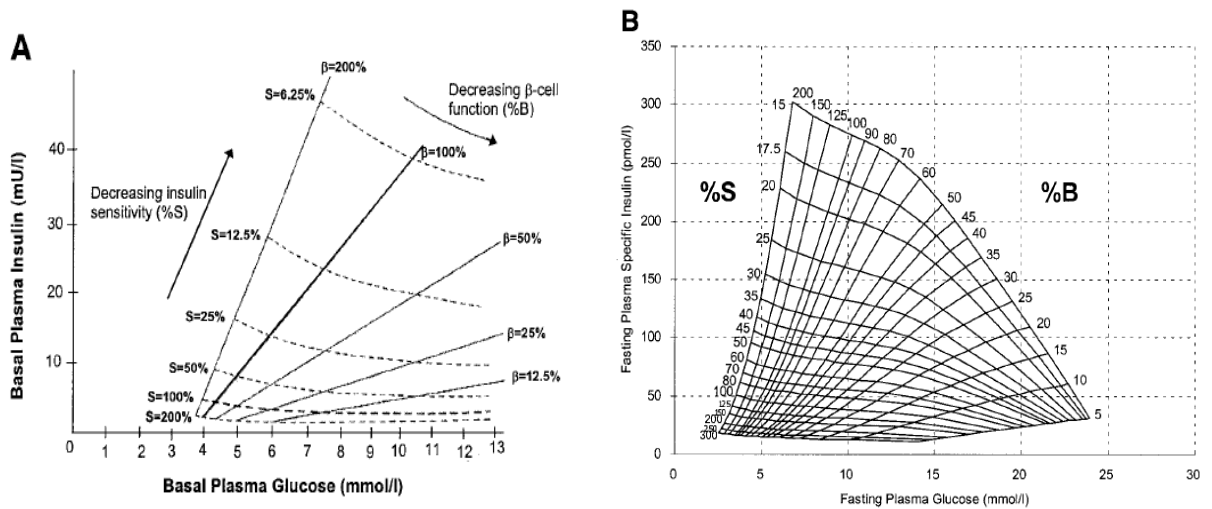


Figure 1.4. The 1985 HOMA Model (A) and the 1996 HOMA computer model (B)⁽⁹⁰⁾

The advantages of HOMA values are that the calculations are relatively simple, and they use parameters commonly analysed during routine clinical and laboratory examinations.⁽⁵⁾ The HOMA model is considered robust, easy to use and is relatively inexpensive, making it suitable for both large epidemiological and clinical treatment studies.^(5, 90) Additionally, HOMA has been validated against a variety of complex procedures, including the hyperglycaemic clamp technique^(5, 90), and has been reported in over 500 publications.⁽⁹⁰⁾ The physiological information provided by HOMA however is limited to steady state conditions, and therefore information is lacking in relation to daily fluctuations in glucose homeostasis.⁽⁵⁾ Finally, caution is recommended when comparing HOMA values across cultures/ethnicities, because the prevailing 'normal' value in different population groups will vary based on differing genetics and environmental factors.⁽⁵⁾

1.5 Measures of glycaemic control

Findings from the UKPDS confirmed the importance of glycaemic control in the prevention of diabetes related complications.⁽⁴⁴⁾ Chronic, sustained hyperglycaemia is a well-known risk factor for the development of micro and macrovascular complications (see Section 1.6) in type 1 and type 2 diabetes.^(44, 93) Glycaemic markers, such as glycated haemoglobin (HbA1c), fasting and postprandial (postmeal) plasma glucose are essential in routine practice, as well as clinical trials, to guide therapy and to investigate the efficacy of medication on glycaemic control in diabetes management.⁽⁹³⁾

1.5.1 Fasting plasma glucose

The measurement of fasting plasma glucose provides an acute assessment of glycaemia for an eight- to 10-hour period (for example, an overnight fast) and is useful for monitoring and assessing glycaemic parameters such as hepatic glucose output, and the effectiveness of antihyperglycaemic agents.⁽⁹³⁾ Measured in units of mmol/L or mg/dL⁽⁵⁵⁾, fasting plasma glucose is generally the lowest plasma glucose level of the day.⁽⁵⁰⁾ Research has shown that impaired fasting plasma glucose is an independent predictor of cardiovascular mortality⁽⁹⁴⁾, and that reductions in fasting plasma glucose is related to a decrease in cardiovascular mortality.⁽⁹⁵⁾

1.5.2 Postprandial plasma glucose

Postprandial or postmeal plasma glucose is also a measure of acute glycaemia, and estimates glycaemic control over periods of two to four hours.⁽⁹³⁾ Reports suggest that whilst elevations in postprandial plasma glucose are due to a number of causes, such as loss of first phase insulin secretion, decreased insulin sensitivity and increased hepatic glucose output, they are also associated with deficiencies in GLP-1 and GIP incretin hormone production.⁽⁹⁶⁾

Postprandial plasma glucose, measured in units of mmol/L or mg/dL⁽⁵⁵⁾, is useful in assessing

meal induced glucose excursions.⁽⁹³⁾ Reports suggest that gradual loss of daytime, postprandial glycaemic control with worsening diabetes precedes deterioration in fasting, overnight glycaemia control.⁽⁹⁶⁾ There is also a growing body of evidence on the relationship between postprandial hyperglycaemia and oxidative stress, carotid intima-media thickness and endothelial dysfunction.⁽⁹⁶⁾ Elevated postprandial plasma glucose has been shown to increase the risk of cardiovascular disease or the occurrence of cardiovascular events by approximately threefold; however the authors⁽⁹³⁾ cautioned that evidence supporting the use of postprandial plasma glucose as a marker of cardiovascular events is currently lacking, and that further studies targeting postprandial hyperglycaemia are needed to better establish the contribution of this parameter to overall cardiovascular risk in patients with diabetes.⁽⁹⁵⁾

1.5.3 Glycated haemoglobin (HbA1c)

Glycated haemoglobin (HbA1c), also referred to as glycohaemoglobin⁽⁹⁷⁾, is a product of non-enzymatic interaction between glucose and haemoglobin within erythrocytes.^(98, 99) Formation of glycated haemoglobin is irreversible⁽⁹⁹⁾, and the level is dependent on blood glucose concentrations over the life span of the erythrocyte, which ranges between 60 and 140 days.^(98, 100) Glycated haemoglobin has been used as a biomarker for monitoring glycaemic control for more than 30 years and it represents an indicator for overall glucose exposure integrating both fasting and postprandial hyperglycaemia.⁽⁹³⁾

It is noteworthy that glycated haemoglobin reflects an average of glucose control over one to three months, and therefore does not capture acute glucose fluctuations.⁽⁹³⁾ Nevertheless, it is well documented that glycated haemoglobin can be used as a risk predictor for diabetes related cardiovascular complications.⁽¹⁰¹⁻¹⁰³⁾ Cardiovascular complications include atherosclerotic congestive heart disease, diabetic cardiomyopathy, ischaemic heart disease, stroke and peripheral vascular disease.^(45, 104) A review of studies suggested that for every 1%

increase in HbA1c, there was a 10-20% increase in cardiovascular risk.⁽¹⁰¹⁾ Whilst glycated haemoglobin is considered the gold standard to assess glycaemic control^(46, 93), several conditions may interfere with HbA1c measurements causing erroneous values. Such conditions include high erythrocyte turnover such as episodes of internal bleeding, haemolytic anaemia, blood transfusion, chronic renal or liver disease.⁽⁹³⁾

The International Diabetes Federation⁽⁴⁴⁾ reported that high performance liquid chromatography assays for the measurement of HbA1c are precise and aligned to an international reference method. Additionally, recommendations from the International HbA1c Consensus Committee have seen the adoption of new reporting methods for HbA1c.⁽¹⁰⁵⁾ International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) units are now being used to report HbA1c worldwide.⁽¹⁰⁵⁾ This has seen HbA1c being expressed as millimole HbA1c per mole of unglycated haemoglobin (mmol/mol).⁽⁴⁴⁾ Previously, HbA1c was expressed as a percentage of total haemoglobin.⁽¹⁰⁵⁾ The International Diabetes Federation⁽⁴⁴⁾ has published recommended levels of glycaemic control for HbA1c, as well as fasting and postprandial blood glucose levels, which are listed in Table 1.5.

Table 1.5. Recommended glucose control levels for glycaemic markers glycated haemoglobin (HbA1c) and fasting and postprandial plasma glucose levels⁽⁴⁴⁾

	Normal Non-diabetes Levels	Target Levels for Diabetes
HbA1c	<6.0% (<42 mmol/mol)	<7.0% (<53 mmol/mol)
Fasting plasma glucose	5.5 mmol/L (100mg/dL)	6.5 mmol/L (115mg/dL)
Postprandial plasma glucose	7.8mmol/L (140mg/dL)	9.0 mmol/L (160mg/dL)

1.6 Diabetes related complications

Despite an enormous amount of research, the exact underlying pathology that causes diabetes related complications is still unclear.⁽¹⁰⁶⁾ Whilst research has primarily focused on the harmful effects of elevated plasma glucose levels, reports suggest that there are

differences in individual susceptibility to complications.⁽¹⁰⁶⁾ It is well documented that high HbA1c is associated with an increased risk of complications^(96, 101-103, 106); however individual differences in HbA1c only explain about 11% of the differences in complication risk.⁽¹⁰⁶⁾ Regardless of the underlying pathophysiology, the metabolic alterations that arise from hyperglycaemia cause functional and/or structural changes within tissues and organs.⁽¹⁰⁶⁾ The most notable damage is to the vascular endothelium which plays an important part in the pathogenesis of macrovascular disease, vision loss, renal failure and neuropathy.⁽⁹⁶⁾

Research suggests that complications are commonly present at the time of diagnosis of type 2 diabetes; however actual rates vary between studies.⁽⁴⁴⁾ The International Diabetes Federation⁽⁴⁴⁾ reports that in The Netherlands, retinopathy was found in 7.6% of people with newly diagnosed type 2 diabetes, impaired foot sensitivity in 48.1%, microalbuminuria in 17.2%, myocardial infarction in 13.3%, ischaemic heart disease in 39.5% and peripheral arterial disease in 10.6%.⁽⁴⁴⁾ The development of retinopathy, for example, is related to the duration of the diabetes, and it has been estimated that type 2 diabetes may have its onset up to 12 years before it is clinically diagnosed.⁽⁴⁴⁾

1.6.1 Retinopathy

Diabetic retinopathy is the most common cause of visual impairment amongst working adults in developed nations.^(44, 107, 108) Screening programs have allowed early diagnosis and consequently prompt treatment of sight-threatening retinopathy⁽¹⁰⁷⁾; however despite this, the prevalence of diabetic retinopathy remains high at 40%.⁽¹⁰⁷⁾ Biochemical mechanisms due to hyperglycaemia have been implicated in the pathogenesis of diabetic retinopathy.⁽¹⁰⁷⁾ Reports suggest that diabetic retinopathy is a 'neurovascular' condition as well as having a microvascular presentation, and that neural changes run parallel with vascular changes in terms of structural and functional involvement.⁽¹⁰⁷⁾

Diabetic retinopathy starts with small retinal changes, where blood vessels in the retina become weaker and microaneurysms occur, causing leakage of clear fluid and blockage of blood vessels.⁽¹⁰⁷⁾ This condition is referred to as non-proliferative diabetic retinopathy, and vision loss does not normally occur.⁽¹⁰⁸⁾ Leakage of fluid from damaged blood vessels may result in oedema of the retina, and if oedema occurs in the central macular area, the result is diabetic macular oedema causing progressive loss of detailed central vision.⁽¹⁰⁸⁾ Diabetic macular oedema is the most common cause of vision loss in individuals with diabetic retinopathy, and frequently affects both eyes at the same time.⁽¹⁰⁸⁾ Whilst it will not cause total blindness, it may cause legal blindness⁽¹⁰⁸⁾, making driving illegal.⁽¹⁰⁹⁾ With the blockage of retinal blood vessels, macular function is disrupted.⁽¹⁰⁸⁾ A reduction of oxygen supply to the retina causes ischaemia, and consequently new blood vessels are formed, which are abnormal and very fragile.⁽¹⁰⁸⁾ The new, weaker blood vessels tend to break, causing vitreous haemorrhage and obstruction to vision.⁽¹⁰⁸⁾ Known as proliferative diabetic retinopathy⁽¹⁰⁸⁾, the condition is progressive, and devoid of any symptoms until the haemorrhage actually occurs.⁽¹⁰⁸⁾ Formation of scar tissue within the damaged vessels may cause tightening on the retina, resulting in possible retinal detachment.⁽¹⁰⁸⁾ If proliferative diabetic retinopathy is not treated early enough, total blindness may occur.⁽¹⁰⁸⁾

Management of non-proliferative diabetic retinopathy involves treatment with the medication fenofibrate which has been shown to reduce the risk of retinopathy progression by 30%.⁽¹⁰⁸⁾ For more advanced vision-threatening diabetic retinopathy, laser treatment or a series of injections into the eye to prevent blood vessel leakage and abnormal blood vessel growth are administered.⁽¹⁰⁸⁾ Surgery may also be needed in severe cases of proliferative diabetic retinopathy.⁽¹⁰⁸⁾

1.6.2 Neuropathy

Diabetic neuropathy is a common complication of type 2 diabetes, and whilst its pathogenesis is still poorly understood⁽¹⁰⁶⁾, it is thought to be caused, in part, by pathological microvascular changes to the small nerve fibres.⁽¹¹⁰⁾ Two main forms can be identified: peripheral neuropathy (usually distal and symmetrical), and autonomic neuropathy that can affect the normal functioning of many organs.⁽¹⁰⁶⁾

In peripheral neuropathy, changes in the small nerve fibres in the feet and hands cause pain and paraesthesia in a 'glove and stocking' distribution that is spontaneous and unpredictable.^(44, 110) The pain is not related to exercise, and is usually worse at night.⁽¹¹⁰⁾ The pain associated with peripheral neuropathy is difficult to manage⁽⁴³⁾, and usually involves pharmacological interventions such as tricyclic antidepressants and analgesics, various forms of physical activity and psychological measures to assist with pain coping strategies.^(43, 110) Peripheral neuropathy and associated connective tissue damage can cause foot deformities which present in subtle ways such as limited joint mobility, or in a more destructive ways such as Charcot's foot.⁽¹⁰⁶⁾ In Charcot's foot, the deformed foot is more prone to pressure ulcers which are often not noticed due to a lack of sensory sensations.⁽¹⁰⁶⁾ Ulcers occur more readily because the underlying vascular pathology impedes oxygen supply to tissues, slowing down the healing process.⁽¹⁰⁶⁾ Consequently, ulcers are more prone to infection, and subsequently treatment with antibiotics is difficult due to poor perfusion to the infected area.⁽¹⁰⁶⁾ Amputation risk is high⁽¹⁰⁶⁾ and usually precedes a foot ulcer.⁽⁴⁴⁾

When the autonomic nervous system is affected, there are a number of manifestations including gastroparesis, diarrhoea, faecal incontinence, erectile dysfunction, bladder disturbances and orthostatic hypotension.⁽⁴⁴⁾ Early recognition and management of neuropathy is important⁽⁴³⁾, including improving glycaemic control.⁽¹⁰⁶⁾

1.6.3 Nephropathy

Long standing hyperglycaemia is known to be a significant risk factor for the development of diabetic nephropathy⁽¹¹¹⁾ and is a leading cause of chronic kidney disease in many developed countries.⁽⁴⁴⁾ Hyperglycaemia can directly cause injury, thickening and scarring of the cellular properties of the glomerular microvascular bed within the renal nephrons, damaging their filtering integrity.⁽¹¹²⁾

The earliest clinical evidence of nephropathy, incipient nephropathy, is the appearance of low, but abnormal levels of albumin in the urine ($\geq 30\text{mg/day}$ or $20\mu\text{g/min}$) referred to as microalbuminuria.⁽¹¹³⁾ Microalbuminuria is also a marker of greatly increased cardiovascular morbidity and mortality for individuals with diabetes.⁽¹¹³⁾ Noteworthy is the fact that up to 90% of kidney function may be lost before symptoms are present.⁽¹¹⁴⁾ Data has shown that early intervention can slow down the progression of nephropathy and cardiovascular risk by up to 50% and may improve quality of life.⁽¹¹⁴⁾

Without specific interventions, nearly half of type 2 diabetes cases with microalbuminuria will progress to overt nephropathy or clinical albuminuria, defined as $\geq 300\text{mg/day}$ or $\geq 200\mu\text{g/minute}$ of albumin in urine.⁽¹¹³⁾ If overt nephropathy is left untreated, GFR, the best measure of renal function, gradually declines over time.⁽¹¹⁴⁾ A GFR of $<60\text{ml/minute}/1.73\text{m}^2$ is associated with increased risk of adverse renal, cardiovascular and other clinical outcomes, irrespective of an individual's age.⁽¹¹⁴⁾ Management of nephropathy includes such interventions as improving glycaemic control and reducing cardiovascular risk factors, lowering low density lipoprotein (LDL) cholesterol and managing hypertension, ceasing smoking and engaging in regular physical activity.^(113, 114)

1.7 Why a systematic review is needed

1.7.1 Current evidence for the comparison of GLP-1 analogues with DPP-4 inhibitors on beta cell function and diabetes related complications in adults with type 2 diabetes

A search of the literature uncovered many reviews and meta-analyses documenting the clinical efficacy and safety of DPP-4 inhibitors and GLP-1 analogues either alone or in combination with other antihyperglycaemic agents^(37, 54, 64, 77, 115-117), but few head to head comparisons were identified. However, one systematic review by Shyangdan et al.⁽¹⁰⁾ in 2010 aimed to provide evidence on the clinical effectiveness of GLP-1 analogues compared to placebo and other antihyperglycaemic agents, including two DPP-4 inhibitor /GLP-1 analogue head to head comparisons.^(34, 118) Inconsistencies in data were evident however, when in the same year, Davidson⁽¹¹⁾ published a supplemental article on the differences between GLP-1 analogues and DPP-4 inhibitors which located an additional study.⁽¹⁸⁾ Later, in 2012, McIntosh et al.⁽¹¹⁹⁾ compared the safety and efficacy of all antihyperglycaemic agents, but no head to head comparative effectiveness studies were included using GLP-1 analogues and DPP-4 inhibitors. Similarly, Amori et al.⁽¹⁶⁾ in 2007 and Aroda et al.⁽⁷⁸⁾ in 2012 both analysed only incretin- based therapies for efficacy and safety, but again no comparative studies were included. Mudaliar⁽¹⁾ in 2013 conducted a systematic review on the impact of antihyperglycaemic agents including DPP-4 inhibitors and GLP-1 analogues on beta cell function. Original research and review articles from January 2000 to August 2012 were used. No comparisons were drawn between any of the agents. Hence, given the lack of head to head effectiveness data, the dynamic nature with which further incretin-based therapies are being developed, and the publication of recent research using newer agents that were not available when the previous reviews were completed (for example, Nauck et al.⁽⁷⁶⁾, and unpublished work by pharmaceutical company Sanofi⁽¹²⁰⁾), it is timely to synthesise all available evidence in a systematic process.

Given the increasing popularity and use of GLP-1 analogues and DPP-4 inhibitors in the management of type 2 diabetes, it is timely to compare the clinical effectiveness of these two incretin-based agents in a systematic review, one that will assess the methodological quality of included studies, explore the differences that typically emerge in study results, and quantitatively synthesise these results.⁽¹²¹⁾ These two treatments have important similarities and differences, and clinicians treating individuals with diabetes must be aware of factors that might favour one treatment approach over the other.⁽¹¹⁾ It is important to bring together in a single document, a comprehensive, transparent synthesis of scientific studies using a rigorous and transparent approach.⁽¹²²⁾ The systematic review presented in this thesis focuses specifically on adults over the age of 18 years with type 2 diabetes, and assess the effectiveness of GLP-1 analogues compared to DPP-4 inhibitors for beta cell function and diabetes related complications. The protocol for the research conducted in this thesis is published and available online⁽¹²³⁾ and presented in Appendix I.

1.8 Review question

The review question addressed by the research in this thesis is:

What is the effectiveness of GLP-1 analogues compared to DPP-4 inhibitors for beta cell function and diabetes related complications among adults with type 2 diabetes?

Chapter 2: Systematic review methods

Chapter 2 outlines the inclusion criteria for the systematic review: types of participants, types of interventions, types of outcomes and types of studies. This chapter also details the systematic review methods used, including a description of the search strategy, as well as an overview of the processes used to critically appraise studies, extract study characteristics and results, and synthesise outcome data.

2.1 Types of participants

The review considered studies that included adults over 18 years of age with type 2 diabetes. The diagnosis of type 2 diabetes should have been made using standard criteria that were valid at the time of the study, clearly described and consistent with changes in classification and diagnosis over the years (refer Table 1.3). In the event that diagnostic criteria were not described, the author's definition of diabetes was used.

2.2 Types of interventions and comparators

The primary interventions of interest were any short acting or long acting GLP-1 analogue. GLP-1 analogue injectable preparations considered were albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide and semaglutide. Active comparators were the DPP-4 inhibitor oral preparations: sitagliptin, saxagliptin, linagliptin, alogliptin, vildagliptin, gemigliptin, anagliptin and teneligliptin. Consideration was given to treatment with either class of drug for a minimum of eight weeks, either alone or in combination with metformin (any dose).

2.3 Types of outcomes

This review considered studies that included the following primary outcome measures: beta cell function assessed by a range of measurements, namely, hyperglycaemic clamp

technique, homeostasis model assessment-beta (HOMA-beta), proinsulin to insulin (PI/I) plasma concentration ratio and measures of plasma C-peptide (refer Section 1.4). Glycated haemoglobin (HbA1c), fasting plasma glucose and postprandial plasma glucose were also primary outcomes of interest (refer Section 1.5).

Secondary outcomes of interest were diabetes related complications: retinopathy, neuropathy and nephropathy (refer Section 1.6). Adverse events of a gastrointestinal nature, infection, headache, pancreatitis and mortality were of interest. Adverse events such as 'gastrointestinal' and 'infection' were deliberately considered broadly to accommodate the diverse classification of these effects by the authors of primary studies. Gastrointestinal adverse events considered included nausea, vomiting, diarrhoea, constipation, abdominal pain, abdominal distension and dyspepsia; infection adverse events considered included nasopharyngitis, upper respiratory tract infection, urinary tract infection and influenza.

2.4 Types of studies

Experimental studies under consideration for this review included randomised controlled trials (RCTs), non-randomised controlled trials, quasi-experimental and controlled before-after studies.

2.5 Search strategy

In accordance with Joanna Briggs Institute (JBI) method guidelines for a systematic review assessing the effectiveness of an intervention or therapy⁽¹²⁴⁾, the suitability of the proposed review topic was determined by conducting a preliminary investigation of major electronic databases. Results of searches of the *JBI Database of Systematic Reviews and Implementation Reports*, Cochrane Database of Systematic Reviews and the biomedical

bibliographic citation database, PubMed, showed there had been no recently published systematic reviews on the same topic.

2.5.1 Search method

The search strategy developed used a three-step process and was designed to find published and unpublished studies. No date restrictions were applied. An initial search of international biomedical bibliographic citation databases, PubMed and EMBASE, allowed identification of key words in titles and abstracts. Initial key words or terms employed in various combinations included glucagon-like peptide 1, GLP-1 analogues, dipeptidyl-peptidase IV inhibitors, DPP-4 inhibitors, diabetes mellitus, type 2, type 2 diabetes, retinopathy, nephropathy, neuropathy, beta-cell function, beta cell preservation and insulin-secreting cells, along with individual drug names. A second search of the databases was conducted utilising all identified searching terms and key words found in titles and abstracts ensuring as comprehensive a search as possible. When searching, consideration was given to each databases' unique indexing language to ensure all relevant indexing terms were identified. Included in the search of international databases were clinical trial registries, as well as websites of pharmaceutical industries, international diabetes federation and government organisations involved in the regulation of therapeutic goods. A detailed list of all databases searched is provided in Table 2.1. Using citations that were identified based on keywords in abstracts and titles, full papers were retrieved and scanned to determine whether inclusion criteria had been met. Thirdly, to ensure that all relevant studies were identified, the reference list of retrieved papers was scanned to detect any additional studies. Appendix II provides detailed search strategies for each database, registry and website source. Results of database searching were managed using the bibliography software Endnote x7⁽¹²⁵⁾ (Thomson Reuters, USA 2015). The Endnote library created was used to facilitate screening of titles and abstracts of citations to assess eligibility for the review (refer Section 2.1 - 2.4).

Table 2.1. Databases searched, including search dates and location details

Database	Date searched	Website URL
PubMed	26/05- 26/06/2014	http://www.ncbi.nlm.nih.gov/pubmed
EMBASE	18/05- 26/06/2014	http://www.elsevier.com/online-tools/embase
Cochrane Central Register of Controlled Trials	26/05/2014	http://www.cochranelibrary.com/about/central-landing-page.html
US Clinical Trials Registry	23/06/2014	https://clinicaltrials.gov/
WHO Clinical Trials Registry	28/06/2014	http://www.who.int/trialsearch/
European Union Clinical Trials Registry	23/06/2014	https://www.clinicaltrialsregister.eu/ctr-search/
Current Controlled Trials	22/06/2014	http://www.controlled-trials.com/search?q=&filters=conditionCategory%3ANutritional%5C%2C+Metabolic%5C%2C+Endocrine
Australian New Zealand Clinical Trials Registry	23/06/2014	http://www.anzctr.org.au/rialSearch.aspx
Canadian Institutes of Health Research	23/06/2014	http://cihr-irsc.gc.ca/e/193.html
Novo Nordisk	23/06/2014	http://www.novonordisk-trials.com
Sanofi	19/08/2014	http://en.sanofi.com/rd/clinical_trials/clinical_trials.aspx
International Diabetes Federation	24/06/2014	www.idf.org
Therapeutic Goods Administration	24/06/2014	https://www.tga.gov.au/health-professionals

Full details of the search strategy employed at each database/site are presented in Appendix II.

2.6 Assessment of methodological quality

The papers selected for retrieval were assessed for methodological quality by two independent reviewers to ensure transparency and minimise risk of bias.⁽¹²⁶⁾ The appraisal tool, designed to assess the internal validity and methodological quality of the studies, was used to allow consideration of the extent to which each study had addressed the likelihood of

bias in the design, conduct and analysis.⁽¹²⁶⁾ The standard tool from the Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument (JBI-MASARI) for randomised controlled trials was used⁽¹²⁴⁾ (refer Appendix III). The ten quality assurance questions that made up the critical appraisal tool could be answered 'yes', 'no', 'unclear' or 'not applicable'. Qualifying criteria were developed around each of the appraisal questions to ensure consistency and transparency in interpretation between reviewers (refer Appendix III). A 'yes' answer deemed that the study met the requirements of the question, a 'no' meant it did not meet the requirements and an 'unclear' indicated that insufficient study information had been provided to enable a conclusive decision about its inclusion. 'Yes' answers were allocated a score of '1' while 'no' and 'unclear' were both scored as '0'. Before the commencement of critical appraisal, a decision was made on the scoring system and the cut off for inclusion of studies. For this review, studies that scored four out of ten or less were rated as being at high risk of bias, and were excluded from the review.

Following each reviewer's independent appraisal, the primary reviewer (Susan Bellman) identified any discrepancies in the study appraisal outcomes between the two reviewers. In cases where there was discrepancy, discussion was held between the two reviewers to determine if a consensus could be reached. As the two reviewers were able to agree on all items, a third reviewer was not required to resolve any discrepancies around study appraisal.

2.7 Data extraction

Descriptive and outcome data was abstracted from included studies using the standardised data extraction tool from JBI-MASARI presented in Appendix IV. The data extracted included specific details about the interventions, their strengths and dosages, study participants, study setting, study methods and outcomes of beta cell function, glycated haemoglobin and plasma glucose concentration, diabetes related complications and adverse events. Data on each

study included in the systematic review is presented in tabular format. A request for additional outcome data was made to the corresponding author of one RCT⁽⁷⁶⁾ and data from one of the unpublished studies⁽¹²⁰⁾ was sourced from the Sanofi clinical trials website after making contact with the company's Medical Advisor (refer Appendix V). Interpretation of data from one unpublished study⁽¹²⁷⁾ sponsored by AstraZeneca and Amylin pharmaceutical companies was challenging as information was minimal or lacking. When additional information requested from the study author was not forthcoming, the study was excluded for consideration in the review.

2.8 Data synthesis

2.8.1 Data conversions

All HbA1c data was reported as measures of % and mmol/mol in this review. For studies that only reported outcomes as %, conversion of HbA1c measures from % to mmol/mol was performed using the National Glycohaemoglobin Standardisation Program (NGSP) converter.⁽¹²⁸⁾ On occasions when conversion using the online converter was not possible due to the values being too low, a ratio equation presented by Nauck et al.⁽⁷⁶⁾ was used, where 1.22% was equal to 13.3mmol/mol. All data on plasma glucose concentration outcomes was reported as mmol/L and mg/dL. For those studies that only reported glucose outcomes as mg/dL, an online conversion calculator from the Society of Biomedical Diabetes Research was used to make the conversion to mmol/L.⁽⁵⁵⁾

2.8.2 Meta-analysis

The included studies used varying dosing regimens of GLP-1 analogue, therefore two types of analysis were conducted. One included the lowest maintenance dose of GLP-1 analogue used in the studies, and the other included the highest dose used. Groups contained both long and short acting GLP-1 analogues, where long acting GLP-1 analogues were those requiring only

once a week dosing. Low dose GLP-1 analogues included dulaglutide 0.75mg once a week and liraglutide 1.2mg once a day. High dose GLP-1 analogues included exenatide 10 µg twice a day, exenatide 2mg once a week, dulaglutide 1.5mg once a week, liraglutide 1.8mg once a day and lixisenatide 20 µg once a day. Only one DPP-4 inhibitor, sitagliptin 100mg daily, was used as the active comparator in all seven included studies (refer Table 2.2). Where possible, quantitative data was pooled in statistical meta-analysis using RevMan v5.3 software⁽¹²⁹⁾ (Cochrane Collaboration, Copenhagen). Heterogeneity was assessed statistically using the standard Chi^2 and I^2 . Interpretation of I^2 was based on Cochrane Handbook⁽¹³⁰⁾ guidelines where I^2 values 0% to 40% were not considered important, 30% to 60% represented moderate heterogeneity, 50% to 90% represented substantial heterogeneity and 75% to 100% represented considerable heterogeneity. For continuous data, the statistical analysis in this systematic review employed a fixed effect model except where statistical heterogeneity was present (I^2 values greater than 50%). In these cases a random effects model was also used. The effect sizes were expressed as weighted mean differences and their 95% confidence intervals were calculated. Dichotomous data was analysed using the Mantel-Haenszel fixed effect model and expressed as odds ratios, with calculation of 95% confidence interval. Sensitivity analysis was planned to assess the potential impact of outliers to determine how much they dominated the results. For the three multi-arm studies^(3, 60, 118), as outlined in the Cochrane Handbook⁽¹³¹⁾, only those intervention groups that were relevant to this systematic review were included in the meta-analysis.

Table 2.2. High dose and low dose glucagon-like peptide-1 (GLP-1) analogues and dipeptidyl peptidase-4(DPP-4) inhibitor

High dose GLP-1 analogue Injection	Low dose GLP-1 analogue Injection	DPP-4 inhibitor Tablet
Dulaglutide 1.5mg once a week ⁽⁷⁶⁾	Dulaglutide 0.75mg once a week ⁽⁷⁶⁾	Sitagliptin 100mg once a day used throughout all included studies ^(3, 34, 60, 61, 76, 118, 120)
Liraglutide 1.8mg once a day ^(34, 61)	Liraglutide 1.2mg once a day ^(34, 61)	
Exenatide 2mg once a week ^(60, 118)		
Exenatide 10 micrograms twice a day ⁽³⁾		
Lixisenatide 20 micrograms once a day ⁽¹²⁰⁾		

Chapter 3: Results

3.1 Study inclusion process

The search strategy outlined in Section 2.5 identified 467 potentially relevant studies (Figure 3.1). Of these, 20 were duplicate citations, and a further 430 were excluded on the basis of title and abstract. A total of 17 studies were retrieved for detailed examination, and of those nine were excluded on basis of full text (refer Figure 3.1 for reasons for exclusion). Eight RCTs^(3, 34, 60, 61, 76, 118, 120, 132) including 1 unpublished study⁽¹²⁰⁾ and 3 multi-arm studies^(3, 60, 118) met the eligibility criteria for the review and were selected for critical appraisal. Of those eight RCTs, seven were included in the systematic review following critical appraisal. Figure 3.1 outlines the study inclusion process.

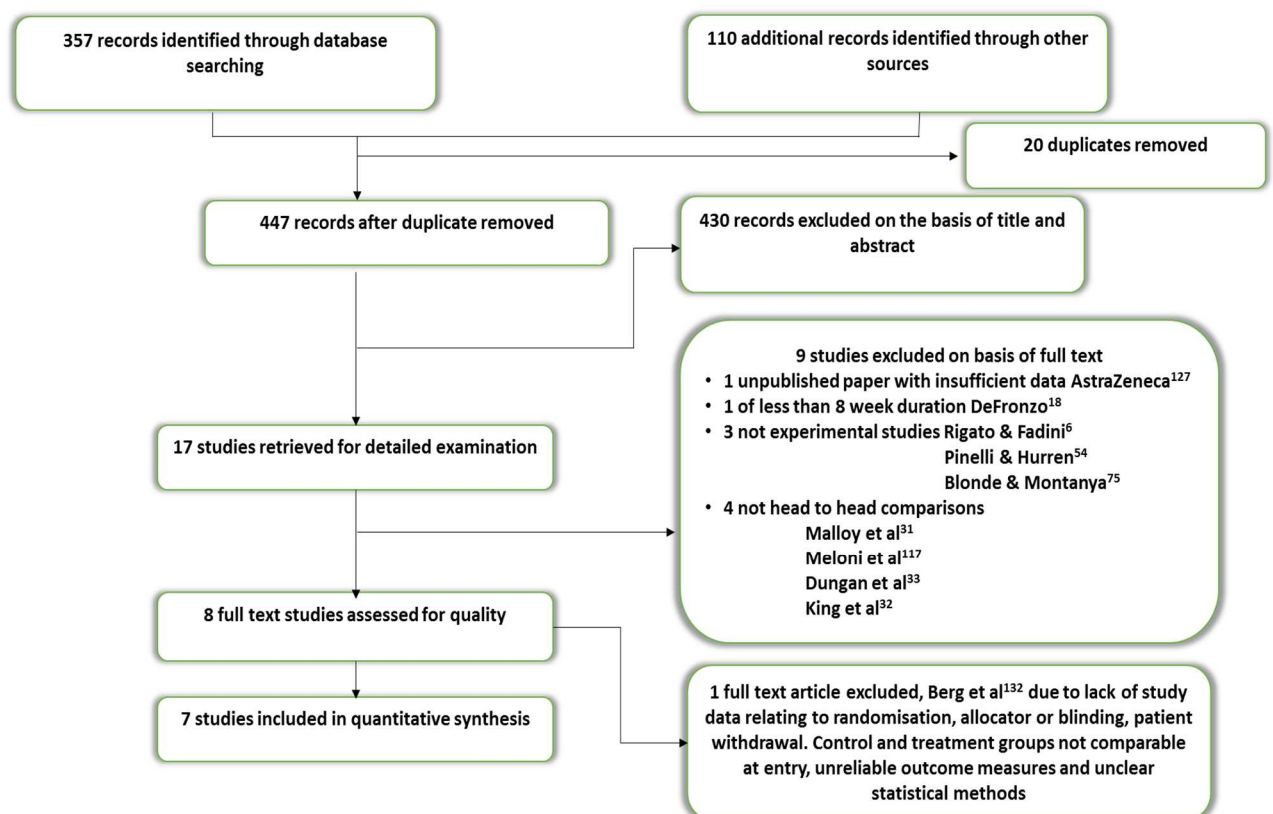


Figure 3.1. PRISMA flow diagram outlining study selection process⁽¹³³⁾

3.2 Methodological quality

The overall quality of the studies included in the review was good. The appraisal scores of the seven included RCTs are presented in Table 3.1. The only consistent shortfall was that six out of the seven included studies scored 'No' or 'Unclear' for question three which assessed concealment of treatment groups to the allocator. Concealment of allocation prevents the influence of confounders, balancing the known and unknown factors that might influence outcomes in each intervention group so that any observed differences would be attributed to the effect of the intervention rather than to intrinsic differences between groups.⁽¹³⁴⁾ Lack of allocation concealment may increase the risk of selection bias in these studies.⁽¹²⁴⁾ There is evidence to show that effects of interventions can be exaggerated if the randomisation sequence is not concealed from the investigators⁽¹³⁵⁾, with one study estimating that inadequate allocation concealment in RCTs could exaggerate the estimate of effect size of interventions by as much as 40%.⁽¹³⁶⁾

One full text article⁽¹³²⁾ did not meet the minimum quality criteria for inclusion, scoring four in all ten critical appraisal questions. As outlined in Figure 3.1, the reasons for study exclusion included the lack of clarity around whether assignment to treatment group was truly random, as well as whether or not allocation to treatment groups was concealed from the allocator. Additionally, the interpretation of the outcomes of those participants who withdrew from the study was also unclear. Finally, baseline data of groups at entry was not comparable and it was unclear who was responsible for the measurement of some of the reported outcome measures.

Table 3.1. Critical appraisal scores for studies that met eligibility criteria

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Total
Included Studies											
Bergental et al. 2010 ⁽¹¹⁸⁾	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10
Gudipaty et al. 2014 ⁽³⁾	Y	N	N	N	N	N	Y	Y	Y	Y	5
Nauck et al. 2014 ⁽⁷⁶⁾	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	9
Pratley et al. 2010 ⁽³⁴⁾	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	9
Pratley et al. 2011 ⁽⁶¹⁾	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	9
Russell-Jones et al. 2012 ⁽⁶⁰⁾	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	9
Sanofi 2014 ⁽¹²⁰⁾	U	Y	N	Y	Y	U	Y	Y	Y	Y	7
Excluded study											
Berg et al. 2011 ⁽¹³²⁾	U	Y	U	U	Y	N	Y	Y	N	N	4

The Joanna Briggs Institute (JBI) critical appraisal tool with criteria for this review is presented in Appendix III. Y= Yes; N= No; U=Unclear. Each Yes accrues 1 point.

3.3 Description of included studies

In the seven RCTs included in this review, the trial duration ranged from 24 to 52 weeks. Two studies were of a 52-week^(61, 76) duration, four studies ran for 26 weeks^(3, 34, 60, 118) and one study for 24 weeks.⁽¹²⁰⁾ The included unpublished study was a Phase 3 study⁽¹²⁰⁾, and the most recent update by the sponsoring pharmaceutical company was in 2014 (refer Table 3.2).

A total of 2661 participants received either GLP-1 analogue or DPP-4 inhibitor treatment across the seven included studies (range 26 to 921 participants); one of the studies had less than 100 participants⁽³⁾, while the remaining six RCTs^(34, 60, 61, 76, 118, 120) all had participant numbers greater than 300. The two included studies by Pratley et al. which ran for 26⁽³⁴⁾ and 52⁽⁶¹⁾ weeks used the same study participants; after completion of 26 weeks, many participants continued for another 26 weeks in their originally assigned treatment groups. For this reason, the number of participants involved in the 52 week study⁽⁶¹⁾ were not included in

the overall participant total mentioned above. Six of the seven included studies^(34, 60, 61, 76, 118, 120) were multicentre studies, where their geographical locations were situated in offices, hospitals and clinics around the world. One of the studies⁽³⁾ was located only in America, in Pennsylvania (refer Table 3.2).

Participants' average age in six of the included studies^(3, 34, 60, 61, 76, 118) ranged from 52 to 57 years, average duration of type 2 diabetes ranged from 2.7 to 7 years, average BMI ranged from 31 to 33kg/m² and average baseline HbA1c ranged from 6.4 to 8.6% (46 to 70mmol/mol). The inclusion criteria for one study⁽³⁾ stipulated that study participants be diagnosed with 'early' type 2 diabetes defined as plasma glucose concentration between 6.1mmol/L (110mg/dL) and 8.8mmol/L (159mg/dL). The inclusion criteria for all the other studies were based on HbA1c values (See Table 3.2). No baseline characteristics of study participants for the unpublished study⁽¹²⁰⁾ were provided. For the three included multi-arm studies^(3, 60, 118), the study arms involving participants not taking GLP-1 analogues or DPP-4 inhibitors were excluded from the analysis. However, as recommended in the Cochrane Handbook⁽¹³¹⁾, all intervention groups of the multi-arm studies are detailed in the study characteristics Table 3.2. In five^(34, 61, 76, 118, 120) out of seven studies, metformin therapy was administered in combination with either GLP-1 analogue or DPP-4 inhibitor. The other two studies^(3, 60) examined GLP-1 analogue or DPP-4 inhibitor as monotherapy without the concurrent administration of metformin, whilst one study⁽⁶⁰⁾ included participants who were naïve to antihyperglycaemic drugs but suboptimally managed with diet and exercise.

3.3.1 Interventions and comparators

The GLP-1 analogues and DPP-4 inhibitor used in the seven studies or study arms being compared in this review are listed below:

- Exenatide 10µg twice a day versus sitagliptin 100mg daily⁽³⁾

- Liraglutide 1.8mg or liraglutide 1.2mg once a day versus sitagliptin 100mg daily⁽³⁴⁾
- Liraglutide 1.8mg or liraglutide 1.2mg once a day versus sitagliptin 100mg daily⁽⁶¹⁾
- Lixisenatide 20µg once a day versus sitagliptin 100mg daily⁽¹²⁰⁾
- Exenatide 2mg once a week versus sitagliptin 100mg daily⁽¹¹⁸⁾
- Exenatide 2mg once a week versus sitagliptin 100mg daily⁽⁶⁰⁾
- Dulaglutide 1.5mg or dulaglutide 0.75mg once a week versus sitagliptin 100mg daily.⁽⁷⁶⁾

As can be seen above, of the GLP-1 analogues used in the included studies, two were long acting with once weekly dosing regimens (exenatide 2mg and dulaglutide), and three were short acting (exenatide 10µg, liraglutide and lixisenatide) involving daily or twice daily dosing.

Table 3.2. Study characteristics of the included randomised controlled trials

<p>Citation: Nauck et al. 2014⁽⁷⁶⁾</p> <p>Study design: Adaptive, double-blind, parallel-arm, randomised study</p> <p>Setting: Multicentre study; unclear where subjects were recruited from</p> <p>Duration of follow-up: Treatment period lasted 104 weeks, with 26 week and 52 week primary end point data</p> <p>Randomisation: Assigned to treatment by one of two sequential randomisation schemes: 1) adaptive randomisation during the dose-finding portion, where one of</p>	<p>Inclusion criteria: Patients 18-75 years old, type 2 diabetes for ≥ 6 months, HbA1c $> 8\%$ and $\leq 9.5\%$ (> 64 mmol/mol and ≤ 80 mmol/mol) on diet and exercise alone or $\geq 7\%$ and $\leq 9.5\%$ (≥ 53 mmol/mol and ≤ 80 mmol/mol) on monotherapy (metformin or other AHA) or combination therapy (metformin plus oral AHA/s), body mass index 25-40 kg/m² and stable weight 3 months prior to study. Patients required to be treated with metformin monotherapy (minimum dose ≥ 1500 mg/day) for ≥ 6 weeks prior to randomisation and to be continued during treatment period; all</p>	<p>Number of participants and intervention groups:</p> <p>Intervention A: (Number randomised and treated n=304) Dulaglutide 1.5mg injection injected subcutaneously once a week</p> <p>Intervention B: (Number randomised and treated n=302) Dulaglutide 0.75mg injection injected subcutaneously once a week</p> <p>Intervention C: (Number randomised and treated n=315) Sitagliptin 100mg tablet swallowed once a day</p> <p>Placebo: (Number randomised and treated n=177)</p>	<p>Outcome measures:</p> <p>Primary: Mean changes from baseline to 26 and 52 weeks in: beta cell function estimated by HOMA-beta; HbA1c; fasting plasma glucose measured by central laboratory measure</p> <p>Secondary: Adverse events from baseline to 26 and 52 weeks: gastrointestinal side effects, infections, headache, pancreatitis and mortality</p>	<p>Results: Mean changes from baseline to 26 weeks and 52 weeks. All data are least squares mean (+/- standard error)</p> <p>Beta cell function (HOMA-beta) Dulaglutide 1.5mg: 26 weeks 32.3% ($\pm 2.7\%$); 52 weeks 33.6% ($\pm 2.5\%$) Dulaglutide 0.75mg: 26 weeks 27.0% ($\pm 2.6\%$); 52 weeks 22.3% ($\pm 2.5\%$) Sitagliptin 100mg: 26 weeks 10.8% ($\pm 2.7\%$); 52 weeks 6.7% ($\pm 2.5\%$) Placebo: 1.6% ($\pm 4.0\%$) (26 week data only)</p> <p>HbA1c Dulaglutide 1.5mg: 26 weeks -1.22% ($\pm 0.05\%$) (-13.3 ± 0.6 mmol/mol); 52 weeks -1.10% ($\pm 0.06\%$) (-12.0 ± 0.7 mmol/mol) Dulaglutide 0.75mg: 26 weeks -1.01% ($\pm 0.06\%$) (-11.0 ± 0.7 mmol/mol); 52 weeks -0.87% ($\pm 0.06\%$) (-9.5 ± 0.7 mmol/mol) Sitagliptin: 26 weeks -0.61% ($\pm 0.05\%$) (-6.7 ± 0.6 mmol/mol); 52 weeks -0.39% ($\pm 0.06\%$) (-4.3 ± 0.7 mmol/mol) Placebo: 0.03% ($\pm 0.07\%$) (0.3 ± 0.8 mmol/mol) (26 week data only)</p> <p>Fasting plasma glucose Dulaglutide 1.5mg: 26 weeks -2.38 ± 0.13 mmol/L (-42.84 ± 2.2 mg/dL); 52 weeks -2.38 ± 0.13 mmol/L (-42.84 ± 2.3 mg/dL)</p>
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<p>two dulaglutide doses (1.5mg and 0.75mg) were selected, followed by 2) fixed randomisation after dose selection into study arms dulaglutide 1.5mg, dulaglutide 0.75mg; sitagliptin 100mg or placebo (replaced with sitagliptin after 26 weeks) in a 2:2:2:1 ratio.</p>	<p>other oral AHAs discontinued.</p> <p>Exclusion criteria: Patients were excluded if they were taking GLP-1 analogues during the 6 months prior to screening or on chronic insulin therapy.</p>	<p>For 26 weeks only; replaced with sitagliptin after 26 weeks to keep blinding 2:2:2:1</p> <p>All patients randomised received at least one dose of study drug.</p>	<p>Dulaglutide 0.75mg: 26 weeks -1.97 ± 0.12 mmol/L (-35.46 ± 2.2 mg/dL); 52 weeks -1.63 ± 0.13 mmol/L (-29.34 ± 2.3 mg/dL) Sitagliptin: 26 weeks -0.97 ± 0.11 mmol/L (-17.46 ± 2.0 mg/dL); 52 weeks -0.90 ± 0.13 mmol/L (-16.20 ± 2.3 mg/dL)</p> <p>Adverse events Data is number of adverse events through 26 weeks and 52 weeks respectively.</p> <p><i>Gastrointestinal events</i> Dulaglutide 1.5mg 26 weeks 116 ; 52 weeks 126 Dulaglutide 0.75mg 26 weeks 97 ; 52 weeks 111 Sitagliptin 26 weeks 55 ; 52 weeks 73 Placebo 41 (26 week data only)</p> <p><i>Infections</i> Dulaglutide 1.5mg 26 weeks 89 ; 52 weeks 111 Dulaglutide 0.75mg 26 weeks 71 ; 52 weeks 97 Sitagliptin 26weeks 74 ; 52 weeks 101 Placebo 36 (26 week data only)</p> <p><i>Headache</i> Dulaglutide 1.5mg 26 weeks 20 ; 52 weeks 26 Dulaglutide 0.75mg 26 weeks 20 ; 52 weeks 23 Sitagliptin 26 weeks 19 ; 52 weeks 23 Placebo 9 (26 week data only)</p> <p><i>Mortality</i> Dulaglutide: 1.5mg 26 weeks 1 ; 52 weeks 1 Dulaglutide: 0.75mg 26 weeks 0; 52 weeks 0 Sitagliptin: 26 weeks 0; 52 weeks 2 Placebo: 0 (26 week data only)</p>
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				<p>Patient on Dulaglutide 1.5mg died of non haemorrhagic stroke; for other deaths there was no reported causative data</p> <p><i>Pancreatitis</i></p> <p>There were no cases of pancreatitis for dulaglutide; two cases for sitagliptin and 1 case for placebo</p>
<p>Notes: Gastrointestinal events defined as nausea, vomiting, diarrhoea, abdominal pain, dyspepsia, abdominal distension. Infections defined as nasopharyngitis, upper respiratory infection, urinary tract infection.</p>				
<p>Funding source: Eli Lilly and Company</p>				
<p>Legend: AHA/s = antihyperglycaemic agent/s; GLP-1 = glucagon-like peptide-1; HbA1c = glycated haemoglobin; HOMA = homoeostasis model assessment; conversion of HbA1c from % to mmol/mol using National Glycohemoglobin Standardization Program (NGSP) converter⁽¹²⁸⁾; conversion of fasting plasma glucose from mg/dL to mmol/L using Society for Biomedical Diabetes Research converter⁽⁵⁵⁾</p>				

<p>Citation: Pratley et al. 2010⁽³⁴⁾</p> <p>Study design: Randomised, active comparator, parallel-group, open-label trial</p> <p>Setting: 158 office-based sites in 11 European countries</p> <p>Duration of follow-up: 26 weeks</p>	<p>Inclusion criteria: Participants 18-80 years old, type 2 diabetes, HbA1c of between 7.5-10% (58-86 mmol/mol), body mass index of 45kg/m² or lower, and had been treated with metformin (≥1500mg daily) for 3 months or longer</p> <p>Exclusion criteria: Previous treatment with any AHA apart</p>	<p>Number of participants and intervention: Intervention A: (Number allocated n=221; number that received treatment n=218) Liraglutide 1.8mg injection injected subcutaneously once a day</p> <p>Intervention B: (Number allocated n=225; number that</p>	<p>Outcome measures: Primary: Mean changes from baseline to week 26 of: beta cell function estimated by HOMA-beta, fasting C-peptide concentration and fasting proinsulin-to-insulin ratio, HbA1c, fasting plasma glucose and postprandial plasma glucose</p> <p>Secondary:</p>	<p>Results: All data are least mean change from baseline to 26 weeks (95% confidence interval)</p> <p>Beta cell function (HOMA-beta) Liraglutide 1.8mg: 28.70% (21.34 to 36.06%) Liraglutide 1.2mg: 27.23% (19.73 to 34.73%) Sitagliptin: 4.18% (-3.27 to 11.62%)</p> <p>Fasting C-peptide Liraglutide 1.8mg: 0.09 nmol/L (0.03 to 0.15 nmol/L) Liraglutide 1.2mg: 0.09 nmol/L (0.03 to 0.15 nmol/L) Sitagliptin: -0.04 nmol/L (-0.10 to 0.02 nmol/L)</p> <p>Fasting proinsulin-to-insulin ratio: Liraglutide 1.8mg: -0.10 (-0.12 to -0.07)</p>
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<p>Randomisation: Randomisation sequence was computer-generated by pharmaceutical company Novo Nordisk. Participants were randomly assigned in a 1:1:1 ratio, stratified by country. Consecutive allocation of the randomisation code to individual participants was concealed by use of a telephone-based or web-based randomisation system. Study was open-label, but data were masked from the statistician until database release.</p>	<p>from metformin within 3 months of the trial; recurrent major hypoglycaemia or hypoglycaemic unawareness; present use of any drug except metformin that could affect glucose; contraindication to trial drugs; impaired renal or hepatic function; clinically significant cardiovascular disease or cancer</p>	<p>received treatment n=221) Liraglutide 1.2mg injection injected subcutaneously once a day</p> <p>(All liraglutide doses were started at 0.6mg/day and escalated by 0.6mg/week to the allocated dose)</p> <p>Intervention C: (Number allocated n=219; number that received treatment n=219) Sitagliptin 100mg tablet swallowed once a day</p> <p>Background treatment with metformin remained stable</p>	<p>Adverse events from baseline to 26 weeks: gastrointestinal side effects, infections, headache, pancreatitis and mortality</p>	<p>Liraglutide 1.2mg: -0.08 (-0.11 to -0.05) Sitagliptin: -0.03 (-0.06 to -0.00)</p> <p>HbA1c Liraglutide 1.8mg: -1.50% (-1.63 to -1.37%); -16.4mmol/mol (-17.8 to -14.9mmol/mol) Liraglutide 1.2mg: -1.24% (-1.37 to -1.11%); -13.5mmol/mol (-14.9 to -12.1mmol/mol) Sitagliptin: -0.90% (-1.03 to -0.77%); -9.8 mmol/mol (-11.2 to -8.4mmol/mol)</p> <p>Fasting plasma glucose Liraglutide 1.8mg: -2.14mmol/L (-2.43 to -1.84mmol/L); -38.56mg/dL (-43.78 to -33.15mg/dL) Liraglutide 1.2mg: -1.87mmol/L (-2.16 to -1.57mmol/L); -33.69mg/dL (-38.9 to -28.29mg/dL) Sitagliptin: -0.83mmol/L (-1.13 to -0.54mmol/L); -14.96mg/dL (-20.36 to -9.73 mg/dL)</p> <p>Postprandial plasma glucose Author reported that data was difficult to interpret, and no data was provided.</p> <p>Adverse events Data is number of adverse events during weeks 0 to 26</p> <p><i>Gastrointestinal events</i> Liraglutide 1.8mg: 88 Liraglutide 1.2mg: 73 Sitagliptin: 46</p> <p><i>Infections</i> Liraglutide 1.8mg: 59 Liraglutide 1.2mg: 62</p>
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				<p>Sitagliptin: 63 <i>Headache</i> Liraglutide 1.8mg: 25 Liraglutide 1.2mg: 20 Sitagliptin: 22 <i>Mortality</i> Liraglutide: 1.8mg: 1 (pancreatic carcinoma) Liraglutide: 1.2mg 0 Sitagliptin: 1 (fatal cardiac arrest) <i>Pancreatitis</i> No pancreatitis reported in this study (one case of diabetic retinopathy in liraglutide 1.8mg treatment group)</p>
Notes: Gastrointestinal events defined as nausea, vomiting, diarrhoea, constipation, dyspepsia. Infections defined as nasopharyngitis, influenza				
Funding Source: Novo Nordisk				
Legend: AHA/s = antihyperglycaemic agent/s; HbA1c = glycated haemoglobin; HOMA = homoeostasis model assessment; conversion of HbA1c from % to mmol/mol using National Glycohemoglobin Standardization Program (NGSP) converter ⁽¹²⁸⁾ ; for small HbA1c values used ratio 1.22% equals 13.3mmol/L ⁽⁷⁶⁾ ; conversion of fasting plasma glucose from mmol/L to mg/dL using Society for Biomedical Diabetes Research converter ⁽⁵⁵⁾				

<p>Citation: Pratley et al. 2011⁽⁶¹⁾ (this is an extension of Pratley et al. 2010)⁽³⁴⁾</p> <p>Study design: Randomised, active comparator, parallel- group, open-label trial</p> <p>Setting:</p>	<p>Inclusion criteria: Participants 18-80 years old, type 2 diabetes, HbA1c of between 7.5-10% (58- 86 mmol/mol), body mass index of 45kg/m² or lower, and had been treated with metformin (≥1500mg daily) for 3 months or longer</p>	<p>Number of participants and intervention groups: Intervention A: Number that were enrolled/exposed in the extension (n=176) Liraglutide 1.8mg injection injected subcutaneously once</p>	<p>Outcome measures: Primary: Mean changes from baseline to week 52 of: beta cell function estimated HOMA-beta, fasting C-peptide concentration and fasting proinsulin-to- insulin ratio, HbA1c, fasting plasma glucose</p>	<p>Results: All data is least mean change from baseline to 52 weeks (95% confidence interval) Beta cell function (HOMA-beta) Liraglutide 1.8mg: 25.76% (19.39 to 32.13%) Liraglutide 1.2mg: 22.58% (16.09 to 29.07%) Sitagliptin: 3.98% (-2.45 to 10.45%) Fasting C-peptide Liraglutide 1.8mg: 0.09 nmol/L (0.03 to 0.15 nmol/L) Liraglutide 1.2mg: 0.05 nmol/L (-0.01 to 0.11</p>
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<p>158 office-based sites in 11 European countries</p> <p>Duration of follow-up: 52 weeks</p> <p>Randomisation: Randomisation sequence was computer-generated by pharmaceutical company Novo Nordisk. Participants were randomly assigned in a 1:1:1 ratio, stratified by country. Consecutive allocation of the randomisation code to individual participants was concealed by use of a telephone-based or web-based randomisation system. Study was open-label, but data were masked from the statistician until database release.</p>	<p>Exclusion criteria: Additional withdrawal criteria during the extension were: elevated fasting plasma glucose > 11 mmol/L (200 mg/dL) with no treatable intercurrent cause or acute pancreatitis (defined as a minimum two out of three of the following: abdominal pain, amylase and/or lipase > 3 x upper normal range or characteristic findings on computed tomography/magnetic resonance imaging).</p>	<p>a day</p> <p>Intervention B: Number that were enrolled/exposed in the extension (n=155) Liraglutide 1.2mg injection injected subcutaneously once a day</p> <p>Intervention C: Number that were enrolled/exposed in the extension (n=166) Sitagliptin 100mg tablet swallowed once a day</p> <p>Background treatment with metformin remained stable</p>	<p>and postprandial plasma glucose</p> <p>Secondary: Adverse events from baseline to 52 weeks: gastrointestinal side effects, infections, headache, pancreatitis and mortality</p>	<p>nmol/L) Sitagliptin: 0.01 nmol/L (-0.05 to 0.07 nmol/L)</p> <p>Fasting proinsulin-to-insulin ratio: Liraglutide 1.8mg: -0.09 (-0.13 to -0.05) Liraglutide 1.2mg: -0.07 (-0.11 to -0.03) Sitagliptin: -0.01 (-0.05 to -0.03)</p> <p>HbA1c Liraglutide 1.8mg: -1.51% (-1.65 to -1.37%); -16.5 mmol/mol (-18.0 to -14.9 mmol/mol) Liraglutide 1.2mg: -1.29% (-1.43 to -1.15%); -14.1 mmol/mol (-15.6 to -12.5 mmol/mol) Sitagliptin: -0.88% (-1.02 to -0.74%); -9.6 mmol/mol (-11.1 to -8.1 mmol/mol)</p> <p>Fasting plasma glucose Liraglutide 1.8mg: -2.04 mmol/L (-2.37 to -1.71 mmol/L); -36.72 mg/dL (-42.72 to -30.72 mg/dL) Liraglutide 1.2mg: -1.71 mmol/L (-2.04 to -1.38 mmol/L); -30.78 mg/dL (-36.78 to -24.78 mg/dL) Sitagliptin: -0.59 mmol/L (-0.92 to -0.26 mmol/L); -10.62 mg/dL (-16.62 to -4.62 mg/dL)</p> <p>Postprandial plasma glucose Author reported that data was difficult to interpret, and no data was provided.</p> <p>Adverse Events Data are number of adverse events during weeks 0 to 52</p> <p><i>Gastrointestinal events</i> Liraglutide 1.8mg: 94 Liraglutide 1.2mg: 80</p>
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				<p>Sitagliptin: 52</p> <p><i>Infections</i></p> <p>Liraglutide 1.8mg: 77</p> <p>Liraglutide 1.2mg: 74</p> <p>Sitagliptin: 75</p> <p><i>Headache</i></p> <p>Liraglutide 1.8mg: 29</p> <p>Liraglutide 1.2mg: 21</p> <p>Sitagliptin: 27</p> <p><i>Mortality</i></p> <p>Liraglutide 1.8mg: 1 (pancreatic carcinoma)</p> <p>Liraglutide 1.2mg: 0</p> <p>Sitagliptin: 2 (fatal cardiac arrest x 2)</p> <p><i>Pancreatitis</i></p> <p>One case of 'non-acute' pancreatitis reported with liraglutide 1.8mg (one case of diabetic retinopathy in liraglutide 1.8mg treatment group)</p>
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Notes: Gastrointestinal events defined as nausea, vomiting, diarrhoea, constipation, dyspepsia. Infections defined as nasopharyngitis, influenza

Funding source: Novo Nordisk.

Legend: HbA1c = glycated haemoglobin; HOMA = homoeostasis model assessment; conversion of HbA1c from % to mmol/mol using National Glycohemoglobin Standardization Program (NGSP) converter⁽¹²⁸⁾; for small HbA1c values used ratio 1.22% equals 13.3mmol/L⁽⁷⁶⁾; conversion of fasting plasma glucose from mmol/L to mg/dL using Society for Biomedical Diabetes Research converter⁽⁵⁵⁾

<p>Citation: Bergenstal et al. 2010⁽¹¹⁸⁾</p> <p>Study design: Randomised, double-</p>	<p>Inclusion criteria: Patients aged 18 years or older with type 2 diabetes but otherwise healthy, and had been</p>	<p>Number of participants and intervention groups: Intervention A: (Number allocated n=170; number that</p>	<p>Outcomes measures: Primary: Mean changes from baseline to week 26 of: HbA1c, fasting plasma glucose</p>	<p>Results: All data are least square mean change from baseline to 26 weeks (95% confidence interval)</p> <p>HbA1c Exenatide 2mg: -1.5% (-1.7 to -1.4%); -16.4mmol/mol (-18.5 to -15.3mmol/mol)</p>
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<p>blind, double-dummy multi-arm superiority trial</p> <p>Setting: 72 hospitals and clinics in the USA India and Mexico</p> <p>Duration of follow-up: 26 week</p> <p>Randomisation: Assigned centrally via an interactive voice response system to conceal allocation and was independent of the sponsor, investigators, study-site staff and patients. The randomisation sequence was computer-generated, and patients were randomly allocated in a 1:1:1 ratio. Placebo medications were identical in appearance to study treatment.</p>	<p>treated with a stable metformin regimen for at least 2 months before screening; HbA1c of 7.1-11.0% (54-97mmol/mol) and a body mass index of 25-45kg/m²</p> <p>Exclusion criteria: Previous exposure to GLP-1 analogues; gastroparesis; cardiovascular disease; hepatic disease; macular oedema</p>	<p>received treatment n=160 Exenatide 2mg injection injected subcutaneously once a week plus oral placebo once a day</p> <p>Intervention B: (Number allocated n=172; number that received treatment n=166) Sitagliptin 100mg tablet swallowed once a day plus placebo as a once weekly injection</p> <p>Intervention C: (Number allocated n=172; number that received treatment n=165) 45mg oral pioglitazone once daily plus placebo as a once weekly injection</p> <p>Stable doses of metformin were</p>	<p>Secondary: Adverse events from baseline to 26 weeks: gastrointestinal side effects, infections, headache, pancreatitis and mortality</p>	<p>Sitagliptin: -0.9% (-1.1 to -0.7%); -9.8mmol/mol (-12.0 to -7.6mmol/mol) Pioglitazone: -1.2% (-1.4 to -1.0%); -13.1mmol/mol (-15.3 to -10.9mmol/mol)</p> <p>Fasting plasma glucose Exenatide 2mg: -1.8mmol/L (-2.2 to -1.3mmol/L); -32.43mg/dL (-39.64 to -23.42mg/dL) Sitagliptin: -0.9mmol/L (-1.3 to -0.5mmol/L); -16.21mg/dL (-23.42 to -9.01mg/dL) Pioglitazone: -1.5mmol/L (-1.9 to -1.1mmol/L); -27.03mg/dL (-34.23 to -19.82mg/dL)</p> <p>Adverse events Data is number of patients (number of events) to 26 weeks <i>Gastrointestinal events</i> Exenatide 2mg: 94 (139) Sitagliptin: 39 (106) Pioglitazone: 27 (31) <i>Infections</i> Exenatide 2mg: 21 (22) Sitagliptin: 26 (28) Pioglitazone: 34 (39) <i>Headache</i> Exenatide 2mg: 15 (16) Sitagliptin: 15 (19) Pioglitazone: 7 (9) <i>Mortality</i> Exenatide 2mg: 0 Sitagliptin: 1 (uncontrolled hypertension)</p>
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<p>Randomisation was stratified by country and by HbA1c at screening (<9.0% (<75mmol/mol) vs >9.0% (>75mmol/mol). All patients, study-site staff, investigators and the sponsor were masked to treatment allocation during the double-blind treatment period. After finalisation of the statistical analysis plan and subsequent database lock, the sponsor was unmasked to treatment allocation.</p>		<p>received throughout the study</p>		<p>Pioglitazone: 0 <i>Pancreatitis</i> One case of necrotising pancreatitis was reported with pioglitazone</p>
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Notes: Gastrointestinal events defined as nausea, diarrhoea, vomiting and constipation. Infections defined as upper respiratory tract infection and urinary tract infection and sinusitis.

Funding source: Amylin Pharmaceuticals and Eli Lilly

Legend: GLP-1 = glucagon-like peptide-1; HbA1c = glycated haemoglobin; conversion of HbA1c from % to mmol/mol using National Glycohemoglobin Standardization Program (NGSP) converter⁽¹²⁸⁾; for small HbA1c values used ratio 1.22% equals 13.3mmol/L⁽⁷⁶⁾; conversion of fasting plasma glucose from mmol/L to mg/dL using Society for Biomedical Diabetes Research converter⁽⁵⁵⁾

Citation:	Inclusion criteria:	Number of intent to	Outcome measures:	Results:
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<p>Russell-Jones et al. 2012⁽⁶⁰⁾</p> <p>Study design: Randomised, double-blind, multi-arm study</p> <p>Setting: Multicentre study in 22 countries</p> <p>Duration of follow-up: 26 weeks</p> <p>Randomisation: Randomisation was determined by computer-generated random sequence using an interactive voice response system. Treatment assignments were stratified by country</p>	<p>Adults with type 2 diabetes and HbA1c 7.1-11.0% (54-97mmol/mol), body mass index 23-45kg/m² and history of stable weight. Patients had to be suboptimally treated with diet and exercise, but naïve to antihyperglycaemic agents.</p> <p>Exclusion criteria: Treatment with any AHA for >7 days within 3 months of screening.</p>	<p>treat participants and intervention groups:</p> <p>Intervention A: (n=248) Exenatide 2mg subcutaneous injection injected once weekly</p> <p>Intervention B: (n=163) Sitagliptin 100mg tablet swallowed once a day</p> <p>Intervention C: (n=246) Metformin oral tablet swallowed once a day increased in weekly increments up to target of 2000mg/day (Metformin could be increased to 2500mg/day based on glycaemic control)</p> <p>Intervention D: (n=163) Pioglitazone oral tablet swallowed once a day increased in weekly increments up to target of 45mg/day</p>	<p>Primary: Mean changes from baseline to week 26 of: beta cell function assessed by HOMA-beta, HbA1c and fasting plasma glucose</p> <p>Secondary: Adverse events from baseline to 26 weeks: gastrointestinal side effects, infections, headache, pancreatitis and mortality</p>	<p>Data was presented as least squares mean reduction (\pm standard error) from baseline to 26 weeks</p> <p>Beta cell function (HOMA-beta) Mean (standard error) HOMA-beta (ratio of end point [last observation carried forward] to baseline) was significantly (all $P < 0.001$) improved in patients treated with exenatide 2mg [+1.8 (0.006)] compared with sitagliptin [+1.3 (0.04)], metformin [+1.4 (0.04)] and pioglitazone [+1.3 (0.05)]</p> <p>HbA1c Exenatide 2mg: -1.53% \pm 0.07%; (-16.7mmol/mol \pm 0.76mmol/mol) Sitagliptin: -1.15% \pm 0.08%; (-12.5mmol/mol \pm 0.87mmol/mol) Metformin: -1.48% \pm 0.07%; (-16.1mmol/mol \pm 0.76mmol/mol) Pioglitazone: -1.63% \pm 0.08%; (-17.8mmol/mol \pm 0.87mmol/mol)</p> <p>Fasting plasma glucose Exenatide 2mg: -2.3mmol/L \pm 0.1mmol/L; (-41.44mg/dL \pm 1.80mg/dL) Sitagliptin: -1.1mmol/L \pm 0.2mmol/L; (-19.82mg/dL \pm 3.60mg/dL) Metformin: -2.0mmol/L \pm 0.1mmol/L; (-36.04mg/dL \pm 1.80mg/dL) Pioglitazone: -2.6mmol/L \pm 0.2mmol/L; (-46.85mg/dL \pm 3.60mg/dL)</p> <p>Adverse events</p>
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		Standard diet and exercise counselling was provided in each treatment group		<p>Data are number of patients of intent to treat population</p> <p><i>Gastrointestinal</i></p> <p>Exenatide 2mg: 94</p> <p>Sitagliptin: 22</p> <p>Metformin: 64</p> <p>Pioglitazone: 24</p> <p><i>Infection</i></p> <p>Exenatide 2mg: 19</p> <p>Sitagliptin: 16</p> <p>Metformin:11</p> <p>Pioglitazone: 14</p> <p><i>Headache</i></p> <p>Exenatide 2mg: 20</p> <p>Sitagliptin: 15</p> <p>Metformin: 30</p> <p>Pioglitazone: 13</p> <p><i>Mortality</i></p> <p>One death reported with metformin which was not considered due to the study drug</p> <p><i>Pancreatitis</i></p> <p>One reported case of pancreatitis with sitagliptin</p>
Funding Source: Amylin Pharmaceuticals and Eli Lilly				
Notes: Gastrointestinal events defined as diarrhoea, nausea, dyspepsia and constipation. Infections defined as nasopharyngitis				
Legend: AHA = antihyperglycaemic agent; HbA1c = glycated haemoglobin; HOMA = homoeostasis model assessment; conversion of HbA1c from % to mmol/mol using National Glycohemoglobin Standardization Program (NGSP) converter ⁽¹²⁸⁾ ; for small HbA1c values used ratio 1.22% equals 13.3mmol/L ⁽⁷⁶⁾ ; conversion of fasting plasma glucose from mmol/L to mg/dL using Society for Biomedical Diabetes Research converter ⁽⁵⁵⁾				
Citation: Gudipaty et al. 2014 ⁽³⁾	Inclusion criteria: Patients age 18-70	Number of participants and intervention	Outcome measures: Primary:	Results: Data are means (\pm standard error) change from

<p>Study design: Randomised, active comparator, open label, multi-arm study</p> <p>Setting: University of Pennsylvania Clinical and Translational Research Centre</p> <p>Duration of follow-up: Six months</p> <p>Randomisation: Randomisation was performed with stratification designed to balance sex and tiers of age (18-44 and 45-70 years), fasting glucose level (110-126 mg/dL) (6.1-7.0 mmol/L) and 127-159mg/dL) (7.1-8.8mmol/L) and body mass index (<35 and 35-44kg/m²) among the three groups.</p>	<p>years with impaired fasting plasma glucose or early type 2 diabetes as defined by a plasma glucose concentration between 110 and 159mg/dL (6.1-8.8mmol/L) following a >12 hour overnight fast performed off any AHA for ≥ 2 weeks (6 weeks for thiazolidinediones) and of stable body weight (±5%) for at least 2 weeks</p> <p>Exclusion Criteria: any prior exposure to GLP-1 analogues or DPP-4 inhibitors and active cardiovascular, liver or kidney disease</p>	<p>groups:</p> <p>Intervention A: Number treated (n=14) Exenatide 5µg subcutaneous twice a day, increasing to 10µg twice a day after one month</p> <p>Intervention B: Number treated (n=12) Sitagliptin oral tablet 100mg daily</p> <p>Intervention C: Number treated (n=14) Glimepiride oral tablet 0.5mg daily, increasing by 0.5-1.0mg increments in the morning or evening at weekly intervals (maximum total daily dose 4.0mg divided) to achieve an average fasting glucose level <110mg/dL (<6.1mmol/L) while avoiding any hypoglycemia.</p>	<p>Mean changes from baseline to six months of: beta cell function assessed by plasma proinsulin-to-insulin ratio, HbA1c and fasting plasma glucose</p>	<p>baseline to 6 months</p> <p>Beta cell function: Plasma Proinsulin to insulin ratio Proinsulin to insulin ratios were unchanged from baseline to 6 months with no significant differences between the exenatide or sitagliptin and glimepiride groups (data not shown in the study)</p> <p>HbA1c Exenatide 10 µg: -0.2% ±0.1%; (-2.2 mmol/mol ± 1.1mmol/mol) Sitagliptin: -0.01% ±0.1%; (-0.1 mmol/mol ±1.1mmol/mol) Glimepiride: -0.5% ±0.2%; (-5.5mmol/mol ± 2.2mmol/mol)</p> <p>Fasting plasma glucose Exenatide: -0.10mmol/L ±0.3mmol/L; (-2mg/dL ±5mg/dL) Sitagliptin: +0.06mmol/L ±0.5mmol/L; (+1mg/dL ±9mg/dL) Glimepiride: -0.44mmol/L ±0.33mmol/L; (-8mg/dL ±6mg/dL)</p>
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<p>Notes: Small study size and the standard deviations were wide for some of the intervention groups. There were a number of spelling errors in paper. This study measured beta cell function from the glucose-potentiated arginine test, which was not part of the inclusion criteria for this systematic review. Proinsulin-to-insulin ratio data was not reported.</p>				
<p>Funding source: Study did not receive any sponsorship</p>				
<p>Legend: AHA = antihyperglycaemic agent; GLP-1 = glucagon-like peptide-1; DPP-4 = dipeptidyl peptidase-4; HbA1c = glycated haemoglobin; for small HbA1c values used ratio 1.22% equals 13.3mmol/L⁽⁷⁶⁾; conversion of plasma glucose levels from mg/dL to mmol/L using Society for Biomedical Diabetes Research converter⁽⁵⁵⁾</p>				

<p>Citation: Sanofi Pharmaceutical Company date of issue 2014⁽¹²⁰⁾</p> <p>Study design: Phase 3 randomised, double-blind, double-dummy, active comparator, 2-arm parallel-group, multicentre study</p> <p>Setting: 92 centres in 13 countries</p> <p>Duration of follow-up: 24 weeks</p> <p>Randomisation:</p>	<p>Inclusion criteria: Patients aged from 18 years to less than 50 years with type 2 diabetes diagnosed at least 1 year before the screening visit; insufficiently controlled with metformin at a stable dose of at least 1500mg/day for at least 3 months prior to screening; obese body mass index $\geq 30\text{kg/m}^2$; aged from 18 years to less than 50 years; and HbA1c $\geq 7.0\%$ and $\leq 10\%$ ($\geq 53\text{ mmol/mol}$ and 86 mmol/mol) at screening</p>	<p>Number of participants and intervention groups:</p> <p>Intervention A: Number treated (n=158) lixisenatide or volume-matched placebo 10μg injection once daily for 1 week, then 15μg once daily for one week, followed by the maintenance dose of 20μg once daily</p> <p>Intervention B Number treated (n=161) sitagliptin and matching placebo as a 100mg tablet once daily oral administration.</p>	<p>Outcome measures:</p> <p>Primary: Mean change from baseline to week 24 in beta-cell function (assessed by HOMA-beta, fasting plasma C-peptide and fasting plasma proinsulin-to-insulin ratio); HA1c, fasting plasma glucose, postprandial plasma glucose</p> <p>Secondary Outcomes: Adverse events from baseline to 24 weeks: gastrointestinal side effects, infections, headache, pancreatitis and mortality</p>	<p>Results: Data is least squares mean difference for lixisenatide versus sitagliptin from baseline to 24 weeks</p> <p>Beta cell function: Fasting plasma proinsulin to insulin ratio Least square (LS) mean difference for lixisenatide versus sitagliptin was 0.08 (95% confidence interval (CI) 0.001 to 0.167)</p> <p>HOMA-beta and plasma C-peptide: No significant difference was observed between the lixisenatide and sitagliptin treatment groups in beta cell function assessed by HOMA-beta . No relevant differences were observed between the lixisenatide and sitagliptin treatment groups in C-peptide levels. No study data was provided.</p> <p>HbA1c: LS mean HbA1c changes from baseline to week 24 (-0.66% and -0.72%) (-7.2mmol/mol and -7.8mmol/mol) in the lixisenatide and sitagliptin treatment groups respectively; the LS mean</p>
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<p>No documentation on randomisation process</p>	<p>Exclusion criteria: None noted</p>	<p>Patients received either lixisenatide and sitagliptin-matched placebo or sitagliptin and lixisenatide-matched placebo. Study was double-blind with regard to treatment. However, for lixisenatide or volume-matched placebo the injected volume differed according to dose being received (dose increase or maintenance period) and therefore was not blinded.</p> <p>Stable doses of metformin were received throughout the study</p>	<p>difference versus sitagliptin was 0.06% (95%CI - 0.179 to 0.308)</p> <p>Fasting plasma glucose No significant difference was observed between the lixisenatide and sitagliptin treatment groups. No study data was provided.</p> <p>Postprandial plasma glucose The LS mean change from baseline to week 24 in 2-hour postprandial plasma glucose was -3.35mmol/L (-60.36mg/dL) in lixisenatide treatment group compared with -1.44mmol/L (-25.95mg/dL) in the sitagliptin treatment groups (LS mean difference versus sitagliptin -1.91mmol/L (95% CI -2.88 to -0.94mmol/L) - 34.41mg/dL (95% CI -51.89 to -16.94mg/dL)</p> <p>Adverse events Data are number of patients with at least one adverse event</p> <p><i>Gastrointestinal</i> Lixisenatide: 28 Sitagliptin: 11</p> <p><i>Infections</i> No reports</p> <p><i>Headache</i> Lixisenatide: 20 Sitagliptin: 15</p> <p><i>Mortality</i> There were no cases of death</p> <p><i>Pancreatitis</i> No confirmed diagnoses of pancreatitis</p>
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Funding Source: Sanofi				
Notes: This was a Phase 3 unpublished study. Gastrointestinal event defined as nausea.				
Legend: HbA1c = glycated haemoglobin; HOMA = homoeostasis model assessment; conversion of HbA1c from % to mmol/mol using National Glycohemoglobin Standardization Program (NGSP) converter ⁽¹²⁸⁾ ; for small HbA1c values used ratio 1.22% equals 13.3mmol/L ⁽⁷⁶⁾ ; conversion of plasma glucose levels from mg/dL to mmol/L using Society for Biomedical Diabetes Research converter ⁽⁵⁵⁾				

3.4 Effects on pancreatic beta cell function

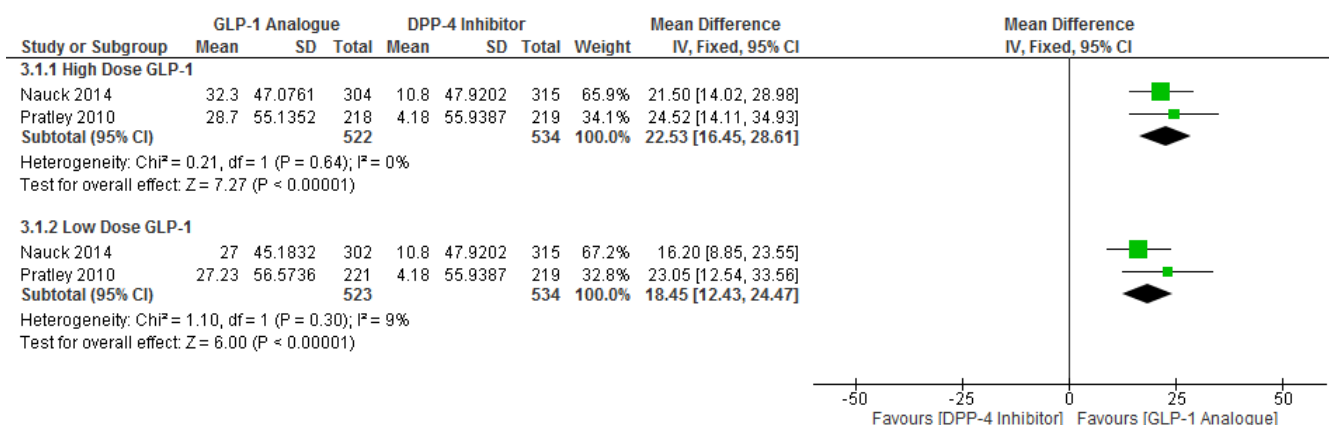
3.4.1 HOMA-beta (%)

Five of the included RCTs^(34, 60, 61, 76, 120), which included one unpublished study⁽¹²⁰⁾, assessed pancreatic beta cell function using HOMA-beta. Three of these studies^(34, 61, 76) presented data as the mean change in beta cell function (as a percentage) from baseline to endpoint, while another study⁽⁶⁰⁾ presented results from HOMA-beta as a ratio of endpoint to baseline. For the unpublished study⁽¹²⁰⁾, details of analysis for measures of HOMA-beta were not reported.

3.4.1.1 High dose and low dose GLP-1 analogue compared to DPP-4 inhibitor for duration of 26 weeks

Meta-analysis of two RCTs^(34, 76) showed a statistically significant improvement in beta cell function with GLP-1 analogues compared to administration of DPP-4 inhibitor as measured by HOMA-beta with 26 weeks of treatment for both high and low dose GLP-1 analogues (refer Figure 3.2). Different GLP-1 analogues were used in each study. Figure 3.2 indicates little difference attributable to differences in dosage in the magnitude of the effect size; high dose GLP-1 analogue had a slightly greater effect compared to the low dose GLP-1 analogue estimate (23% versus 18.5%). Results of Chi² and I² analysis showed no statistical heterogeneity (refer Figure 3.2). The results presented in Figure 3.2 are consistent with the multi-arm RCT conducted by Russell-Jones et al.⁽⁶⁰⁾ (see Table 3.2), which showed that high dose GLP-1 analogue (exenatide, 2mg once weekly) improved beta cell function at 26 weeks compared to DPP-4 inhibitor. These authors used a different measure of HOMA-beta (mean HOMA-beta ratio of endpoint to baseline) to show mean standard error (SE) HOMA-beta (ratio of endpoint [last observation carried forward] to baseline) was significantly (p<0.001) improved in patients treated with GLP-1 analogue [+1.8 (0.06)] compared to DPP-4 inhibitor [+1.3(0.04)]. Conversely, an unpublished 24-week study sponsored by pharmaceutical

company Sanofi⁽¹²⁰⁾, manufacturer of GLP-1 analogue (see Table 3.2), found no statistically significant difference (effect size and p value not reported) between high dose GLP-1 analogue (lixisenatide 20µg once daily) and DPP-4 inhibitor on beta cell function using the same measure of beta cell function, HOMA-beta. The difference observed in HOMA-beta in the Sanofi sponsored study was difficult to explain, as the authors gave no clear description of randomisation methods used, and baseline data for study participants was not described, preventing comparisons to be drawn on treatment groups (see Table 3.1 for critical appraisal of study). It is noteworthy that the GLP-1 analogue used was different in each study.



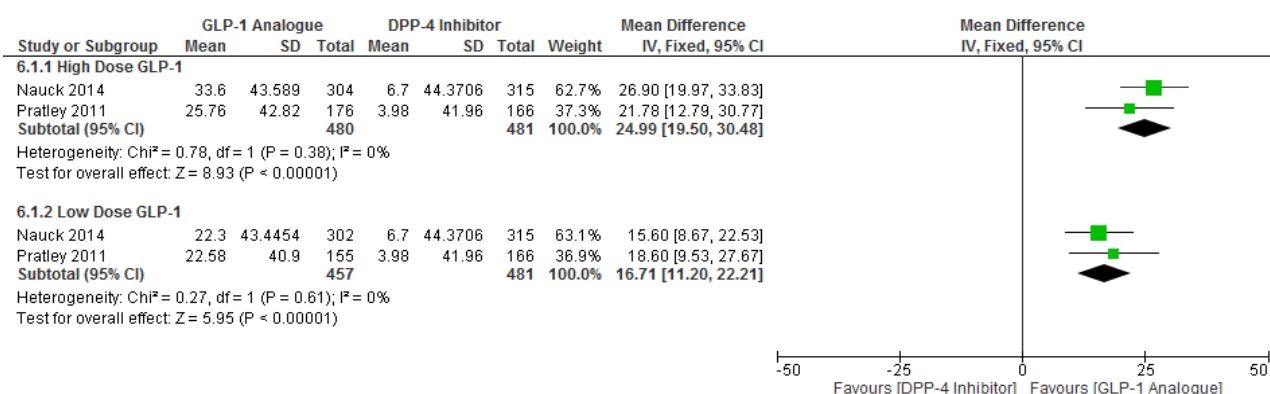
High dose GLP-1 analogue dulaglutide 1.5mg once weekly (Nauck et al.)⁽⁷⁶⁾ and liraglutide 1.8mg once daily (Pratley et al.)⁽³⁴⁾; low dose GLP-1 analogue dulaglutide 0.75mg once weekly (Nauck et al.)⁽⁷⁶⁾ and liraglutide 1.2mg once daily (Pratley et al.)⁽³⁴⁾

Figure 3.2. Meta-analysis of effects on beta cell function after 26 weeks as measured by HOMA-beta (homeostasis model assessment-beta) (%) for GLP-1 analogue high dose (top) and low dose (bottom) compared to DPP-4 inhibitor, sitagliptin, 100mg once daily

3.4.1.2 High dose and low dose GLP-1 analogue compared to DPP-4 inhibitor for duration of 52 weeks

The same trials^(61, 76) reported HOMA-beta at 52 weeks. Similar to results after 26 weeks (Figure 3.2), meta-analysis showed statistically significant greater improvement in beta cell function with administration of GLP-1 analogues than DPP-4 inhibitor at both high and low doses (refer Figure 3.3). Mean difference at 52 weeks for high dose GLP-1 analogue was comparable to corresponding data at 26 weeks (25 versus 23%) (refer Figure 3.2). Similarly,

mean difference at 52 weeks for low dose GLP-1 analogue was similar to the corresponding data at 26 weeks (16.7% versus 18.5% – refer Figures 3.2 and 3.3). The results of Chi² and I² in these meta-analyses indicated no statistically significant heterogeneity (refer Figure 3.3).



High dose GLP-1 analogue dulaglutide 1.5mg once weekly (Nauck et al.)⁽⁷⁶⁾ and liraglutide 1.8mg once daily (Pratley et al.)⁽⁶¹⁾; low dose GLP-1 analogue dulaglutide 0.75mg once weekly (Nauck et al.)⁽⁷⁶⁾ and liraglutide 1.2mg once daily (Pratley et al.)⁽⁶¹⁾

Figure 3.3. Meta-analysis of effects on beta cell function after 52 weeks as measured by HOMA-beta (homeostasis model assessment-beta) (%) for GLP-1 analogue high dose (top) and low dose (bottom) compared to DPP-4 inhibitor, sitagliptin 100mg once daily

3.4.2 Plasma proinsulin to insulin (PI/I) ratio

Three out of four RCTs^(3, 34, 61, 120) assessing beta cell function using measures of plasma proinsulin to insulin (PI/I) ratio showed GLP-1 analogues improved beta cell function compared to DPP-4 inhibitors; data from all studies was presented as mean change from baseline to endpoint (refer Table 3.2). A meta-analysis was not conducted for this outcome due to a combination of insufficient data reporting and data heterogeneity. An unpublished study⁽¹²⁰⁾ sponsored by pharmaceutical company Sanofi concluded GLP-1 analogues showed a significant treatment difference when compared to DPP-4 inhibitor after 24 weeks (refer Table 3.2). Similarly, Pratley et al.⁽³⁴⁾ showed low and high dose GLP-1 analogues after 26 weeks were associated with statistically significant improvements in PI/I ratio compared to DPP-4 inhibitor, and this improvement was maintained for 52 weeks⁽⁶¹⁾ (refer Table 3.2). Conversely, Gudipaty et al.⁽³⁾ reported that after 26 weeks, PI/I ratio was unchanged from

baseline, with no significant differences between high dose GLP-1 analogue and DPP-4 inhibitor. The authors did not provide any data to support their conclusion. The difference in result by Gudipaty et al.⁽³⁾ may be explained by the small number of study participants recruited in the study, and the diabetes eligibility criteria for this study was for 'early' diabetes. By contrast, the other studies^(34, 61, 120) had larger participant numbers, and different inclusion criteria for type 2 diabetes, whereby participants' glycaemic control was poorer at baseline. Also, for the study by Gudipaty et al.⁽³⁾, the two treatment groups were not comparable at entry; there were sizeable differences in duration of diabetes (GLP-1 analogue 3.3 years \pm 0.6 years compared to DPP-4 inhibitor 5.3 years \pm 1.7 years), fasting insulin levels (GLP-1 analogue 24 μ U/mL \pm 6 μ U/mL compared to DPP-4 inhibitor 17 μ U/mL \pm 2 μ U/mL) and fasting glucagon levels (GLP-1 analogue 40pg/mL \pm 4pg/mL compared to DPP-4 inhibitor 50pg/mL \pm 6pg/mL).

3.4.3 Plasma C-peptide levels

Fasting plasma C-peptide (nmol/L) was measured in three RCTs^(34, 61, 120) to assess beta cell function. All measures were expressed as mean change from baseline to endpoint. Two studies published by Pratley et al. on the same patients^(34, 61) demonstrated statistically significant improvements in fasting C-peptide concentrations with both high and low dose GLP-1 analogues compared to DPP-4 inhibitor at 26 weeks, but only high dose GLP-1 analogues showed statistically significant improvements at 52 weeks (refer Table 3.2). The unpublished study⁽¹²⁰⁾ sponsored by Sanofi reported no observed differences in C-peptide between high dose GLP-1 analogue and DPP-4 inhibitor, but no study data was provided (refer Table 3.2). As previously noted in section 3.4.1.1, reasons for the difference in the Sanofi sponsored study are difficult to explain due to lack of available information on both study randomisation and participants.

3.5 Effects on glycaemic control

3.5.1 Glycated haemoglobin (HbA1c)

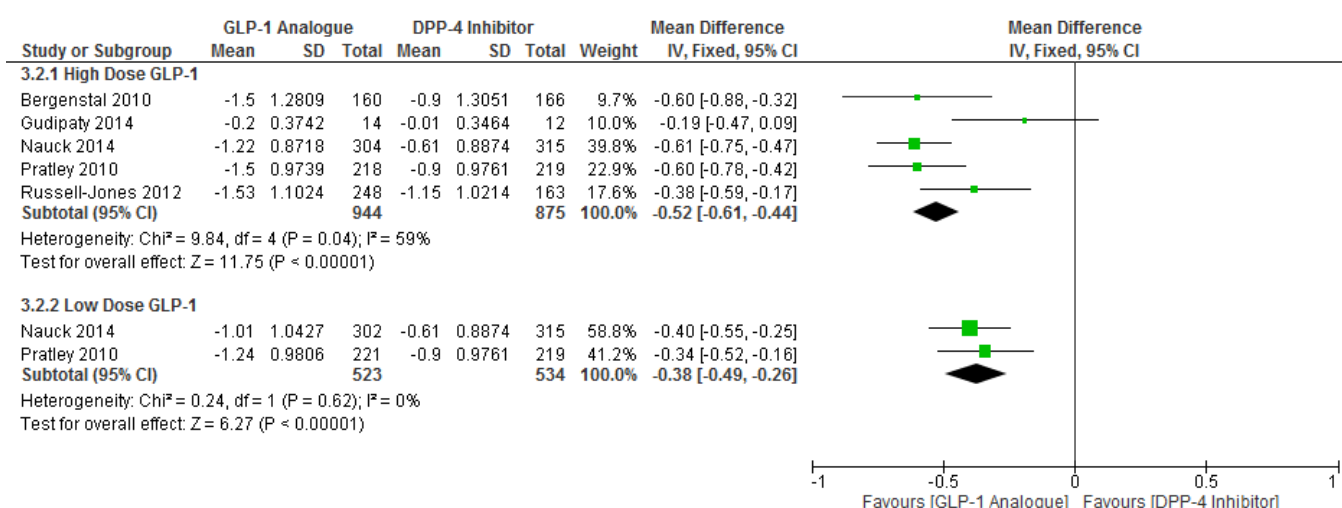
All seven studies provided outcome data on mean changes in HbA1c from baseline to endpoint. Two of these studies^(3, 76) expressed results of HbA1c as a percentage and the new reporting methods mmol/mol (refer Section 1.5.3), while the remaining studies^(34, 60, 61, 118, 120) expressed HbA1c as a percentage only. Therefore, HbA1c data was meta-analysed as a percentage change, however overall results in this section have also been expressed in mmol/mol, including data presented in Table 3.2.

3.5.1.1 High dose and low dose GLP-1 analogue compared to DPP-4 inhibitor for duration of 26 weeks

Meta-analysis of five RCTs^(3, 34, 60, 76, 118) showed a statistically significant greater reduction in HbA1c with high dose GLP-1 analogue compared to DPP-4 inhibitor after 26 weeks (Figure 3.4). Although the meta-analysis showed a statistically significant reduction in HbA1c, there was a substantial level of heterogeneity, as indicated by Chi^2 of 9.84 and I^2 of 59% (refer Figure 3.4). All five studies favoured GLP-1 analogue treatment, however one study⁽³⁾ had small participant numbers and showed a non-statistically significant change in HbA1c. When the study by Gudipaty et al.⁽³⁾ was excluded from the meta-analysis, results of sensitivity analysis (for both fixed and random effect model) showed a statistically significant mean difference in HbA1c of -0.56% (-6.10mmol/mol) (fixed effect 95% CI -0.65 to -0.47%; -7.09 to -5.12mmol/mol); (random effect 95% CI -0.66 to -0.45%; -7.20 to -4.91mmol/mol). Similar results for Chi^2 of 3.63 and I^2 of 17% suggested no statistically significant heterogeneity, indicating that the majority of the heterogeneity was attributable to this study Gudipaty et al.⁽³⁾ Potential areas of clinical and methodological heterogeneity in the Gudipaty et al.⁽³⁾ study included variability in participant baseline demographic and clinical characteristics, (refer Section 3.4.2) differences in inclusion criteria (refer Table 3.2) and risk of bias due to

lack of concealment of participants, allocators and assessors to study drugs (refer Table 3.1 for critical appraisal scores).

There appeared to be little difference in the magnitude of the effect size between low dose and high dose, although the effect of high dose GLP-1 analogue was slightly greater when compared to the low dose GLP-1 analogue estimates (-0.52% versus -0.38%; -5.67 mmol/mol versus -4.14mmol/mol) (refer Figure 3.4). The unpublished study⁽¹²⁰⁾, which ran for a shorter period of 24 weeks, showed no significant difference in HbA1c between GLP-1 analogue and DPP-4 inhibitor (refer Table 3.2).



High dose GLP-1 analogue exenatide 2mg once weekly (Bergenstal et al.⁽¹¹⁸⁾ and Russell-Jones et al.)⁽⁶⁰⁾ exenatide 10µg twice daily (Gudipaty et al.)⁽³⁾ dulaglutide 1.5mg once weekly (Nauck et al.)⁽⁷⁶⁾ and liraglutide 1.8mg once daily (Pratley et al.)⁽³⁴⁾; low dose GLP-1 analogue dulaglutide 0.75mg once weekly (Nauck et al.)⁽⁷⁶⁾ and liraglutide 1.2mg once daily (Pratley et al.)⁽³⁴⁾

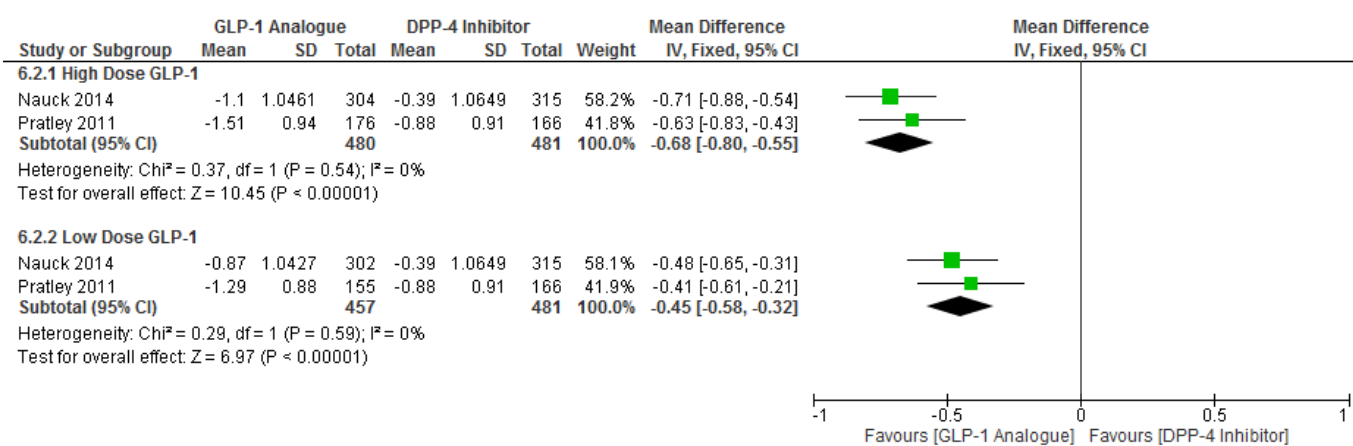
Figure 3.4. Meta-analysis of effects on glycated haemoglobin (HbA1c) (%) after 26 weeks for GLP-1 analogue high dose (top) and low dose (bottom) compared to DPP-4 inhibitor, sitagliptin, 100mg once daily

3.5.1.2 High dose and low dose GLP-1 analogue compared to DPP-4 inhibitor for duration of 52 weeks

After 52 weeks, high dose and low dose GLP-1 analogue resulted in statistically significant reductions in HbA1c compared to DPP-4 inhibitors with meta-analysis of two RCTs.^(61, 76)

Figure 3.5 indicates little difference in the magnitude of the effect size, although the effect

of high dose GLP-1 analogue was slightly greater when compared to the low dose GLP-1 analogue estimates (-0.68% versus -0.45%; -7.41mmol/mol versus -4.91mmol/mol). There was no statistical heterogeneity observed (refer Figure 3.5).



High dose GLP-1 analogue dulaglutide 1.5mg once weekly (Nauck et al.)⁽⁷⁶⁾ and liraglutide 1.8mg once daily (Pratley et al.)⁽⁶¹⁾; low dose GLP-1 analogue dulaglutide 0.75mg once weekly (Nauck et al.)⁽⁷⁶⁾ and liraglutide 1.2mg once daily (Pratley et al.)⁽⁶¹⁾

Figure 3.5. Meta-analysis of effects on glycated haemoglobin (HbA1c) (%) after 52 weeks for GLP-1 analogue high dose (top) and low dose (bottom) compared to DPP-4 inhibitor, sitagliptin 100mg once daily

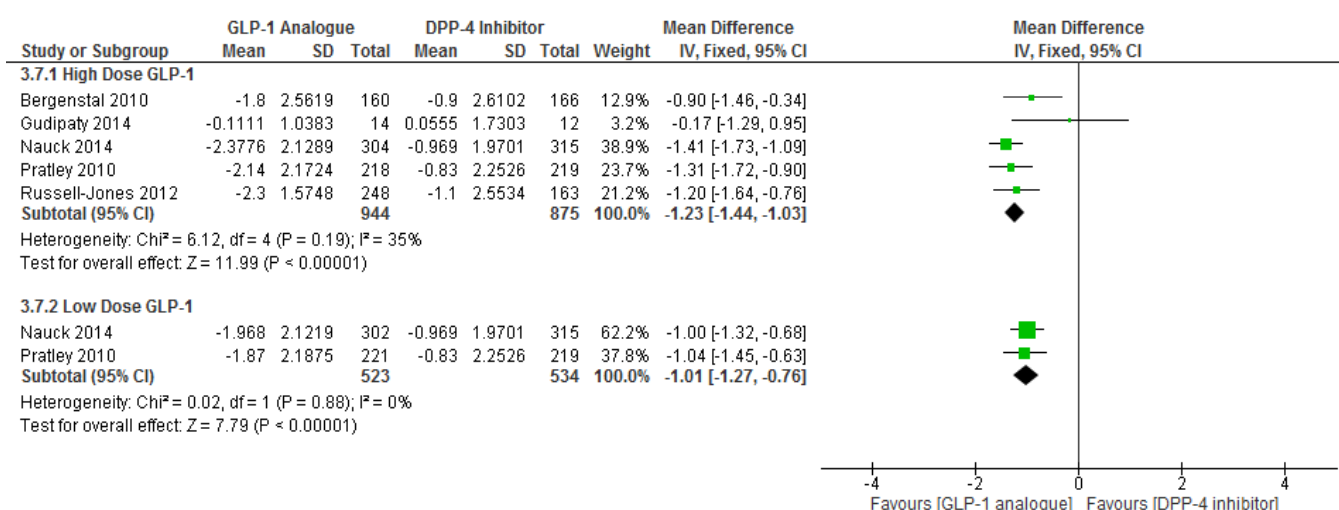
3.5.2 Fasting plasma glucose

All seven included studies^(3, 34, 60, 61, 76, 118, 120) reported fasting plasma glucose as a mean change from baseline to endpoint.

3.5.2.1 High dose and low dose GLP-1 analogue compared to DPP-4 inhibitor for duration of 26 weeks

Meta-analysis showed that GLP-1 analogues, irrespective of dose, significantly reduced fasting plasma glucose compared to DPP-4 inhibitor after a study duration of 26 weeks (refer Figure 3.6). There was little difference in the magnitude of the effect size seen at each dose, although high dose GLP-1 analogue was slightly greater when compared to the low dose GLP-1 analogue estimates (-1.23mmol/L versus -1.01mmol/L; -22.16mg/dL versus

-18.20mg/dL). Whilst all five RCTs^(3, 34, 60, 76, 118) in the analysis of high dose GLP-1 analogue showed an effect in a similar direction with no substantial heterogeneity, (refer Figure 3.6) Gudipaty et al.⁽³⁾ was the only study that found a non-statistically significant reduction in fasting plasma glucose compared to DPP-4 inhibitor treatment. When this study was excluded from the meta-analysis, results of sensitivity analysis, using both random and fixed effect models, showed the same mean difference in fasting plasma glucose of -1.27mmol/L (-22.88mg/dL) (95%CI -1.48 to -1.07mmol/L; -26.67 to -19.28mg/dL) with Chi² of 2.51 and I² of 0%. These results suggested no statistically significant heterogeneity (refer Figure 3.6). Possible explanations for the difference in the outcome finding by Gudipaty et al.⁽³⁾ are outlined in Section 3.4.2 and 3.5.1.



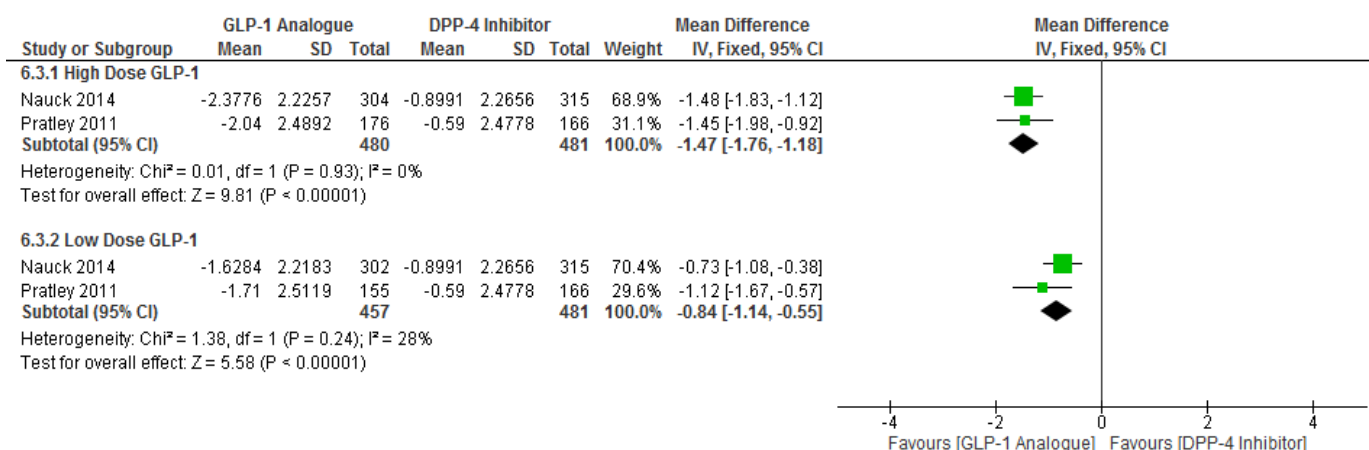
High dose GLP-1 analogue exenatide 2mg once weekly (Bergenstal et al.)⁽¹¹⁸⁾ and Russell-Jones et al.)⁽⁶⁰⁾ exenatide 10µg twice daily (Gudipaty et al.)⁽³⁾ dulaglutide 1.5mg once weekly (Nauck et al.)⁽⁷⁶⁾ and liraglutide 1.8mg once daily (Pratley et al.)⁽³⁴⁾; low dose GLP-1 analogue dulaglutide 0.75mg once weekly (Nauck et al.)⁽⁷⁶⁾ and liraglutide 1.2mg once daily (Pratley et al.)⁽³⁴⁾

Figure 3.6. Meta-analysis of effects on fasting plasma glucose after 26 weeks for GLP-1 analogue high dose (top) and low dose (bottom) compared to DPP-4 inhibitor, sitagliptin 100mg once daily

3.5.2.2 High dose and low dose GLP-1 analogue compared to DPP-4 inhibitor for duration of 52 weeks

Two RCTs^(61, 76) were included in a meta-analysis to determine effects on fasting plasma glucose after 52 weeks (refer Figure 3.7). Low dose and high dose GLP-1 analogue both

showed a statistically significant greater reduction in fasting plasma glucose compared to DPP-4 inhibitor (refer Figure 3.7). High dose GLP-1 analogue may have been more effective at reducing fasting plasma glucose than low dose GLP-1 analogues, as it showed a greater magnitude of effect size (-1.47 mmol/L versus -0.84mmol/L; -26.49mg/dL versus -15.13mg/dL). No statistically significant heterogeneity was observed (refer Figure 3.7).



High dose GLP-1 analogue dulaglutide 1.5mg once weekly (Nauck et al.)⁽⁷⁶⁾ and liraglutide 1.8mg once daily (Pratley et al.)⁽⁶¹⁾; low dose GLP-1 analogue dulaglutide 0.75mg once weekly (Nauck et al.)⁽⁷⁶⁾ and liraglutide 1.2mg once daily (Pratley et al.)⁽⁶¹⁾

Figure 3.7. Meta-analysis of effects on fasting plasma glucose after 52 weeks for GLP-1 analogue high dose (top) and low dose (bottom) compared to DPP-4 inhibitor, sitagliptin 100mg once daily

3.5.3 Postprandial plasma glucose

Three studies^(34, 61, 120) reported on postprandial plasma glucose; however meta-analysis was not performed due to a lack of sufficient detail provided in the included studies. Two studies by Pratley et al.^(34, 61) discussed that change in postprandial plasma glucose data was difficult to interpret, citing variability in monitoring times of postprandial plasma glucose and meal patterns across different sites of the multicentre trials as possible reasons for the high discrepancies in their results. No results were reported. On the other hand, the results of the Sanofi sponsored unpublished RCT⁽¹²⁰⁾ demonstrated that treatment with GLP-1 analogue (lixisenatide 20µg once daily) significantly improved postprandial glycaemic control

compared to DPP-4 inhibitor by a mean difference of -1.91mmol/L (-34.41mg/dL) (refer Table 3.2). For this unpublished study⁽¹²⁰⁾, however, there is potential risk of bias. As described in the assessment of methodological quality (refer Table 3.1), the study was determined to be at risk of selection bias as well as allocation bias and recruitment bias.⁽¹³⁵⁾

3.6 Outcomes of diabetes related complications using GLP-1 analogue compared to DPP-4 inhibitor

Diabetes related complications, retinopathy, neuropathy and nephropathy, were not reported by any of the seven included RCTs. Pratley et al.^(34, 61) reported a single case of diabetic retinopathy in the high dose GLP-1 analogue treatment group (liraglutide 1.8mg); however the study authors did not elaborate as to whether it was present before the study period or had developed during the study.

3.7 Adverse events using GLP-1 analogue compared to DPP-4 inhibitor

Six of the seven included studies^(34, 60, 61, 76, 118, 120) reported adverse events that were of interest for this review (refer Table 3.2).

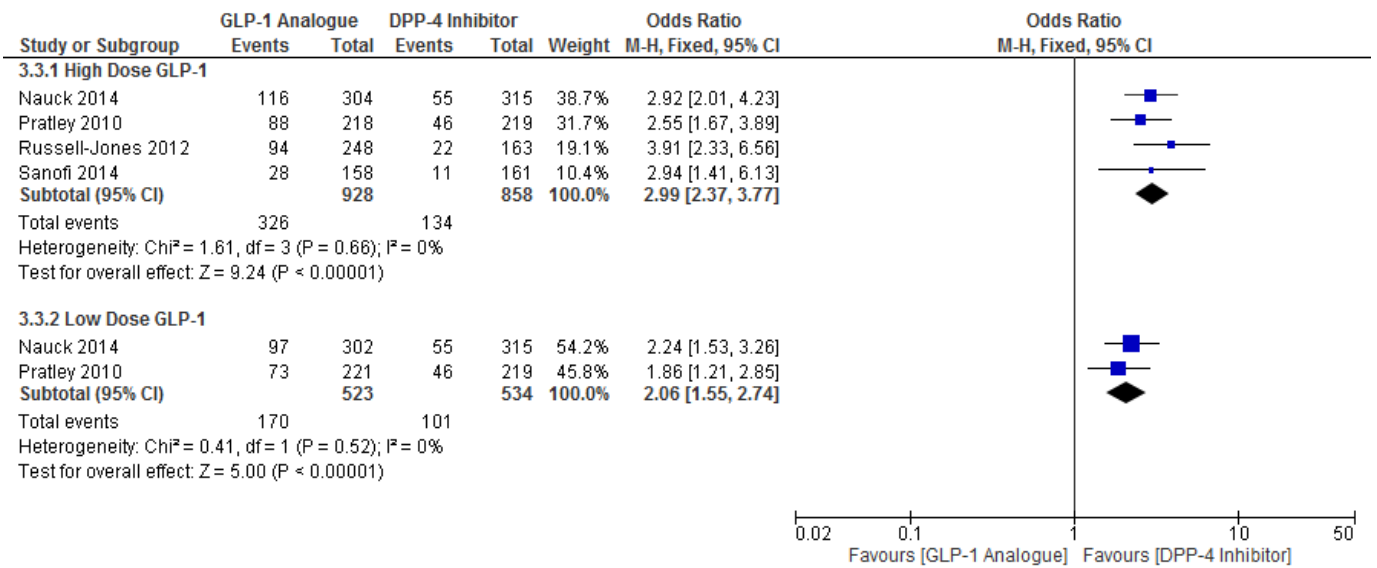
3.7.1 Gastrointestinal adverse events

3.7.1.1 High dose and low dose GLP-1 analogue compared to DPP-4 inhibitor for a duration of 24 to 26 weeks

Patients from both the GLP-1 analogue and DPP-4 inhibitor treatment groups experienced gastrointestinal adverse events. The odds of gastrointestinal adverse events in patients receiving high dose GLP-1 analogue was nearly three times that of the DPP-4 inhibitor however, compared to two times increased odds seen in patients receiving low dose GLP-1 analogue (refer Figure 3.8). Both of these results were statistically significant. In three out of four studies^(34, 76, 120), participants were taking metformin adjunctive treatment in addition to

the study drugs and the dose of GLP-1 analogue was titrated upwards until the study dose was achieved, per manufacturer recommendations, to improve drug tolerability and reduce the risk of gastrointestinal adverse events.^(137, 138, 139, 140) Of particular interest, the study by Russell-Jones et al.⁽⁶⁰⁾ involving participants naïve to antihyperglycaemic agents showed nearly a four-fold increased odds of gastrointestinal adverse event with high dose GLP-1 analogue exenatide 2mg once weekly. For this product, dose titration is not required according to product information provided by the manufacturers.⁽⁸¹⁾

A study by Bergenstal et al.⁽¹¹⁸⁾ which was not included in the analysis presented in Figure 3.8 also showed increased odds of high dose GLP-1 analogue (exenatide 2mg once a week) causing gastrointestinal adverse events (nausea, diarrhoea, vomiting, constipation) compared to DPP-4 inhibitor when used as an adjunct to metformin. This study could not be included in the meta-analysis because the authors reported the number of patients from each group that had individual types of gastrointestinal adverse events separately, and did not provide data on patients with any gastrointestinal adverse event overall. Due to the possibility that patients experiencing one adverse event would have also experienced another, these numbers could not be combined.

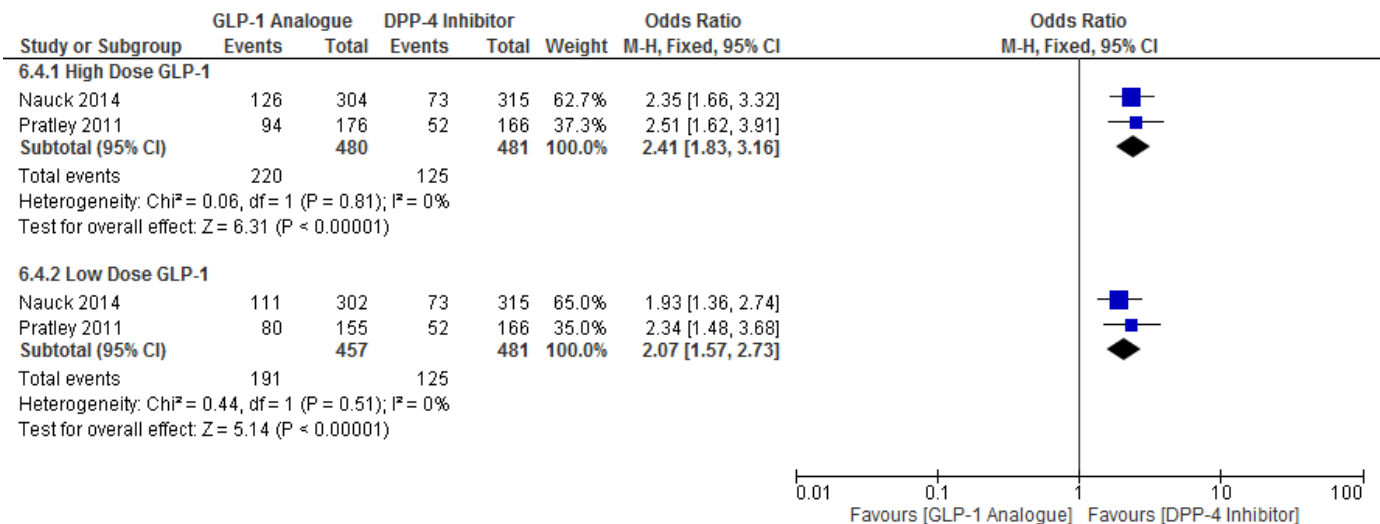


High dose GLP-1 analogue dulaglutide 1.5mg once weekly (Nauck et al.)⁽⁷⁶⁾; liraglutide 1.8mg once daily (Pratley et al.)⁽³⁴⁾; exenatide 2mg once weekly (Russell-Jones et al.)⁽⁶⁰⁾ and lixisenatide 20µg once daily (Sanofi)⁽¹²⁰⁾; low dose GLP-1 analogue dulaglutide 0.75mg once weekly (Nauck et al.)⁽⁷⁶⁾ and liraglutide 1.2mg once daily (Pratley et al.)⁽³⁴⁾ Sanofi⁽¹²⁰⁾ was a 24-week study, all other studies were 26 weeks.

Figure 3.8. Meta-analysis of outcomes of gastrointestinal adverse events after 24 to 26 weeks for GLP-1 analogue high dose (top) and low dose (bottom) compared to DPP-4 inhibitor sitagliptin 100mg once daily

3.7.1.2 High dose and low dose GLP-1 analogue compared to DPP-4 inhibitor for duration of 52 weeks

Meta-analysis showed that the difference in gastrointestinal adverse events did not diminish with use of GLP-1 analogue and DPP-4 inhibitor treatments after 52 weeks. There was still a 141% greater risk of gastrointestinal adverse events occurring with high dose GLP-1 analogue compared to DPP-4 inhibitor, whilst for low dose GLP-1 analogue there was an 107% increased risk compared to DPP-4 inhibitor (refer Figure 3.9).

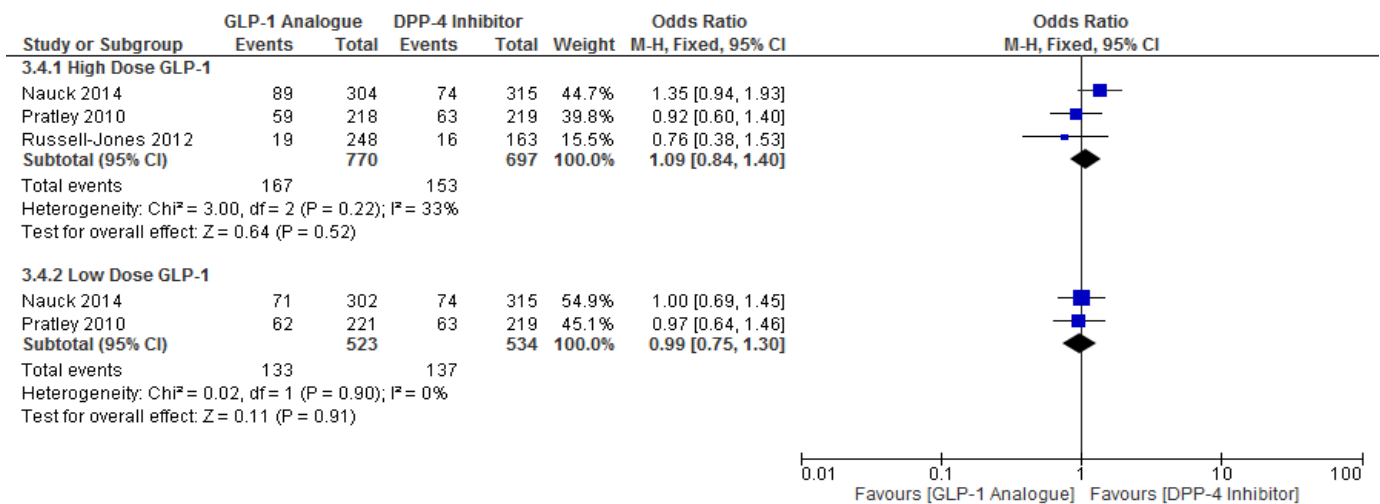


High dose GLP-1 analogue dulaglutide 1.5mg once weekly (Nauck et al.)⁽⁷⁶⁾ and liraglutide 1.8mg once daily (Pratley et al.)⁽⁶¹⁾; low dose GLP-1 analogue dulaglutide 0.75mg once weekly (Nauck et al.)⁽⁷⁶⁾ and liraglutide 1.2mg once daily (Pratley et al.)⁽⁶¹⁾

Figure 3.9. Meta-analysis of outcomes of gastrointestinal adverse event after 52 weeks for GLP-1 analogue high dose (top) and low dose (bottom) compared to DPP-4 inhibitor sitagliptin 100mg once daily

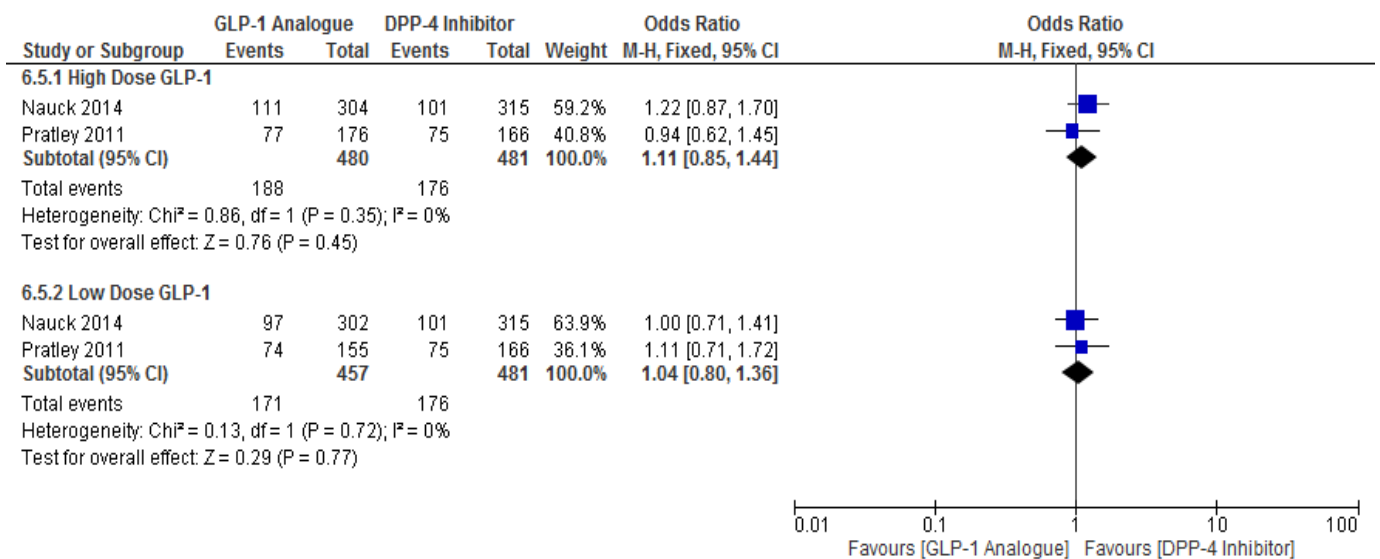
3.7.2 Headache, infection, pancreatitis and mortality

For adverse events, headache and infection, results of pooled data in a meta-analysis showed there was no statistically significant difference between GLP-1 analogue (high dose and low dose) and DPP-4 inhibitor treated patients after 26 weeks or 52 weeks (refer Figures 3.10 to 3.13). Three studies reported isolated cases of pancreatitis^(60, 61, 76), as discussed in Table 3.2. The number of deaths reported by two study authors^(34, 61, 76) in both the GLP-1 analogue and DPP-4 inhibitor groups were small (refer to Table 3.2). One author⁽⁶¹⁾ concluded that the deaths were not likely related to the study drugs.



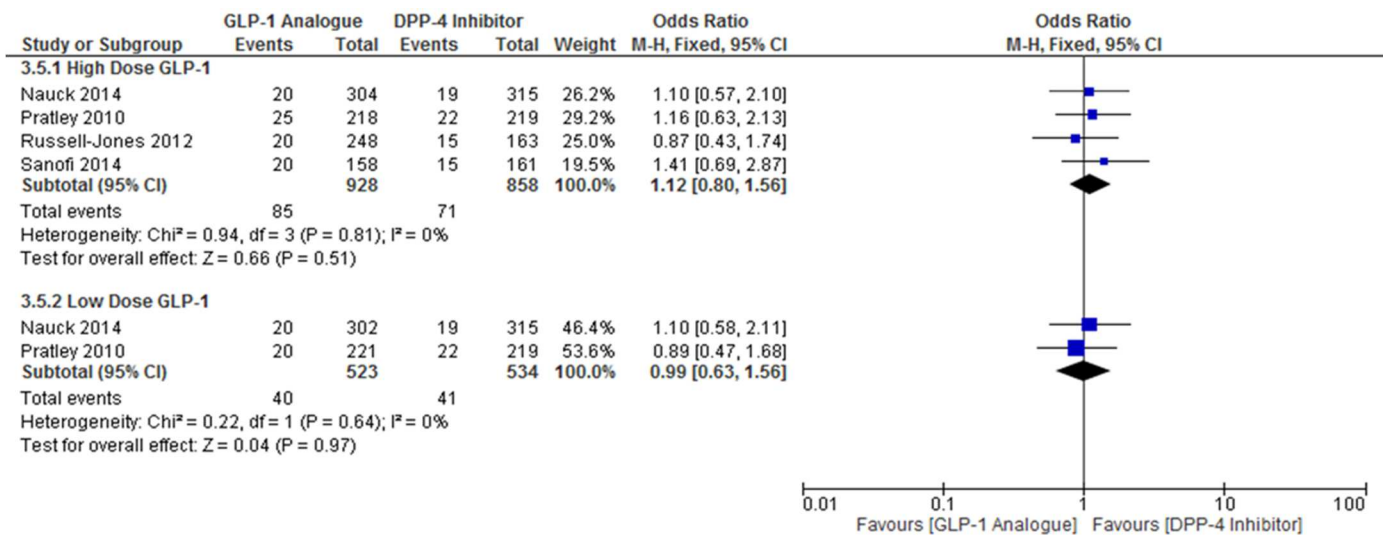
High dose GLP-1 analogue dulaglutide 1.5mg once weekly (Nauck et al.)⁽⁷⁶⁾ liraglutide 1.8mg once daily (Pratley et al.)⁽³⁴⁾ and exenatide 2mg once weekly (Russell-Jones)⁽⁶⁰⁾; low dose GLP-1 analogue dulaglutide 0.75mg once weekly (Nauck et al.)⁽⁷⁶⁾ and liraglutide 1.2mg once daily (Pratley et al.)⁽³⁴⁾

Figure 3.10. Meta-analysis of outcomes of infection adverse event after 26 weeks for GLP-1 analogue high dose (top) and low dose (bottom) compared to DPP-4 inhibitor sitagliptin 100mg once daily



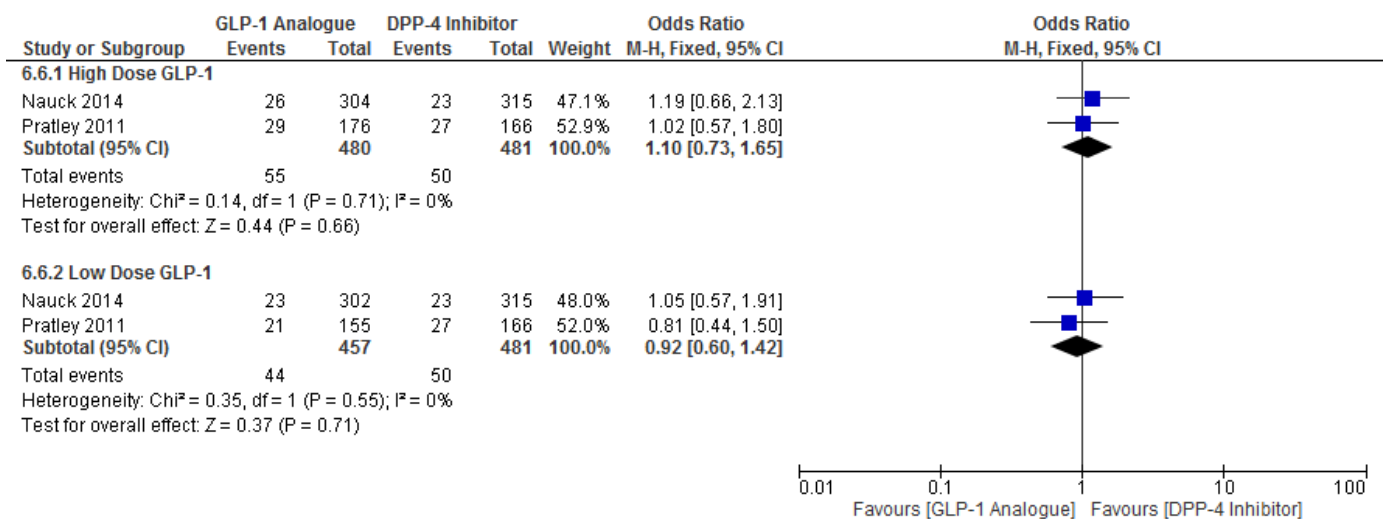
High dose GLP-1 analogue dulaglutide 1.5mg once weekly (Nauck et al.)⁽⁷⁶⁾ and liraglutide 1.8mg once daily (Pratley et al.)⁽⁶¹⁾; low dose GLP-1 analogue dulaglutide 0.75mg once weekly (Nauck et al.)⁽⁷⁶⁾ and liraglutide 1.2mg once daily (Pratley et al.)⁽⁶¹⁾

Figure 3.11. Meta-analysis of outcomes of infection adverse event after 52 weeks for GLP-1 analogue high dose (top) and low dose (bottom) compared to DPP-4 inhibitor sitagliptin 100mg once daily



High dose GLP-1 analogue dulaglutide 1.5mg once weekly (Nauck et al.)⁽⁷⁶⁾ liraglutide 1.8mg once daily (Pratley et al.)⁽³⁴⁾ exenatide 2mg once weekly (Russell-Jones et al.)⁽⁶⁰⁾ and lixisenatide 20µg once daily (Sanofi)⁽¹²⁰⁾; low dose GLP-1 analogue dulaglutide 0.75mg once weekly (Nauck et al.)⁽⁷⁶⁾ and liraglutide 1.2mg once daily (Pratley et al.)⁽³⁴⁾ Sanofi⁽¹²⁰⁾ was a 24-week study, all other studies were 26 weeks.

Figure 3.12. Meta-analysis of outcomes of headache adverse event after 24-26 weeks for GLP-1 analogue high dose (top) and low dose (bottom) compared to DPP-4 inhibitor sitagliptin 100mg once daily



High dose GLP-1 analogue dulaglutide 1.5mg once weekly (Nauck et al.)⁽⁷⁶⁾ and liraglutide 1.8mg once daily (Pratley et al.)⁽⁶¹⁾; low dose GLP-1 analogue dulaglutide 0.75mg once weekly (Nauck et al.)⁽⁷⁶⁾ and liraglutide 1.2mg once daily (Pratley et al.)⁽⁶¹⁾

Figure 3.13. Meta-analysis of outcomes of headache adverse events after 52 weeks for GLP-1 analogue high dose (top) and low dose (bottom) compared to DPP-4 inhibitor sitagliptin 100mg once daily

Chapter 4: Discussion

The results of the systematic review presented in this thesis suggest that, irrespective of dose, GLP-1 analogues are more effective at improving beta cell function and have more favourable effects on markers of glycaemic control than DPP-4 inhibitors, but at the expense of increased likelihood of gastrointestinal adverse events.

4.1 General discussion

These results are supported by a similar systematic review by Shyangdan et al.⁽¹⁰⁾ who investigated the effectiveness of GLP-1 analogues compared to other antihyperglycaemic agents, including DPP-4 inhibitors, in patients with type 2 diabetes on beta cell function and other metabolic markers. This previous review showed that all GLP-1 analogues led to significant improvements in HOMA-beta when compared to placebo and the active comparators, insulin, thiazolidinediones and DPP-4 inhibitors.⁽¹⁰⁾ The systematic review by Shyangdan et al.⁽¹⁰⁾ included two studies^(34, 118) that have also been included in the current systematic review; this review located and included a further five relevant studies^(3, 60, 61, 76, 120) to inform the effectiveness of GLP-1 analogues compared to DPP-4 inhibitors. For other measures of beta cell function beyond HOMA-beta, results of a study by Vilsboll et al.⁽¹⁴¹⁾ showed that while various daily doses of GLP-1 analogue (liraglutide) significantly improved PI/I ratio when compared to placebo, Garber et al.⁽¹⁴²⁾ showed that there was no significant difference in PI/I ratio between liraglutide and sulfonylureas treatments. These authors^(141, 142) did not report on any comparative data for DPP-4 inhibitors, and therefore could not contribute data to inform the current systematic review which showed that GLP-1 analogue treatment improved both PI/I ratio and C-peptide measures compared to DPP-4 inhibitor at 26 and 52 weeks. It is noteworthy that the HOMA-beta measure of beta cell function was

validated against the highly reproducible hyperglycaemic clamp method unlike PI/I ratio and C-peptide.^(5, 90)

For markers of glycaemic control, Shyangdan et al.⁽¹⁰⁾ concluded that GLP-1 analogues significantly reduced HbA1c compared to placebo and DPP-4 inhibitors, but HbA1c results were varied when GLP-1 analogues of differing strengths and dosages were compared to insulin, sulfonylureas and thiazolidinediones.⁽¹⁰⁾ For fasting plasma glucose, Shyangdan et al.⁽¹⁰⁾ reported that whilst GLP-1 analogues significantly reduced fasting plasma glucose compared to placebo and DPP-4 inhibitors, there was a non-statistical difference compared to thiazolidinediones. Shyangdan et al.⁽¹⁰⁾ reported that the overall difference between the three studies⁽¹⁴³⁻¹⁴⁵⁾ showed favourable results for long acting insulin compared to GLP-1 analogue (exenatide 10µg twice a day), whilst another study⁽¹⁴⁶⁾ showed GLP-1 analogue (liraglutide 1.8mg daily) to be more effective than long acting insulin, although the difference was not significant.

Possible explanations for the increased efficacy of GLP-1 analogues on beta cell function and glycaemic control compared to DPP-4 inhibitors shown in this systematic review relate to the persistently elevated GLP-1 analogue concentrations^(34, 76) that result from their longer plasma half-lives⁽³⁴⁾, and the consequent greater GLP-1 receptor stimulation.⁽¹⁸⁾ Research suggests that administration of GLP-1 analogues can increase plasma GLP-1 concentration four to five times more than DPP-4 inhibitors.^(34, 147) This may suggest that high pharmacological levels of exogenously administered GLP-1 are more effective than a drug that modestly increases concentration of endogenous GLP-1.⁽³⁴⁾

Results of this systematic review showed that the magnitude of the effect size for GLP-1 analogue treatment in reducing HbA1c was consistently greater than 1% (10.9mmol/mol),

except in the case of one low dose dulaglutide GLP-1 analogue treatment after 52 weeks (-0.87%; -9.5mmol/mol).⁽⁷⁶⁾ Putting these results into perspective, the UKPDS demonstrated that a 1% reduction in HbA1c was associated with a 37% decreased risk of microvascular complications and a 21% decreased risk of death related to diabetes.^(34, 56)

With regards to diabetes related complications, retinopathy, neuropathy and nephropathy, none of the included studies reported on these important, patient centred outcome measures. This may be due to the fact that these diabetes related complications are difficult to measure in a trial with a duration of one year, when typically these complications develop 20 years after diagnosis.⁽⁶²⁾ Additionally, it is also consistent with a general mismatch between patient centred outcomes and outcomes reported in clinical trials.^(148, 149)

Both GLP-1 analogue and DPP-4 inhibitor treatments caused gastrointestinal adverse events, including nausea, vomiting and diarrhoea. Whilst both high and low dose GLP-1 analogue treatments were statistically more likely to cause gastrointestinal adverse events than DPP-4 inhibitors, the occurrence with high dose GLP-1 analogue appeared greater than the low dose. Interestingly, study authors^(34, 60, 118) reported there were few withdrawals from their studies due to gastrointestinal adverse events. As mentioned, the effectiveness of GLP-1 analogues may be attributed to their ability to increase plasma GLP-1 concentration up to levels five times greater than DPP-4 inhibitors, and this may explain the increased reports of gastrointestinal adverse events⁽⁶¹⁾ caused by the increased stimulation of GLP-1 receptors mediating systemic effects, in addition to the insulinotropic and glucagonostatic action.⁽⁸³⁾ The systemic effects include delayed gastric emptying that may result in the sensation of 'fullness' or nausea.⁽⁸³⁾ Results suggested that the odds of high dose GLP-1 analogues causing gastrointestinal adverse events became closer to the odds for DPP-4 inhibitor treatments the longer treatment was continued. This observation is consistent with the

findings of other studies^(10, 11, 78) that suggest gastrointestinal adverse events were worst at the initiation of GLP-1 analogue treatment and tended to reduce with the length of the duration of treatment⁽¹⁰⁾ without diminishing the beneficial effects on beta cell function and glycaemic control. When GLP-1 analogues are used in the clinical setting, dietary counselling is often provided to reduce the risk of gastrointestinal adverse events by acknowledging the delay in gastric emptying and explaining strategies for its accommodation.⁽¹⁵⁰⁾

Recommendations include eating smaller meals, and stopping eating at the first sign of satiation; patients sometimes describe experiencing gastrointestinal disturbances after meals, but it may actually just be a feeling of 'fullness'.⁽¹⁵⁰⁾ It was noted that reports of general dietary counselling was provided as part of study protocol in only one⁽⁶⁰⁾ of the seven included studies.

The incidence of the adverse events, headache, infection, pancreatitis and reported mortalities (refer Table 3.2), did not statistically significantly differ between the two study drugs, regardless of duration of treatment. Results from other studies showed that both DPP-4 inhibitors and GLP-1 analogues had been associated with acute pancreatitis^(54, 150, 151), with one population-based matched case control study⁽¹⁵¹⁾ finding significantly increased odds of hospitalisation for acute pancreatitis with GLP-1 analogues and DPP-4 inhibitors. Additionally, results from an analysis of the United States Food and Drug Administration (FDA) adverse events database reported an increased risk of pancreatitis associated with these drugs^(152, 153), but this reported association has been refuted by vendors, who claim that pancreatitis is associated with the pathophysiology of type 2 diabetes.⁽¹⁵³⁾

It is important to consider pitfalls that arise when systematic reviews and meta-analyses report on adverse events from clinical trials, particularly when adverse events are not primary outcomes of the trials.⁽¹⁵⁴⁾ In contrast to beneficial outcomes for which there are

structured and standardised protocols, detecting adverse events often requires patient or study investigator awareness and diligence in enquiring about the event, and judgement around reporting the event.⁽¹⁵⁴⁾ Factors including inconsistent definitions of adverse events, and incomplete information due to participant loss to follow up, increase the risk of over or under reporting adverse events.⁽¹⁵⁴⁾ Whilst well conducted RCTs generally produce unbiased estimates of treatment effect, there is often no RCT data around adverse events due to study impracticalities, expense and ethical difficulties around investigating long term adverse events.⁽¹⁵⁵⁾ Also, the generalisability of RCT data may be limited if, as is often the case, trials specifically exclude patients with a high risk of adverse events, for example, the elderly or those with multiple comorbidities.⁽¹⁵⁵⁾ Given these limitations, the importance of evaluating the use of data from non-randomised studies in systematic reviews of adverse events has been proposed, as analysis has found little evidence of systematic differences in adverse events obtained from a meta-analysis of RCTs and from a meta-analysis of observational studies.⁽¹⁵⁵⁾ Whilst it can be argued that the lack of randomisation has the potential to increase the risk of bias of observational studies, in some instances they may be the only available source of data for a particular adverse event.⁽¹⁵⁵⁾ Finally, confounding in observational studies may be less likely to occur for outcomes that are not the intended result of the treatment (adverse events) compared to the intended effects of the treatment.⁽¹⁵⁵⁾ The future direction for conducting a systematic review of harm associated with treatments such as antihyperglycaemic agents may involve analysing a broad range of study types that can help build a complete picture of potential harms and improve the generalisability of the review without loss of validity.⁽¹⁵⁵⁾

The number of approved antihyperglycaemic agents has grown significantly in the past two decades, (refer Section 1.3) but despite hundreds of millions of dollars being spent each year in the pursuit of improved diabetes therapies⁽¹⁵⁶⁾, diabetes continues to be associated with a

range of serious complications resulting in reduced quality of life and premature mortality.⁽⁴⁴⁾ Literature suggests this is partially attributed to the use of diabetes therapy options that have limited efficacy, inconvenient adverse events and unfavourable delivery methods.⁽¹⁵⁶⁾ Patients want antihyperglycaemic agents that are effective, easy to use, safe, tolerable and affordable.⁽¹⁵⁶⁾ Additionally, in the context of diabetes, efficacy can mean a number of things.⁽¹⁵⁶⁾ Whilst a maximally effective agent would address the underlying cause of diabetes, more commonly, an agent's efficacy is measured by how robustly it provides glycaemic control, how durable it is and what benefits beyond glucose lowering it provides. For example, will it promote weight loss and what effect does it have on beta cell function?⁽¹⁵⁶⁾ Results of the A Diabetes Outcome Progression Trial (ADOPT) suggest that the treatment of type 2 diabetes with antihyperglycaemic agents that favourably influence beta cell function soon after diagnosis may improve treatment durability.⁽⁶⁷⁾ Whilst the results of the systematic review presented in this thesis have shown GLP-1 analogues are significantly more effective at improving beta cell function and improving glycaemic control than DPP-4 inhibitors, it is important to consider the effectiveness of the other antihyperglycaemic agents for improving beta cell function.

As outlined in Section 1.3, currently there are another seven classes of antihyperglycaemic agents aside from GLP-1 analogues and DPP-4 inhibitors on the market. Of those seven classes of drugs, only thiazolidinediones and insulin have been shown to significantly improve beta cell function in clinical trials. Whilst thiazolidinediones have been shown to improve beta cell function compared to metformin, sulfonylureas and acarbose^(1, 12, 67, 157), they have been found to be less effective than the GLP-1 analogue, exenatide.⁽⁶⁰⁾ Early intensive insulin therapy in patients with newly diagnosed type 2 diabetes was shown to have favourable outcomes on beta cell function compared with sulfonylureas and metformin⁽¹⁵⁸⁾, but not when compared with the GLP-1 analogue, exenatide.⁽¹⁴³⁾ Metformin,

recommended as first line therapy in type 2 diabetes^(58, 59, 159), has little or no effect on beta cell function in overt diabetes despite showing significant improvements in beta cell function in individuals with prediabetes.^(1, 12) Although the class of antihyperglycaemic agents, sulfonylureas, have historically been used as second line therapy, they have been associated with higher rates of monotherapy failure than alternative treatments.⁽¹⁵⁶⁾ The proposed mechanism of reduced efficacy relates to their pharmacological action of inducing insulin secretion via beta cell stimulation, and subsequently causing beta cell functional decline or beta cell 'burnout'.⁽¹⁵⁶⁾ There is no data available regarding the effects on beta cell function for glinides and SGLT-2 inhibitors.

Despite the more favourable beta cell effects conferred by GLP-1 analogue injections, an orally administered treatment like a DPP-4 inhibitor is still considered to be the preferred patient option due to ease of administration, and perceived lack of pain.⁽¹⁵⁶⁾ As discussed in Section 1.3, however, all agents have notable limitations due to their related adverse events. Whilst GLP-1 analogues are shown to cause significant initial gastrointestinal adverse events^(34, 58, 61, 150, 160) which are shown to diminish with time⁽¹⁰⁾ and can be attenuated with patient counselling⁽¹⁵⁰⁾, their ability to delay gastric emptying may promote weight loss and contribute to better glycaemic control.^(1, 21, 53, 58) Both insulin and thiazolidinediones are less likely to cause gastrointestinal adverse events, but are more likely to cause undesirable weight gain.^(58, 59, 71, 74) It is also well documented that thiazolidinediones have been associated with cardiovascular adverse events and bone fractures which has seen a decline in their use in clinical practice.^(1, 58, 59, 64)

4.2 Limitations of included studies

Since systematic reviews often bring together studies that are both clinically and methodologically diverse, heterogeneity in their results is to be expected.⁽¹⁶¹⁾ Key methodological differences identified included differences in study design, treatment dose and duration, sample size and treatment used prior to study. Only five of the seven included studies^(3, 34, 60, 61, 76) described a ‘wash out’ period of other antihyperglycaemic agents before commencement of the study, while in five of the seven studies^(34, 61, 76, 118, 120), the study drugs were administered in combination with metformin, and as monotherapy in the remaining two studies.^(3, 60) The primary processes used to compare differences in the study drugs may give rise to important differences in methodology, e.g. differences in measuring beta cell function and glycaemic outcomes. Examples of these include assays used to measure HOMA-beta varying between different laboratories, and target values varying across different cultures and ethnicities due to differing genetics and environmental factors.⁽⁵⁾ Measures of HbA1c may vary between laboratories and between countries as a number of factors influence HbA1c assays, and currently measures are not well standardised.⁽⁴⁶⁾ One included study was unpublished⁽¹²⁰⁾, and interpretation of study design and results was difficult due to ambiguities and missing data.

The majority of the studies ran for 26 weeks or less^(3, 34, 60, 118, 120), with only two studies^(61, 76) running for 52 weeks. This duration may not be long enough for gathering meaningful evidence on long-term outcomes.⁽¹⁰⁾ Although RCTs are the gold standard with regard to level of evidence and establishing causality of treatment effects, questions are often raised regarding the extent to which their results can be extrapolated to the wider patient population (external validity) because standardised and controlled study conditions do not adequately reflect the clinical setting.⁽¹⁶²⁾ Another limitation of the evidence included in this thesis was the scarcity of head to head comparisons of the two therapies. Few studies have

directly compared GLP-1 analogues and DPP-4 inhibitors, and in fact, of the DPP-4 inhibitors, only sitagliptin has been studied in comparison with GLP-1 analogue treatments.^(19, 150)

Despite this, however, the head-to-head data that was obtained should represent a fair comparison of GLP-1 analogue and DPP-4 inhibitor in general, as individual agents within the DPP-4 inhibitor class have achieved similar efficacy in clinical trials.⁽¹⁵⁰⁾

Finally, six of the seven clinical papers were sponsored by the pharmaceutical industry.^(34, 60, 61, 76, 118, 120) A systematic review by Lexchin et al.⁽¹⁶³⁾ found that studies financed by industry, always found outcomes favourable to the sponsoring company, and the results were inconsistent with the quality of study methods used.⁽¹⁶³⁾

4.3 Limitations of the review process

Only studies published in English were included in this review which introduces a risk of language bias. The consequence of this may be the exclusion of some important studies, producing a review with conclusions that may be distorted or invalid.⁽¹²¹⁾ The scanning of citations and reading of full text papers to determine eligibility for inclusion in the review was only performed by the primary reviewer and author of this thesis, increasing the potential for errors of omission. Reports suggest that usually two or more reviewers need to work independently to apply the inclusion criteria, and to make sure the criteria are clearly, objectively and consistently applied.⁽¹²¹⁾ Whilst critical appraisal was done by two reviewers, this systematic review was limited by the use of only one data extractor (Susan Bellman). Similar safeguards should be in place when abstracting data from studies, where data abstraction should be carried out as a duplicated, independent process⁽¹²¹⁾ to reduce the possibility of error or bias.

A further limitation to the synthesis of data in this thesis relates to the lack of consideration afforded to potential differences in the efficacy of the GLP-1 analogues within the high and low dose subgroups presented. For example, in head-to-head studies, liraglutide 1.8mg administered once a day has been shown to provide greater reduction in HbA1c than both shorter acting exenatide 10µg administered twice a day and long acting exenatide 2mg administered once a week.^(138, 164) In this review, these treatments were collectively included in the high dose subgroup, based on the fact that this was the maximum dose for each preparation. Similarly, as previously discussed in Section 1.3.8, findings of recent research have shown that long acting GLP-1 analogues have more favourable fasting plasma glucose outcomes than short acting GLP-1 analogues.^(79, 80) This difference in efficacy was not considered when developing GLP-1 analogue subgroups in the included studies.

4.4 Implications for clinical practice

Despite improvements in glycaemic control with their administration, it has been demonstrated that not all antihyperglycaemic agents improve beta cell function⁽¹⁾, which reportedly declines at a rate of approximately 4% each year in the type 2 diabetes population.⁽⁴⁹⁾ Agents that slow or prevent the ongoing decline in beta cell function could potentially confer treatment durability and alter the course of type 2 diabetes by reducing morbidity and ultimately also mortality.⁽¹⁾ Two conventional antihyperglycaemic agents, insulin and thiazolidinediones, have shown beneficial effects on beta cell function in clinical trials, but have an increased risk of significant adverse effects, including weight gain and hypoglycaemia for insulin^(1, 71-74), peripheral oedema, heart failure and bone fractures, particularly in women on thiazolidinediones.^(1, 58, 59, 64) Results presented in this thesis show that whilst both GLP-1 analogues and DPP-4 inhibitors improve glycaemic markers and beta cell function with minimal adverse events, GLP-1 analogues are significantly more effective than DPP-4 inhibitor at improving beta cell function and measures of glycaemic control.

Importantly, research has shown that the effectiveness of GLP-1 analogues on beta cell function is sustained for a period of three years⁽¹⁶⁵⁾, while similar data for DPP-4 inhibitors is lacking.⁽³⁷⁾

While metformin is recommended as the first line treatment for most people with type 2 diabetes, due to declining beta cell function over time, therapy invariably needs to be intensified with additional antihyperglycaemic agents to attain and maintain glycaemic control.⁽²²⁾ There is no specific guidance for a particular add-on agent once metformin has lost its effectiveness; only various options are provided, leaving the final decision with the clinician.⁽²²⁾ Whilst this is due in part to the many factors that clinicians need to consider when selecting additional antihyperglycaemic agents (e.g. cost, modality of delivery, adverse events), this is also due to the general lack of comparative effectiveness research in this area.⁽²²⁾ Commencing a treatment that addresses the underlying pathological decline in beta cell function associated with type 2 diabetes, rather than solely focusing on managing hyperglycaemia, should be the ideal.⁽⁵⁾ Given the economic and social burden associated with diabetes related complications, there are potential savings to be made through the ability of GLP-1 analogue to improve glycaemic control, thereby reducing health care costs associated with complication management.^(20, 34)

As injectable therapies are associated with barriers to uptake and adherence, the route of GLP-1 analogue administration is considered a disadvantage.⁽²²⁾ In an internet survey study of American and European individuals with type 2 diabetes, who were already receiving metformin monotherapy, more than 80% of patients preferred to add on an oral medication like DPP-4 inhibitor than an injectable therapy like GLP-1 analogue.^(20, 22) However, when individuals understood that greater glycaemic efficacy could be achieved with an injectable agent, then their preference was for injectable therapy compared to oral therapy.^(20, 22)

Additionally, in a treatment satisfaction survey, greater satisfaction was reported in an open-label study of patients treated with GLP-1 analogue compared with DPP-4 inhibitor in a head-to-head trial directly comparing these agents.⁽¹⁶⁶⁾ This was despite GLP-1 analogues being associated with more adverse events, typically gastrointestinal in nature.⁽¹⁶⁶⁾ Measures of convenience or flexibility did not differ between treatments, suggesting that the route of administration did not influence overall treatment satisfaction.⁽¹⁶⁶⁾ Treatment satisfaction is important, as it is associated with increased treatment adherence and improved clinical outcomes.⁽¹¹⁸⁾

The results of this thesis showed that there was little difference in the effectiveness between high and low dose GLP-1 analogues, but that the odds of high dose GLP-1 analogues causing gastrointestinal adverse events was greater than low dose. By reducing the dose of GLP-1 analogue, it appears the same effectiveness could be achieved, whilst reducing the odds of gastrointestinal adverse events. Additionally, in a clinical setting, patient education would most likely be provided regarding recommended dietary modification and specific strategies to reduce the occurrence of gastrointestinal adverse events with GLP-1 treatment⁽¹⁶⁰⁾, something that was not done in the studies included in this review, and which would influence their tolerability. The fact that five studies^(34, 61, 76, 118, 120) included participants taking metformin concurrently with the two treatment groups, however, is noteworthy. Gastrointestinal adverse events are also a very common side effect of metformin, occurring in $\geq 1/10$ patients⁽¹⁶⁷⁾; however it is difficult to determine what effect, if any, this had on the overall results. Hence, given its positive effects on the beta cell function as well as its glucose lowering capabilities and transient adverse event profile, GLP-1 analogue seems a likely choice for early introduction in the treatment algorithm for type 2 diabetes. Current treatment algorithms recommend that GLP-1 analogues can, along with other antihyperglycaemic agents, such as DPP-4 inhibitor and sulphonylureas^(58, 59), be

considered at multiple points throughout the treatment of type 2 diabetes.⁽⁷⁹⁾ Metformin is the standard first drug treatment after diagnosis of diabetes, and is the only antihyperglycaemic agent that has been shown to decrease adverse cardiovascular outcomes⁽⁶³⁾, achieving statistically significant reductions in myocardial infarction.⁽⁴⁹⁾ However, given that metformin does not improve beta cell function the way GLP-1 analogue treatment does, it stands to reason that GLP-1 analogues should be started early in diabetes management as the preferred second line therapy in otherwise healthy individuals, in the absence of diabetes related complications, rather than being simply a consideration.

4.5 Implications for research

4.5.1 Cost effectiveness of adding GLP-1 analogues to metformin monotherapy

Whilst GLP-1 analogues have been shown to be superior to DPP-4 inhibitor treatment for beta cell function and glycaemic control, and these findings support the use of GLP-1 analogues as an effective agent to add to the widely used first line metformin therapy, the value of GLP-1 analogues needs to be quantified in the framework of cost effectiveness analysis.⁽¹⁶⁸⁾ Patients want therapies that are not only effective, easy to use, tolerable and safe, but also affordable. The antihyperglycaemic agents that achieve the most favourable balance of these characteristics will have the highest appeal for patients.⁽¹⁵⁶⁾ Informed decisions by public and private health care authorities regarding optimal prescribing and reimbursement of second-line antihyperglycaemic agents, after metformin has lost its effectiveness, requires information about their clinical benefit, costs and cost-effectiveness.⁽¹⁶⁹⁾ A Canadian study⁽¹⁶⁹⁾ determined the cost-effectiveness of treatment with second-line antihyperglycaemic agents added to metformin in patients with type 2 diabetes. Consideration was given to the agents sulfonylureas, DPP-4 inhibitors, glinides, alpha-glucosidase inhibitors and insulin, and whilst it was concluded that the addition of sulfonylureas to metformin was associated with the most favourable cost-effectiveness

results, it is important to recall that sulfonylureas exhaust beta cell function^(2, 23) and their clinical usefulness declines over time⁽⁶⁵⁾ (refer Section 1.3.2). GLP-1 analogues were not included in the analysis.⁽¹⁶⁹⁾ Whilst GLP-1 analogues are more costly per patient than DPP-4 inhibitors⁽¹⁷⁰⁾, results of studies^(168, 170) evaluating the short and long term cost-effectiveness of GLP-1 analogue (liraglutide) versus DPP-4 inhibitor (sitagliptin) when added to metformin showed that the GLP-1 analogue was associated with a lower mean cost per patient when the benefits of both costs and effects were considered, compared to DPP-4 inhibitor. It was noted however that potential patient barriers to the use of injectable medication, patient preference and patient satisfaction were not incorporated into the cost-effectiveness analysis.⁽¹⁶⁸⁾ Evaluating the cost effectiveness of antihyperglycaemic agents is challenging, requiring diabetes models that are often complex, where the effectiveness analyses are run long term to adequately capture end-stage complications.⁽¹⁷⁰⁾ Nevertheless, cost effectiveness estimates need to be regularly updated as new clinically important outcomes that demonstrate differences in glycaemic durability between different agents over time become available.⁽¹⁶⁹⁾

4.5.2 Use of GLP-1 analogue in prediabetes

Prediabetes, characterised by higher than normal blood glucose levels, but below the diagnostic cut-off for type 2 diabetes, manifests as impaired fasting glucose and/or impaired glucose tolerance.^(171, 172) It is considered an underlying aetiology of metabolic syndrome: a cluster of conditions that synergistically increase the risk of cardiovascular disease, type 2 diabetes and premature mortality.^(20, 171, 172) Approximately 40% of subjects with prediabetes will develop type 2 diabetes within five to 10 years.⁽¹⁷²⁾ Research supports the fact that a decline in beta cell function begins some 10 to 12 years before diabetes diagnosis⁽⁸⁾, therefore early intervention during the prediabetes period is desirable to prevent this progression.^(20, 172) Preclinical research has shown that GLP-1 analogue treatment can

effectively suppress the diabetes onset and reverse impaired glucose levels in nearly 50% of obese rats.⁽¹⁷²⁾ In the clinical setting, it still remains unclear whether GLP-1 analogues can effectively help to mitigate the effects of prediabetes and thereby prevent the onset of diabetes and its associated morbidity and mortality.⁽¹⁷²⁾ Further research is warranted in this area. This sentiment was backed up by Garber⁽²⁰⁾ who explained that a range of further studies were ongoing or planned with GLP-1 analogues in relation to prediabetes.

4.5.3 Use of GLP-1 analogue in beta cell preservation and regeneration

The main interest or hope in the research field has been in regard to whether GLP-1 analogues may enhance beta cell survival and stimulate beta cell growth.^(2, 10, 14, 143, 165) Preclinical evidence suggests that GLP-1 analogues have the potential to stimulate proliferation and neogenesis of beta cells and suppress beta cell apoptosis.^(2, 14, 15, 173) Bunck et al.⁽¹⁶⁵⁾ concluded that three years of GLP-1 analogue treatment in individuals with type 2 diabetes resulted in sustained improvement in beta cell function, but recommended that long-term follow-up in a wide range of patients at earlier stages of type 2 diabetes was needed to examine possible diabetes modifying effects of GLP-1 analogues.⁽¹⁶⁵⁾ If GLP-1 analogues can preserve and rescue beta cells, they may reverse disease progression and ultimately reduce the diabetes epidemic.⁽²⁾

4.5.4 Long term safety data for GLP-1 analogues

Emerging evidence in literature and opinions of regulatory agencies, notably United States FDA and the European Medicines Agency (EMA), about the risk of GLP-1 analogues are conflicting, and there are many open questions in particular on their pancreatic and cardiovascular effects.⁽¹⁷⁴⁾ New guidelines from the FDA and EMA require that all new type 2 diabetes agents and their risks of major cardiovascular events be assessed through large randomised clinical trials.⁽¹⁷⁵⁾ Currently, results from dedicated cardiovascular outcome trials

are only available for one GLP-1 analogue, lixisenatide^(79, 176), which demonstrated lixisenatide had a neutral effect on cardiovascular safety compared to placebo⁽¹⁷⁷⁾ and therefore met the pre-specified criterion of non-inferiority versus placebo in terms of cardiovascular outcomes.⁽⁷⁹⁾ However, the cardiovascular safety of other GLP-1 analogues in subjects with type 2 diabetes and high cardiovascular risk is unclear as long term outcome trial data is pending.^(63, 178, 179) Likewise, little is known about long term adverse effects of the GLP-1 analogues on the pancreas.⁽¹⁵³⁾ Thus it is important to continue to monitor closely the use of these antihyperglycaemic agents in clinical practice to improve knowledge on their long-term safety if they are going to cement their place in diabetes therapy.⁽¹⁷⁴⁾

4.6 Conclusion

The results of the review presented in this thesis suggest that GLP-1 analogues more effectively improve beta cell function compared to DPP-4 inhibitors, with significantly greater reductions in markers of glycaemic control, but gastrointestinal adverse events are significantly increased. Longer term safety data based on analysing a broad range of studies is required to not only better define the contribution of GLP-1 analogues in reducing diabetes related microvascular complications based on their effects on beta cell function, but also determine their long term pancreatic and cardiac effects.

Appendix I

Systematic Review Protocol

Review title

The Effectiveness of GLP-1 Analogues Compared to DPP-4 Inhibitors for Beta Cell Function and Diabetes Related Complications Among Adults with Type 2 Diabetes.

Reviewers

Susan Bellman ¹

Edoardo Aromataris ¹

¹ Joanna Briggs Institute, School of Translation Health Science, University of Adelaide, 5005

Corresponding Author: Susan Bellman susan.bellman@adelaide.edu.au

Review question/objective

What is the effectiveness of GLP-1 analogues compared to DPP-4 inhibitors for beta cell function and diabetes related complications among adults with type 2 diabetes?

Background

Diabetes mellitus is a global health burden,¹ and in 2013 an estimated 382 million people worldwide had diabetes.² This figure is expected to rise to 592 million by 2035.² In Australia, approximately 990,000 people have diabetes,² and type 2 diabetes accounts for approximately 85% of diabetes cases.³

The natural history of type 2 diabetes is characterized by insulin resistance and a progressive loss of pancreatic beta cell function.⁴ This decrease in beta cell function progressively damages the first phase insulin response,⁵ allowing blood glucose levels to rise.⁶ The primary aim of treatment for diabetes is to control blood glucose levels and reduce the development of diabetes-associated secondary microvascular (retinopathy, nephropathy and neuropathy) and macrovascular (cardiovascular disease) complications.⁷

Research has indicated that beta cell failure begins early in the course of type 2 diabetes.⁴ The UK Prospective Diabetes Study (UKPDS),⁸ a randomized controlled trial of 5102 individuals with type 2 diabetes, showed that those individuals with newly diagnosed type 2 diabetes, had a reduction in their beta cell function of approximately 50%.^{6, 9} Extrapolation of the observed rate of decline of beta cell function showed that the loss of function began some 10-12 years before type 2 diabetes was actually diagnosed.⁸

Additionally, in patients with type 2 diabetes, beta cell function continues to decline despite treatment with commonly prescribed antihyperglycaemic agents, and ultimately exogenous

insulin administration is required to maintain optimal blood glucose control.⁴ Therefore, interventions to address the early decline in beta cell function could potentially alter the course of type 2 diabetes, by preventing or delaying its onset and decreasing the incidence of complications.⁴

There are a number of oral and injectable antihyperglycaemic agents available on the market to manage type 2 diabetes.¹⁰ Pharmacological treatment options including metformin, insulin and a class of drugs known as sulfonylureas have been available for many years. In more recent times, a number of new agents have been introduced onto the market. These agents fall into a number of different drug classes including alpha-glucosidase inhibitors, thiazolidinediones, sodium glucose co-transporter-2 inhibitors and the incretin therapies; the incretin therapies include both dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon like peptide-1 (GLP-1) analogues.¹⁰ These provide new treatment options for people with type 2 diabetes. Currently, the oral medication, metformin is the first line therapy in people with type 2 diabetes.¹⁰ There is little evidence in the literature that metformin has an impact on beta cells.¹¹ However, several studies have linked the loss of beta cell mass and function to decreased levels of incretin hormones.⁵ There is some evidence from animal models that the incretin hormones increase pancreatic islet beta cell mass and reduce beta cell apoptosis.^{7, 12, 13} Introduced in 2005,¹⁴ the incretin therapies (GLP-1 analogues and DPP-4 inhibitors) target these beta cell associated incretin hormones.⁵ The incretin therapies and their effect on beta cell function in adults with type 2 diabetes will be the focus of this systematic review.

The incretin hormones are a group of hormones produced by the gastrointestinal system¹³ and released in response to food⁷ that enhance insulin secretion¹³ while inhibiting glucagon release, but only when glucose levels are elevated, thus offering the potential to lower plasma glucose levels while reducing the likelihood of hypoglycaemia.¹² The combined incretin response accounts for 50-70% of total postprandial insulin production.¹³ However, in individuals with type 2 diabetes incretin response is reduced to 20-35%.¹⁵ The two main human incretins are glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP).^{12, 13} In addition to enhancing insulin secretion and inhibiting glucagon release, GLP-1 also promotes satiety, exerts a motility-inhibiting effect, and slows gastric emptying.¹³ In individuals with type 2 diabetes, the insulinotropic activity of GIP is thought to be negligible in contrast to the activity of GLP-1.⁵ GLP-1 does retain efficacy in type 2 diabetes,¹⁶ and therefore attempts to modulate the incretin system are directed at GLP-1.⁵

GLP-1 analogues are administered by subcutaneous injection to avoid degradation by gastrointestinal enzymes, and mimic the action of the endogenous gastrointestinal hormone GLP-1.^{7, 13} They regulate blood glucose levels by stimulating glucose dependent insulin secretion and suppressing glucagon secretion, delaying gastric emptying and promoting satiety.⁷ However, unlike endogenous GLP-1 that has a short half-life of 1-2 minutes due to degradation by dipeptidyl peptidase enzyme DPP-4, GLP-1 analogues are resistant to DPP-4 degradation.¹³ There are several GLP-1 analogues available, including albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide and semaglutide.¹⁷ All of these agents will be investigated in this systematic review, although only three of them, namely exenatide, liraglutide and lixisenatide are registered with the Australian Therapeutic Goods Administration (effective March 2014).¹⁸

Exenatide and lixisenatide are synthetic forms of the naturally occurring exendin-4,¹³ a

peptide identified in the saliva of the Gila monster (*Heloderma suspectum*)¹⁴ that shares 50% sequence homology with human GLP-1.^{13, 14} Exenatide is available in several different strengths and is generally administered twice a day or once a week depending on the strength being administered. Lixisenatide is also available as once a day formulation.¹⁸ Liraglutide, albiglutide, semaglutide and dulaglutide are human GLP-1 analogues that share >90% amino acid sequence identity with native GLP-1.¹⁷ Liraglutide reversibly binds to albumin, increasing half-life and allowing once daily dosing.¹³ Albiglutide, semaglutide and dulaglutide are all once weekly GLP-1 analogues in late clinical development phases.¹⁷

While GLP-1 analogues directly affect the incretin system by mimicking the effects of endogenous GLP-1, DPP-4 inhibitors, on the other hand, are described as incretin enhancers as they prevent the inactivation of endogenous incretins by the DPP-4 enzyme.¹⁹ They elicit their effect via competitive, reversible inhibition of DPP-4.¹⁹ This action elevates active incretin levels, and is dependent on a functioning endogenous incretin secretory system.¹⁹ The DPP-4 inhibitors are small molecular weight drugs that inhibit approximately 90% of DPP-4 activity, and are taken orally once or twice a day.^{13, 19} The DPP-4 inhibitors that will be investigated in this systematic review will be sitagliptin, saxagliptin, linagliptin, alogliptin, vildagliptin, gemigliptin, anagliptin and teneligliptin.^{14, 17} Five DPP-4 inhibitors (sitagliptin, saxagliptin, linagliptin, alogliptin and vildagliptin) are listed on the Australian Therapeutic Goods Administration database (effective March 2014).¹⁸

GLP-1 has become an attractive pharmacological target, and consequently the incretin based therapies (GLP-1 analogues and DPP-4 inhibitors) represent an important step forward in the treatment of type 2 diabetes.²⁰ Due to ongoing interest in the benefits of incretin based therapies¹⁴ and the fact that they are establishing a foothold in the diabetes armamentarium,²⁰ the aim of this systematic review is to compare the effectiveness of GLP-1 analogues and DPP-4 inhibitors for beta cell function among adults with type 2 diabetes. A search of the literature databases to determine whether such a systematic review had already been completed identified two systematic reviews; one by Richter et al²¹ assessing the effectiveness of DPP-4 inhibitors (sitagliptin and vildagliptin) on beta cell function, and the other by Shyangdan et al⁷ examining the effectiveness of GLP-1 analogues. Both of these reviews compared these classes of drugs against other type 2 therapies and identified few studies with GLP-1 analogues versus DPP-4 inhibitors head to head comparisons. More recently, Mudaliar⁴ conducted a systematic review on antihyperglycaemic agents including DPP-4 inhibitors and GLP-1 analogues on the impact of beta cell preservation, however no comparisons were drawn between the two agents. A review by Davidson,¹⁴ examined the differences between GLP-1 analogues and DPP-4 inhibitors. In this article, Davidson¹⁴ identified the two studies already reviewed by Shyangdan et al⁷ as discussed above, but he also identified another comparative study by DeFronzo et al²² which looked at a DPP-4 and GLP-1 analogue. The article by Davidson¹⁴ was not a systematic review and therefore did not document any comparative findings between the two agents. In light of these studies being identified across several different reviews, it is timely to synthesize all available evidence from reputable sources in a systematic process.

Inclusion criteria

Types of participants

This review will include adults (over 18 years of age) with type 2 diabetes mellitus.

The diagnosis of type 2 diabetes mellitus should have been made using standard criteria that were valid at the beginning of the study. Ideally, diagnostic criteria should have been described, and should be consistent with changes in classification and diagnosis over the years. The author's definition of diabetes will be used, if necessary.

Types of intervention(s)

The interventions of interest for this review will be treatment with a GLP-1 analogue (primary intervention) and DPP-4 inhibitor (active comparator). GLP-1 analogue injectable preparations include exenatide, liraglutide and lixisenatide. The GLP-1 analogues still in the developmental stage, albiglutide, semaglutide and dulaglutide will also be of interest.

The DPP-4 inhibitor tablet preparations of interest include alogliptin, linagliptin, saxagliptin, sitagliptin, gemigliptin, anagliptin, teneligliptin or vildagliptin.

Treatment with either class of drug should be for a minimum of eight weeks, either alone or in combination with metformin (any dose).

Types of outcomes

Primary Outcomes

Primary outcomes of interest for this review will focus on beta cell function, and this will be assessed by a range of measurements. Firstly, the total amount of glucose metabolized during a glucose infusion will be used to quantify the response of beta cells. This is measured by the hyperglycaemic clamp technique.²⁴

Beta cell function will also be measured indirectly using homeostasis model assessment (HOMA). This is achieved by measuring fasting plasma insulin and glucose concentrations which reflects the balance between hepatic glucose output and insulin secretion, where insulin secretion is a measure of beta cell function. This model can also use radioimmunoassay insulin or C-peptide (which is also a measure of insulin secretion) in place of plasma insulin.²⁵

Plasma proinsulin and insulin levels are measured by immunoradiometric assays to calculate the Proinsulin to Insulin (P/I) Ratio which is used as a marker of the degree of beta cell secretory capacity. An increase in plasma proinsulin concentrations is a marker of defective beta cell insulin secretion and the proinsulin:insulin ratio correlates inversely with maximum beta cell secretory capabilities.²⁶

A further measure of insulin secretion are C-peptide levels. The C-peptide minimal model reflects the balance between hepatic glucose output and insulin secretion, where insulin secretion is a measure of beta cell function.²⁷ Glycated haemoglobin (HbA1c), fasting plasma glucose and postprandial plasma glucose will also be primary outcomes of interest.

Secondary Outcomes

Secondary outcomes of interest will be diabetes related complications including but not limited to retinopathy, neuropathy and nephropathy. Adverse events including mortality, and

also incidence of gastrointestinal side effects, infections, headache and pancreatitis will also be noted.

Types of studies

This review will consider any experimental study design including randomized controlled trials, non-randomized controlled trials, quasi-experimental and controlled before and after studies.

Search strategy

The search strategy aims to find both published and unpublished studies. A three-step search strategy will be utilised in this review. An initial limited search of MEDLINE and Cochrane Central will be undertaken followed by analysis of the text words contained in the title and abstract, and of the index terms used to describe article. A second search using all identified keywords and index terms will then be undertaken across all included databases. Thirdly, the reference list of all identified reports and articles will be searched for additional studies. Studies published in English will be considered for inclusion in this review.

The databases to be searched include:

PubMed

EMBASE

Cochrane Central trials register

Government clinical trials register including but not limited to Australia and New Zealand Clinical trials registry, United States clinical trials, Canadian Institutes of Health Research, The WHO Registry Network, Clinical trials registry, Pharmaceutical Industry Initiative

Current Controlled trials

International Diabetes Federation

Therapeutic Goods Administration

Initial keywords to be used will be:

type 2 diabetes

beta-cell function

beta-cell preservation

dipeptidyl peptidase-4 inhibitors

DPP-4 inhibitors

glucagon-like peptide analogues

GLP-1 analogues

Assessment of methodological quality

Papers selected for retrieval will be assessed by two independent reviewers for methodological validity prior to inclusion in the review using standardised critical appraisal instruments from the Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI) (Appendix I). Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer.

Data collection

Data will be extracted from papers included in the review using the standardised data extraction tool from JBI-MAStARI (Appendix II). The data extracted will include specific details about the interventions, populations, study methods and outcomes of significance to the review question and specific objectives.

Data synthesis

Quantitative data will, where possible, be pooled in statistical meta-analysis using RevMan (Cochrane Collaboration <http://tech.cochrane.org/revman>). For the majority of outcomes listed, effect sizes expressed as weighted mean differences (for continuous data) and their 95% confidence intervals will be calculated for analysis. Incidence of diabetes complications and adverse events as a result of taking these agents will, where possible, be expressed as odds ratios and their 95% confidence interval. Heterogeneity will be assessed statistically using the standard Chi-square and I-square. Where statistical pooling is not possible the findings will be presented in narrative form including tables and figures to aid in data presentation where appropriate.

Conflicts of interest

No conflict of interest

Acknowledgements

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Appendix II

Search strategies

PubMed search strategy (conducted 26/05/2014 to 26/06/2014)

- #1 Diabetes Mellitus, Type 2[mh] OR diabetes mellitus type 2[tw] OR type 2 diabetes[tw] OR maturity onset diabetes[tw] OR Adult Onset Diabetes Mellitus[tw] OR Diabetes Mellitus Type II[tw] OR NIDDM[tw] OR non insulin dependent diabetes[tw] OR diabetic retinopath*[tw] OR diabetic nephropath*[tw] OR diabetic kidney disease[tw] OR diabetic neuropathy[tw] OR diabetic glomerulosclerosis[tw] OR insulin independent diabetes[tw]
- #2 Insulin-Secreting Cells[mh] OR insulin secreting cell*[tw] OR beta cell*[tw] OR B cell*[tw] OR beta islet cell*[tw]
- #3 Dipeptidyl-Peptidase IV Inhibitors[mh] OR alogliptin[tw] OR linagliptin[tw] OR saxagliptin[tw] OR sitagliptin[tw] OR gemigliptin[tw] OR anagliptin[tw] OR teneligliptin[tw] OR vildagliptin[tw] OR Linagliptin[Supplementary Concept] OR saxagliptin[Supplementary Concept] OR sitagliptin[Supplementary Concept] OR vildagliptin[Supplementary Concept]
- #4 Glucagon-Like Peptide 1[mh] OR Glucagon-Like Peptide 1[tw] OR exenatide[tw] OR liraglutide[tw] OR lixisenatide[tw] OR albiglutide[tw] OR semaglutide[tw] OR dulaglutide[tw] OR DAPD peptide[Supplementary Concept] OR exenatide[Supplementary Concept] OR GLP 1[tw]
- #5 #1 AND #2 AND #3 AND #4

EMBASE search strategy (conducted 18/05/2014 to 26/06/2014)

#1.1 'glucagon like peptide 1'/syn OR 'glucagon like peptide 1' OR 'exendin 4'/syn OR 'exendin 4' OR 'liraglutide'/syn OR 'liraglutide' OR 'lixisenatide'/syn OR 'lixisenatide' OR 'albiglutide'/syn OR 'albiglutide' OR 'semaglutide'/syn OR 'semaglutide' OR 'dulaglutide'/syn OR 'dulaglutide'

#1.2 'dipeptidyl peptidase iv inhibitor'/syn OR 'dipeptidyl pepidase iv inhibitor' OR 'alogliptin'/syn OR 'alogliptin' OR 'linagliptin'/syn OR 'linagliptin' OR 'saxagliptin'/syn OR 'saxagliptin' OR 'sitagliptin'/syn OR 'sitagliptin' OR 'gemigliptin'/syn OR 'gemigliptin' OR 'anagliptin'/syn OR 'anagliptin' OR 'teneligliptin'/syn OR 'teneligliptin' OR 'vildagliptin'/syn OR 'vildagliptin'

#1.3 'pancreas islet beta cell'/syn OR 'pancreas islet beta cell'

#1.4 'non insulin dependent diabetes'/syn OR 'non insulin dependent diabetes'

#1.5 #1.1 AND #1.2 AND #1.3 AND #1.4 AND [embase]/lim NOT [medline]/lim

Cochrane Central Trials Register search strategy (conducted 26/05/2014)

#1 glucagon like peptide 1 or GLP-1 or GLP-1 agonist or albiglutide or dulaglutide or exenatide or liraglutide or lixisenatide or semalgutide

#2 dipeptidyl peptidase IV or DPP-4 inhibitor or anagliptin or gemigliptin or linagliptin or saxagliptin or sitagliptin or teneligliptin or vildagliptin

#3 beta cell function or beta cell functions

#4 diabetes mellitus or diabetes mellitus, adult onset or diabetes mellitus, Type 2 or diabetes mellitus, non insulin dependent

#5 #1 and #2 and #3 and #4

US Clinical Trials Registry search strategy (conducted 23/06/2014)

Search was done by drug class and individual drug name

GLP-1 receptor agonists OR Glucagon like peptide agonists AND DPP-4 inhibitors OR dipeptidyl peptidase inhibitors

Individual key words alogliptin OR anagliptin OR gemigliptin OR linagliptin OR saxagliptin OR sitagliptin OR teneligliptin OR vildagliptin OR albiglutide OR dulaglutide OR exenatide OR liraglutide OR lixisenatide OR semaglutide

WHO Clinical Trials Registry search strategy (conducted 28/06/2014)

Search was done by drug class and individual drug name

GLP-1 receptor agonists AND DPP-4 inhibitors

Individual key words alogliptin OR anagliptin OR gemigliptin OR linagliptin OR saxagliptin OR sitagliptin OR teneligliptin OR vildagliptin OR albiglutide OR dulaglutide OR exenatide OR liraglutide OR lixisenatide OR semaglutide

European Union Clinical Trials Registry search strategy (conducted 23/06/2014)

Search was done by drug class and individual drug name

GLP-1 analogues AND DPP-4 inhibitors

Individual key words alogliptin OR anagliptin OR gemigliptin OR linagliptin OR saxagliptin OR sitagliptin OR teneligliptin OR vildagliptin OR albiglutide OR dulaglutide OR exenatide OR liraglutide OR lixisenatide OR semaglutide

Current Controlled Trials search strategy (conducted 22/06/2014)

Search was done by individual drug name

Individual key words alogliptin OR anagliptin OR gemigliptin OR linagliptin OR saxagliptin OR sitagliptin OR teneligliptin OR vildagliptin OR albiglutide OR dulaglutide OR exenatide OR liraglutide OR lixisenatide OR semaglutide

Australian New Zealand Clinical Trials Registry search strategy (conducted 23/05/2014)

Search was done by drug class and individual drug name

DPP-4 inhibitors OR dipeptidyl peptidase-4 inhibitors AND GLP-1 agonist OR glucagon-like peptide-1 receptor agonist

Individual key words alogliptin OR anagliptin OR gemigliptin OR linagliptin OR saxagliptin OR sitagliptin OR teneligliptin OR vildagliptin OR albiglutide OR dulaglutide OR exenatide OR liraglutide OR lixisenatide OR semaglutide

Canadian Institutes of Health Research search strategy (conducted 23/06/2014)

Search was done by drug class

DPP-4 inhibitor OR dipeptidyl peptidase-4 inhibitor AND GLP-1 analogue OR glucagon-like peptide analogue

Novo Nordisk search strategy (conducted 23/06/2014)

Search was done by individual drug name

Individual key words alogliptin OR anagliptin OR gemigliptin OR linagliptin OR saxagliptin OR sitagliptin OR teneligliptin OR vildagliptin OR albiglutide OR dulaglutide OR exenatide OR liraglutide OR lixisenatide OR semaglutide

Sanofi search strategy (conducted 19/08/2014)

Search was done by individual drug name

Individual key words alogliptin OR anagliptin OR gemigliptin OR linagliptin OR saxagliptin OR sitagliptin OR teneligliptin OR vildagliptin OR albiglutide OR dulaglutide OR exenatide OR liraglutide OR lixisenatide OR semaglutide

International Diabetes Federation search strategy (conducted 24/06/2014)

Search was done by individual drug name

Individual key words alogliptin OR anagliptin OR gemigliptin OR linagliptin OR saxagliptin OR sitagliptin OR teneligliptin OR vildagliptin OR albiglutide OR dulaglutide OR exenatide OR liraglutide OR lixisenatide OR semaglutide

Therapeutic Goods Administration search strategy (conducted 24/06/2015)

Search was done by individual drug name

Individual key words alogliptin OR anagliptin OR gemigliptin OR linagliptin OR saxagliptin OR sitagliptin OR teneligliptin OR vildagliptin OR albiglutide OR dulaglutide OR exenatide OR liraglutide OR lixisenatide OR semaglutide

Appendix III

Joanna Briggs Institute (JBI) critical appraisal tool – randomised trials

1. Was the assignment to treatment groups truly random?

Yes	Method by which randomisation to intervention or control group described by author(s). (e.g. random allocation using number generator, stratification randomisation). Randomisation needs to be described with sufficient detail to enable reviewers to determine whether the method used is sufficient to minimise selection bias.
No	Methods other than randomisation used to allocate patients to Intervention or control groups.
Unclear	General terms like “random”, “random allocation” and “randomisation” used but method by which this was achieved not clearly described.

Reviewer’s response/comment:

2. Were participants blinded to treatment allocation?

Yes	Participants unaware that they have been allocated to either the intervention or control group.
No	Participants aware of which group they have been allocated to even although blinding may have been possible.
Unclear	Description of above unclear or unsatisfactory.

Reviewer’s response/comment:

3. Was allocation to treatment groups concealed from the allocator?

Yes	Allocator unaware of whether they were allocating participants to intervention or control group.
No	Allocator aware of which group they were allocating participants to.
Unclear	Description of above unclear or unsatisfactory.

Reviewer’s response/comment:

4. Were the outcomes of people who withdrew described and included in the results and analysis?

Yes	<p>Withdrawn participants reported and reasons for the withdrawal described.</p> <p>Withdrawn participants analysed in the groups to which they were originally allocated (Intention to treat analysis/ ITT).</p> <p>All participants included in final calculations including withdrawn participants, regardless of whether their final outcomes were measured.</p>
No	<p>No explanation of withdrawn patients or the significance of these withdrawals.</p> <p>Withdrawn patients not analysed in the groups to which they were originally allocated.</p>
Unclear	<p>Withdrawn patients incompletely described.</p> <p>Numbers of included/withdrawn patients do not match result figures.</p> <p>Description of above unclear or unsatisfactory.</p>

Reviewer's response/comment:

5. Were those assessing outcomes blind to the treatment allocation?

Yes	<p>Data collectors were blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met).</p> <p>In diagnostic study, were test results blinded to patient history and other test results?</p>
No	<p>Data collectors were aware of which group the patient belonged to.</p>
Unclear	<p>Description of above unclear or unsatisfactory.</p>

Reviewer's response/comment:

6. Were the control and treatment groups comparable at entry?

Yes	<p>At a minimum, the following baseline data for the patients was reported and comparable:</p> <ul style="list-style-type: none"> • Age • Sex • Duration of diabetes • HbA1c.
No	<p>At minimum the baseline data of age, sex, duration of diabetes, HbA1c are present, but they are not comparable.</p>
Unclear	<p>Description of above unclear or unsatisfactory.</p>

Reviewer's response/comment:

7. Were groups treated identically other than for the named interventions?

Yes	Participants in both the intervention and control groups were treated identically for all other aspects of care other than the diabetes treatment.
No	Participants in each group were treated differently in respect to other aspects of care.
Unclear	Description of above unclear or unsatisfactory.

Reviewer's response/comment:

8. Were outcomes measured in the same way for all groups?

Yes	Description of how data was measured and collected was provided and consistent between participant groups. Assessors were the same people or trained in the same way.
No	Description of how outcome data was measured and collected was different for each group. Assessors were different types of health professionals or trained in different ways.
Unclear	Description of above unclear or unsatisfactory.

Reviewer's response/comment:

9. Were outcomes measured in a reliable way?

Yes	<p>All outcomes measured used standardised methods or instruments (including units of measure, types of equipment). Authors mention the reliability and/or validity of the measurements they use (including trained data collectors) or piloted within the trial.</p> <ul style="list-style-type: none"> • Beta cell function measured by either: • HOMA • Hyperglycaemic clamp technique • C-peptide measures • Proinsulin to Insulin Ratio <p>Clearly stated description of adverse effects as a consequence of the diabetes treatment. Percentage of change and baseline data reported. P values and confidence intervals given.</p>
No	<p>Incorrect or non-standardised methods or instruments used, absence of clear definitions for measurements of outcome measures. No reporting on the reliability and/or validity of the methods used for measuring outcome or training provided for data collectors. Percentage of change <u>and</u> baseline data is not reported. P values <u>and</u> confidence intervals are not reported.</p>
Unclear	Description of above unclear or unsatisfactory.

Reviewer's response/comment:

10. Was appropriate statistical analysis used and reported?

Yes	Appropriate statistical methods used, described and reported.
No	Statistical methods not described or inappropriate methods used. Missing patient data not reported or accounted for.
Unclear	Description of above unclear or unsatisfactory.

Reviewer's response/comment:

Author's conclusion:

Appendix IV

Joanna Briggs Institute (JBI) data extraction tool

JBI Data Extraction Form for Experimental / Observational Studies

Reviewer Date

Author Year

Journal Record Number

Study Method

RCT Quasi-RCT Longitudinal
Retrospective Observational Other

Participants

Setting _____

Population _____

Sample size

Group A _____ Group B _____

Interventions

Intervention A _____

Intervention B _____

Authors Conclusions:

Reviewers Conclusions:

Study results

Dichotomous data

Outcome	Intervention () number / total number	Intervention () number / total number

Continuous data

Outcome	Intervention () number / total number	Intervention () number / total number

Appendix V

Details of additional data obtained for included studies from study authors

Citation	Contact Details	Query	Response																
Nauck M, Weinstock RS, Umpierrez, GE. Efficacy and safety of dulaglutide versus sitagliptin after 52 weeks in type 2 diabetes in a randomized controlled trial (AWARD-5). Diabetes Care. 2014;37(8):2149-58 ⁽⁷⁶⁾	Vicky Foster Medical Information Consultant Eli Lilly Australia Pty Ltd foster_vicky@lilly.com Received by email on 23/12/14 and 05/02/2015	Outcome data for change from baseline in fasting plasma glucose (+/-SE) after 26 and 52 weeks for dulaglutide 1.5mg and 0.75mg and sitagliptin 100mg	Fasting plasma glucose mg/dL (+/-SE) DU= dulaglutide SITA = sitagliptin <table border="1"> <thead> <tr> <th colspan="2">Week 26</th> </tr> </thead> <tbody> <tr> <td>DU 1.5 mg (mg/dL)</td> <td>-42.84 (2.2)</td> </tr> <tr> <td>DU 0.75 mg (mg/dL)</td> <td>-35.46 (2.2)</td> </tr> <tr> <td>SITA (mg/dL)</td> <td>-17.46 (2.0)</td> </tr> <tr> <th colspan="2">Week 52</th> </tr> <tr> <td>DU 1.5 mg (mg/dL)</td> <td>-42.84 (2.3)</td> </tr> <tr> <td>DU 0.75 mg (mg/dL)</td> <td>-29.34 (2.3)</td> </tr> <tr> <td>SITA (mg/dL)</td> <td>-16.20 (2.3)</td> </tr> </tbody> </table>	Week 26		DU 1.5 mg (mg/dL)	-42.84 (2.2)	DU 0.75 mg (mg/dL)	-35.46 (2.2)	SITA (mg/dL)	-17.46 (2.0)	Week 52		DU 1.5 mg (mg/dL)	-42.84 (2.3)	DU 0.75 mg (mg/dL)	-29.34 (2.3)	SITA (mg/dL)	-16.20 (2.3)
Week 26																			
DU 1.5 mg (mg/dL)	-42.84 (2.2)																		
DU 0.75 mg (mg/dL)	-35.46 (2.2)																		
SITA (mg/dL)	-17.46 (2.0)																		
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DU 1.5 mg (mg/dL)	-42.84 (2.3)																		
DU 0.75 mg (mg/dL)	-29.34 (2.3)																		
SITA (mg/dL)	-16.20 (2.3)																		
Sanofi. A randomized, double-blind, double-dummy, 2-arm parallel-group, multicentre 24-week study comparing the efficacy and safety of AVE0010 to sitagliptin as add-on to metformin in obese type 2 diabetic patients younger than 50 and not adequately controlled with metformin (EFC10780)[Internet]. 2014 Jan 29 [cited 2014 Aug 19]. ⁽¹²⁰⁾	Dr Philip Henderson Medical Advisor Sanofi Philip.Henderson@sanofi.com Received by email 19/08/2014	Results of the phase III unpublished clinical trial	Summary of results at URL http://en.sanofi.com/img/content/study/EFC10780_summary.pdf																

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