Incretin-Based Therapies in Patients with Type 2 Diabetes Mellitus and Renal Impairment

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ABSTRACT

The objective of this thesis is to add to literature addressing the safety and effectiveness of incretin-based agents in patients with diabetes and chronic kidney disease.

Methods:

Two complementary studies were conducted, a systematic review and meta-analysis and a population-based cohort study.

Results:

The systematic review and meta-analysis demonstrated in patients with diabetes and moderate or severe chronic kidney disease (CKD), incretin-based therapies effectively reduced glycated hemoglobin compared to placebo (WMD -0.53; 95%CI -0.64, -0.42). The pooled relative risk (RR) for all-cause mortality indicated no evidence of effect for incretin vs. placebo (RR 1.02; 95%CI 0.50, 2.06). In the cohort study dipeptidyl peptidase-4 (DPP-4) inhibitors, as second-line therapy were not significantly associated with a reduction in all-cause mortality (adjusted hazard ratio 0.74 [95%CI 0.52-1.04] vs. SU initiators).

Conclusion:

The meta-analysis supports incretin-based therapies as effectively reducing glycemia without substantial increased risk of hypoglycemia. The cohort study demonstrated second-line DPP4 inhibitor therapy was not significantly associated with a reduction in all-cause mortality when compared to sulfonylureas. Despite their introduction to the pharmaceutical market in 2007, there is still much to be understood regarding incretin therapy.

General Summary

The purpose of this thesis is to add to research addressing the usefulness of a group of medications, (incretins) in patients with diabetes and chronic kidney disease (CKD).

Two studies were completed, one reviewed existing published research and the other used a large set of previously collected data, each with specific objectives.

The first study showed that in patients with diabetes and CKD, incretin medications are successful in reducing blood sugar. The second study showed that one incretin medication subgroup was not connected with a change in all-cause mortality risk.

This thesis demonstrates that incretin medications lower blood sugar without dropping it dangerously low in patients with diabetes and CKD. It also showed no change in risk of all-cause mortality for one group of incretin medications compared to other antidiabetic medications in patients with CKD. There remains much to learn about incretin medication, especially in patients with diabetes and CKD.

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Table of Contents

List of Tables

List of Figures

List of Abbreviations

A1C	Glycated hemoglobin
AC	Active comparator
ACE	Angiotensin converting enzyme
ACR	Albumin creatinine ratio
ACS	Acute coronary syndrome
ARB	Angiotensin receptor blocker
CCI	Charlson Comorbidity Index
CI	Confidence interval
CKD	Chronic kidney disease
CPRD	Clinical practice research datalink
CV	Cardiovascular
DPP-4	Dipeptidyl peptidase 4
eGFR	Estimated glomerular filtration rate
EHR	Electronic health record
ESKD	End stage kidney disease
FPG	Fasting plasma glucose
GFR	Glomerular filtration rate
GIP	Glucose-dependent insulinotropic polypeptide
GLP-1	Glucagon-like peptide 1
GLP-1RA	Glucagon-like peptide-1 receptor agonist
HES	Hospital episode statistics
MACE	Major adverse cardiovascular events

MD	Mean difference
MeSH	Medical Subject Heading
MI	Myocardial infarction
ONS	Office for national statistics
RCT	Randomized control trial
RR	Relative risk
SD	Standard deviation
SGLT-2	Sodium-glucose co-transporter-2
SU	Sulfonylurea
T2DM	Type 2 diabetes mellitus
TZD	Thiazolidinedione
WMD	Weighted mean difference

List of Appendices

List of Supplementary Files

Chapter 1: Introduction

1.1 OVERVIEW

This chapter will review the epidemiology, management, and burden of disease for both diabetes and chronic kidney disease. It will also cover background information on the incretin system and incretin-based therapies as the primary antihyperglycemic agents of interest for the thesis. This thesis document is presented in the manuscript style of presentation.

1.2 DIABETES

1.2.1 Epidemiology

Diabetes is a chronic disease characterized by high glucose levels that, without proper management, can cause microvascular complications of the eyes, kidneys, and nerves, in addition to increasing the risk of cardiovascular disease.[2,3] Diabetes occurs when the body's requirement for insulin is not met, either through impaired insulin secretion, defective insulin action, or both.[4, 5] According to the International Diabetes Federation, there were approximately 415 million people with diabetes in 2015, with the number expected to rise to 642 million by 2040.[6]

The complexity of diabetes has led to changing definitions and diagnostic factors over time. Diabetes is often classified into two broad categories, Type 1 and Type 2, and is generally based on thresholds of glycemia, although other forms exist. Type 1 diabetes, formerly known as "childhood onset diabetes" and "insulin dependent diabetes" is an autoimmune disease that is largely a result of pancreatic cell destruction, leading to insulin deficiency.[4, 7] Management of Type 1 diabetes requires regular glucose monitoring, dietary maintenance, and daily insulin treatment.[4, 6] Type 2 diabetes, formerly known as "adult onset diabetes", is a metabolic disorder which includes

predominant insulin resistance with relative insulin deficiency as well as predominant secretory defect with insulin resistance. Prediabetes refers to elevated blood glucose levels, identified by either impaired fasting glucose, impaired glucose tolerance, or a glycated hemoglobin (A1C) of 6.0% to 6.4%. The term categorizes individuals who are at an increased risk for developing type 2 diabetes.[4, 7]

Type 2 diabetes accounts for approximately 90% of all individuals with diabetes, Type 1 accounts for approximately 9%, with the other types (including gestational diabetes) accounting for the remaining 1%.[6, 8] Venous samples and various laboratory tests, including fasting plasma glucose (FPG), 2-hour plasma glucose (2hPG), and A1C, may be used to diagnose and classify diabetes.[4] The Diabetes Canada 2018 Guidelines identify meeting any one of four markers as diagnostic for diabetes: 1) FPG ≥7.0 mmol/L, where fasting means no caloric intake for 8 hours, 2) A1C ≥6.5% (in adults), 3) 2hPG in a 75 g oral glucose tolerance test ≥11.1 mmol/L, or 4) random plasma glucose ≥11.1 mmol/L.[4]

1.2.1 Management

While Type 1 diabetes requires treatment with insulin, the management of type 2 diabetes is individualized and may include lifestyle modification, oral medications, injectable medications, insulin agents, or a combination of therapies.[4, 6] Initiating lifestyle therapy – which includes diet, exercise, and medically assisted weight loss – with the goal of achieving glycemic control is the fundamental first-line therapy. Pharmacological management is recommended either if glycemic targets are not met or upon diagnosis of diabetes, depending on initial glycemic values, and should be discussed with the patient in addition to continued lifestyle therapy.[4, 9]

Several classes of antidiabetic agents are available in North America for the management of type 2 diabetes (Table 1.1). Diabetes Canada and the American Diabetes Association recommends that metformin, a biguanide, be started as first-line pharmacotherapy unless there are contraindications, such as severe chronic kidney disease (CKD) and hepatic failure.[4, 10] Other broad classes of antidiabetic agents include incretins (dipeptidyl peptidase 4 (DPP-4) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists), sodium-glucose co-transporter-2 (SGLT-2) inhibitors, alpha-glucosidase inhibitors, insulin, insulin secretagogues (sulfonylureas and meglitinides), and thiazolidinediones (TZDs).[4, 10] While most patients with type 2 diabetes are started on metformin, insulin may be initiated for those with an initial A1C of >9.0%.[4, 11] Patients may eventually experience a decline in glycemic control, requiring dual-therapy, triple-therapy, or more intensive insulin regimes to meet glycemic targets.[10]

1.2.2 Complications

Diabetes and the associated hyperglycemia proportionately lead to increased risk for severe microvascular and macrovascular complications affecting numerous organ systems. Hypertension (both systolic and diastolic) and dyslipidemia are common co-existing risk factors that contribute to both microvascular and macrovascular complications.[4, 10, 12] Intensive glycemic control, maintaining A1C ≤7.0% for most patient, has been shown to provide protective benefits.[4, 11, 13]

The development of cardiovascular disease is escalated by diabetes and has been shown to be the leading cause of morbidity and mortality in patients with diabetes. Cardiovascular disease may include stable ischemic heart disease (SIHD) (previously known as angina), acute coronary syndrome (ACS) (previously known as myocardial infarction), heart failure, and stroke. Both diabetes and hyperglycemia are independent risk factors for macrovascular complications,

including acute coronary events.[4, 6, 10, 13, 14] In individuals with diabetes there is a 2- to 4-fold increase in the risk of vascular disease, a 3-fold increase in acute coronary syndrome (ACS) risk, and a 2-fold increase in mortality compared to those without diabetes.[4, 15]

Major microvascular complications include retinopathy, neuropathy, and nephropathy. Retinopathy in those with type 2 diabetes is estimated to be present in approximately 21% to 39%, although severe sight-threatening diabetic retinopathy is thought to be relatively low.[4] Persistent hyperglycemia is the primary cause of retinopathy and can lead to the damage of vascular supply of the retina. Screening for diabetic retinopathy should be initiated at diagnosis and continue every 1-2 years in those with type 2 diabetes. While diabetic retinopathy can become advanced before vision is affected, it remains the leading cause of blindness in Canada.[3, 4, 6]

Neuropathy, most commonly peripheral, is another microvascular complication of prolonged hyperglycemia and is likely to develop in up to 50% of people with type 2 diabetes within 10 years of onset.[4, 6] Diabetic neuropathy may present as a sharp or burning pain, tingling, or loss of sensation typically in the feet, which can lead to ulceration, infection, or amputation. The associated pain often restricts physical activity, work and affects quality of life. Other potential neuropathies include erectile dysfunction, loss of bladder sensation, incontinence, and gastrointestinal dysfunction, including constipation, and diarrhea.[4, 6, 16] Screening for peripheral neuropathy, with 10g monofilament or loss of sensation to vibration at the great toe, should be conducted annually, beginning at diagnosis.[4] Glycemic control has been shown to help reduce the risk of diabetic neuropathy and subsequent complications such as ulceration and amputation.[4, 16, 17]

Concomitant hypertension, as well as hyperglycemia, smoking, dyslipidemia, and obesity, are risk factors that contribute to the development of diabetic nephropathy, as with other microvascular complications of diabetes. While diabetic nephropathy is a common cause for CKD in people with diabetes, CKD has a number of other causes including hypertensive nephrosclerosis, ischemic nephropathy and other kidney diseases.[18] Treatment of hypertension with an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) to achieve a target blood pressure of <130/80 is recommended as per the Hypertension Canada Guidelines.[19] The renin–angiotensin–aldosterone system (RAAS) blockade has long been the treatment for renoprotection in patients with T2DM. Current practice also utilizes SGLT-2 inhibitors, the newest of the anti-hyperglycemic agents, to aid in slowing the progression of diabetic nephropathy.[20-22] Results of the CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial and the EMPA-KIDNEY trial support the use of SGLT-2 inhibitors in patients with type 2 diabetes mellitus (T2DM) and chronic kidney disease as a treatment option for renal and cardiovascular protection.[23, 24] Of note, the SGLT-2 agents were not yet in clinical use at the time this thesis was conceived.

Additionally, individuals with diabetes and related comorbidities are at increased risk for pregnancy complications, peripheral vascular disease, periodontitis, and infection, as well as decreased quality of life.[4, 6, 13, 25, 26]

1.3 CHRONIC KIDNEY DISEASE

1.3.1 Epidemiology

The term chronic kidney disease (CKD) encompasses abnormalities of the structure or function of the kidney, is present for more than 3 months, and includes a breadth of severity, causes, presentations, and prognoses. The spectrum of CKD ranges from kidney damage to kidney failure or death.[27, 28] CKD is defined by the Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guidelines as "abnormalities of kidney structure or function, present for >3 months, with implications for health." Such abnormalities may include albuminuria; sediment, electrolyte, and structural abnormalities; or history of kidney transplantation.[22, 27] CKD may be diagnosed following persistent eGFR <60 ml/min/1.73m^2, or 2 out of 3 albumin creatinine ratio (ACR) values ≥ 2.0mg/mmol over at least a 3-month span.[18] It is further classified or staged according to the level of impairment of estimated glomerular filtration rate (eGFR) with associated prognoses as outlined by the KDIGO guidelines. (Table 1.2)[4, 27]

Individuals with diabetes are considered a high-risk group for CKD, with diabetic nephropathy being a leading cause of kidney failure. Diabetes and chronic kidney disease create a substantial burden on the health care system, especially with the increasing prevalence.[27, 29] One study estimated the prevalence of CKD to be 12.5% in Canadian adults between 2007-2009.[28]

1.3.2 Morbidity and Mortality

The complications of chronic kidney disease affect all organ systems and CKD is recognized as an independent risk factor or cardiovascular disease.[27] A 2010 meta- analysis showed an increased

relative risk of all-cause mortality and cardiovascular mortality in patients with eGFR less than 60 mL/min/1.73m^2 or, as independent predictors, an ACR greater than 1.1mg/mmol.[30]

Risk factors for kidney disease progression include the presence of diabetes, elevated blood pressure, sustained hyperglycemia, dyslipidemia, obesity, and smoking.[4, 30] Early detection of kidney disease, glycemic control, and management of comorbidities are crucial for slowing the progression of CKD. Optimization of blood pressure is important in the prevention of developing proteinuria and albuminuria and an overall target blood pressure of <130/80, as is recommended for patients with diabetes, offers kidney protection.[4] Cardiovascular protection can be provided through blockade of the renin angiotensin aldosterone system with either an ACE inhibitor or ARB to decrease or prevent worsening albuminuria and nephropathy.[4, 27] Additionally, lipid modification using statin therapy and aspirin for secondary prevention (but not primary prevention) may be utilized for risk factor modification similarly to that of the general population.[27]

1.3.3 Renal impairment and Antihyperglycemic Agents

At reduced glomerular filtration rate (GFR), the pharmacokinetics of drugs that are renally excreted are altered and, variation of drugs that are not renally excreted may also be seen. Therefore, pharmacotherapies often require dose adjustment at lower GFRs to avoid drug accumulation and toxicity.[4] The degree of kidney impairment must be considered when selecting antihyperglycemic agents. According to Diabetes Canada Clinical Practice Guidelines[4], within CKD class 3A (eGFR 45-59 mL/min/1.73m^2), use of sulfonylureas is cautioned, but dose adjustment is not required for most other agents (Metformin, most GLP-1 receptor agonists, most DPP-4 inhibitors, insulins). The use of SGLT-2 inhibitors are cautioned in those with CKD stage

3A or greater due to limited glycemic efficacy.[4, 31] However, the CREDENCE trial demonstrated renal and cardiovascular protection in patients with T2DM and CKD, including those with an eGFR of 30 to <60 mL/min/1.73m^2, approximately 60% of the study population.[23] The KDIGO 2022 Clinical Practice Guideline also recommends use of an SGLT-2 inhibitor in patients with T2DM, CKD, and an eGFR ≥20 ml/min/1.73m^2 for cardiorenal protection, also noting that it is reasonable to continue even if the eGFR falls below 20 ml/min/1.73m^2.[21, 22]

Some GLP-1 Receptor Agonists (GLP-1RA) (dulaglutide, lixisenatide, liraglutide) do not require any dose adjustment within CKD 3A and 3B (eGFR 30-44 mL/min/1.73m^2), and liraglutide is approved for routine use in CKD class 4 (eGFR 15-29 mL/min/1.73m^2). DPP-4 inhibitors can be considered without dose adjustment for linagliptin and at a lowered dose for saxagliptin in patients with CKD class 3A-4, while alogliptin and sitagliptin may be continued within CKD 5 (eGFR <15 mL/min/1.73m^2 or dialysis) at reduced dosing.[4, 31]

While the need for dialysis or transplantation in patients with CKD is quite low, the treatment presents a significant financial burden, noted by the KDIGO Organization, as 5% of annual budgets consumed by less than 1% of the population.[27]

1.4 INCRETIN-BASED THERAPIES

1.4.1 The incretin system

The incretin hormones, consisting of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), function as gastrointestinal factors which are released by the body post-prandially and stimulate insulin secretion.[32, 33] The incretin effect is a phenomenon explaining the variation in the body's response to oral glucose absorbed from the gut compared to

intravenous glucose administration, even at the same plasma glucose ("isoglycaemia"). Oral glucose (or meals) stimulate secretion of the incretin hormones (GIP and GLP-1) which regulate the incretin effect, triggering glucose-induced insulin secretion and suppressing glucagon secretion from the pancreas, thereby lowering blood glucose. Individuals with type 2 diabetes have an impaired incretin effect (impaired glucose tolerance), and thereby a reduction in insulin secretion by the body following oral glucose consumption. However, because the insulinotropic effects of incretin hormones are dependent on blood glucose concentrations, they do not cause hypoglycemia.[32, 33] Incretin-based therapies, which include GLP-1 receptor agonists (GLP-1RA) (injectable/oral) and DPP-4 inhibitors (oral), target the incretin axis, augmenting its glucose-sensing mechanism and improving glucoregularion.

1.4.2 GLP-1 receptor agonists

GLP-1 receptor agonists (GLP-1RAs) are one of two classes of incretin-based agents approved for the treatment of type 2 diabetes. They can be further divided into short-acting agents (exenatide and lixisenatide), which have a half-life of 2–3hr, and longer-acting agents (dulaglutide, exenatide extended-release, liraglutide, and semaglutide) which have a half-life of up to one week.[32, 34] GLP-1RAs are primarily administered as subcutaneous injections with dosing ranging from twice daily to once weekly, depending on the agent and its half-life. All medications within this class are well established as glucose-lowering agents for the treatment of type 2 diabetes and are associated with low risk of hypoglycemia. Significant A1C reductions in the range of 0.6-1.4% and increased odds of achieving target A1C have been demonstrated by many studies.[35-41] Oral semaglutide is the first orally available GLP-1RA yet it's effect on cardiovascular outcomes had not been determined at the time this thesis was conceived.[41] Since that time, the Peptide Innovation for Early Diabetes Treatment (PIONEER) 6 trial has demonstrated noninferior cardiovascular safety of oral

semaglutide when compared to placebo.[39] GLP-1RAs tend to be well-tolerated with gastrointestinal side effects (nausea, vomiting, diarrhea) being most prominent. GLP-1RAs are contraindicated in patients with a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2 and cautioned in those with a history of pancreatitis or pancreatic cancer.[4, 42, 43]

The pleiotropic effects of the GLP-1 hormone are thought to provide some renal benefit, and prior studies have demonstrated renal safety (no significant difference in renal outcomes) with the use of GLP-1RAs when compared with placebo.[40, 44] The REWIND trial found reduced composite renal outcomes in treatment with dulaglutide versus placebo in patients with type 2 diabetes.[45] Additionally, some GLP-1RAs (dulaglutide, liraglutide, and subcutaneous semaglutide) have been shown to provide cardiovascular outcome benefit.[45, 46]

1.4.3 DPP-4 inhibitors

DPP-4 inhibitor therapies are thought to overcome the impaired incretin effect that occurs with T2DM by inhibiting the DPP-4 enzyme, which cleaves the incretin hormones, thereby promoting insulin production and release.[47-49] This glucose-dependent pathway therefore reduces risk of hypoglycemia. Like other antidiabetic agents, DPP-4 inhibitors have shown glycemic efficacy in patients with type 2 diabetes and reduced kidney function, with an A1C reduction in the range of 0.5-0.7% and an added benefit of being weight neutral.[41, 50, 51] Although DPP-4 inhibitors are renally cleared, the extent of renal excretion varies greatly among those available (6-75%). Therefore, dose adjustment to avoid accumulation is recommended in those therapies with significant renal excretion, such as sitagliptin.[4, 47] DPP-4 inhibitors are listed as a second-line antihyperglycemic therapy option in the 2018 Diabetes Canada Clinical Practice Guidelines for

their glucose-lowering effects, lack of effect on weight, and low risk of hypoglycemia; however, they tend to be less effective than their GLP-1RA counterpart in terms of A1C lowering.[4, 41, 52] While DPP-4 inhibitors are generally well tolerated without any major side effects, there have been rare reports of pancreatitis and severe joint pain. Additionally, they are cautioned for use in patients with a history of pancreatitis or pancreatic cancer and a risk of heart failure has been reported with saxagliptin.[4, 41, 53]

1.4.4 Review of evidence

Incretin therapies were included in the Canadian Diabetes Association (now Diabetes Canada) 2013 Clinical Practice Guidelines as second-line antihyperglycemic agents which could be used as adjuvant therapy with metformin in patients not meeting glycemic targets.[54] At this time, the long-term safety and efficacy data were very limited. Since then, incretin agents have been well established as glucose-lowering agents, demonstrating reduction of A1C in the range of 0.5-1.4%.[36, 41, 50] By the time of publication of the 2018 Clinical Practice Guidelines, clinical trials were demonstrating efficacy and safety for both DPP-4 inhibitors and GLP-1 receptor agonists, including the reduction in major adverse cardiovascular events (MACE) and CV death for patients with cardiovascular disease treated with liraglutide.[4] Diabetes Canada's 2020 update on the "Pharmacologic Glycemic Management of Type 2 Diabetes in Adults" recommends therapeutic regimes that include GLP-1RA (with the exception of lixisenatide) or SGLT-2 inhibitor agents in patients with type 2 diabetes and atherosclerotic cardiovascular disease; >60 years old and 2 or more CV risk factors; or, GFR >30mL/min/1.73m^2, given the demonstrated cardiorenal benefits.[41] The evidence favors subcutaneous liraglutide, dulaglutide and semaglutide in terms of both CV safety and CV benefits. Additionally, the SUSTAIN-6 trial showed no significant treatment interactions among patients with CKD and therefore could be used to reduce the risk of MACE in

that population.[46, 55] The 2020 update also reviews additional cardiovascular outcome trials, including the PIONEER 6 trial of once-daily oral semaglutide versus placebo, which was considered an exploratory analysis, leaving the consideration of MACE outcome benefit unproven.[39, 41]

At the time of this study, there was limited pooling of data from individual studies or subgroup analyses, which can provide stronger evidence when considering efficacy. Previous systematic reviews found that incretin-based therapies, particularly DPP-4 inhibitors are effective and comparable alternatives to metformin and other oral antidiabetic medications for blood glucose management. These reviews also showed incretin therapies to be tolerable in patients with type 2 diabetes and CKD, with appropriate dose adjustment.[47, 48, 56-58] However, the majority of studies included in systematic reviews used placebo comparators.[59-62] Several large clinical trials address the effect of incretin therapies on all-cause mortality and cardiovascular outcomes in patients with diabetes.[40, 63-65] While some of these trials reported CKD subgroups, few have focused on the specific cohort of patients with CKD, specifically moderate to severe CKD (stages 3, 4, or 5).

Between the time of this study and completion of this thesis, several systematic reviews have been published, reporting on the effect of incretin agents in the context of CKD. [58, 66-68]

1.5 OBJECTIVES AND RATIONALE

1.5.1 Objectives

The overarching objective of this thesis is to add to the limited literature addressing the safety and effectiveness of incretin-based agents in patients with diabetes and established chronic kidney disease. This research will contribute to the existing literature using two different study designs:

(1) a systematic review and meta-analysis and a (2) population-based cohort study, each with specific objectives.

Study 1: The primary objective of the systematic review and meta-analysis is to synthesize the literature (available as of March 2016) on the efficacy and safety of incretin-based agents in patients with type 2 diabetes and moderate or severe chronic kidney disease. This primary efficacy and safety outcome measures of interest are change in A1C and proportion of hypoglycemic events, accordingly. Secondary outcome measures of interest include change in FPG, all-cause mortality, acute MI, stroke, end stage kidney disease (ESKD)/kidney transplant/dialysis, and MACE. MACE was defined as a 3-point composite outcome of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke.

Study 2: The primary objective of the population-based cohort study is to comparatively assess population-based rates of all-cause mortality and cardiovascular outcome among patients using DPP-4 inhibitors compared to other antidiabetic medications in patients with type 2 diabetes and chronic kidney disease. The source population provides data in a timeframe of 2001 to 2012. The primary research question of this study is: Does exposure to a DPP-4 inhibitor as a second-line antidiabetic medications (incretin-based therapies, insulin, TZDs, sulfonylureas, others) increase or decrease the risk of all-cause mortality and cardiovascular morbidity in patients with type 2 diabetes and chronic kidney disease? Cardiovascular morbidity was operationalized as major adverse cardiovascular events. Additional outcomes include cardiovascular disease, non-fatal myocardial infarction, and non-fatal stroke as discrete outcomes.

1.5.2 Rationale

In summary, this thesis discusses the effects of incretin-therapies in patients with moderate to severe CKD to close the gap of limited efficacy and safety data that included a comparison to other anti-diabetic agents using real world data. This will provide additional knowledge and evidence to inform physicians and other prescribers when making recommendations on therapy for diabetes management while taking into consideration the growing risks of chronic kidney disease associated with type 2 diabetes.

It is important to note that a version of Study 1, the systematic review and meta-analysis, has previously been published in the American Journal of Kidney Diseases via an open access license and written permission was not required for re-use in this thesis.[1]

Table 1.1: Antihyperglycemic agents for the management of type 2 diabetes*

Class	Drug(s)		
Biguanides	Metformin Metformin extended-release		
Incretins	**DPP-4 inhibitors** Alogliptin Linagliptin Saxagliptin Sitagliptin	**GLP-1 receptor agonists** *Short-acting:* Exenatide Lixisenatide *Longer-acting:* Dulaglutide Exenatide extended-release Liraglutide Semaglutide	
SGLT-2 inhibitors	Canagliflozin Dapagliflozin Empagliflozin		
∝-glucosidase inhibitor	Acarbose		
Insulin	**Bolus (prandial) Insulins** *Rapid-acting* Aspart Aspart (faster-acting) Glulisine Lispro *Short-acting* Regular	**Basal Insulins** *Intermediate-acting* NPH *Longer-acting* Degludec Detemir Glargine	**Premixed Insulins** Regular-NPH Biphasic insulin aspart Lispro/lispro protamine suspension
Insulin secretagogues	**Sulfonylureas** Gliclazide Gliclazide modified release Glimepiride Glyburide	**Meglitinides** Repaglinide	
TZDs	Pioglitazone Rosiglitazone		

**Adapted with permission from Diabetes Canada 2018 Clinical Practice Guidelines*[4]*

Table 1.2: CKD definition as used by KDIGO

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012				Persistent albuminuria categories Description and range		
				A1	**A2**	**A3**
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min/1.73 m2) Description and range	**G1**	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); yellow: moderately increased risk; orange: high risk; red: very high risk.

**Used with permission from KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease*[22]

Chapter 2: Safety and Efficacy of Incretin-based Therapies in Patients with Type 2 Diabetes Mellitus and Chronic Kidney Disease: Systematic Review and Meta-analysis[†]

This chapter was a collective effort with contributions from all co-authors, Patricia M. Howse, Lyudmila N. Chibrikova, Laurie K. Twells, Brendan J. Barrett, and John-Michael Gamble, detailed as follows: research area and study design: PH, BB, LT, JMG; data acquisition: PH, LC; data analysis/ interpretation: PH, JMG; statistical analysis: PH, JMG; supervision and mentorship: JMG, BB, LT; manuscript preparation: primarily PH with support from JMG, BB, LT. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

2.1 INTRODUCTION

Diabetes is the leading cause of chronic kidney disease; and, as the rate of diabetes increases, CKD and associated cardiovascular outcomes are a growing public health concern.[69, 70] Diabetes itself, and in combination with CKD, is associated with increased rates of cardiovascular disease and cardiovascular-related death, emphasizing the importance of appropriate treatment for patients in this population.[4, 71] Increased albuminuria and reduced renal function, as measured by the GFR, are both independent risk factors for cardiovascular events and other adverse effects.[72, 73] Although

[†]This chapter has been previously published.

1. Howse PM, Chibrikova LN, Twells LK, et al. Safety and Efficacy of Incretin-Based Therapies in Patients With Type 2 Diabetes Mellitus and CKD: A Systematic Review and Meta-analysis. Am J Kidney Dis. 2016;68(5):733-742. DOI: 10.1053/j.ajkd.2016.06.014.

many anti-diabetic therapies are available to manage hyperglycemia in patients with type 2 diabetes mellitus, the pharmacokinetics and pharmacodynamics of these medications are often altered in the context of CKD.[74]

Incretin-based therapies are a novel class of anti-diabetic medications, increasingly used in the treatment of hyperglycemia in patients with type 2 diabetes.[75] The Canadian Diabetes Association (CDA) 2013 Clinical Practice Guidelines, the Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes, and the Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology recommend incretin-based therapies, DPP-4 inhibitors and GLP-1 receptor agonists, as an option for add-on therapy to first-line therapy metformin or other anti-diabetic medications.[54, 76, 77] However, there is limited evidence about the relative clinical effectiveness and safety of incretin-based therapies in patients with diabetes and CKD.

Other reviews have found that incretin-based therapies, particularly DPP-4 inhibitors, are effective and comparable alternatives to metformin and other oral anti-diabetic medications for blood glucose management and are tolerable in patients with type 2 diabetes and CKD with appropriate dose adjustment.[47, 48, 56-58] One study's pooled analysis of linagliptin found that dose adjustment was not necessary in patients with type 2 diabetes and renal impairment.[56] However, there are limited studies that focus on incretin-based therapies in patients with moderate to severe CKD (Stages 3, 4 or 5), and previous reviews of this patient population have not included a meta-analysis.[47, 48, 58, 75] We aimed to conduct a systematic review and meta-analysis of randomized

controlled trials (RCTs) to assess the safety and efficacy of incretin-based therapies in patients with type 2 diabetes and moderate or severe CKD.

2.2 METHODS

2.2.1 Literature Search

Database searches included The Cochrane Library, PubMed, EMBASE and International Pharmaceutical Abstracts from inception to March 9, 2016. The articles were not restricted based on language or publication status. Studies were limited to RCTs using a tested highly sensitive search strategy for each database.[78] Alternative sources searched for published and unpublished trials included the CDA 2013 Clinical Practice Guidelines reference list, the National Kidney Foundation Guidelines reference list, clinical trial registries and the references of associated systematic reviews and meta-analyses.

Both MeSH and keyword searches were performed in The Cochrane Library and PubMed. EMTREE and keyword searches were completed in EMBASE and keyword searches were conducted in International Pharmaceutical Abstracts. The search terms included 'kidney disease', 'renal impairment', 'incretin', 'dipeptidyl-peptidase 4' and 'glucagon-like peptide 1', which were adjusted according to the requirements of each database. A sample search strategy is provided in the supplementary material (Appendix 2.B).

2.2.2 Review methods and selection criteria

Eligible trials were listed and assessed independently by two reviewers (PH, LC) using pre-defined inclusion criteria. Studies were included if they met the following criteria: 1) randomized controlled design; 2) patients with type 2 diabetes; 3) patients ≥18 years of age; 4) patients with

moderate CKD, severe CKD, or ESKD, as defined by the individual study; 5) the intervention group received either a DPP-4 inhibitor or GLP-1 receptor agonist; 6) the comparison group received placebo or an active comparator (AC), the later defined as an anti-diabetic medication other than an incretin-based therapy; and 7) reported at least one outcome of interest. There were no restrictions on length of follow-up. In the case of multiple publications from the same population, we included the report with the longer follow-up period.[79, 80]

2.2.3 Outcomes of Interest

Outcome measures included change in A1C (%) as the primary measure of efficacy, and the proportion of patients experiencing a hypoglycemic event as the primary measure of safety. Secondary outcomes included change in FPG (mmol/L), all-cause mortality, acute MI, stroke, ESKD/kidney transplant/dialysis, and major adverse cardiovascular events.[81] MACE was defined as a composite outcome of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke.[82, 83]

2.2.4 Data extraction

Two authors (PH, LC) used pre-defined forms to extract data from the studies, including: study and design characteristics; number of subjects; participant baseline characteristics (e.g. age, sex, duration of diabetes); follow-up period; intervention and comparison particulars (e.g. drug, dose); and outcomes (e.g. A1C, adverse events). A1C did not have to be the primary outcome and could have been reported as either pre- and post-intervention values, or change in A1C from baseline to endpoint. The quality of each study was independently assessed by two authors (PH, LC) using the Cochrane Collaboration's risk of bias assessment tool.[84] In the case of any disagreement, a third author (JMG) also assessed the study.

2.2.5 Statistical analyses

For each outcome measure of interest, random effects meta-analyses were conducted to pool mean differences (MDs) for continuous outcomes and relative risks (RRs) for dichotomous outcomes, in order to determine the effect of DPP-4 inhibitors or GLP-1 receptor agonists vs. placebo and active comparator. The random effects model was used to account for statistical heterogeneity, particularly as the intervention particulars (e.g. drug, dose, frequency) varied among studies.[84, 85] We used a restricted likelihood estimation approach to calculate 95% confidence intervals.[86] For dichotomous outcomes, we used an exact binomial likelihood estimator to calculate the variance. For groups with zero events, we added 0.5 to each cell.[84] Forest plots were used to display the mean difference or relative risk and 95% CI for each study, and the pooled summary treatment effect. The I^2 statistic was used to measure heterogeneity across studies.[84, 87] Heterogeneity was explored through subgroup analyses whereby results were stratified by the type of incretin-based therapy, CKD stage, and risk of bias. All data analyses were performed using R version 3.3.0 (R Foundation for Statistical Computing, Vienna, Austria). The study protocol is included as Appendix 2.A.

2.3 RESULTS

2.3.1 Included studies

A detailed summary of the identification and selection of studies is provided in Figure 2.1. Through our comprehensive search we identified 1619 unique citation records from which 13 studies were selected for inclusion in the meta-analysis.[40, 59, 60, 62-65, 80, 88-92] Only 11 of the 13 were full-text studies and subsequently included in the risk of bias assessment.[40, 59, 60, 63-65, 80, 88, 89, 91, 92] Authors of the full-text articles were contacted for additional outcome data; however, only one reply was

received.[92] Characteristics of the 13 studies included in this review are presented in Table 2.1. Study-level patient characteristics can be found in Appendix 2.C. Study interventions included DPP-4 inhibitors (sitagliptin, vildagliptin, linagliptin, saxagliptin, alogliptin, and gemigliptin) and GLP-1 receptor agonists (albiglutide and liraglutide). Most studies used placebo comparators[40, 59, 60, 62, 65, 80, 88-92] and those with active comparators[60, 63, 64, 90] were sulfonylureas (glipizide or glimepiride). None of the studies included metformin as a comparator due to the contraindication for creatinine clearances below 60mL/min/1.73m^2, despite the thoughts that these guidelines may be overly restrictive.[93] Two of the studies started the trial with a placebo comparator and switched to a sulfonylurea at week 12.[60, 90] Eleven of the included studies reported a change in A1C[40, 59, 60, 62-64, 80, 88-91] and 10 reported hypoglycemia[40, 60, 63-65, 80, 88-91], although definitions of hypoglycemia differed among studies (Appendix 2.D). All eleven full-text studies reported baseline demographic and anthropometric traits to be generally well balanced between groups.[40, 59, 60, 63-65, 80, 88, 89, 91, 92] Each study reported that participants were to continue their background anti-diabetic therapy while participating in the study.

2.3.2 Risk of Bias Assessment

A summary of study quality is presented in Figure 2.2. In accordance with the Cochrane Collaboration's tool for assessing risk of bias[84], an overall 'High risk of bias' classification was given to studies that had been scored as high risk for one or more of the six domains. High risk of bias indicates possible bias that weakens confidence in the results. An overall 'Low risk of bias' classification was assigned to studies that had been scored as low risk for all key domains, indicating that any possible bias is unlikely to alter the results. For a domain to be classified as 'Unclear risk of bias' there must have been insufficient information to allow judgment of either 'low risk' or 'high risk'. Nine studies reported adequate random sequence generation[40, 59, 60, 63-65,

[80, 88, 92] while only six reported adequate allocation concealment.[40, 59, 65, 80, 88, 92] All studies reported blinding of participants and personnel. Risk of attrition bias (incomplete outcome data) was detected in seven of the selected studies, earning the status of 'high risk'.[60, 63, 64, 80, 88, 89, 91] Funnel plots were constructed for primary outcomes; however, there were an inadequate number of included studies (<10) for either outcome to properly assess publication bias through a funnel plot, or employ other tests (e.g. Egger's regression test).[94] Therefore, publication bias cannot be excluded as a factor affecting the results of this meta-analysis.

2.3.3 Quantitative Analysis

Thirteen studies that included a total of 6848 patients with data for at least one outcome were included in the meta-analysis (Table 2.1).[40, 59, 60, 62-65, 80, 88-92] Eleven studies used a DPP-4 inhibitor as the intervention drug[59, 60, 62-65, 80, 89-92], nine of which were compared to a placebo.[59, 60, 62, 65, 80, 89-92] Two studies used GLP-1 receptor agonists as the intervention, both of which were compared to a placebo.[40, 88] Chan et al.[60] and Laakso et al.[90] started their trials with a placebo comparator and switched to glipizide and glimepiride, respectively, at week 12. In our analysis we included these studies with the DPP-4 inhibitor vs. placebo group using the 12-week endpoint values and with the DPP-4 inhibitor vs. sulfonylurea group using the 52-week endpoint values.

2.3.4 Primary Outcomes

Eleven studies reported change in A1C from baseline[40, 59, 60, 62-64, 80, 88-91]. The pooled mean difference of the change in A1C from baseline was significantly greater in the incretin-based group vs. placebo group (weighted mean difference (WMD) -0.64%; 95%CI -0.79, -0.48; $p<0.001$; I^2= 43%). In contrast, there was no difference for the change in A1C when DPP-4 inhibitors were compared to sulfonylurea (WMD -0.07; 95%CI -0.25, 0.12; $p=0.5$; I^2= 38%) (Figure 2.3).

The pooled relative risk of hypoglycemic events indicated a statistically significant risk for the incretin vs. placebo group (RR 1.38; 95%CI 1.01, 1.89; p=0.05), but no effect in the incretin vs. sulfonylurea (RR 0.24; 95%CI 0.03, 1.94; p=0.2). The incretin vs. placebo analyses for hypoglycemia exhibited no heterogeneity (I^2=0%) while the incretin vs. sulfonylurea analysis exhibited moderate heterogeneity (I^2=52%). One study[88] reported no incidents of hypoglycemia in either group Chan et al.[60] and Laakso et al.[90] were included in the incretin vs. sulfonylurea analysis for hypoglycemic events as the outcome was only reported following the comparator switch at the 52-week endpoint.

2.3.5 Secondary Outcomes

The pooled mean difference of the change in FPG between treatment and comparison groups was found to be significant in the incretin vs. placebo analysis (WMD -0.61 mmol/L; 95%CI -1.16, -0.06; p=0.03; I^2=43%), favouring incretins. In contrast, there was no difference for the change in FPG in the incretin vs. sulfonylurea analysis (WMD 0.28mmol/L; 95%CI -0.12, 0.68; p=0.2; I^2=0%), favouring the active comparator. (Table 2.2)

The pooled RR for all-cause mortality indicated no evidence of effect in either the incretin vs. placebo group (RR 1.21; 95%CI 0.64, 2.29; p=0.6; I^2=0%) or the incretin vs. sulfonylurea group (RR 0.70; 95%CI 0.32, 1.54; p=0.4; I^2=0%). Chan et al.[60] was included in the incretin vs. placebo incretin analysis using the 12-week values and in the incretin vs. sulfonylurea analysis using the 52-week values. The pooled RR for the ESKD, dialysis, or transplant outcome indicated no evidence of effect in the incretin vs. placebo analysis (RR 1.07; 95%CI 0.78, 1.47; p=0.7; I^2=0%);

however, only two studies[65, 80] reported this outcome. No studies in the incretin vs. sulfonylurea group reported the outcome.

Nine studies were included in the pooled RR for myocardial infarctions: six for incretin vs. placebo[40, 60, 65, 80, 90, 91] (RR 1.23; 95%CI 0.88, 1.73; p=0.2; I^2=0%) and three in the incretin vs. sulfonylurea analysis[63, 64, 90] (RR 1.02; 95%CI 0.21, 5.07; p=0.9; I^2=0%). Stroke was only reported as an outcome in three studies[65, 90, 91] and MACE was reported as an outcome in four[65, 90-92] of the thirteen studies. Forest plots for secondary outcomes are illustrated in the supplementary material (Appendix 2.E).

2.3.6 Subgroup Analyses

A subgroup analysis was conducted using the Risk of Bias categories. The results for mean change in A1C were found to be consistent across risk of bias categories. The results for hypoglycemia when incretins were compared with placebo gave significant evidence of effect for 'Low Risk' studies (RR 1.54; 95%CI 1.07, 2.22; p=0.02; I^2=0%) but no evidence of effect for 'High Risk' studies (RR 0.93; 95%CI 0.38, 2.27; p=0.9; I^2=18%). The results for hypoglycemia when incretins were compared with sulfonylureas were found to be consistent with those when all studies were combined. (Appendix 2.F)

A subgroup analysis comparing study data based on patient CKD Stage was also conducted. When incretins were compared with placebo for mean change in A1C, the results were found to be consistent with the overall results, significant evidence of effect, for all CKD Stages except the ESKD group (Stage 5). These results for incretins vs. active comparator for mean change in A1C were found to be consistent with those when CKD Stages were combined, as provided in each

individual study. The results for hypoglycemia when incretins were compared with placebo gave significant evidence of effect for the CKD Stage 3 group but showed no evidence of effect for the other CKD Stages. The results for hypoglycemia when incretins were compared with active comparator were found to be consistent with those when all studies were combined. (Appendix 2.G)

2.4 DISCUSSION

The results of this systematic review and meta-analysis of thirteen RCTs indicate that incretin-based therapies are effective in reducing glycated hemoglobin compared to placebo in patients with an eGFR <60mL/min/1.73m^2. Importantly, we found that neither DPP-4 inhibitors nor GLP-1 receptor agonists were associated with hypoglycemia compared to placebo or active comparator; however, there was a minimal increased risk of hypoglycemia when incretin-based agents were combined versus placebo. Furthermore, our findings regarding all-cause mortality, ESKD, and cardiovascular events are limited given the lack of events, short follow-up of included studies, and lack of formal adjudication of cardiovascular events within all studies.

Our analysis provides more precise evidence than previous studies[47, 48, 58] that incretin-based therapies are effective in reducing glycemia without substantially increasing the risk of hypoglycemia within a subgroup of patients with eGFR <60 mL/min/1.73m^2. Ramirez et al.[48] conducted a review to evaluate the use of DPP-4 inhibitors in patients with type 2 diabetes and CKD. However, the review only included six studies of patients with eGFR <60 mL/min/1.73m^2 and the results were not pooled.[48] Davis[47] conducted a systematic review to determine the efficacy, tolerability, and safety of DPP-4 inhibitors in patients with type 2 diabetes and renal impairment. The study indicated that DPP-4 inhibitors could be used, and well tolerated, in patients with type

2 diabetes and renal impairment, and were comparable to other oral therapies in terms of glycemic efficacy. Davis stated there was no clear indication of safety (renal toxicity, hypoglycemia) from the included long-term efficacy studies of people with CKD and suggested that dose adjustment of DPP-4 inhibitors is recommended in this subgroup to avoid drug accumulation.[47] Cooper et al.[95] conducted a pooled analysis of large clinical trials to investigate the renal safety of linigliptin in patients with type 2 diabetes. Their study found that linigliptin was not associated with increased risk of kidney disease; however, it did not assess other safety measures, such as hypoglycemia or cardiovascular events. Our meta-analysis expands on these studies by evaluating cardiovascular outcomes in this clinically important subgroup of patients, which has not been previously reported.

Important questions remain regarding the safety of incretin-based therapies in terms of cardiovascular events in patients with CKD. The SAVOR TIMI 53[65] and EXAMINE[92] trials included in this study, reported CKD subgroups for cardiovascular outcomes; however, patient-level data was unavailable for all outcomes. Additional data from other ongoing trials should provide a more precise assessment of the risks of cardiovascular outcomes, particularly in patients with CKD. The CAROLINA trial[96] is an ongoing study comparing linagliptin and glimepiride with respect to cardiovascular outcomes in patients with type 2 diabetes. Given that change in eGFR from baseline is reported as a secondary outcome, special patient groups, such as CKD, may be reported in this and other trials providing additional data for future meta-analyses.

Although our review is the most comprehensive meta-analyses to date regarding the safety and efficacy of incretin-based therapies aimed at patients with CKD there are limitations that should be considered when interpreting the results. First, there was variation among studies in the

intervention drug used. Although the effective dosage, metabolism and excretion differ among incretin therapies, they are understood to be similar in terms of their efficacy in A1C reduction and safety and tolerability profiles.[97-101] Dose adjustments are not required for CKD patients taking linagliptin or albiglutide.[54, 102] However, studies with shorter follow-up time may favor agents with less glycemic durability. Additionally, the relatively small number of studies available limited our ability to account for between-study variation, particularly in the incretin vs. active comparator group. The wide confidence intervals for effects on hypoglycemia and mortality prevent us from making definition conclusions. Although two abstracts that contained sufficient results were included in this meta-analysis[62, 90], a number of studies were identified in our search that met the primary inclusion criteria, but were eliminated during the screening process due to limited availability of results (e.g. abstracts without outcomes of interest, trials in progress without any published results, etc.). As the results of these studies become available and further research is conducted on the use of incretins in patients with CKD, an updated meta-analysis could provide additional power. There was considerable heterogeneity between the studies included in some of the analyses, particularly those comparing incretins and other anti-diabetic therapies (sulfonylureas). Although the different anti-diabetic therapies may explain this heterogeneity, there were not enough studies to conduct informative subgroup analyses or meta-regression based on different active comparators. Seven of the included studies were given a grade of 'high risk' for the attrition bias (incomplete outcome data). This was largely due to the lack of information provided by authors on the amount or imbalance of missing data and how it was handled in the analysis. This meta-analysis carries a risk of reporting bias as not all studies reported each outcome of interest. Although a number of the studies had registered protocols, most reported on our primary outcomes while very few studies reported the cardiovascular outcomes. Finally, we were

unable to completely separate all studies into explicit groups based on CKD Stage, which may have provided valuable information regarding the differences in the safety and efficacy of incretins among patients with moderate versus severe renal impairment. However, a subgroup analysis was conducted based on the information available.

Since the publication of this study in 2016, there have been three primary systematic reviews and meta-analyses assessing cardiorenal outcomes with GLP-1 receptor agonists: Sattar et al.[103], Kristensen et al.[68], and Giugliano et al.[104] While none of these studies focused explicitly on patients with chronic kidney disease, they all included a form of broad composite kidney outcome. Their conclusions were unanimous that GLP-1 receptor agonists have beneficial effects on cardiovascular outcomes (MACE), all-cause mortality, and kidney outcomes (e.g. no progression of diabetic renal disease) in patients with type 2 diabetes.[68, 103, 104]

This systematic review and meta-analysis focused on the safety and efficacy of incretin-based therapies as anti-diabetic agents when compared to placebo or active comparators in patients with moderate or severe renal impairment. Our meta-analysis confirms several clinically relevant effects of the incretin-based therapies, including effective reduction of glycemia without a substantial increased risk of hypoglycemia within a clinically important subgroup of patients. However, given the wide confidence intervals for effects on hypoglycemia and mortality, we are unable preclude definition conclusions. Uncertainty still exists regarding the effects of DPP-4 inhibitors and GLP-1 receptor agonists on the risk of all-cause mortality and other long-term outcomes including cardiovascular disease and ESKD. Despite the number of studies published, more data is needed to precisely quantify associations with all-cause mortality, cardiovascular

events, and ESKD. Future collaborative meta-analyses, particularly those that incorporate subgroup analysis based on CKD stage or patient level analysis, would help to further characterize the safety and efficacy of incretin-based therapies in patients with type 2 diabetes and CKD.

Table 2.1 Characteristics of trials included in the systematic review and meta-analysis

Study	Study Size	Length of Follow-up (weeks)	Intervention*	Comparator*	A1C	FPG	Hypo§	Death	MI	Stroke	MACE§	ESKD
Arjona Ferreira 2013a[63]	n=129	54	Sitagliptin 25mg daily	Glipizide Initiated at 2.5mg daily with titrated to a max of 10mg twice daily	X	X	X	X	X			
Arjona Ferreira 2013b[64]	n=423	54	Sitagliptin Mod: 50mg/day (two 25mg tablets) Sev: 25mg/day (one 25mg tablet)	Glipizide starting with dose of 2.5mg/day, titrated to a max of 20mg/day	X	X	X	X	X			
Barnett 2013[59]	n=65 subgroup	24	Linagliptin 5mg qd	Placebo	X							
Chan 2008[60]	n=91	52	Sitagliptin Mod: 50mg qd Sev: 25mg qd	Placebo switched to Glipizide week 12	X	X	X	X	X			
Davies 2016[40]	n=279	26	Liraglutide 1.8mg: initiated 0.6mg/day and increased by 0.6mg/day each week	Placebo	X	X	X	X	X			
Idorn 2016[88]	n=47	12	Liraglutide titrated dose of 0.6mg, 1.2mg or 1.8mg	Placebo	X		X	X				
Kothny 2012[89]	n=525	52	Vildagliptin 50mg qd	Placebo	X		X	X				
Laakso 2013[90]	n=235	52	Linagliptin 5mg qd	Placebo switched to glimepiride (1-4mg qd) week 12	X	X	X	X	X	X	X	

Study	Study Size	Length of Follow-up (weeks)	Intervention*	Comparator*	A1C	FPG	Hypo§	Death	MI	Stroke	MACE§	ESKD
McGill 2013[91]	n=133	52	Linagliptin 5mg/ day	Placebo	X	X	X	X	X	X	X	
Nowicki 2011[80]	n=170	52	Saxagliptin 2.5mg	Placebo	X	X	X	X	X			X
Scirica 2014[65, 105]	n=2576 subgroup	109 (median)	Saxagliptin 2.5mg daily	Placebo			X		X	X	X	X
White 2013[92, 106]	n=1585 subgroup	72 (median)	Alogliptin Mod: 12.5mg Sev: 6.25mg	Placebo							X	
Yoon 2015[107]	n=132	12	Gemigliptin 50mg	Placebo	X							

*All treatments and comparators were in addition to anti-hyperglycemic background therapy. §Outcome definitions are provided in the supplementary material (Appendix 2.D).
Mod = eGFR <60 mL/min/1.73m^2, Sev = eGFR <30 mL/min/1.73m^2, A1C = glycated hemoglobin, FPG = fasting plasma glucose, Hypo = hypoglycemia, Death = all-cause mortality, MI = myocardial infarction, MACE = major adverse cardiovascular events, ESKD = end stage kidney disease.

Table 2.2 Summary of meta-analysis results for secondary analyses

Comparison	Number of Events	Number of Patients	Effect Size	I^2	Number of Studies
Change in FPG from baseline			WMD [95% CI]		
Incretin vs. Placebo	N/A	828	-0.61 [-1.16, -0.06]	43%	5
Incretin vs. Active Comparator	N/A	677	0.28 [-0.12, 0.68]	0%	4
All-cause Mortality			RR [95% CI]		
Incretin vs. Placebo	40	1439	1.21 [0.64, 2.29]	0%	7
Incretin vs. Active Comparator	26	642	0.70[0.32, 1.54]	0%	3
Stroke			RR [95% CI]		
Incretin vs. Placebo	54	2944	0.99 [0.58, 1.69]	0%	3
Incretin vs. Active Comparator	N/A	N/A	N/A	N/A	0
Myocardial Infarction			RR [95% CI]		
Incretin vs. Placebo	136	3482	1.23 [0.88, 1.73]	0%	6
Incretin vs. Active Comparator	4	786	1.02 [0.21, 5.07]	0%	3
MACE			RR [95% CI]		
Incretin vs. Placebo	553	4509	1.02 [0.86, 1.20]	0%	4
Incretin vs. Active Comparator	N/A	N/A	N/A	N/A	0
ESKD/Dialysis/Transplant			RR [95% CI]		
Incretin vs. Placebo	154	2746	1.07 [0.78, 1.47]	0%	2
Incretin vs. Active Comparator	N/A	N/A	N/A	N/A	0

*CI = confidence interval; MD = mean difference; N/A = not applicable; RR = relative risk

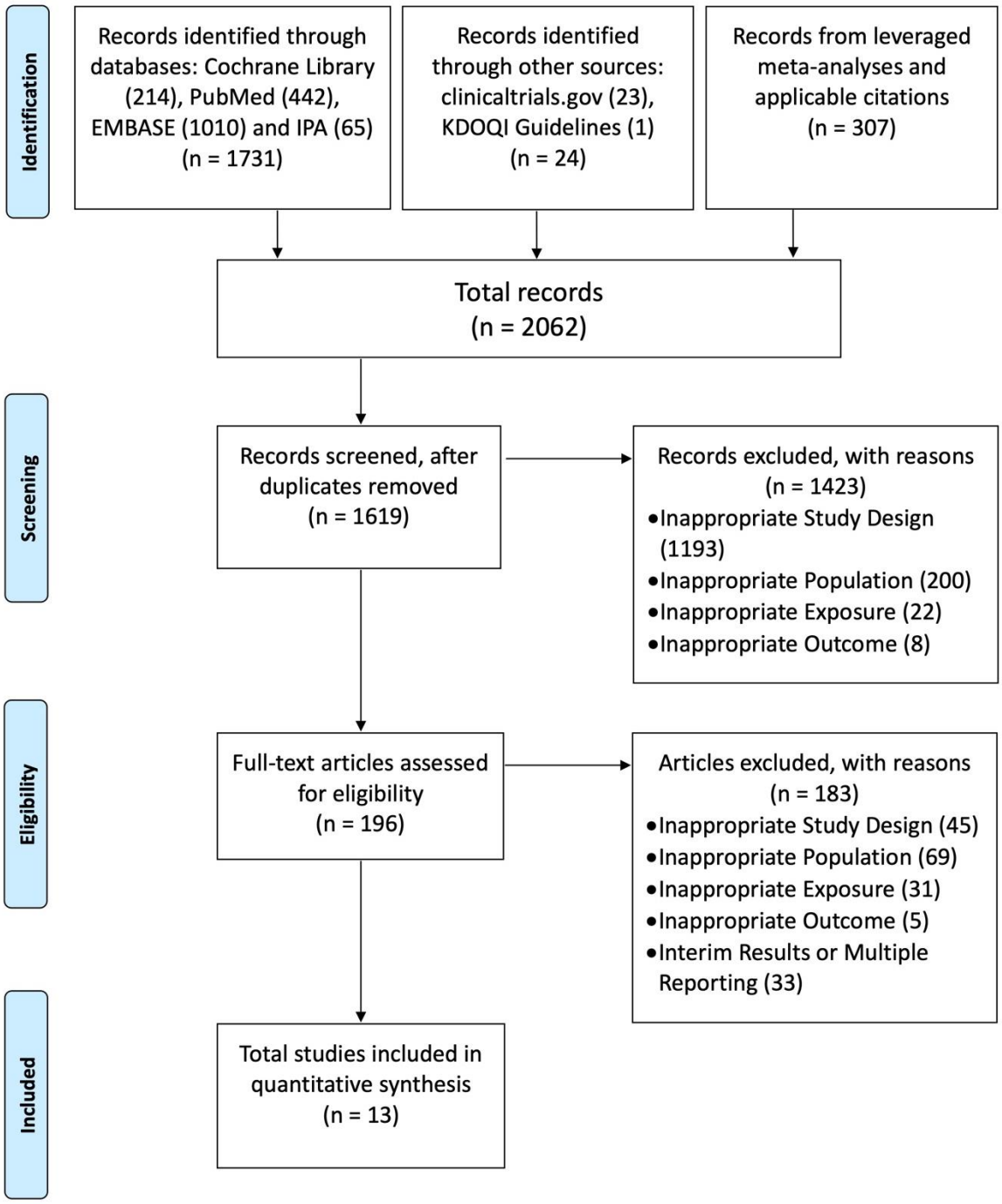

Figure 2.1: Systematic review study flow diagram

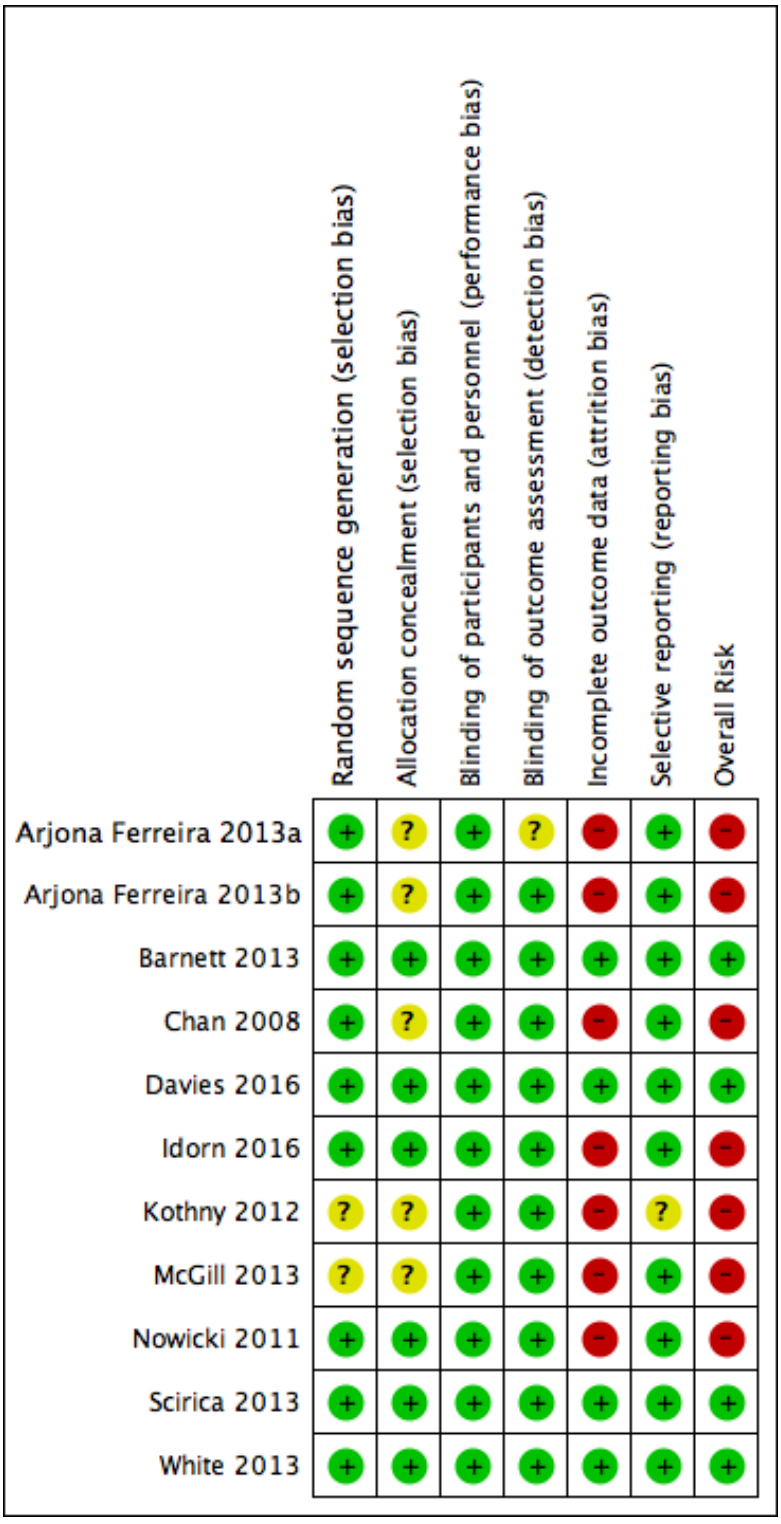

Figure 2.2: Systematic review risk of bias summary for included studies

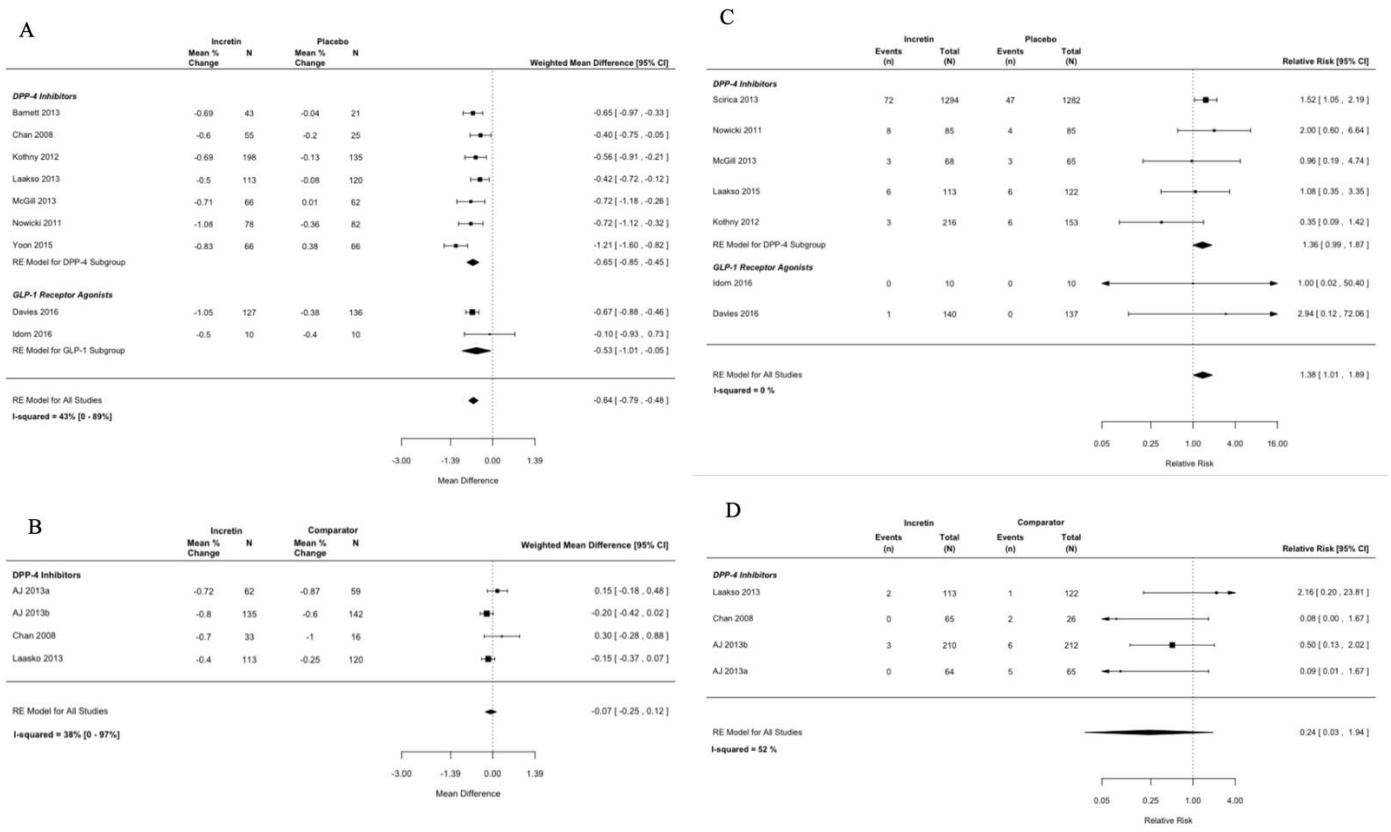

Figure 2.3: Forest plots for relative treatment effect of incretins versus placebo and active comparators for primary outcomes: A) Change in A1C (%) for Incretin vs. Placebo B) Change in A1C (%) for Incretin vs. Active Comparator C) Hypoglycemia for Incretin vs. Placebo D) Hypoglycemia for Incretin vs. Active Comparator. Weights are from random effects analysis.

Chapter 3: Risk of all-cause mortality and cardiovascular morbidity associated with DPP-4 inhibitor therapies in metformin users with chronic kidney disease: a population-based cohort study

3.1 INTRODUCTION

In 2015 the number of adults (aged 20–79 years) with diabetes worldwide was estimated at 415 million which as of 2021 had increased to 537 million adults worldwide.[6, 108] With increasing prevalence, diabetes has become one of the biggest global health concerns. Diabetes is associated with a variety of complications including macrovascular complications (eg. acute coronary syndrome, stroke) and microvascular complications (eg. retinopathy, neuropathy, and nephropathy). Given that diabetes is the most common underlying cause of chronic kidney disease, treatment and prevention of complications of diabetes are of the utmost importance.[6, 8, 58, 109] Several clinical practice guidelines (e.g. KDOQI Guidelines, Diabetes Canada 2018 Guidelines) recommend a target A1C of less than 7% in order to prevent or delay progression of the microvascular complications of diabetes, including nephropathy.[4, 69] Type 2 diabetes mellitus is the most common type and is associated with insulin resistance and compromised insulin secretion.[6, 8] Along with general lifestyle recommendations (weight control, physical activity, diet), a number of treatment options are available for type 2 diabetics. The prevention and delay of type 2 diabetes has been shown to reduce rates of cardiovascular disease and renal failure.[54, 110]

Metformin is the most well-established medication for type 2 diabetes and is generally recommended as the primary pharmacological agent.[54, 111] Metformin had previously been cautioned for use in patients with chronic kidney disease (eGFR <60 mL/min/1.73m^2); however,

recent guidelines recommend use in patients with T2DM, CKD and an eGFR >30 mL/min/1.73m^2.[10, 22, 54, 76, 77] As type 2 diabetes progresses, an antidiabetic agent, in addition to or instead of metformin, will likely be required to meet glycemic targets, which can include a sulfonylurea, an incretin agent, TZD, insulin, or another second-line therapy.[54, 101] Incretin agents, DPP-4 inhibitors and GLP-1RAs, arrived on the North American market in the mid-2000s and have since been recommended as second-line or third-line agents for the treatment of type 2 diabetes by the CDA 2013 Clinical Practice Guidelines, the Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes, and the Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology.[54, 76, 77] While several studies have indicated that incretin agents display reduction of A1C and low incidence of hypoglycemia, there is limited evidence regarding the comparative safety of antidiabetic agents in a real setting.[99, 112]

Several randomized control trials have aimed to characterize the safety and efficacy of incretin agents in patients with type 2 diabetes, including the LIRA-RENAL, and SAVOR-TIMI trials.[40, 61, 65, 105] However, the large clinical trials tend to focus on all type 2 diabetes patients as their study population, evaluating renal function as a subgroup analysis.[105, 106] Liu et al.[113] conducted a systematic review and meta-analysis assessing the impact of incretins on mortality in patients with type 2 diabetes. Additionally, they reported composite cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stoke) but did not report outcomes based on kidney function.[113] There are few studies that focus on incretin therapies in patients with moderate to severe CKD (Stages 3A, 3B, 4 and 5).[1] We performed an exploratory analysis to evaluate the risk of all-cause mortality and major adverse cardiovascular events with initiation of DPP-4

inhibitor therapy when compared to other anti-diabetic agents, as a second-line agent, in individuals with type 2 diabetes and moderate to severe CKD.

3.2 METHODS

3.2.1 Study Design

We conducted a cohort study using the UK Clinical Practice Research Datalink (CPRD) database. The CPRD includes primary healthcare data from general practitioner Electronic Health Record (EHR) systems in the United Kingdom. CPRD GOLD is a database of anonymized medical records that includes patient demographic information, clinical events, referrals, immunization records, diagnostics, lifestyle information, and other routine care events that participating general practitioner records in the EHR. A subset of patients included within the CPRD GOLD was linked to Hospital Episode Statistics (HES) and the Office for National Statistics (ONS), the latter providing death certificate records.[114]

This study is a pre-specified secondary analysis of metformin users from the primary study who met criteria for chronic kidney disease.[115] The objective is to comparatively assess rates of all-cause mortality and cardiovascular outcomes for 2nd-line DPP-4 inhibitor users compared to users of other antidiabetic medications in in a defined subgroup: patients with type 2 diabetes and chronic kidney disease. The source database provides population data in a timeframe of 2001 to 2012. The analysis was an a priori specified secondary analysis of a predefined subgroup of patients with CKD (ISAC protocol 13_100R).

The primary study[115] compared all-cause mortality and major adverse cardiovascular events (MACEs) among new metformin users who initiated a second antidiabetic agent, either a DPP-4

inhibitor, GLP-1RA, sulfonylurea (SU), TZD, or insulin. The data used was drawn from the CPRD database and included a cohort of 38,233 metformin monotherapy users who started a second antidiabetic agent after January 1, 2007. There was a significant 42% reduction in mortality with the initiation of a DPP-4 inhibitor when compared to an SU. 2nd-line DPP-4 inhibitor use was also associated with a significant reduction in MACE, when compared to 2nd-line SU use. At the time this study was conducted (2016), SUs were the most commonly prescribed 2nd-line antidiabetic agent, representing about 70% of the studied cohort. The primary study[115] received approval from the Health Research Ethics Board at Memorial University.

3.2.2 Study population

The source population for this study consisted of 165,308 patients identified in the CPRD-GOLD database that received a new prescription for any antidiabetic agent between January 1, 2001 and December 31, 2012 with a minimum of 12 months of up-to-standard medical history (based on CPRD quality indices). New user status was defined as patients with no prescription record for any antidiabetic drug for 1-year prior to the initial antidiabetic agent prescription. The study cohort included patients from the source population who were metformin monotherapy users, at least 30 years of age (to limit misclassification of type 2 diabetes), and met criteria for CKD. CKD status was defined by an individual having at least two eGFR values <60mL/min/1.73m^2 at least 90-days apart prior to the index date (the date at which they initiated their second-line agent). Patients with CKD were further classified by Stages (3A, 3B, 4 and 5) per the National Kidney Foundation's 2002 K/DOQI Clinical Practice Guidelines Chronic Kidney Disease.[116] Second-line agents included the primary exposure group of interest, DPP-4 inhibitors, as well relevant comparators: sulfonylureas, glucagon-like peptide-1 receptor agonists (GLP-1RA), insulin, TZDs, and 'other', which included α-glucosidase inhibitors (eg. acarbose) and meglitinides (repaglinide and

nateglinide). A cut-off date of January 1, 2007 was used as incretin therapies were first introduced to the pharmaceutical market in November 2006.

3.2.3 Exposure definitions

Patients were excluded if they met any of the following exclusion criteria: 1) pregnant, diagnosed with gestational diabetes or polycystic ovarian syndrome anytime within the study period; 2) date of second anti-diabetic agent occurred before January 1, 2007 or no second agent prescribed; 3) first anti-diabetic agent not metformin; 4) eGFR ≥60 mL/min/1.73m^2 or no reported serum creatinine tests (Figure 3.1).

3.2.4 Outcome definitions

Our co-primary outcomes were risk of all-cause mortality and major adverse cardiovascular events (3-point MACE: composite of non-fatal stroke, non-fatal myocardial infarction (MI), and cardiovascular disease (CVD)). Subgroup analyses were performed on the complete study cohort in the strata of interest to assess potential effect modification: age (<65 years and ≥65 years), sex (male and female), and eGFR (<45 and 45-60 mL/min/1.73m^2). Secondary outcomes included individual components of the MACE composite outcome. Cardiovascular outcomes were only available through data linked to HES hospital records and death certificates (ONS mortality data). Therefore, this sub-cohort was used in the assessment of cardiovascular (secondary) outcomes only.

3.2.5 Statistical analysis

We used appropriate descriptive statistics to identify the baseline characteristics of the study population at the time the second-line agent was initiated. Values were displayed as percentages for categorical variables and mean (SD) for continuous variables. Values for baseline

characteristics were based on the most recent value prior to the index date, or if missing, the most recent value after the index date was used. We used multivariable Cox hazard regression models to assess the association between exposure to a DPP-4 inhibitors compared to SU, GLP-1RA, insulin, TZDs, and 'other' (α-glucosidase inhibitors and meglitinides) as second-line agents. The study entry date was defined as the start of metformin monotherapy. The cohort entry or index date was defined as the start date of a second antidiabetic agent, as a switch from or as an add-on to the initial metformin monotherapy. We censored follow-up time for each patient at the earliest of either: date of exposure to a third antidiabetic agent, emigration from a CPRD practice, or end of study period. Analyses were performed on an intention-to-treat basis, according to the assignment of second-line antidiabetic agent, regardless of subsequent changes in antidiabetic therapies. To adjust for potential confounding, we incorporated clinically relevant covariates into our analysis as independent baseline variables, including: age, sex, smoking status, duration of diabetes, A1C, and others (Appendix 3.A). These were adjusted for in the multivariable Cox proportional hazard regression models. We reported results as hazard ratios with 95% confidence intervals (CI) and considered a p-value of <0.05 statistically significant. All data analyses were conducted using RStudio version 0.99.902 (RStudio: Integrated Development for R. RStudio, Inc., Boston, MA).

3.3 RESULTS

New users of metformin, 38,283 individuals, were identified as from the CPRD Gold Source Population (n=165,308). From the new metformin user population, we identified 7,773 patients with CKD prior to initiating their second-line agent [1,023 (13%) DPP4i, 5,688 (73%) SU, 70 (1%) GLP-1RA, 161 (2%) insulin, 754 (10%) TZD, and 77 (1%) other]. The 7,773 new metformin users with CKD comprised the overall cohort for our study (Figure 3.1).

Baseline characteristics were identified in new-users of second-line antidiabetic agents in a cohort of metformin users with CKD (Table 3.1). There were 6413 patients with Stage 3A (eGFR 45-<60); 1235 with Stage 3B (30-<45); 113 with Stage 4 (15-<30); and 12 with Stage 5 (<15) CKD. Mean age was 71 years, 46% were male, mean A1C was 8.3%, mean follow-up was 1.5 years, mean duration of diabetes prior to cohort entry was 3.3 years, and no difference in smoking status was identified. Metformin users that initiated a DPP-4 inhibitor as second-line therapy were on average younger (70 vs. 72 years), had more females (56% vs. 54%), had lower A1C (8.1% vs. 8.3%), had a higher eGFR (53 vs. 51 mL/min/1.73m^2), and a lower Charlson Comorbidity Index (CCI) score (88% vs. 86% with score of 1), compared to those with SU second-line therapy.

There was a total of 705 deaths during the study period. All-cause mortality rates were 22.1 deaths/1000 person-years for DPP-4 inhibitor initiators; 39.9 deaths/1000 person-years for SU; 141.6 deaths/1000 person-years for insulin; 7.2 deaths/1000 person-years for GLP-1RA; 14.9 deaths/1000 person-years for TZD; and, 149.7 deaths/1000 person-years for other (Table 3.2). The adjusted hazard ratio for mortality, when compared to SU initiators, was 0.74 [95%CI 0.52-1.04, p=0.08] among second-line DPP-4 inhibitor initiators; 0.58 [95%CI 0.08-4.13] among GLP-1RA initiators; 2.60 [95%CI 1.89-3.56] among insulin initiators; and 0.77 [95%CI 0.52-1.13] among TZD initiators. No significant subgroup treatment effects were observed for the strata (age, sex, and eGFR) that were hypothesized to have a potential effect modification on all-cause mortality. All interaction terms had a p-value >0.15 (Table 3.3).

We identified 4,650 patients with CKD prior to initiating their second-line agent in the HES/ONS linked data and noted a total of 481 MACE occurrences within this sub-cohort during the study period. Cardiovascular events, including MACE and other secondary outcomes, are displayed in Table 3.4. Incident rates for MACE were 55.3 deaths/1000 person-years for DPP-4 inhibitor; 56.8 deaths/1000 person-years for SU; 144.8 deaths/1000 person-years for insulin; 14.7 deaths/ 1000 person-years for GLP-1RA; 33.2 deaths/ 1000 person-years for TZD; and, 100.2 deaths/ 1000 person-years for other antidiabetic agents. The adjusted hazard ratio for MACE, when compared to SU initiators, was 1.07 [95% CI 0.78-1.47, p-value >0.05] among second-line DPP-4 inhibitor initiators; 0.43 [95% CI 0.06-3.10, p >0.05] among GLP-1RA initiators; 2.33 [95% CI 1.54-3.55, p <0.001] among insulin initiators; 0.92 [95% CI 0.66-1.29, p >0.05] among TZD initiators; 1.23 [95% CI 0.63-2.41, p >0.05] among initiators of other second-line agents. Subgroup analyses were attempted for each of the secondary outcomes. Interaction terms included age, sex, and eGFR in the regression models for MACE, MI, stroke, and cardiovascular death. There was a significant interaction found for sex in the MACE and stoke outcomes; however, these analyses yielded very few events and therefore any interaction found would have very little confidence.

3.4 DISCUSSION

The findings of our cohort study of new-users of metformin with CKD showed second-line DPP-4 inhibitor therapy was associated with a non-significant reduction in the risk of all-cause mortality when compared to SUs and TZDs. The adjusted HRs illustrated a protective effect (72% reduction in all-cause mortality) when second-line DPP-4 inhibitor therapy was compared to second-line insulin use. DPP-4 inhibitors were non-inferior to SUs in the risk of MACE, while GLP-1RAs demonstrated a non-significant reduction. There was a non-significant reduction in MI, stroke and cardiovascular death for incretin therapies when compared to SUs; however, the cardiovascular

outcomes (Table 3.4) were limited by small number of events. Once again, there was a protective effect illustrated by the adjusted HRs for all cardiovascular outcomes when second-line DPP-4 inhibitor therapy was compared to second-line insulin use. These findings are consistent with the primary large scale cohort previously reported.[115] Gamble et al. found that second-line DPP-4 inhibitor use was associated with a reduction in all-cause mortality when compared with second-line SU, insulin, or TZD use.[115] Additionally, the non-inferior DPP-4 inhibitor therapy results for both mortality and MACE outcomes are consistent with other large cardiovascular outcome trials, including the SAVOR-TIMI 53 [105], EXAMINE[117], and TECOS trials[118].

Current guidelines recommend the use of metformin with caution in patients with renal impairment when the eGFR is <60 mL/min/1.73m^2 and advise against its use when eGFR is <30 mL/min/1.73m^2.[54] The addition of, or switch to, incretin therapy represents one of the limited treatment options for patients with type 2 diabetes and moderate to severe renal impairment (eGFR is <60 mL/min/1.73m^2), although some drugs within the class may require downward dose adjustments.[54, 69] Therefore, understanding the safety and efficacy of incretin therapies as it related to reduced renal function is of great importance.

Several trials assessing the safety and efficacy of DPP-4 inhibitors in type 2 diabetics have shown evidence of reduced A1C without increasing risk of hypoglycemia when compared to other therapies.[101, 119, 120] Fewer studies have assessed safety and efficacy in patients with reduced renal function. A number of clinical trials have attempted to characterize the safety and efficacy of incretin agents in patients with type 2 diabetes, analyzing patients with renal impairment as a subgroup.[40, 61, 65, 105] Our cohort was comparable in size to these trials in terms of CKD subgroups.

The SAVOR-TIMI 53 trial analyzed cardiovascular outcomes in type 2 diabetics with renal impairment receiving either saxagliptin, a DPP-4 inhibitor, or placebo.[65, 105] Within the stratified cohort, 2,240 patients with T2DM had moderate renal impairment (30–50 mL/min/1.73m^2) and another 336 had severe renal impairment (<30 mL/min/1.73m^2). Death from cardiovascular causes (reported as 2 year survival rate) in saxagliptin-users was slightly reduced (non-significant) when compared to placebo in both moderate and severe renal impairment patient groups (moderate CKD: 11.0% saxagliptin vs. 11.5% placebo; severe CKD: 14.7% saxagliptin vs. 17.2% placebo). This is in keeping with our identified protective effect of DPP-4 inhibitors. All-cause mortality was not reported for the renal subgroups. The SAVOR-TIMI 53 trial[105] compares a DPP-4 inhibitor to placebo, whereas our study uses other antidiabetic agents as comparators. Similarly, the TECOS trial investigated the effect of sitagliptin or placebo when added to existing therapy in patients with diabetes and mild to severe CKD. This study's assessment of cardiovascular outcomes - which included CV deaths, MI, stroke, and hospitalization for unstable angina and heart failure - observed more frequent CV events in patients with lower levels of kidney function, yet no clinically significant effect of the sitagliptin treatment on CV outcomes.[118, 121]

Our study expands on a larger population using a robust database to identify a population with an adequate number of outcomes for all-cause mortality, specifically in DPP-4 inhibitor users. We identify a clinically relevant population of new users of metformin who developed CKD, as the rate of diabetes-related kidney disease increases.[6, 54] As type 2 diabetes progresses and patients with renal impairment switch from or add-on to metformin for glycemic control, the safety and efficacy of second-line agents is of increasing concern.

3.4.1 Limitations

Despite its strengths, including use of a large representative data set that is considered valid and reliable, there are limitations of this study that must be addressed. While our analysis adjusted for a range of demographic and clinical characteristics, as with other observational studies we are unable to dismiss the possibility of confounding by unknown or unmeasured variables not adjusted for in our model. Second, we did not account for potential changes in antidiabetic treatment following the initiated second-line therapy. Third, there were a small number of events (deaths) in some of the second-line agent groups, particularly for the CV death subgroup analysis, limiting our interpretation of the adjusted hazards ratios presented. Fourth, an assumption was made for the purposes of our statistical model and analysis that patients adhered to medications and took them as prescribed. Fiftly, our patient population was limited to those who first initiated metformin monotherapy and started a second agent, as a switch to or add-on to metformin after January 1, 2007. While this patient population was defined to reflect the current guidelines and pharmaceutical market, it may limit our study's generalizability. Finally, a short follow-up period of 1.5 years is not long enough to thoroughly observe the outcomes of all-cause mortality and MACE.

3.4.2 Conclusions

In conclusion, a large database of patients with type 2 diabetes and chronic kidney disease was used to compare second-line antidiabetic agents, defined as an add-on to or switch from metformin primary therapy. Second-line DPP-4 inhibitor therapy was not associated with a significant reduction in mortality compared to sulfonylureas or TZDs but showed a protective effect compared to insulin in patients with CKD. While more data is needed to precisely quantify associations with mortality as well as other outcomes, future studies could consider risk of cardiovascular outcomes.

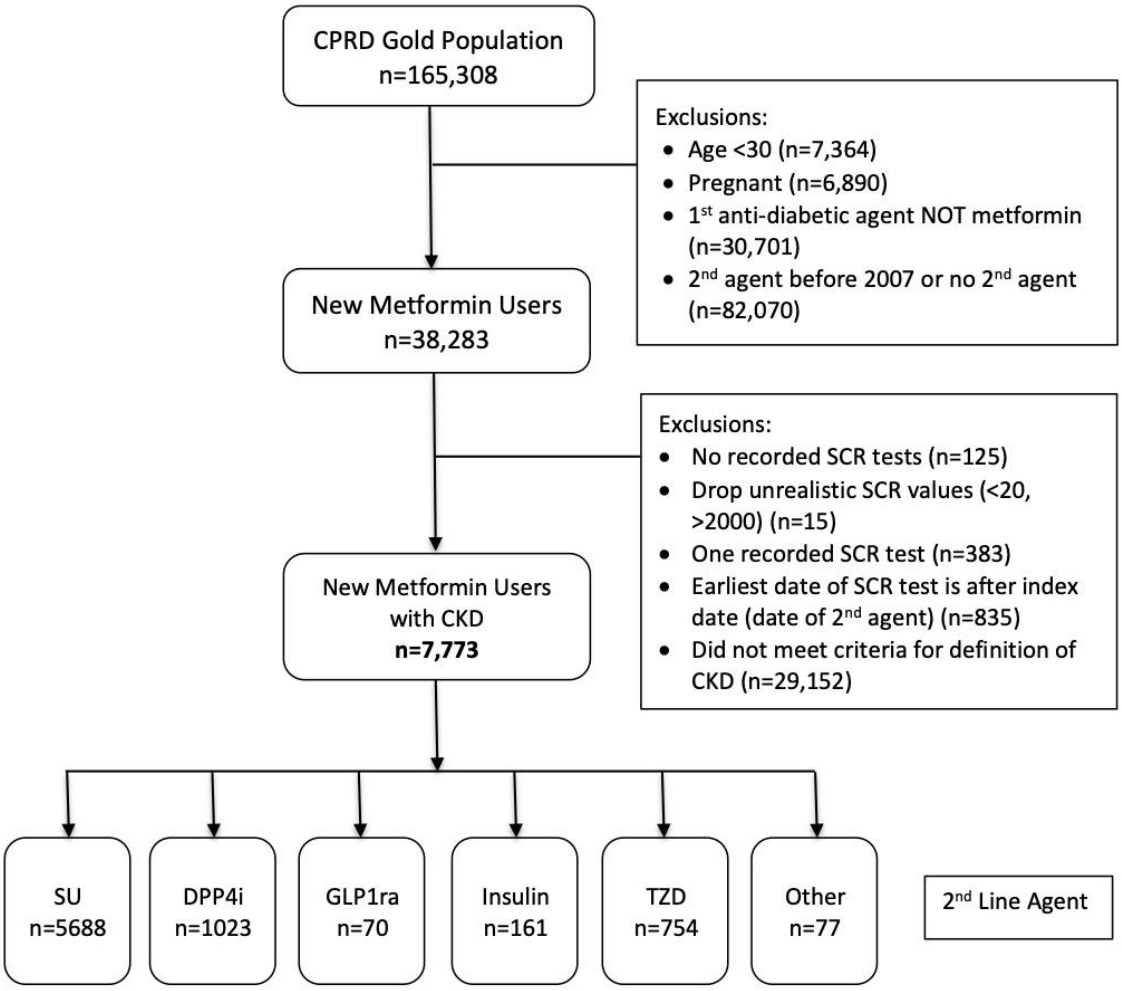

Figure 3.1 Flow diagram indicating patient cohort derived from CPRD Gold patient population.

CPRD = Clinical Practice Research Datalink; SCR = serum creatinine; SU = Sulfonylurea; DPP4i = Dipeptidyl peptidase-4 inhibitors; GLP1ra = glucagon-like peptidase-1 receptor agonist; TZD = thiazolidinedione

Table 3.1 Baseline characteristics of new-users of second-line antidiabetic therapies in a cohort of metformin users with CKD (n=7,773)

Factor	SU n=5,688	DPP4i n=1,023	GLP1ra n=70	Insulin n=161	TZD n=754	Other n=77	Total Cohort n=7,773	p-value
Age in years at Index, mean (SD)	72 (10)	70 (10)	61 (9)	72 (10)	68 (10)	68 (12)	71 (10)	<0.001
Male, n (%)	2606 (46%)	452 (44%)	22 (31%)	92 (57%)	352 (47%)	29 (38%)	3553 (46%)	<0.01
Smoking Status, n (%)								0.18
Current	474 (8%)	77 (8%)	5 (7%)	20 (12%)	67 (9%)	10 (13%)	653 (8%)	
Former	2161 (38%)	408 (40%)	30 (43%)	57 (35%)	264 (35%)	30 (39%)	2950 (38%)	
Non	2147 (38%)	376 (37%)	21 (30%)	50 (31%)	310 (41%)	27 (35%)	2931 (38%)	
Unknown	906 (16%)	162 (16%)	14 (20%)	34 (21%)	113 (15%)	10 (13%)	1239 (16%)	
Diabetes duration in years, mean (SD)	3.3 (2.4)	4.0 (2.6)	3.8 (2.4)	2.9 (2.5)	2.9 (2.1)	2.7 (2.0)	3.3 (2.4)	<0.001
Charlson Comorbidity Index, n (%)								<0.001
1	4902 (86%)	905 (88%)	69 (99%)	126 (78%)	707 (94%)	68 (88%)	6777 (87%)	
2	554 (10%)	97 (9%)	NR	23 (14%)	32 (4%)	7 (9%)	713 (9%)	
3+	232 (4%)	21 (2%)	NR	12 (7%)	15 (2%)	NR	283 (4%)	
HbA1c (%), mean (SD)	8.3 (1.8)	8.1 (1.4)	8.0 (2.1)	8.9 (2.7)	8.2 (1.4)	8.7 (2.0)	8.3 (1.7)	<0.001
eGFR (mL/min/1.73m^2), mean (SD)	51 (7.7)	53 (6.4)	53 (6.2)	50 (8.9)	53 (7.1)	50 (8.0)	52 (7.5)	
CKD Stage, n (%)								<0.001
3a	4609 (81%)	899 (87%)	60 (86%)	122 (76%)	667 (88%)	56 (73%)	6413 (83%)	
3b	977 (17%)	120 (12%)	10 (14%)	33 (20%)	76 (10%)	19 (25%)	1235 (16%)	
4	93 (2%)	NR	NR	NR	10 (1%)	NR	113 (1%)	
5	9 (<1%)	NR	NR	NR	NR	NR	12 (<1%)	
Socioeconomic Indicator (IMD)*, n (%)								<0.001
1 = Least Deprived	742 (13%)	112 (11%)	9 (13%)	21 (13%)	103 (14%)	6 (8%)	993 (13%)	
2	847 (15%)	122 (12%)	NR	22 (14%)	109	6	1108 (14%)	
3	735 (13%)	100 (10%)	12 (17%)	25 (16%)	88	9	969 (12%)	
4	727 (13%)	107 (10%)	NR	12	87	13	950 (12%)	
5 = Most Deprived	544 (10%)	112 (11%)	9 (13%)	22 (14%)	88 (12%)	11 (14%)	786 (10%)	

Factor	SU n=5,688	DPP4i n=1,023	GLP1ra n=70	Insulin n=161	TZD n=754	Other n=77	Total Cohort n=7,773	p-value
Unknown	2093 (37%)	470 (46%)	34 (49%)	59 (37%)	279 (37%)	32 (42%)	2967 (38%)	
BMI (kg/m^2), n (%)								<0.001
<30	2660 (47%)	364 (36%)	NR	62 (39%)	287 (38%)	24 (31%)	3398 (44%)	
30 to <40	2561 (45%)	516 (50%)	26 (37%)	76 (47%)	383 (51%)	44 (57%)	3606 (46%)	
≥40	398 (7%)	138 (13%)	43 (61%)	14 (9%)	81 (11%)	9 (12%)	683 (9%)	
Missing	69 (1%)	5 (<1%)	NR	9 (6%)	NR	NR	86 (1%)	
Systolic Blood Pressure (mmHg), n (%)								0.02
<90	13 (<1%)	NR	NR	NR	NR	NR	14 (<1%)	
90 to <140	3380 (59%)	634 (62%)	43 (61%)	98 (61%)	419 (56%)	45 (58%)	4619 (59%)	
≥140	2147 (38%)	345 (34%)	25 (36%)	53 (33%)	318 (42%)	29 (38%)	2917 (38%)	
Missing	148 (3%)	44 (4%)	NR	9 (6%)	17 (2%)	NR	223 (3%)	
Physician Visits, n (%)								<0.001
1 to 12	2354 (41%)	449 (44%)	19 (27%)	30 (19%)	443 (59%)	31 (40%)	3326 (43%)	
13 to 24	2116 (37%)	397 (39%)	36 (51%)	63 (39%)	237 (31%)	28 (36%)	2877 (37%)	
24 or more	1218 (21%)	177 (17%)	15 (21%)	68 (42%)	74 (10%)	18 (23%)	1570 (20%)	
Statins, n(%)	4666 (82%)	871 (85%)	60 (86%)	137 (85%)	628 (83%)	68 (88%)	6430 (83%)	0.11
NSAIDs, n(%)	1604 (28%)	278 (27%)	33 (47%)	49 (30%)	212 (28%)	22 (29%)	2198 (28%)	0.02
Calcium Channel Blockers, n(%)	2157 (38%)	364 (36%)	27 (39%)	62 (39%)	288 (38%)	26 (34%)	2924 (38%)	0.75
Beta-Blockers, n(%)	2209 (39%)	373 (36%)	24 (34%)	60 (37%)	241 (32%)	34 (44%)	2941 (38%)	<0.01
Anticoagulants, n(%)	694 (12%)	98 (10%)	NR	19 (12%)	44 (6%)	10 (13%)	869 (11%)	<0.001
Antiplatelets, n(%)	3139 (55%)	502 (49%)	37 (53%)	90 (56%)	415 (55%)	36 (47%)	4219 (54%)	<0.01
ACE/ARB/Renin, n(%)	4287 (75%)	744 (73%)	53 (76%)	120 (75%)	551 (73%)	56 (73%)	5811 (75%)	0.45
Diuretics, n(%)	3084 (54%)	490 (48%)	44 (63%)	91 (57%)	331 (44%)	46 (60%)	4086 (53%)	<0.001

*2010 English Index of Multiple Deprivation for England; §NR = Not reportable due to small sample size; CKD = chronic kidney disease; SU = sulfonylurea; DDP1i = dipeptidyl peptidase-4 inhibitor; GLP1ra = glucagon-like peptide-1 receptor agonist; TZD = thiazolidinedione; SD = standard deviation

Table 3.2 All-cause mortality rate, unadjusted and adjusted hazard ratios for new-users of second-line antidiabetic therapies in a sub-cohort of metformin users with CKD using HES and ONS data (n=7,773)

Antidiabetic Therapy	Deaths (n)	Person-Years (PY)	Incidence Rate, per 1000 PY [95% CI]	Unadjusted HR [95% CI]	Adjusted HR§ [95% CI]
SU	554	13,987	39.9 [36.7-43.3]	-- reference --	-- reference --
DPP-4	38	1718	22.1 [16.1-30.4]	0.54 [0.39-0.75]**	0.74 [0.52-1.04]
GLP-1	NR	139	7.2 [1.7-40.0]	0.18 [0.02-1.26]	0.58 [0.08-4.13]
Insulin	45	318	141.6 [105.9-189.4]	3.54 [2.61-4.79]**	2.60 [1.89-3.56]**
TZD	30	2011	14.9 [10.5-21.3]	0.38 [0.26-0.55]**	0.77 [0.52-1.13]
Other	37	247	149.7 [108.8-206.4]	3.82[2.74-5.33]**	5.00 [3.30-7.57]**

* CKD = chronic kidney disease; HR = hazard ratio; CI = confidence interval; SU = sulfonylurea; DDP-1 = dipeptidyl peptidase-4 inhibitor; GLP-1 = glucagon-like peptide-1 receptor agonist; TZD = thiazolidinedione; NR = not reportable

** p-value ≤0.001

§ Covariates include: age at index date, sex, index of deprivation, HbA1C, smoking status, CKD stage, BMI, systolic blood pressure, number of physician visits in the year prior to index, Charlson comorbidity index, history of cardiovascular disease, duration of treated diabetes, duration of metformin overlap, and prescription medications in the year prior to index known to affect mortality and the cardiovascular system (statins, NSAIDs, calcium channel blockers, beta blockers, anticoagulants, antiplatelets, agents that at on the renin-angiotensin system [ACE-inhibitors, ARBs, and renin inhibitors], and diuretics,

Table 3.3 Cohort study subgroup analysis for all-cause mortality

Group	Deaths (n)	Events: SU (n)	Events: DPP4i (n)	Patients (n)	Adjusted HR§ [95% CI]	p-value (interaction)
AGE						0.46
<65	44	26	NR	1848	0.50 [0.16-1.61]	
≥65	530	441	24	5925	0.77 [0.07-8.38]	
SEX						0.20
male	295	242	12	3553	0.90 [0.17-4.77]	
female	279	225	15	4220	1.39 [0.51-3.78]	
eGFR						0.42
<45	167	144	NR	1360	0.51 [0.12-2.10]	
45-60	407	323	23	6413	0.77 [0.53-1.10]	

* NR = not reportable

§ Covariates include: age at index date, sex, index of deprivation, HbA1C, smoking status, CKD stage, BMI, systolic blood pressure, number of physician visits in the year prior to index, Charlson comorbidity index, history of cardiovascular disease, duration of treated diabetes, duration of metformin overlap, and prescription medications in the year prior to index known to affect mortality and the cardiovascular system (statins, NSAIDs, calcium channel blockers, beta blockers, anticoagulants, antiplatelets, agents that at on the renin-angiotensin system [ACE-inhibitors, ARBs, and renin inhibitors], and diuretics,

Table 3.4 Cardiovascular event hazard ratios for new-users of second-line antidiabetic therapies in a cohort of metformin users with CKD (n=4650)

Antidiabetic Therapy	Events (n)	Person-Years (PY)	Incidence Rate, per 1000 PY [95% CI]	Unadjusted HR [95% CI]	Adjusted HR§ [95% CI]
Major Adverse Cardiovascular Events (non-fatal MI, non-fatal stroke, or cardiovascular death)					
SU	385	7,813	56.8 [51.8-62.4]	-- reference --	-- reference --
DPP4i	33	850	55.3 [41.7-73.6]	0.89 [0.66-1.20]	1.07 [0.78-1.47]
GLP1ra	NR	68	14.7 [3.6-82.1]	0.24 [0.03-1.73]	0.43 [0.06-3.10]
Insulin	22	173	144.8 [98.4-213.8]	2.54 [1.69-3.79]**	2.33 [1.54-3.55]**
TZD	33	1,206	33.2 [24.4-45.2]	0.60 [0.44-0.83]***	0.92 [0.66-1.29]
Other	7	130	100.2 [59.0-171.4]	1.86 [1.07-3.22]****	1.23 [0.63-2.41]
Myocardial Infarction					
SU	143	8,193	19.5 [16.7-22.8]	-- reference --	-- reference --
DPP4i	8	876	12.6 [7.1-2.5]	0.56 [0.30-1.03]****	0.66 [0.34-1.26]
GLP1ra	NR	72	NR	NR	NR
Insulin	14	185	92.1 [57.8-147.4]	4.69 [2.84-7.73]**	3.47 [2.04-5.91]**
TZD	9	1241	10.5 [6.2-17.9]	0.56 [0.32-0.99]***	0.93 [0.51-1.68]
Other	NR	134	37.2 [16.4-86.8]	2.04 [0.84-4.98]	1.42 [0.46-4.35]
Stroke					
SU	237	8,027	35.5 [31.6-39.9]	-- reference --	-- reference --
DPP4i	21	864	30.1 [20.6-44.1]	0.78 [0.52-1.17]	0.97 [0.64-1.48]
GLP1ra	NR	68	14.7 [3.6-82.1]	0.39 [0.06-2.81]	0.55 [0.08-3.97]
Insulin	14	184	81.3 [49.6-134.1]	2.28 [1.36-3.84]**	2.33 [1.36-4.00]**
TZD	27	1,215	28.0 [20.1-39.1]	0.81 [0.57-1.15]	1.24 [0.85-1.80]
Other	NR	135	59.5 [30.6-117.2]	1.74 [0.86-3.51]	1.29 [0.55-3.03]

Antidiabetic Therapy	Events (n)	Person-Years (PY)	Incidence Rate, per 1000 PY [95% CI]	Unadjusted HR [95% CI]	Adjusted HR§ [95% CI]
Cardiovascular Death					
SU	70	8,326	8.4 [6.7-10.6]	-- reference --	-- reference --
DPP4i	NR	886	NR	<0.001 [0.00-Inf]	<0.001 [0.00-Inf]
GLP1ra	NR	72	NR	<0.001 [0.00-Inf]	<0.001 [0.00-Inf]
Insulin	11	190	57.8 [32.6-103.5]	6.80 [3.60-12.84]**	5.09 [2.51-10.31]**
TZD	10	1,247	8.0 [4.4-14.7]	1.00 [0.51-1.93]	1.87 [0.88-3.92]****
Other	NR	140	NR	<0.001 [0.00-Inf]	<0.001 [0.00-Inf]

* CKD = chronic kidney disease; HR = hazard ratio; CI = confidence interval; SU = sulfonylurea; DDP-1 = dipeptidyl peptidase-4 inhibitor; GLP-1 = glucagon-like peptide-1 receptor agonist; TZD = thiazolidinedione; NR = not reportable

**p-value ≤0.001

***p-value ≤0.01

****p-value≤0.05

§ Covariates include: age at index date, sex, index of deprivation, HbA1C, smoking status, CKD stage, BMI, systolic blood pressure, number of physician visits in the year prior to index, Charlson comorbidity index, history of cardiovascular disease, duration of treated diabetes, duration of metformin overlap, and prescription medications in the year prior to index known to affect mortality and the cardiovascular system (statins, NSAIDs, calcium channel blockers, beta blockers, anticoagulants, antiplatelets, agents that at on the renin-angiotensin system [ACE-inhibitors, ARBs, and renin inhibitors], and diuretics,

Chapter 4: Summary

4.1 SAFETY AND EFFICACY OF INCRETIN THERAPY

The guidelines for diabetes management are ever-changing with the continuous development and enhancement of anti-hyperglycemic pharmacotherapy, with which comes the need for evidence-based safety and efficacy. The introduction of incretin therapies to the anti-hyperglycemic pharmacotherapy market in 2007 represents one of such developments. This thesis was designed to aid in the available literature on safety and efficacy of incretin agents, particularly in the context of patients with diabetes and established chronic kidney disease. It includes two complementary studies: the first, a systematic review and meta-analysis and the second, a population-based cohort study.

4.1.1 Study Goals

The systematic review and meta-analysis aimed to synthesize the literature on the efficacy and safety of incretin-based agents in patients with type 2 diabetes and moderate or severe chronic kidney disease. Outcome measures included change in A1C level as the primary measure of efficacy, and the proportion of patients having a hypoglycemic event as the primary measure of safety. Secondary outcomes included change in FPG level, all-cause mortality, acute myocardial infarction, stroke, ESKD/kidney transplantation/dialysis, and MACE. MACE was defined as a composite outcome of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke.

The cohort study aimed to comparatively assess population-based rates of all-cause mortality and cardiovascular outcomes among patients using DPP-4 inhibitors compared to other antidiabetic medications in individuals with type 2 diabetes and chronic kidney disease. MACE was once again

used as an outcome indicator for cardiovascular morbidity. Additional outcomes include cardiovascular disease, non-fatal myocardial infarction, and non-fatal stroke as discrete outcomes.

The two studies were designed to complement one another: the systematic review and meta-analysis to synthesize existing literature on the role of incretins in antidiabetic therapy, and the matched cohort study to contribute to evidence for safety and efficacy of incretins in that role. Together, these studies add to the pool of literature.

4.1.2 Overall Results

Our systematic review and meta-analysis included 13 peer-reviewed studies. Overall, in patients with moderate or severe CKD, incretin-based therapies are effective in reducing A1C. Hypoglycemic events are rare and wide confidence intervals observed for mortality, cardiovascular events and ESKD inhibits us from making any definitive conclusions. Since the publication of this systematic review and meta-analysis in 2016, other studies have been conducted assessing the cardiorenal outcomes with GLP-1 receptor agonists. In general, these studies concluded that GLP-1 receptor agonists have beneficial effects on cardiovascular outcomes (MACE), all-cause mortality, and kidney outcomes (e.g. no progression of diabetic renal disease) in patients with type 2 diabetes.[68, 103, 104] Our cohort study identified 7,773 patients with moderate to severe CKD prior to initiating a second-line antidiabetic agent. DPP4-inhibitors as second-line therapy were not associated with significant reduction in mortality.

4.2 RESEARCH AND CLINICAL IMPLICATIONS

Diabetes is a chronic condition that is a public health problem worldwide, playing a major role in premature death, cardiovascular disease, stroke, renal failure, blindness and other significant health

concerns. A better understanding of pharmacologic management of diabetes, particularly the safety and efficacy of therapies, has the potential to help with the prevention of the complications of diabetes. The knowledge generated from this research can be used to further inform researchers and clinicians of the safety and efficacy of incretin therapies, when compared to other antidiabetic agents.

4.2.1 Comparative effectiveness

The results of our systematic review and meta-analysis showed that when compared to placebo, incretin-based therapies significantly reduced A1C; however, compared to active comparators, there was no significant reduction. Incretin-based therapies significantly increased the risk of hypoglycemia compared to placebo, but no effect was observed versus active comparators. We found limited evidence for all-cause mortality as an outcome when comparing incretin-based therapies with placebo or other active therapies. The findings of our cohort study showed that second-line DPP-4 inhibitor therapy was associated with a non-significant reduction in the risk of all-cause mortality when compared to sulfonylureas and thiazolidinediones.

4.2.2 Limitations

There are several limitations that should be considered when interpreting these studies. First, there was a relatively small number of studies available at the time the systematic review was conducted. As such, we noted variation among interventions and heterogeneity between studies, yet our ability to account for between-study variation was limited. As the research in this area has expanded and additional studies are available, an updated meta-analysis could provide additional power when assessing the use of incretins in patients with CKD. One key limitation of the cohort study was the small number of outcomes, particularly for cardiovascular events and in the GLP-1RA users. This

limits interpretation of the presented adjusted hazard ratios and the power of such results. Overall, the most significant limitation is the evolution of treatment and guidelines over the course of this thesis.

4.2.3 Treatment evolution

As the prevalence of diabetes continues to increase, so will the demands on the pharmaceutical industry to provide management options for both treatment and prevention of diabetic complications. Since the analytical part of this thesis was completed, there have been new GLP-1RA agents introduced to the Canadian market, including semaglutide (subcutaneous and oral formulations), dulaglutide, and lixisenatide.[122] Recent evidence has shown an association between GLP1-RA and a risk reduction of MACE among patients with type 2 diabetes and CKD.[46, 55, 68, 103]

Additionally, there has been ongoing research regarding the safety and efficacy of the newest class of antihyperglycemic agents, SGLT-2 inhibitors. Recent studies demonstrate efficacy of SGLT-2 inhibitors on cardiovascular and rental outcomes, including reduction of MACE and the reduction of progression of kidney disease.[123]

Diabetes Canada released a full guideline update in 2018[4], followed by updates to the pharmacologic glycemic management of type 2 diabetes in 2020[41]. The most recent updates cover the demonstrated cardiorenal benefits of SGLT-2 inhibitors and several GLP1-RAs, including liraglutide, semaglutide, and dulaglutide. As such, SGLT-2 inhibitors or GLP1-RA are recommended when adjusting or advancing therapy in type 2 diabetes. The continuous expansion of evidence has led to a shift in the treatment of type 2 diabetes which considers other clinical

outcomes – such as cardiorenal protection, and weight loss – beyond glycemic effects when selecting antihyperglycemic agents.

4.2.4 Future research

With the evolution of antidiabetic treatment, including additional incretin agents and increasing use of GLP-1 receptor agonists, an updated cohort of similar caliber would provide additional data to more precisely quantify the association of incretin agents with mortality and specific cardiovascular outcomes. A similar study with a longer follow-up period is also needed. Future collaborative meta-analyses, particularly those that incorporate CKD state, could help to further characterize the safety and efficacy of incretin-based therapies in a growing population of patients with both type 2 diabetes and chronic kidney disease. Future research may also address such topics as the prohibitive costs of incretins and SGLT-2 inhibitor, access, and other therapeutic considerations.

4.3 CONCLUSION

The results of a systematic review and meta-analysis with a complementary population-based cohort study are reviewed. The meta-analysis supports several clinically relevant effects of the incretin-based therapies, including effective reduction of glycemia without a substantial increased risk of hypoglycemia within a clinically important subgroup of patients. The cohort study demonstrated that second-line DPP-4 inhibitor therapy was not associated with a significant reduction in mortality when compared to sulfonylureas or TZDs in patients with CKD.

This thesis demonstrates the need for a comprehensive understanding of both the patient population and pharmacological data, including safety and efficacy, when considering drug

utilization. This is applicable to both researchers when designing clinical studies and clinicians when prescribing and managing such complex chronic diseases. Despite their introduction to the pharmaceutical market in 2007, there is still much to be understood regarding incretin therapy, particularly in the cohort of patients with diabetes and chronic kidney disease.

References

1. Howse PM, Chibrikova LN, Twells LK, et al. Safety and Efficacy of Incretin-Based Therapies in Patients With Type 2 Diabetes Mellitus and CKD: A Systematic Review and Meta-analysis. Am J Kidney Dis. 2016;68(5):733-742. DOI: 10.1053/j.ajkd.2016.06.014.

2. Herman WH. Diabetes epidemiology: guiding clinical and public health practice: the Kelly West Award Lecture, 2006. Diabetes Care. 2007;30(7):1912-1919. DOI: 10.2337/dc07-9924.

3. Canadian Diabetes Association. Diabetes: Canada at the Tipping Point: Charting a New Path. 2011.

4. Diabetes Canada Clinical Practice Guidelines Expert Committee. Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. Can J Diabetes. 2018;42:S1-S325.

5. Holleman F. Introduction to diabetes mellitus Available: http://www.diapedia.org/1104085113/rev/55. Accessed February 18, 2016. DOI: 10.14496/dia.1104085113.55.

6. International Diabetes Federation. IDF Diabetes Atlas 2015.

7. Public Health Agency of Canada. Diabetes in Canada: Facts and figures from a public health perspective Available: https://www.canada.ca/en/public-health/services/chronic-diseases/reports-publications/diabetes/diabetes-canada-facts-figures-a-public-health-perspective.html. Accessed February 18, 2016.

8. Diabetes Management in Clinical Practice. London: Springer 2014. DOI: 10.1007/978-1-4471-4869-2.

9. Luna B, Feinglos MN. Oral agents in the management of type 2 diabetes mellitus. Am Fam Physician. 2001;63(9):1747-1756, PMID:11352285.

10. American Diabetes A. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2020. Diabetes Care. 2020;43(Suppl 1):S98-S110. DOI: 10.2337/dc20-S009.

11. Alan J. Garber, Martin J. Abrahamson, Joshua I. Barzilay, et al. Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm - 2019 Executive Summary. Endocrine Practice. 2019;25(1):69-100. DOI: 10.4158/CS-2019-0472.

12. American Diabetes Association. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes. Diabetes Care. 2020;43(Suppl 1):S111-134.

13. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ. 2000;321(7258):405-412. DOI: 10.1136/bmj.321.7258.405.

14. Jacobs E, Hoyer A, Brinks R, et al. Burden of Mortality Attributable to Diagnosed Diabetes: A Nationwide Analysis Based on Claims Data From 65 Million People in Germany. Diabetes Care. 2017;40(12):1703-1709. DOI: 10.2337/dc17-0954.

15. Booth GL, Kapral MK, Fung K, et al. Relation between age and cardiovascular disease in men and women with diabetes compared with non-diabetic people: a population-based retrospective cohort study. Lancet. 2006;368(9529):29-36. DOI: 10.1016/S0140-6736(06)68967-8.

16. Kirkman MS, Mahmud H, Korytkowski MT. Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes Mellitus. Endocrinol Metab Clin North Am. 2018;47(1):81-96. DOI: 10.1016/j.ecl.2017.10.002.

17. Ismail-Beigi F, Craven T, Banerji MA, et al. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. Lancet. 2010;376(9739):419-430. DOI: 10.1016/S0140-6736(10)60576-4.

18. Diabetes Canada Clinical Practice Guidelines Expert C, McFarlane P, Cherney D, et al. Chronic Kidney Disease in Diabetes. Can J Diabetes. 2018;42 Suppl 1:S201-S209. DOI: 10.1016/j.jcjd.2017.11.004.

19. Nerenberg KA, Zarnke KB, Leung AA, et al. Hypertension Canada's 2018 Guidelines for Diagnosis, Risk Assessment, Prevention, and Treatment of Hypertension in Adults and Children. Can J Cardiol. 2018;34(5):506-525. DOI: 10.1016/j.cjca.2018.02.022.

20. Gonzalez DE, Foresto RD, Ribeiro AB. SGLT-2 inhibitors in diabetes: a focus on renoprotection. Rev Assoc Med Bras (1992). 2020;66Suppl 1(Suppl 1):s17-s24. DOI: 10.1590/1806-9282.66.S1.17.

21. Rossing P, Caramori ML, Chan JCN, et al. Executive summary of the KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease: an update based on rapidly emerging new evidence. Kidney Int. 2022;102(5):990-999. DOI: 10.1016/j.kint.2022.06.013.

22. Kidney Disease: Improving Global Outcomes Diabetes Work G. KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. Kidney Int. 2022;102(5S):S1-S127. DOI: 10.1016/j.kint.2022.06.008.

23. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N Engl J Med. 2019;380(24):2295-2306. DOI: 10.1056/NEJMoa1811744.

24. The E-KCG, Herrington WG, Staplin N, et al. Empagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. 2023;388(2):117-127. DOI: 10.1056/NEJMoa2204233.

25. Adriaanse MC, Drewes HW, van der Heide I, et al. The impact of comorbid chronic conditions on quality of life in type 2 diabetes patients. Qual Life Res. 2016;25(1):175-182. DOI: 10.1007/s11136-015-1061-0.

26. Abu-Ashour W, Twells L, Valcour J, et al. The association between diabetes mellitus and incident infections: a systematic review and meta-analysis of observational studies. BMJ Open Diabetes Res Care. 2017;5(1):e000336. DOI: 10.1136/bmjdrc-2016-000336.

27. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. Chapter 1: Definition and classification of CKD. Kidney Int Suppl (2011). 2013;3(1):19-62. DOI: 10.1038/kisup.2012.64.

28. Arora P, Vasa P, Brenner D, et al. Prevalence estimates of chronic kidney disease in Canada: results of a nationally representative survey. CMAJ. 2013;185(9):E417-423. DOI: 10.1503/cmaj.120833.

29. Patel UD, Young EW, Ojo AO, et al. CKD progression and mortality among older patients with diabetes. Am J Kidney Dis. 2005;46(3):406-414. DOI: 10.1053/j.ajkd.2005.05.027.

30. Chronic Kidney Disease Prognosis C, Matsushita K, van der Velde M, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet. 2010;375(9731):2073-2081. DOI: 10.1016/S0140-6736(10)60674-5.

31. Canadian Diabetes Association. Therapeutic Considerations for Renal Impairment. Canadian Journal of Diabetes. 2018;42. DOI: 10.1016/j.jcjd.2017.10.044.

32. Rosenberg J, Jacob J, Desai P, et al. Incretin Hormones: Pathophysiological Risk Factors and Potential Targets for Type 2 Diabetes. J Obes Metab Syndr. 2021;30(3):233-247. DOI: 10.7570/jomes21053.

33. Nauck MA, Quast DR, Wefers J, et al. The evolving story of incretins (GIP and GLP-1) in metabolic and cardiovascular disease: A pathophysiological update. Diabetes Obes Metab. 2021;23 Suppl 3:5-29. DOI: 10.1111/dom.14496.

34. van Baar MJB, van Raalte DH. Renoprotection in diabetic kidney disease: can incretin-based therapies deliver? Curr Opin Nephrol Hypertens. 2020;29(1):103-111. DOI: 10.1097/MNH.0000000000000559.

35. Ji L, Dong X, Li Y, et al. Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as add-on to metformin in patients with type 2 diabetes in SUSTAIN China: A 30-week, double-blind, phase 3a, randomized trial. Diabetes Obes Metab. 2021;23(2):404-414. DOI: 10.1111/dom.14232.

36. Hinnen D. Glucagon-Like Peptide 1 Receptor Agonists for Type 2 Diabetes. Diabetes Spectr. 2017;30(3):202-210. DOI: 10.2337/ds16-0026.

37. Trujillo JM, Nuffer W, Smith BA. GLP-1 receptor agonists: an updated review of head-to-head clinical studies. Ther Adv Endocrinol Metab. 2021;12:2042018821997320. DOI: 10.1177/2042018821997320.

38. Htike ZZ, Zaccardi F, Papamargaritis D, et al. Efficacy and safety of glucagon-like peptide-1 receptor agonists in type 2 diabetes: A systematic review and mixed-treatment comparison analysis. Diabetes Obes Metab. 2017;19(4):524-536. DOI: 10.1111/dom.12849.

39. Husain M, Birkenfeld AL, Donsmark M, et al. Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2019;381(9):841-851. DOI: 10.1056/NEJMoa1901118.

40. Davies MJ, Bain SC, Atkin SL, et al. Efficacy and Safety of Liraglutide Versus Placebo as Add-on to Glucose-Lowering Therapy in Patients With Type 2 Diabetes and Moderate Renal Impairment (LIRA-RENAL): A Randomized Clinical Trial. Diabetes Care. 2016;39(2):222-230. DOI: 10.2337/dc14-2883/-/DC1.

41. Diabetes Canada Clinical Practice Guidelines Expert C, Lipscombe L, Butalia S, et al. Pharmacologic Glycemic Management of Type 2 Diabetes in Adults: 2020 Update. Can J Diabetes. 2020;44(7):575-591. DOI: 10.1016/j.jcjd.2020.08.001.

42. Campbell RK, Cobble ME, Reid TS, et al. Distinguishing among incretin-based therapies. Glucose-lowering effects of incretin-based therapies. J Fam Pract. 2010;59(9 Suppl 1):S10-19.

43. Maruthur NM, Tseng E, Hutfless S, et al. Diabetes Medications as Monotherapy or Metformin-Based Combination Therapy for Type 2 Diabetes: A Systematic Review and Meta-analysis. Ann Intern Med. 2016;164(11):740-751. DOI: 10.7326/M15-2650.

44. Hernandez AF, Green JB, Janmohamed S, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. Lancet. 2018;392(10157):1519-1529. DOI: 10.1016/S0140-6736(18)32261-X.

45. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and renal outcomes in type 2 diabetes: an exploratory analysis of the REWIND randomised, placebo-controlled trial. Lancet. 2019;394(10193):131-138. DOI: 10.1016/S0140-6736(19)31150-X.

46. Marso SP, Bain SC, Consoli A, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2016;375(19):1834-1844. DOI: 10.1056/NEJMoa1607141.

47. Davis TM. Dipeptidyl peptidase-4 inhibitors: pharmacokinetics, efficacy, tolerability and safety in renal impairment. Diabetes Obes Metab. 2014;16(10):891-899. DOI: 10.1111/dom.12295.

48. Ramirez G, Morrison AD, Bittle PA. Clinical practice considerations and review of the literature for the Use of DPP-4 inhibitors in patients with type 2 diabetes and chronic kidney disease. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists. 2013;19(6):1025-1034. DOI: 10.4158/EP12306.RA.

49. Andersen ES, Deacon CF, Holst JJ. Do we know the true mechanism of action of the DPP-4 inhibitors? Diabetes Obes Metab. 2018;20(1):34-41. DOI: 10.1111/dom.13018.

50. Gomez-Peralta F, Abreu C, Gomez-Rodriguez S, et al. Safety and Efficacy of DPP4 Inhibitor and Basal Insulin in Type 2 Diabetes: An Updated Review and Challenging Clinical Scenarios. Diabetes Ther. 2018;9(5):1775-1789. DOI: 10.1007/s13300-018-0488-z.

51. Scheen AJ. DPP-4 inhibitors in the management of type 2 diabetes: a critical review of head-to-head trials. Diabetes Metab. 2012;38(2):89-101. DOI: 10.1016/j.diabet.2011.11.001.

52. Canadian Diabetes Association. Table of Contents. Canadian Journal of Diabetes. 2013;37:A1-A2. DOI: 10.1016/s1499-2671(13)00192-5.

53. Pathak R, Bridgeman MB. Dipeptidyl Peptidase-4 (DPP-4) Inhibitors In the Management of Diabetes. P T. 2010;35(9):509-513, PMID:PMC2957740.

54. Canadian Diabetes Association Clinical Practice Guidelines Expert C, Cheng AY. Canadian Diabetes Association 2013 clinical practice guidelines for the prevention and management of diabetes in Canada. Introduction. Can J Diabetes. 2013;37 Suppl 1(Suppl 1):S1-3. DOI: 10.1016/j.jcjd.2013.01.009.

55. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2016;375(4):311-322. DOI: 10.1056/NEJMoa1603827.

56. Friedrich C, Emser A, Woerle H-J, et al. Renal Impairment Has No Clinically Relevant Effect on the Long-Term Exposure of Linagliptin in Patients With Type 2 Diabetes. American Journal of Therapeutics 2013;20(6):618–621. DOI: 10.1097/MJT.0b013e31826232dc.

57. Scheen AJ. Saxagliptin plus metformin combination in patients with type 2 diabetes and renal impairment. Expert Opin Drug Metab Toxicol. 2012;8(3):383-394. DOI: 10.1517/17425255.2012.658771.

58. Scheen AJ. Pharmacokinetics and clinical use of incretin-based therapies in patients with chronic kidney disease and type 2 diabetes. Clin Pharmacokinet. 2015;54(1):1-21. DOI: 10.1007/s40262-014-0198-2.

59. Barnett AH, Huisman H, Jones R, et al. Linagliptin for patients aged 70 years or older with type 2 diabetes inadequately controlled with common antidiabetes treatments: a randomised, double-blind, placebo-controlled trial. Lancet. 2013;382(9902):1413-1423. DOI: 10.1016/S0140-6736(13)61500-7.

60. Chan JC, Scott R, Arjona Ferreira JC, et al. Safety and efficacy of sitagliptin in patients with type 2 diabetes and chronic renal insufficiency. Diabetes, obesity & metabolism. 2008;10(7):545-555. DOI: 10.1111/j.1463-1326.2008.00914.x.

61. Idorn T, Knop FK, Jorgensen MB, et al. Safety and Efficacy of Liraglutide in Patients With Type 2 Diabetes and End-Stage Renal Disease: An Investigator-Initiated, Placebo-Controlled, Double-Blind, Parallel-Group, Randomized Trial. Diabetes Care. 2016;39(2):206-213. DOI: 10.2337/dc15-1025.

62. Yoon S, Han B, Kim S, et al. Abstracts of 51st EASD Annual Meeting. Diabetologia. 2015;58 Suppl 1(Suppl 1):1-607. DOI: 10.1007/s00125-015-3687-4.

63. Arjona Ferreira JC, Corry D, Mogensen CE, et al. Efficacy and safety of sitagliptin in patients with type 2 diabetes and ESRD receiving dialysis: a 54-week randomized trial. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2013;61(4):579-587. DOI: 10.1053/j.ajkd.2012.11.043.

64. Arjona Ferreira JC, Marre M, Barzilai N, et al. Efficacy and safety of sitagliptin versus glipizide in patients with type 2 diabetes and moderate-to-severe chronic renal insufficiency. Diabetes Care. 2013;36(5):1067-1073. DOI: 10.2337/dc12-1365.

65. Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 2013;369(14):1317-1326. DOI: 10.1056/NEJMoa1307684.

66. Yamada T, Wakabayashi M, Bhalla A, et al. Cardiovascular and renal outcomes with SGLT-2 inhibitors versus GLP-1 receptor agonists in patients with type 2 diabetes mellitus and chronic kidney disease: a systematic review and network meta-analysis. Cardiovasc Diabetol. 2021;20(1):14. DOI: 10.1186/s12933-020-01197-z.

67. Giorda CB, Nada E, Tartaglino B. Pharmacokinetics, safety, and efficacy of DPP-4 inhibitors and GLP-1 receptor agonists in patients with type 2 diabetes mellitus and renal or hepatic impairment. A systematic review of the literature. Endocrine. 2014;46(3):406-419. DOI: 10.1007/s12020-014-0179-0.

68. Kristensen SL, Rorth R, Jhund PS, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet Diabetes Endocrinol. 2019;7(10):776-785. DOI: 10.1016/S2213-8587(19)30249-9.

69. National Kidney F. KDOQI Clinical Practice Guideline for Diabetes and CKD: 2012 Update. Am J Kidney Dis. 2012;60(5):850-886. DOI: 10.1053/j.ajkd.2012.07.005.

70. Schernthaner G, Schernthaner GH. Diabetic nephropathy: new approaches for improving glycemic control and reducing risk. J Nephrol. 2013;26(6):975-985. DOI: 10.5301/jn.5000281.

71. Jacobsen LV, Hindsberger C, Robson R, et al. Effect of renal impairment on the pharmacokinetics of the GLP-1 analogue liraglutide. Br J Clin Pharmacol. 2009;68(6):898-905. DOI: 10.1111/j.1365-2125.2009.03536.x.

72. Ninomiya T, Perkovic V, de Galan BE, et al. Albuminuria and kidney function independently predict cardiovascular and renal outcomes in diabetes. J Am Soc Nephrol. 2009;20(8):1813-1821. DOI: 10.1681/ASN.2008121270.

73. Doggen K, Nobels F, Scheen AJ, et al. Cardiovascular risk factors and complications associated with albuminuria and impaired renal function in insulin-treated diabetes. J Diabetes Complications. 2013;27(4):370-375. DOI: 10.1016/j.jdiacomp.2013.02.008.

74. Pinelli NR, Moore CL, Tomasello S. Incretin-based therapy in chronic kidney disease. Adv Chronic Kidney Dis. 2010;17(5):439-449. DOI: 10.1053/j.ackd.2010.06.003.

75. Goossen K, Graber S. Longer term safety of dipeptidyl peptidase-4 inhibitors in patients with type 2 diabetes mellitus: systematic review and meta-analysis. Diabetes Obes Metab. 2012;14(12):1061-1072. DOI: 10.1111/j.1463-1326.2012.01610.x.

76. Inzucchi S, Bergenstal R, Buse J, et al. Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach. Diabetes Care. 2015;38:140–149. DOI: 10.2337/dc14-2441/-/DC1.

77. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm--2016 Executive Summary. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists. 2016;22(1):84-113. DOI: 10.4158/EP151126.CS.

78. CADTH. Strings attached: CADTH database search filters Available: https://www.cadth.ca/resources/finding-evidence/strings-attached-cadths-database-search-filters. Accessed September 29, 2014.

79. Lukashevich V, Schweizer A, Shao Q, et al. Safety and efficacy of vildagliptin versus placebo in patients with type 2 diabetes and moderate or severe renal impairment: a prospective 24-week randomized placebo-controlled trial. Diabetes Obes Metab. 2011;13(10):947-954. DOI: 10.1111/j.1463-1326.2011.01467.x.

80. Nowicki M, Rychlik I, Haller H, et al. Long-term treatment with the dipeptidyl peptidase-4 inhibitor saxagliptin in patients with type 2 diabetes mellitus and renal impairment: a randomised controlled 52-week efficacy and safety study. International journal of clinical practice. 2011;65(12):1230-1239. DOI: 10.1111/j.1742-1241.2011.02812.x.

81. Linnebjerg H, Kothare PA, Park S, et al. Effect of renal impairment on the pharmacokinetics of exenatide. Br J Clin Pharmacol. 2007;64(3):317-327. DOI: 10.1111/j.1365-2125.2007.02890.x.

82. Butalia S, Leung AA, Ghali WA, et al. Aspirin effect on the incidence of major adverse cardiovascular events in patients with diabetes mellitus: a systematic review and meta-analysis. Cardiovasc Diabetol. 2011;10(1):25. DOI: 10.1186/1475-2840-10-25.

83. Gaziano JM, Cincotta AH, Vinik A, et al. Effect of bromocriptine-QR (a quick-release formulation of bromocriptine mesylate) on major adverse cardiovascular events in type 2 diabetes subjects. J Am Heart Assoc. 2012;1(5):e002279. DOI: 10.1161/JAHA.112.002279.

84. Higgins JPT, Green S, (eds). Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 Available: www.cochrane-handbook.org. Accessed May 12, 2015.

85. Sedgwick P. Meta-analyses: tests of heterogeneity. Bmj. 2012;344(jun13 2):e3971-e3971. DOI: 10.1136/bmj.e3971.

86. Cornell JE, Mulrow CD, Localio R, et al. Random-effects meta-analysis of inconsistent effects: a time for change. Ann Intern Med. 2014;160(4):267-270. DOI: 10.7326/M13-2886.

87. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557-560. DOI: 10.1136/bmj.327.7414.557.

88. Idorn T, Knop FK, Jorgensen MB, et al. Safety and Efficacy of Liraglutide in Patients With Type 2 Diabetes and End-Stage Renal Disease: An Investigator-Initiated, Placebo-Controlled, Double-Blind, Parallel-Group, Randomized Trial. Diabetes care. 2016;39(2):206-213. DOI: 10.2337/dc15-1025/-/DC1.

89. Kothny W, Shao Q, Groop PH, et al. One-year safety, tolerability and efficacy of vildagliptin in patients with type 2 diabetes and moderate or severe renal impairment. Diabetes, obesity & metabolism. 2012;14(11):1032-1039. DOI: 10.1111/j.1463-1326.2012.01634.x.

90. Laakso M, Rosenstock J, Groop PH, et al. Linagliptin vs. placebo followed by glimepiride in type 2 diabetes patients with moderate to severe renal impairment. Diabetes. 2013;62:A281-A282.

91. McGill JB, Sloan L, Newman J, et al. Long-term efficacy and safety of linagliptin in patients with type 2 diabetes and severe renal impairment: a 1-year, randomized, double-blind, placebo-controlled study. Diabetes care. 2013;36(2):237-244. DOI: 10.2337/dc12-0706.

92. White WB, Cannon CP, Heller SR, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med. 2013;369(14):1327-1335. DOI: 10.1056/NEJMoa1305889.

93. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approash: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2015;38(1):140-149. DOI: 10.2337/dc14-2441/-/DC1.

94. Egger M, Smith GD, O'Rourke K, et al. Systematic reviews in health care: meta-analysis in context Tavistock Square, London: BMJ Publishing Group 2001.

95. Cooper ME, Perkovic V, McGill JB, et al. Kidney Disease End Points in a Pooled Analysis of Individual Patient-Level Data From a Large Clinical Trials Program of the Dipeptidyl Peptidase 4 Inhibitor Linagliptin in Type 2 Diabetes. Am J Kidney Dis. 2015;66(3):441-449. DOI: 10.1053/j.ajkd.2015.03.024.

96. U.S. National Institutes of Health. Cardiovascular outcome study of linagliptin versus glimepiride in patients with type 2 diabetes (CAROLINA) Available: http://clinicaltrials.gov/ct2/show/NCT00790205?term=TECOS&rank=1. Accessed May 11, 2015.

97. MacCallum L. Optimal medication dosing in patients with diabetes mellitus and chronic kidney disease. Can J Diabetes. 2014;38(5):334-343. DOI: 10.1016/j.jcjd.2014.04.006.

98. Dicker D. DPP-4 inhibitors: impact on glycemic control and cardiovascular risk factors. Diabetes care. 2011;34(Suppl 2):S276-278. DOI: 10.2337/dc11-s229.

99. Ross SA, Ekoe JM. Incretin agents in type 2 diabetes. Can Fam Physician. 2010;56(7):639-648, PMID:PMC2922799.

100. Rossing P, de Zeeuw D. Need for better diabetes treatment for improved renal outcome. Kidney Int Suppl. 2011;79(120):S28-32. DOI: 10.1038/ki.2010.513.

101. Scheen AJ. Pharmacokinetics of dipeptidylpeptidase-4 inhibitors. Diabetes Obes Metab. 2010;12(8):648-658. DOI: 10.1111/j.1463-1326.2010.01212.x.

102. Tanzeum™ (albiglutide) [prescribing information] Available: https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Tanzeum/pdf/TANZEUM-PI-MG-IFU-COMBINED.PDF, Accessed: 2014.

103. Sattar N, Lee MMY, Kristensen SL, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. Lancet Diabetes Endocrinol. 2021;9(10):653-662. DOI: 10.1016/S2213-8587(21)00203-5.

104. Giugliano D, Maiorino MI, Bellastella G, et al. GLP-1 receptor agonists for prevention of cardiorenal outcomes in type 2 diabetes: An updated meta-analysis including the REWIND and PIONEER 6 trials. Diabetes Obes Metab. 2019;21(11):2576-2580. DOI: 10.1111/dom.13847.

105. Udell JA, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes and moderate or severe renal impairment: observations from the SAVOR-TIMI 53 Trial. Diabetes Care. 2015;38(4):696-705. DOI: 10.2337/dc14-1850.

106. White WB, Bakris GL, Bergenstal RM, et al. EXamination of cArdiovascular outcoMes with alogliptIN versus standard of carE in patients with type 2 diabetes mellitus and acute coronary syndrome (EXAMINE): a cardiovascular safety study of the dipeptidyl peptidase 4 inhibitor alogliptin in patients with type 2 diabetes with acute coronary syndrome. Am Heart J. 2011;162(4):620-626 e621. DOI: 10.1016/j.ahj.2011.08.004.

107. Yoon S HB, Kim S, et al. Abstracts of 51st EASD Annual Meeting. Diabetologia. 2015;58 Suppl 1(Suppl 1):1-607. DOI: 10.1007/s00125-015-3687-4.

108. International Diabetes Federation. IDF Diabetes Atlas, 10th Edition 2021.

109. Snyder S, Pendergraph B. Detection and evaluation of chronic kidney disease. Am Fam Physician. 2005;72(9):1723-1732, PMID:16300034.

110. Alberti KG, Zimmet P, Shaw J. International Diabetes Federation: a consensus on Type 2 diabetes prevention. Diabet Med. 2007;24(5):451-463. DOI: 10.1111/j.1464-5491.2007.02157.x.

111. Hung SC, Chang YK, Liu JS, et al. Metformin use and mortality in patients with advanced chronic kidney disease: national, retrospective, observational, cohort study. Lancet Diabetes Endocrinol. 2015;3(8):605-614. DOI: 10.1016/S2213-8587(15)00123-0.

112. Schwartz S. Evidence-based practice use of incretin-based therapy in the natural history of diabetes. Postgrad Med. 2014;126(3):66-84. DOI: 10.3810/pgm.2014.05.2757.

113. Liu J, Li L, Deng K, et al. Incretin based treatments and mortality in patients with type 2 diabetes: systematic review and meta-analysis. BMJ. 2017;357:j2499. DOI: 10.1136/bmj.j2499.

114. Rodriguez LAG, Gutthann SP. Use of the U General Practice Research Database for pharmacoepidemiology. Br J Clin Pharmacol. 1998;45(5):419–425. DOI: 10.1046/j.1365-2125.1998.00701.x.

115. Gamble JM, Thomas JM, Twells LK, et al. Comparative effectiveness of incretin-based therapies and the risk of death and cardiovascular events in 38,233 metformin monotherapy users. Medicine (Baltimore). 2016;95(26):e3995. DOI: 10.1097/MD.0000000000003995.

116. National Kidney F. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002;39(2 Suppl 1):S1-266, PMID:11904577.

117. Zannad F, Cannon CP, Cushman WC, et al. Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a multicentre, randomised, double-blind trial. Lancet. 2015;385(9982):2067-2076. DOI: 10.1016/S0140-6736(14)62225-X.

118. Cornel JH, Bakris GL, Stevens SR, et al. Effect of Sitagliptin on Kidney Function and Respective Cardiovascular Outcomes in Type 2 Diabetes: Outcomes From TECOS. Diabetes Care. 2016;39(12):2304-2310. DOI: 10.2337/dc16-1415.

119. Monami M, Cremasco F, Lamanna C, et al. Predictors of response to dipeptidyl peptidase-4 inhibitors: evidence from randomized clinical trials. Diabetes Metab Res Rev. 2011;27(4):362-372. DOI: 10.1002/dmrr.1184.

120. Fakhoury WK, Lereun C, Wright D. A meta-analysis of placebo-controlled clinical trials assessing the efficacy and safety of incretin-based medications in patients with type 2 diabetes. Pharmacology. 2010;86(1):44-57. DOI: 10.1159/000314690.

121. Green JB, Bethel MA, Armstrong PW, et al. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2015;373(3):232-242. DOI: 10.1056/NEJMoa1501352.

122. Health Canada. Drug Product Database Available: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html#shr-pg0. Accessed May 11, 2022.

123. Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet. 2019;393(10166):31-39. DOI: 10.1016/S0140-6736(18)32590-X.

Appendices

Appendix 2.A Study protocol

Review title

Safety and efficacy of incretin-based therapies in patients with type 2 diabetes mellitus and renal impairment: systematic review and meta-analysis protocol

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Review question/objective

The quantitative objectives are to identify the safety and effectiveness of incretin therapy in patients with type 2 diabetes mellitus and renal impairment.

More specifically, the objectives are to identify:

The safety and effectiveness of dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists in patients with type 2 diabetes mellitus and moderate to severe renal impairment (RI) (eGFR <60 mL/min/1.73m^2).

Background

Diabetes is the leading cause of chronic kidney disease (CKD); and, as the rate of diabetes increases, chronic kidney disease and associated cardiovascular outcomes continue to be a growing public health concern.[1,2] Diabetes itself, and in combination with CKD, is associated with increased rates of cardiovascular disease and cardiovascular-related death, emphasizing the importance of appropriate treatment for patients in this population.[3, 4] Although many anti-diabetic medications are available to manage hyperglycemia in patients with type 2 diabetes mellitus (T2DM), the pharmacokinetics and pharmacodynamics of these medications are often altered in the context of reduced kidney function.[5]

The presence of CKD is determined by kidney damage and level of kidney function and comprises 5 stages, ranging from kidney damage to kidney failure.[1] The glomerular filtration rate [GFR] defines the stage among individuals with CKD. The National Kidney Foundation's KDOQI (Kidney Disease Outcomes Quality Initiative) Guidelines defines moderate (stage 3) CKD as having GFR 30-59 mL/min/1.73m^2; severe (stage 4) CKD as having GFR 15-29 mL/min/1.73m^2; and end-stage renal disease (ESRD) or kidney failure (stage 5) as having GFR <15 mL/min/1.73m^2, or dialysis.[1] As GFR decreases and CKD progresses, people with CKD are at an increased risk for cardiovascular events and other adverse effects.[1, 3]

Incretin-based medications are a new class of anti-diabetic medications, which are increasingly used in the treatment of hyperglycemia in patients with normal renal function. The Canadian Diabetes Association (CDA) Clinical Practice Guidelines recommend incretin agents, dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists, as add-on therapy to first-line agent metformin or other anti-diabetic medications.[3, 6] However, there is limited understanding about the relative clinical effectiveness and safety of incretin-based medications in patients with diabetes and CKD.

Knowledge gained from this study on the real word effects of incretin-based medications will assist physicians when recommending anti-hyperglycemic therapy for diabetics, taking into consideration the growing risks of CKD associated with diabetes. The objective of this study was to perform a systematic review and meta-analysis of randomized controlled trials (RCTs) to assess the safety and efficacy of incretin use in patients with T2DM and renal impairment.

Inclusion criteria

Types of participants

The quantitative and qualitative components of this review will consider studies that include patients who have type 2 diabetes; are ≥18 years of age; and have moderate to severe renal impairment defined as an eGFR <60 mL/min/1.73m^2.

Types of interventions

The quantitative and qualitative components of the review will consider studies that evaluate incretin therapy, including dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists, as monotherapy or add-on therapy to other non-incretin anti-diabetic agents. The review will consider comparison groups of either placebo or an active comparator (other than incretin therapy).

Types of outcomes

This review will consider studies that include at least one of the following outcome measures: differences in change in HbA1c or pre- and post-intervention HbA1c (primary efficacy outcome); number of participants with at least one severe or confirmed hypoglycemic event (primary safety outcome), as defined by the individual study; all-cause mortality; fasting plasma glucose (FPG); myocardial infarction (MI); stroke; ESRD/ Kidney transplant/ permanent dialysis; or major adverse cardiac events (MACE).

Types of studies

The review will consider RCTs for inclusion. There were no restrictions on length of follow-up, publication status, or language.

Search strategy

The search strategy aims to screen both published and unpublished studies through database searches, registries and reference lists.

Database searches will include The Cochrane Library, PubMed, EMBASE and International Pharmaceutical Abstracts (IPA). The articles will not be restricted based on language. Alternative sources will be searched for published and unpublished trials including the CDA Clinical Practice

Guidelines reference list, the National Kidney Foundation Guidelines reference list, clinical trial registries and the references of associated systematic reviews and meta-analyses.

Both MeSH and keyword searches will be completed in The Cochrane Library and PubMed; EMTREE and keyword searches will be completed in EMBASE; and keyword searches will be conducted in IPA. The search terms will include 'kidney disease', 'renal impairment', 'incretin', 'dipeptidyl-peptidase 4' and 'glucagon-like peptide 1', which will be adjusted according to the requirements of each database.

Assessment of methodological quality

Two independent reviewers (P Howse, L Chibrikova) will independently assess the quality of each study using the Cochrane Collaboration's risk of bias assessment tool, which assesses bias in six key areas: selection bias (randomization); selection bias (allocation concealment); performance bias (blinding of participants and personnel); detection bias (blinding of outcome assessment); attrition bias (incomplete outcome data); and reporting bias (selective reporting).[7] Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer (JM Gamble). Quality assessment will be conducted on included studies with a full-published manuscript available (Appendix I).

Data collection

Two reviewers (P Howse, L Chibrikova) will use pre-defined forms to extract data from the studies (Appendix II). Extracted data will include: study and design characteristics; number of subjects; participant baseline characteristics (e.g. age, sex, duration of diabetes); follow-up period; intervention and comparison particulars (e.g. drug, dose); and outcomes (e.g. HbA1c, adverse events).

Data synthesis

Results from included studies will be pooled using random-effects meta-analysis. Study results will be divided into four comparison groups: DPP-4 vs. placebo, DPP-4 vs. active comparator, GLP-1 vs. placebo and GLP-1 vs. active comparator. Pooled treatment effects will be expressed as relative risks for dichotomous outcomes and weighted mean differences for continuous outcomes with associated 95% confidence intervals (95% CI). Forest plots will be used to display

effect size (mean difference or relative risk with a 95% CI) for each study as well as the pooled values. The I^2 statistic will be used to measure heterogeneity across studies. Heterogeneity will be explored through subgroup analysis. Subgroups of interest include degree of renal impairment (moderate vs. severe vs. ESRD) and class of incretin (DPP-4 inhibitors vs. GLP-1 receptor agonists). Data analyses will be performed using Stata/MP version 13.1 (StataCorp, College Station, Texas, USA). Publication bias will be assessed using funnel plots, where appropriate.

Conflicts of interest

The authors declare that there is no duality of interest associated with this manuscript.

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We thank Dr. Marshall Godwin, Jacqueline Fortier, and Michelle Swab for their assistance with the search strategy and study design.

References

1. National Kidney Foundation (2012) KDOQI Clinical Practice Guidelines for Diabetes and CKD: 2012 update. Am J Kidney Dis. 60(5):850-886

2. Schernthaner G, Schernthaner GH (2013) Diabetic nephropathy: new approaches for improving glycemic control and reducing risk. J Nephrol 26(6):975-985

3. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association (2013) Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. Can J Diabetes 37(suppl 1):S1-S212

4. Jacobsen LV, Hindsberger C, Robson R, Zdravkovic (2009) Effect of renal impairment on the pharmacokinetics of the GLP-1 analogue liraglutide. Br J Clin Pharmacol 68(6):898-905

5. Pinelli NR, Moore CL, Tomasello S (2010) Incretin-based Therapy in Chronic Kidney Disease. Adv Chronic Kidney Dis 17(5):419-449

6. Gooßen K, Gräber S (2012) Longer term safety of dipeptidyl peptidase-4 inhibitors in patients with type 2 diabetes mellitus: systematic review and meta-analysis. Diabetes Obes Metab 14:1061–1072

7. Higgins JPT, Green S (editors) (2011) Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration. Available from www.cochrane-handbook.org

Appendix I: Risk of Bias Assessment Table

Reviewer: Study: Date:

	Low Risk	High Risk	Unclear Risk	Support
Random sequence generation (selection bias)				
Allocation concealment (selection bias)				
Blinding of participants and personnel (performance bias)				
Blinding of outcome assessment (detection bias)				
Incomplete outcome data addressed (attrition bias)				
Selective reporting (reporting bias)				
Other bias				
OVERALL				

Comments:

Appendix II: Data Extraction Form

DATA EXTRACTION FORM

STUDY ID _____ REVIEWER _____ Date _____

Study Characteristics

First Author:		
Title:		
Journal citation: (name; volume (issue):pp-pp)		
Year of publication:	Language:	Country(ies) where study conducted:
Funding: ☐ Private industry ☐ Foundation ☐ Government ☐ Internal ☐ Other ☐ Unclear		
Author's primary outcome:		
Author's inclusion criteria:	Author's exclusion criteria:	
Setting: Community ☐ Hospital general care ☐ Unclear ☐ Other specify)_____ Multi site ☐ Single site ☐		

Comments:

Design Characteristics

Study design: ☐ RCT – Parallel ☐ RCT – Crossover	If Crossover, was carryover effect mentioned? ☐ Yes ☐ No
Blinding: ☐ Both patients and physicians ☐ Patients only ☐ Neither / Not Stated – outcome assessment blind ☐ Neither / Not Stated – outcome assessment not blinded	
Intent to treat analysis: ☐ Yes ☐ No ☐ N/A	
Patient or data source	

Interventions

MEDICATION	ROUTE	DOSE	DURATION	NOTES
Treatment (_____)				
Control (_____)				

Number of patients that received full course of treatment as intended:

Tx (n_1 of N_1): **Control (n_2 of N_2):**

Co-Interventions

NAME	ROUTE	DOSE	DURATION	NOTES

Participants

Number of patients enrolled (Treatment/Control):	Number of patients completing the trial (Treatment/Control):
Number excluded after meeting inclusion criteria:	Number lost to follow up:
Length of study	
Reasons for exclusion: *[not the same as exclusion criteria on page 1; ones stated to explain why not included in analysis]*	
Number Withdrawals/Dropouts:	
If yes, reasons:	Intervention (incretin):
	Comparison (active comparator or placebo):
	All participants:
Patient Make-Up: ☐ Consecutive patients ☐ Random Sample ☐ Convenience Sample (by day of week, time, etc.) ☐ Other (volunteers) ☐ Unknown	

Baseline Characteristics

Please indicate the statistic, e.g., %, mean, SD, range, etc AND the units

	Intervention	**Comparison**	**All participants**
Males/females:			
Age (years):			

Race:			
Diabetes Duration (years):			
BMI (kg/m^2):			
A1C (%):			
FPG (mmol/L):			
PPPG (mmol/L)			
Other			

	Drug	**Dosage**	**Directions**
Anti-diabetic regimen at baseline			

Comments regarding baseline characteristics:

Outcomes

Time-points indicate time since RANDOMIZATION in DAYS.
Indicate which period if it's a crossover study or which subgroup where necessary

	Intervention			**Comparison**		
Dichotomous outcomes: **n/N**	Baseline	Time-point	Time-point	Baseline	Time-point	Time-point
Hypoglycemic episodes (count)						

Myocardial Infarction						
Stroke						
All-Cause Mortality						
ESRD/ Kidney Transplant						
MACE						
Other						

	Intervention			**Comparison**		
Continuous outcomes: **n mean(sd)**	Baseline	Time-point	Time-point	Baseline	Time-point	Time-point
A1c (%)						
FBG (mmol/L)						
Weight (kg)						
Serum Creatinine (µmol/L)						
Other						

ASSESSMENT OF Adverse OUTCOMES

Outcomes	Time-point:		Time-point:		Time-point:	
Adverse effects (Name)	**Tx**	**Cont**	**Tx**	**Cont**	**Tx**	**Cont**
1:						
2:						
3:						
4:						

Additional comments:

Appendix 2.B Search Strategy for PubMed

MeSH Search:
1) Kidney Disease [MeSH]
2) Renal Insufficiency [MeSH]
3) Albuminuria [MeSH]
4) Glomerular Filtration Rate [MeSH]
5) Incretin [MeSH]
6) Dipeptidyl Peptidase IV Inhibitors [MeSH]
7) Glucagon Like Peptide 1 [MeSH]
8) (#1 OR #2 OR #3 OR #4) AND (#5 OR #6 OR #7)

Keyword Search:
9) Kidney
10) Renal
11) Albumin*
12) CKD
13) "Glomerular filtration rate"
14) eGFR
15) #9 OR #10 OR #11 OR #12 OR #13 OR #14
16) Incretin*
17) "dipeptidyl peptidase IV inhibitor"
18) "dipeptidyl peptidase 4 inhibitor"
19) sitagliptin
20) Januvia
21) Ristaben
22) Tesavel
23) Xelevia
24) Glativ
25) saxagliptin
26) Onglyza
27) vildagliptin
28) Galvus
29) Zomarist
30) Jalra
31) Xiliarx
32) linagliptin
33) Tradjenta
34) Trazenta
35) alogliptin
36) Nesina
37) Teneligliptin
38) Tenelia
39) Anagliptin
40) Sulny
41) Gemigliptin

42) Zemiglo
43) Dutogliptin
44) #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43
45) "glucagon like peptide 1 receptor agonist"
46) exenatide
47) Byetta
48) Bydureon
49) liraglutide
50) Victoza
51) lixisenatide
52) Lyxumia
53) albiglutide
54) Tanzeum
55) #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54
56) #15 AND (#16 OR #17 OR #18 OR #44 OR #45 OR #55)
57) #8 OR #56

Limit to Randomized Controlled Trials:
58) (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT (animals[mh] NOT humans[mh]) NOT (Editorial[pt] OR Letter[pt] OR Case Reports[pt] OR Comment[pt])
59) #57 AND #58

Appendix 2.C Study-level patient characteristics

Study	Average Ave (years)	% Male	Duration of Diabetes (years)	Degree of Renal Impairment (CKD Stage)	eGFR (mL/min/ 1.73m^2)	A1C (%)	FPG (mmol/L)
Arjona Ferreira 2013a[26]	SITA: 60.5±9.1 GLIP: 58.5±9.9	62.5 56.9	19 16	ESKD (Stage 5)	NR	7.9 ± 0.7 7.8 ± 0.7	8.8 ± 2.7 9.2 ± 3.1
Arjona Ferreira 2013b[27]	SITA: 64.8±10.6 GLIP: 64.3±9.2	59.3 54.9	10.7 10.1	eGFR <50 mL/min/1.73m^2 (Stage 3/4/5)	NR	7.8 ± 0.7 7.8 ± 0.7	8.2 ± 2.2 8.0 ± 2.0
Barnett 2013[28]	NR	NR	NR	eGFR 30 to <60 mL/min/1.73m^2 (Stage 3) eGFR <30 mL/min/1.73m^2 (Stage 4/5)	NR	NR	NR
Chan 2008[29]	SITA: 68.9±9.8 PBO/GLIP: 65.3±9.7	48 62	13.6 ± 9.7 13.2 ± 8.9	*Stratum 1:* eGFR ≥30 to <50 mL/min/1.73m^2, no dialysis (Stage 3) *Stratum 2:* eGFR <30 mL/min/1.73m^2, no dialysis or ESKD on dialysis (Stage 4/5)	NR	7.6 ± 0.9 7.8 ± 0.9	8.9 ± 2.7 8.6 ± 2.0
Davies 2016[30]	LIRA: 68.0±8.3 PBO: 66.3±8.0	NR	15.86 14.17	eGFR 30-59 mL/min/1.73m^2 (Stage 3)	45.4 ± 0.23 45.5 ± 0.25	8.08 ± 0.79 8.00 ± 0.85	9.48 ± 3.27 9.27 ± 2.84
Idorn 2016[31]	LIRA: 68.3±3.1 PBO: 65.9±4.4	85	15.3 ±2.3 13.0 ± 2.4	ESKD on dialysis (Stage 5)	NR	6.7 ± 0.4 6.6 ± 0.4	NR
Kothny 2012[32]	*Mod* VILD: 67.1±9.0 PBO: 69.3±7.2 *Sev* VILD:	57.4 61.8 52.1 51.6	15.9 15.2 17.1 19.6	eGFR ≥30 to <50 ml/min/1.73m^2 and <30 ml/min/1.73m^2 (Stage 3/4/5)	*Mod* 39.5 ± 6.0 40.2 ± 5.6 *Sev* 22.3 ± 5.6 21.0 ± 6.4	*Mod* 7.9 ± 1.0 7.9 ± 1.0 *Sev* 7.7 ± 1.1 7.5 ± 1.1	*Mod* 9.1 ± 3.3 8.6 ± 2.7 *Sev* 8.3 ± 2.9 8.9 ± 3.6

	63.7±9.1 PBO: 65.4±10.5						
Laakso 2013[33]	LINA: 67.3±9.2 PBO/GLIM : 65.9±9.4	61.9 64.8	NR	eGFR <60 mL/min/1.73m^2, no dialysis (Stage 3/4/5)	37.2	8.08 ± 0.89 8.03 ± 0.94	8.6 ± 2.5 8.3 ± 2.9
McGill 2013[34]	LINA: 64.0±10.9 PBO: 64.9±9.6	66.2 53.8	NR	eGFR <30 mL/min/1.73m^2 (Stage 4/5)	22.1±6.3 25.1±6.9	8.2±1.1 8.2±0.9	8.3±4.4 8.9±3.6
Nowicki 2011[35]	SAXA: 66.8±8.3 PBO: 66.2±9.1	37.6 48.2	15.1±7.5 18.2±8.5	eGFR ≤50 mL/min/1.73m^2 or ESKD (Stage 3/4/5)	NR	8.5±1.2 8.1±1.1	10.4±3.9 9.4±3.3
Scirica 2014[36, 48]	*Mod*: 70 *Sev*: 70	57.7 54.8	13.2 15.7	eGFR 30-50 mL/min/1.73m^2 (Stage 3) eGFR <30 mL/min/1.73m^2 (Stage 4/5)	42.9 24.7	7.6 7.6	7.7 7.6
White 2013[37, 49]	NR	NR	NR	eGFR <60 mL/min/1.73m^2 no dialysis (Stage 3/4/5)	*Mod:* ALO: 48.5 PBO: 48.4 *Sev:* ALO: 22.6 PBO: 22.9	NR	NR
Yoon 2015[38]	62.0	NR	16.3	Moderate or Severe (Stage 3/4/5)	33.3	8.4	NR

Data are expressed as mean ± SD.
Mod = eGFR <60 mL/min/1.73m^2, Sev = eGFR <30 mL/min/1.73m^2, MD = mean difference, 95%CI = 95% confidence interval, RR = risk ratio, PBO = placebo, AC = active comparator, ALO = alogliptin, SITA = sitagliptin, GLIP = glipizide, PBO = placebo, VILD = vildagliptin, LINA = linagliptin, SAXA = saxagliptin, ALBI = albiglutide, GLIM = glimepiride, LIRA = liraglutide, NR = not reportable

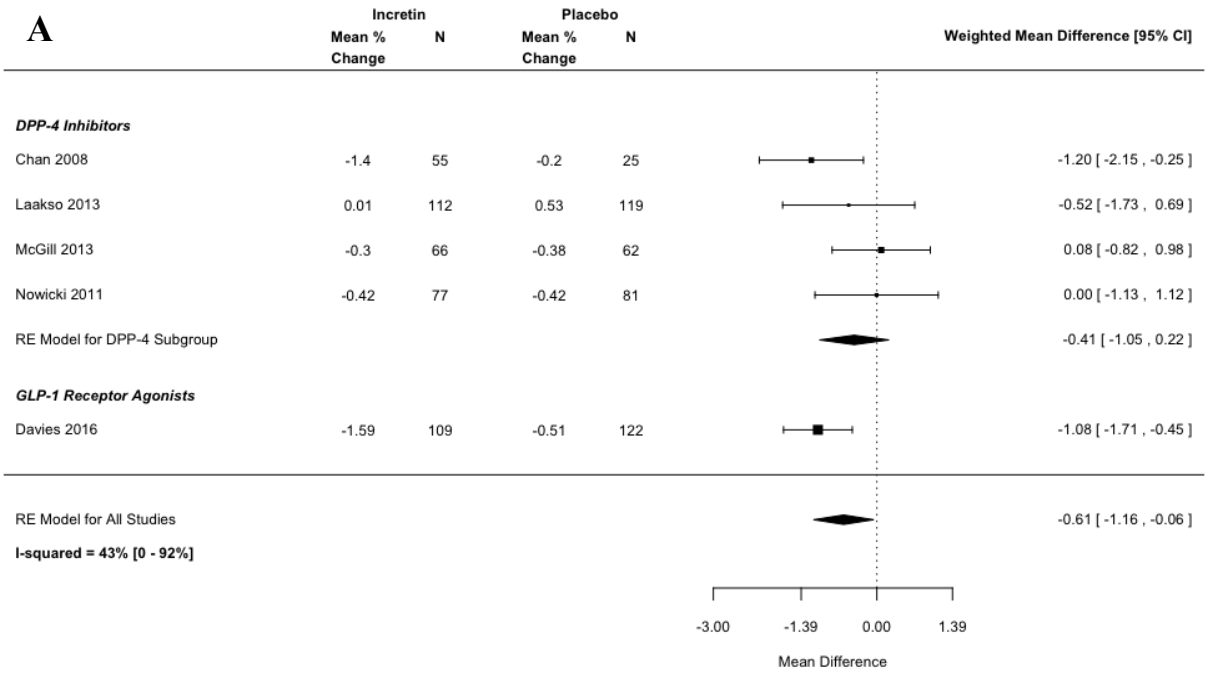
Appendix 2.D Outcome Definitions by Study

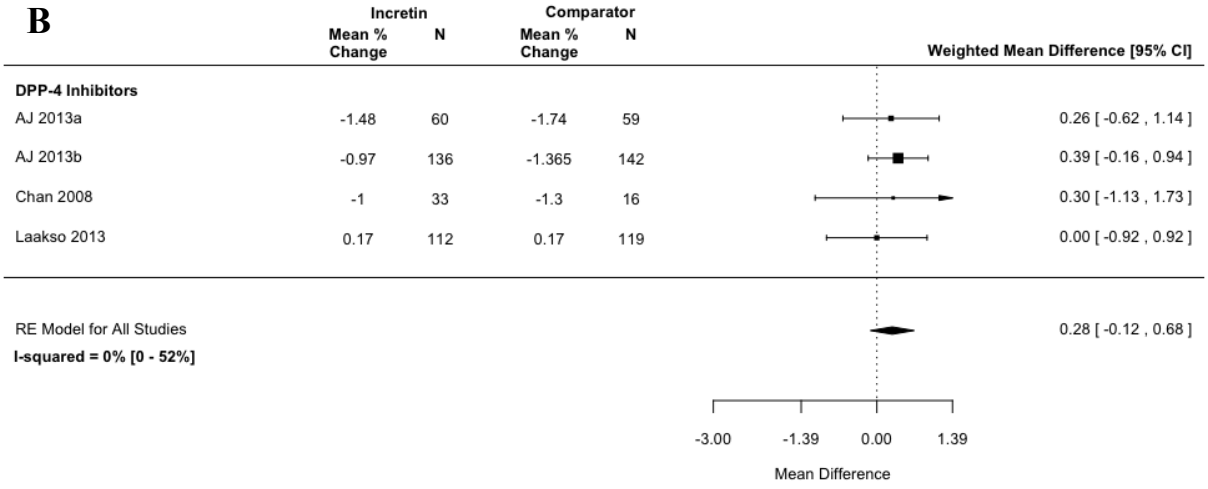
Study	Outcome Definitions
Arjona Ferreira 2013a	*Severe hypoglycemia:* events requiring nonmedical assistance, medical intervention, exhibiting markedly depressed level of consciousness, loss of consciousness or seizure
Arjona Ferreira 2013b	*Severe hypoglycemia:* events requiring nonmedical assistance, medical intervention, exhibiting markedly depressed level of consciousness, loss of consciousness or seizure
Barnett 2013	*NR*
Chan 2008	*Hypoglycemia:* those not requiring assistance, those requiring (non-medical) assistance, those requiring medical intervention or exhibiting markedly depressed level of consciousness, loss of consciousness or seizure.
Davies 2016	*Severe Hypoglycemia*: an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions
Idorn 2016	*Major hypoglycemic episode:* blood glucose <3.1mmol/l and requiring assistance from third person
Kothny 2012	*Severe hypoglycemia:* any episode requiring assistance of another party (whether or not a confirmatory self-monitored blood glucose measure was available)
Laakso 2013	*Severe hypoglycemia*: requiring third party assistance *MACE:* CV death, MI, stroke or hospitalization due to unstable angina
McGill 2013	*Severe hypoglycemia:* event requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions *MACE:* CV death, MI, stroke, and hospitalization for unstable angina
Nowicki 2011	*Confirmed hypoglycemia:* finger-stick glucose value ≤2.8mmol/l with associated symptoms
Scirica 2014	*Major hypoglycemic episode:* events that required a third party to actively intervene *MACE:* CV death, MI, ischemic stroke
White 2013	*MACE:* CV death, non-fatal MI, non-fatal stroke
Yoon 2015	*NR*

MACE = major adverse cardiovascular events, MI = myocardial infarction, NR = not reported

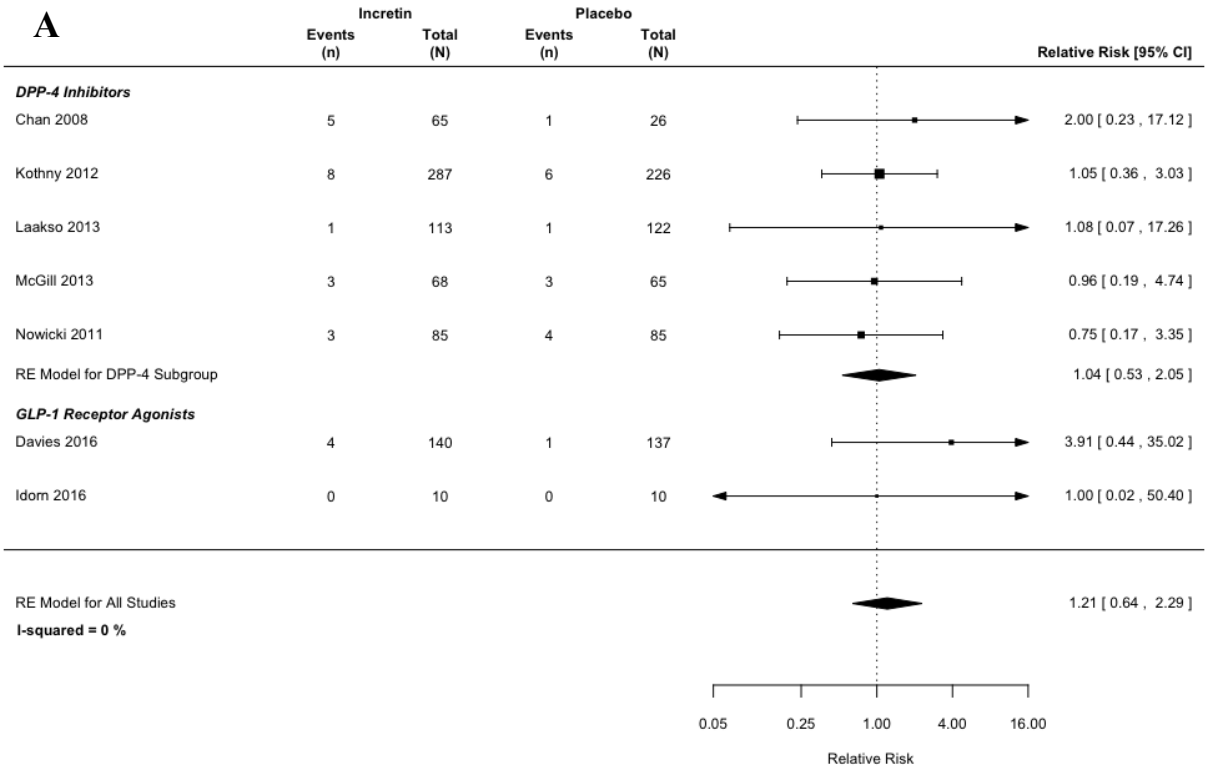
Appendix 2.E Forest plots for relative treatment effect of incretins on secondary outcomes

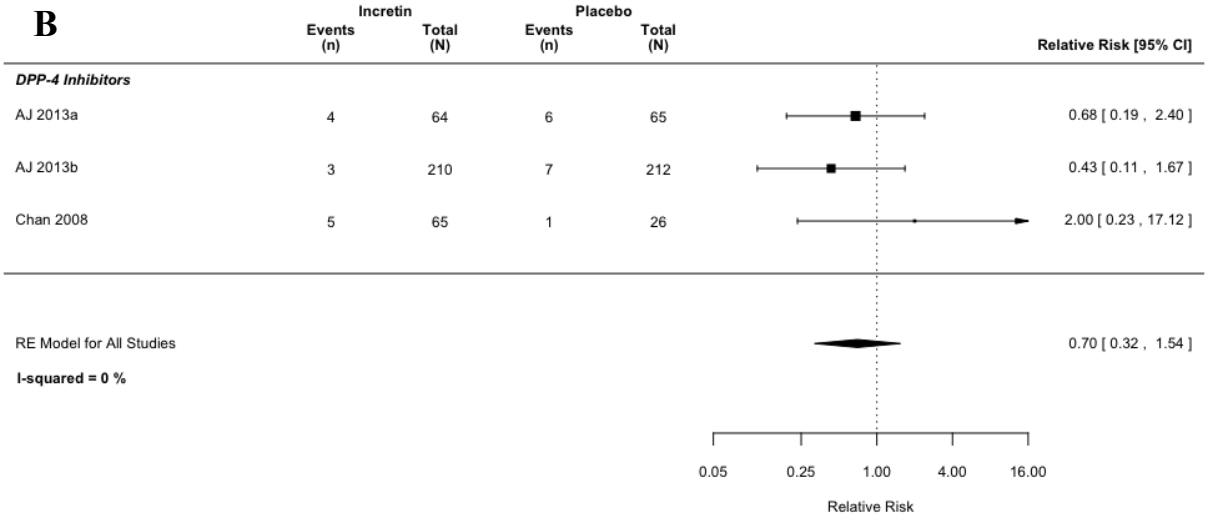
a. Forest plots for relative treatment effect of incretins on fasting plasma glucose versus placebo (A) and active comparator (B). Weights are from random effects analysis.



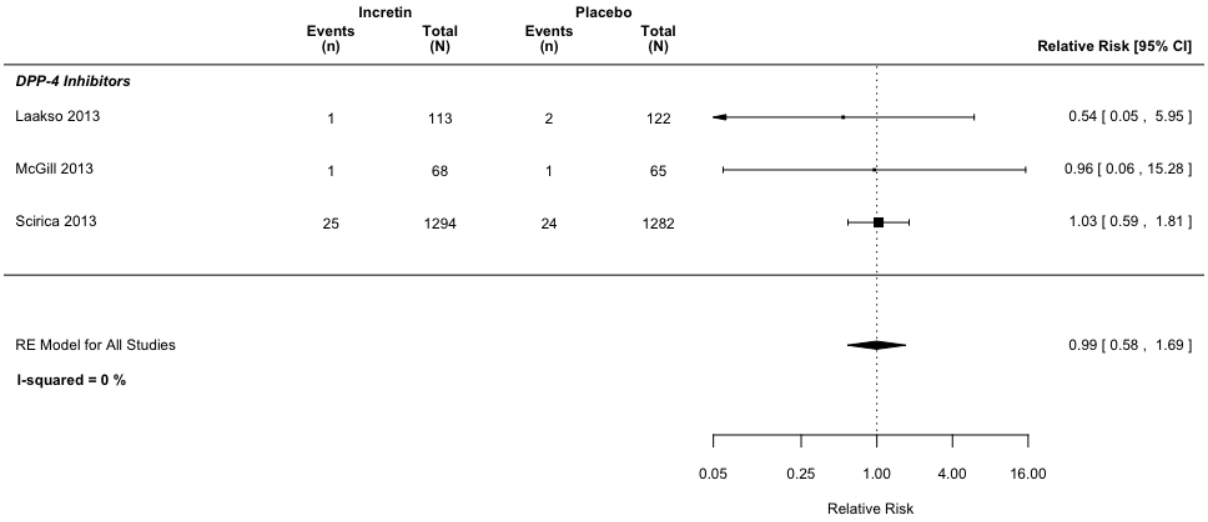


b. Forest plots for relative treatment effect of incretins on all-cause mortality versus placebo (A) and active comparator (B).

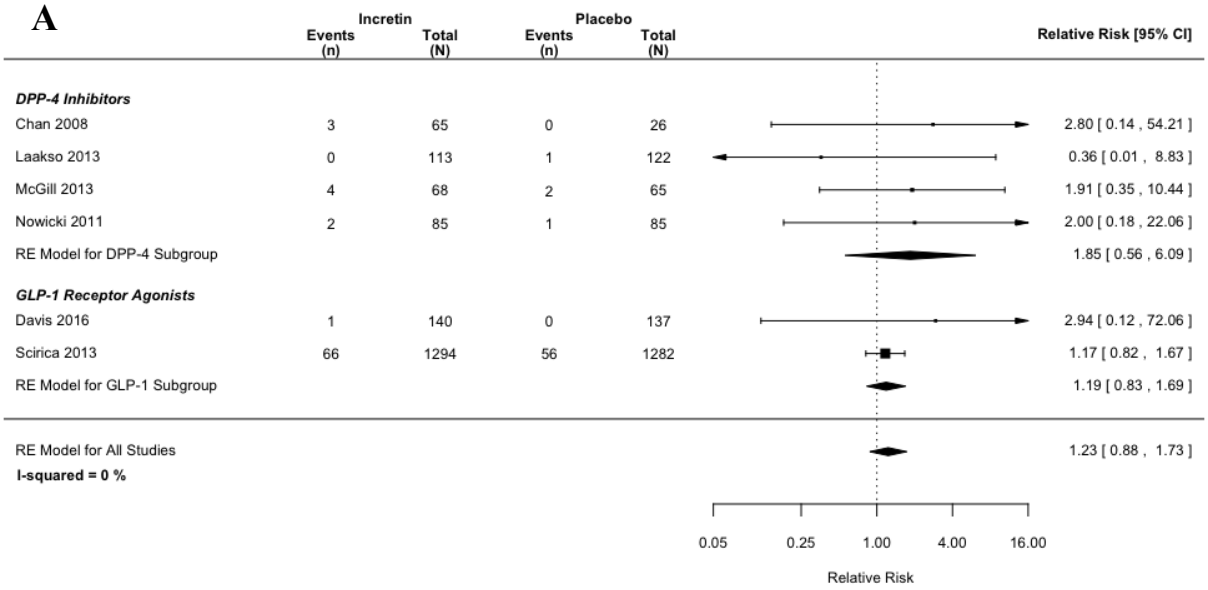


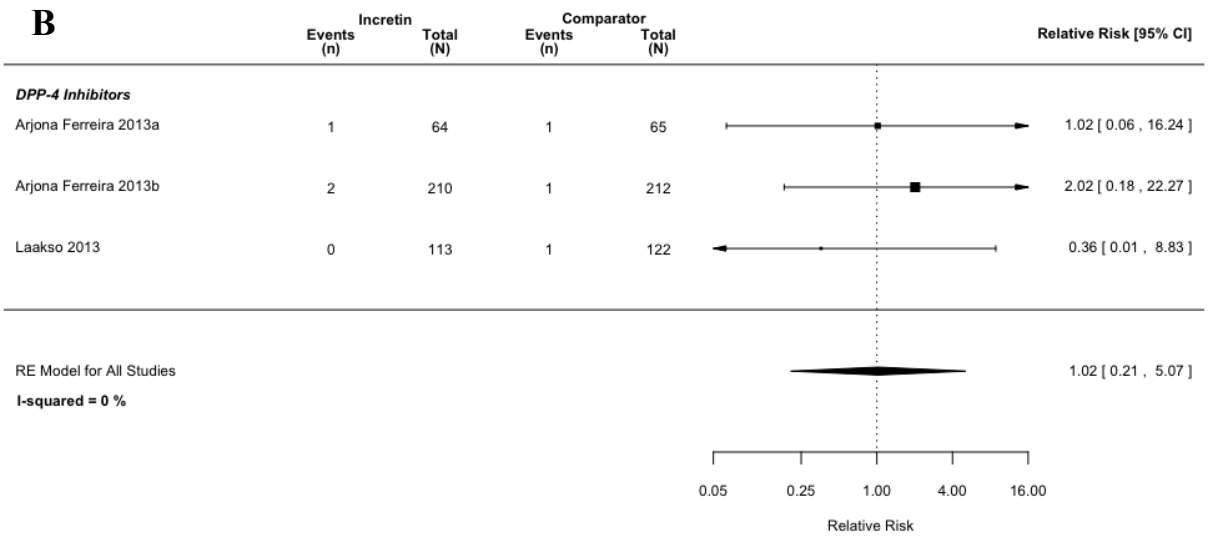


c. Forest plots for relative treatment effect of incretins on stroke versus placebo.

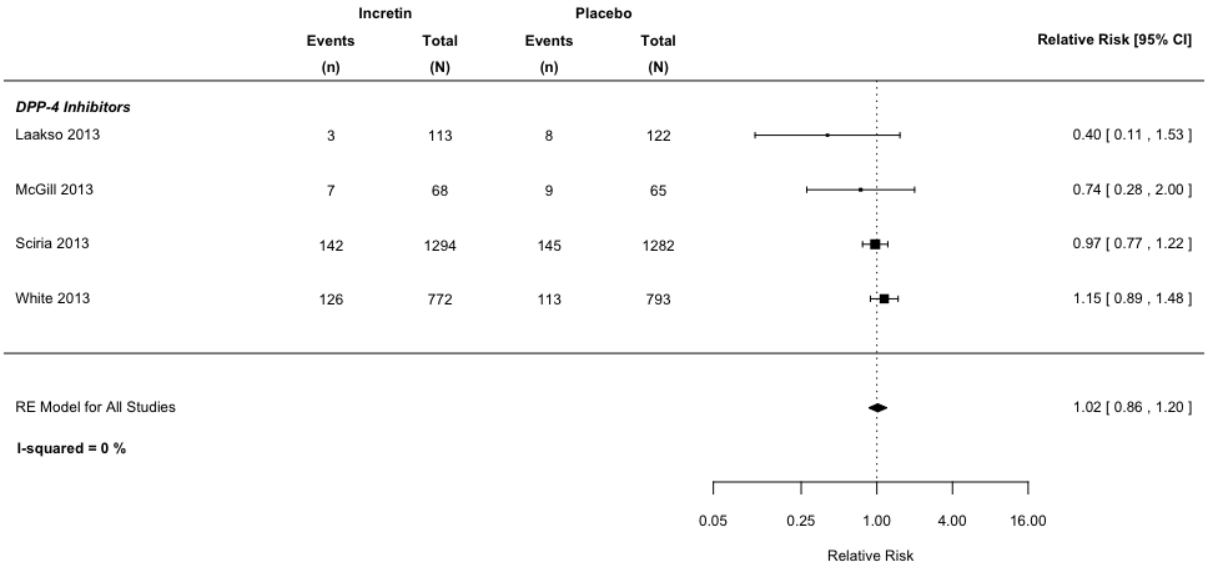


d. Forest plots for relative treatment effect of incretins on myocardial infarction versus placebo (A) and active comparator (B).

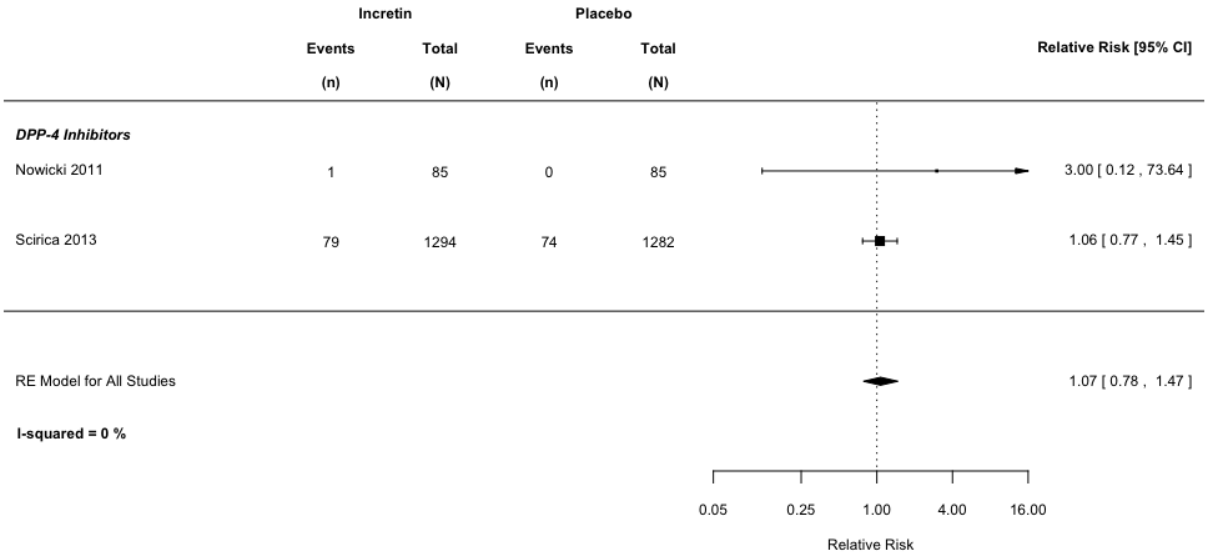




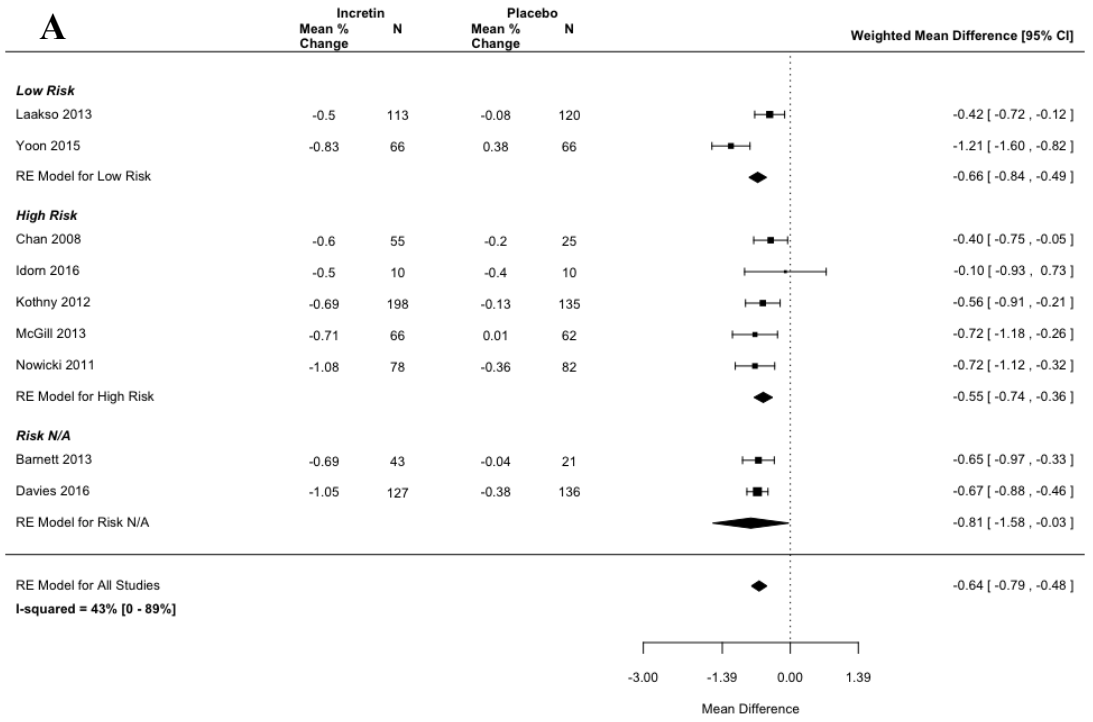
e. Forest plots for relative treatment effect of incretins on major adverse cardiovascular events versus placebo.

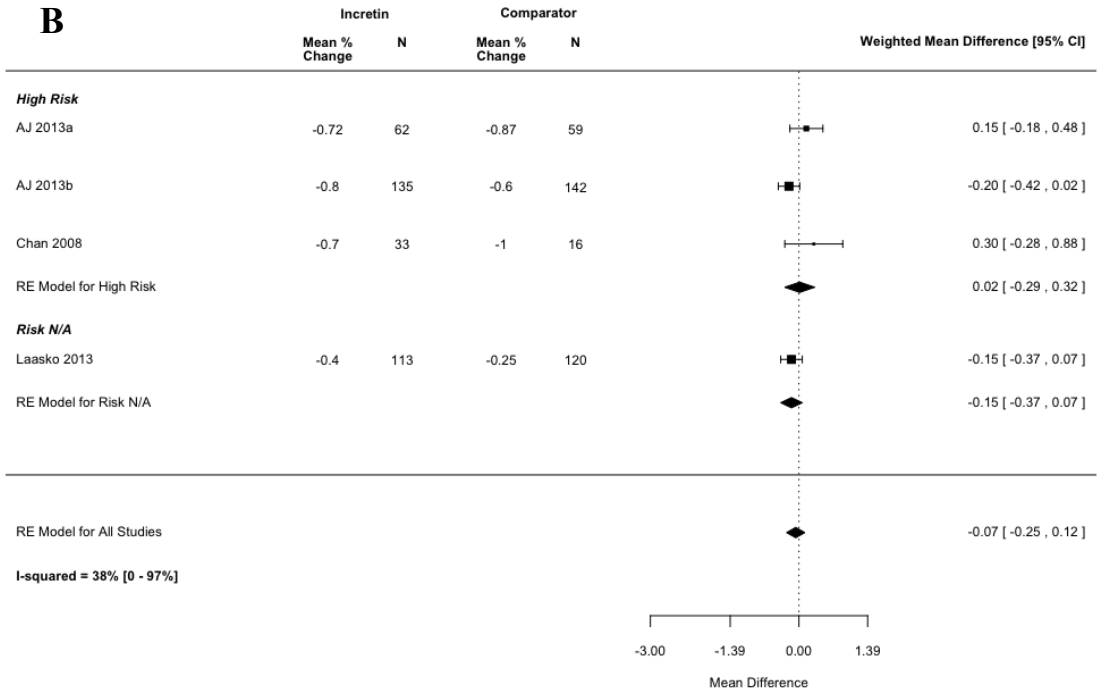


f. Forest plots for relative treatment effect of incretins on end-stage renal disease/ dialysis/ transplant versus placebo.

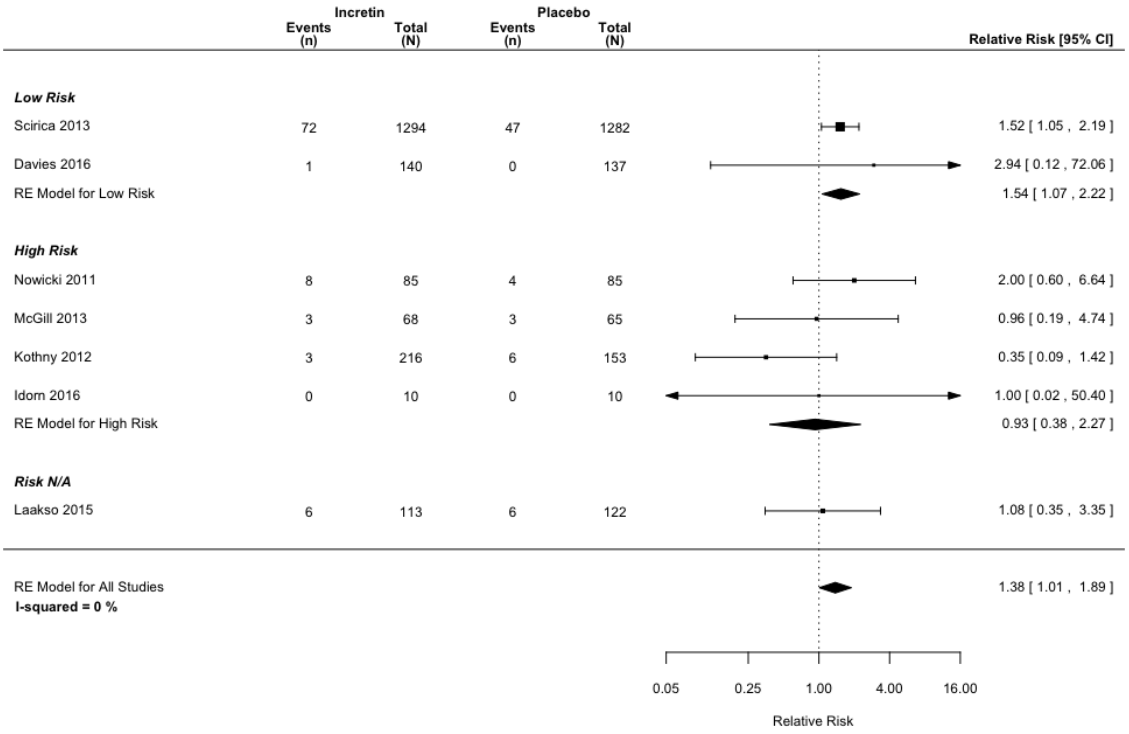


Appendix 2.F Forest plots for subgroup analysis by risk of bias for relative treatment effect of incretins versus placebo and active comparators for primary outcomes: A) Change in A1C (%) for Incretin vs. Placebo B) Change in A1C (%) for Incretin vs. Active Comparator C) Hypoglycemia for Incretin vs. Placebo D) Hypoglycemia for Incretin vs. Active Comparator. Weights are from random effects analysis.

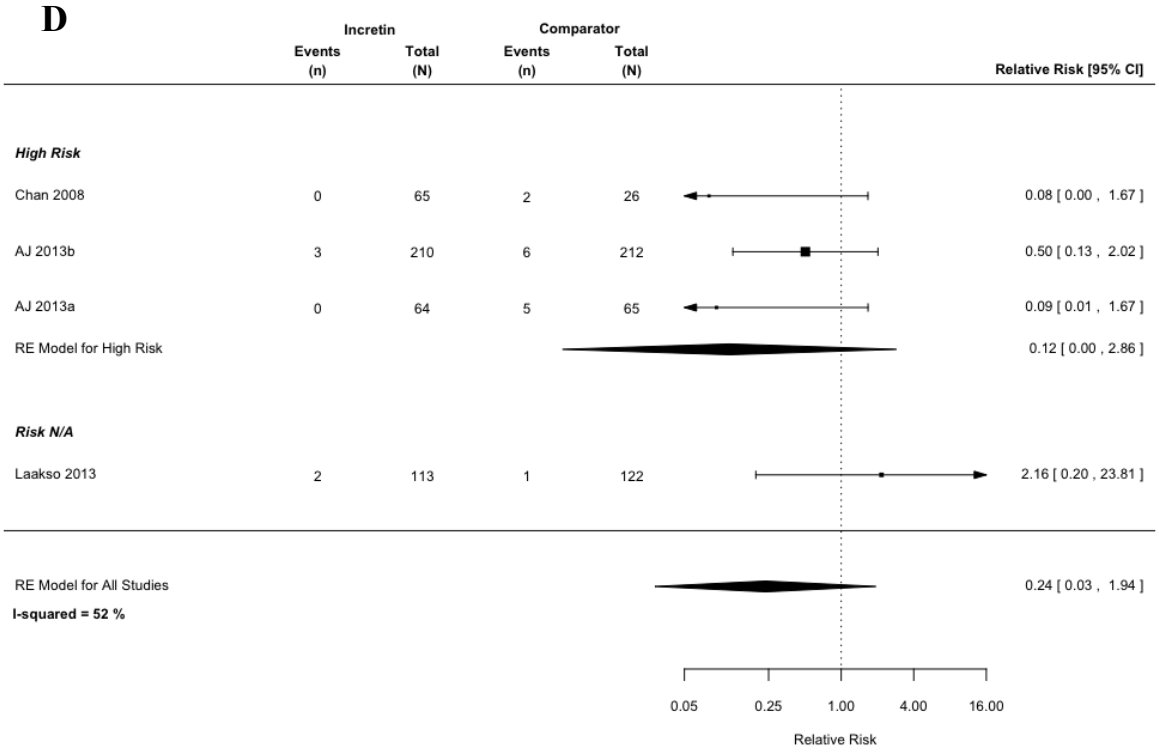




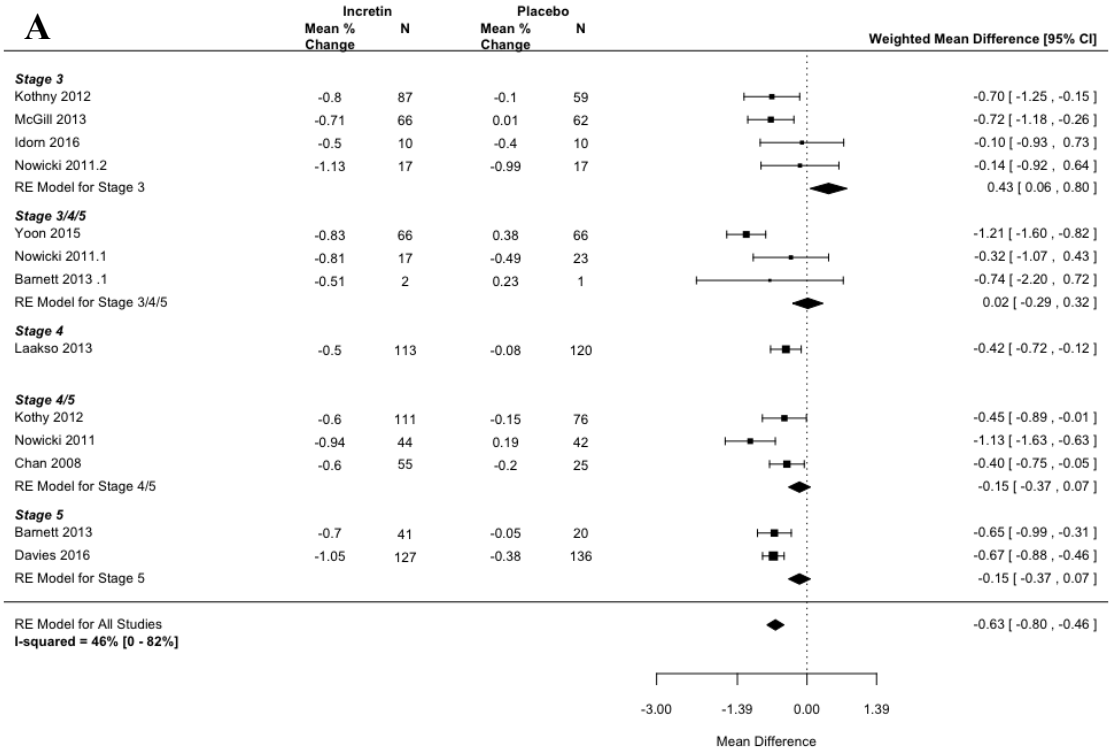
C

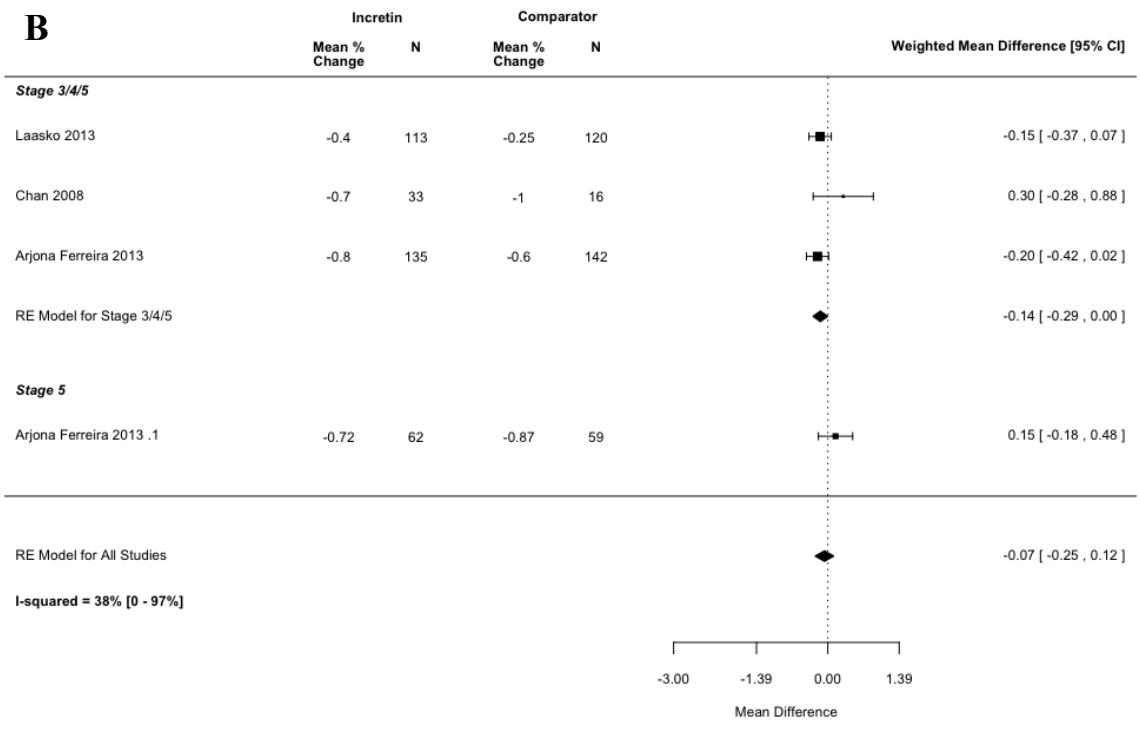

Incretin
Placebo
Events (n)
Total (N)
Events (n)
Total (N)
Relative Risk [95% CI]
Low Risk
Scirica 2013 72 1294 47 1282 1.52 [1.05 , 2.19]
Davies 2016 1 140 0 137 2.94 [0.12 , 72.06]
RE Model for Low Risk 1.54 [1.07 , 2.22]
High Risk
Nowicki 2011 8 85 4 85 2.00 [0.60 , 6.64]
McGill 2013 3 68 3 65 0.96 [0.19 , 4.74]
Kothny 2012 3 216 6 153 0.35 [0.09 , 1.42]
Idom 2016 0 10 0 10 1.00 [0.02 , 50.40]
RE Model for High Risk 0.93 [0.38 , 2.27]
Risk N/A
Laakso 2015 6 113 6 122 1.08 [0.35 , 3.35]
RE Model for All Studies 1.38 [1.01 , 1.89]
I-squared = 0 %
0.05
0.25
1.00
4.00
16.00
Relative Risk

D

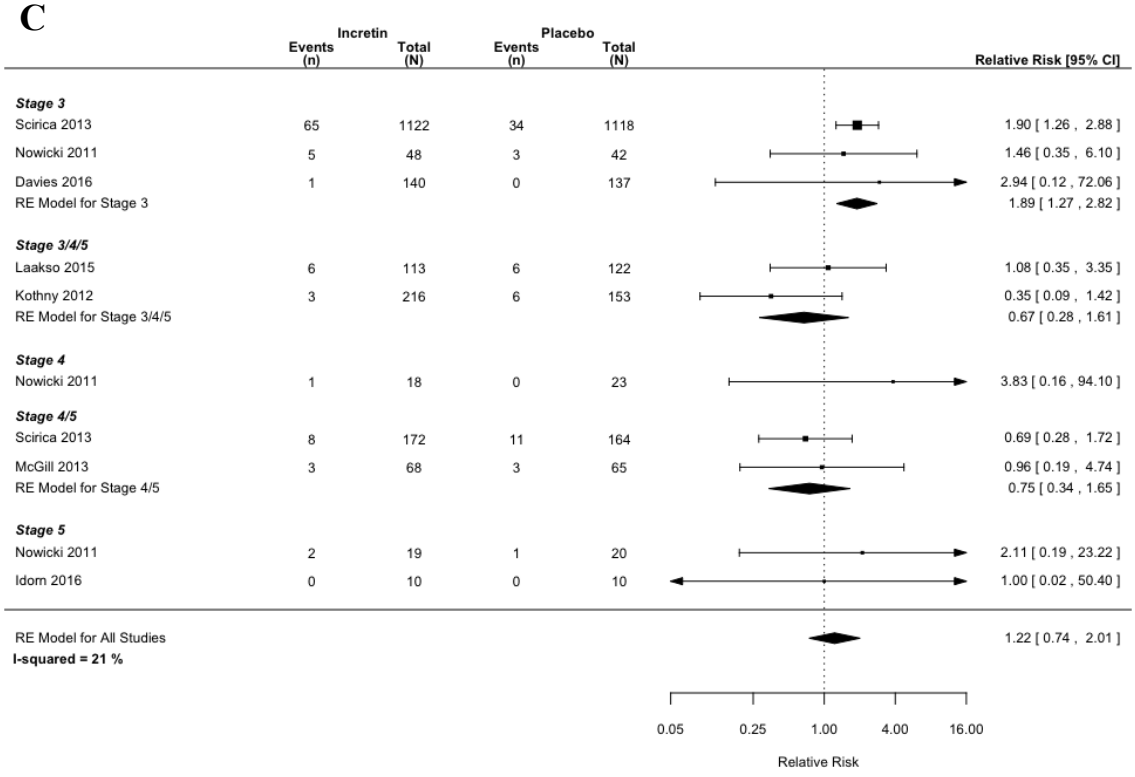

Incretin
Comparator
Events (n)
Total (N)
Events (n)
Total (N)
Relative Risk [95% CI]
High Risk
Chan 2008 0 65 2 26 0.08 [0.00 , 1.67]
AJ 2013b 3 210 6 212 0.50 [0.13 , 2.02]
AJ 2013a 0 64 5 65 0.09 [0.01 , 1.67]
RE Model for High Risk 0.12 [0.00 , 2.86]
Risk N/A
Laakso 2013 2 113 1 122 2.16 [0.20 , 23.81]
RE Model for All Studies 0.24 [0.03 , 1.94]
I-squared = 52 %
0.05
0.25
1.00
4.00
16.00
Relative Risk

Appendix 2.G Forest plots for subgroup analysis by CKD Stage for relative treatment effect of incretins versus placebo and active comparators for primary outcomes: A) Change in A1C (%) for Incretin vs. Placebo B) Change in A1C (%) for Incretin vs. Active Comparator C) Hypoglycemia for Incretin vs. Placebo D) Hypoglycemia for Incretin vs. Active Comparator. Weights are from random effects analysis.

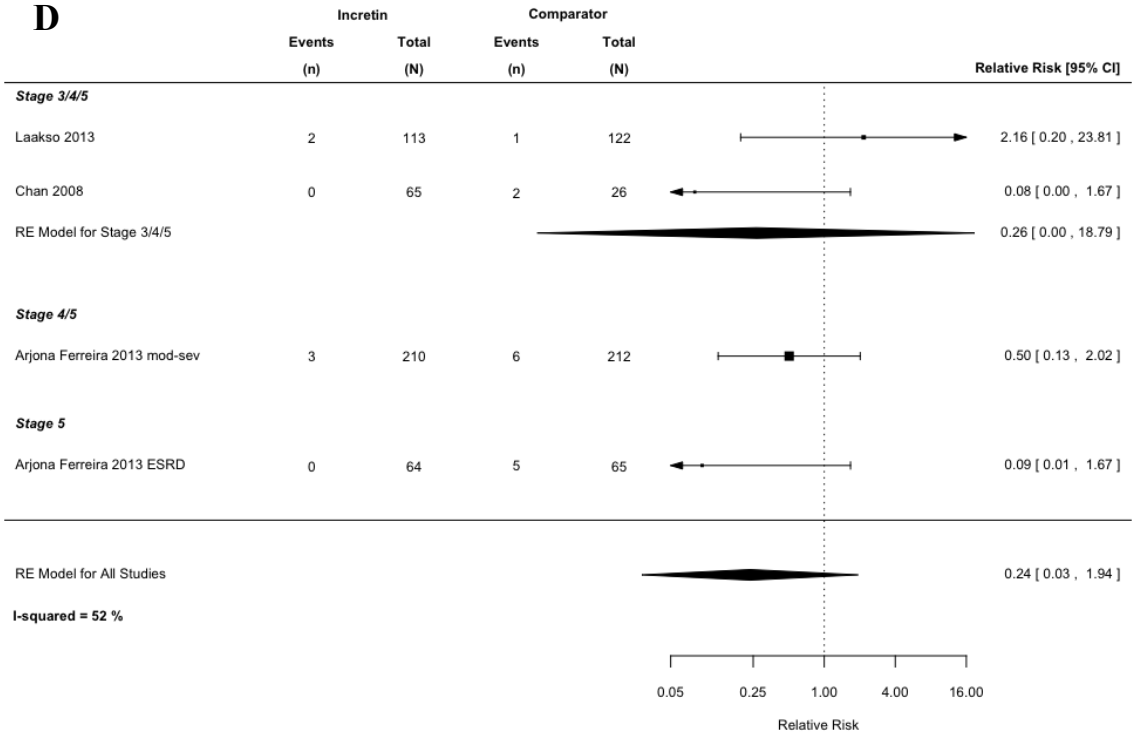




C


Incretin
Placebo
Events (n)
Total (N)
Events (n)
Total (N)
Relative Risk [95% CI]
Stage 3
Scirica 2013 65 1122 34 1118 1.90 [1.26 , 2.88]
Nowicki 2011 5 48 3 42 1.46 [0.35 , 6.10]
Davies 2016 1 140 0 137 2.94 [0.12 , 72.06]
RE Model for Stage 3 1.89 [1.27 , 2.82]
Stage 3/4/5
Laakso 2015 6 113 6 122 1.08 [0.35 , 3.35]
Kothny 2012 3 216 6 153 0.35 [0.09 , 1.42]
RE Model for Stage 3/4/5 0.67 [0.28 , 1.61]
Stage 4
Nowicki 2011 1 18 0 23 3.83 [0.16 , 94.10]
Stage 4/5
Scirica 2013 8 172 11 164 0.69 [0.28 , 1.72]
McGill 2013 3 68 3 65 0.96 [0.19 , 4.74]
RE Model for Stage 4/5 0.75 [0.34 , 1.65]
Stage 5
Nowicki 2011 2 19 1 20 2.11 [0.19 , 23.22]
Idorn 2016 0 10 0 10 1.00 [0.02 , 50.40]
RE Model for All Studies 1.22 [0.74 , 2.01]
I-squared = 21 %
0.05
0.25
1.00
4.00
16.00
Relative Risk

D


Incretin
Comparator
Events (n)
Total (N)
Events (n)
Total (N)
Relative Risk [95% CI]
Stage 3/4/5
Laakso 2013 2 113 1 122 2.16 [0.20 , 23.81]
Chan 2008 0 65 2 26 0.08 [0.00 , 1.67]
RE Model for Stage 3/4/5 0.26 [0.00 , 18.79]
Stage 4/5
Arjona Ferreira 2013 mod-sev 3 210 6 212 0.50 [0.13 , 2.02]
Stage 5
Arjona Ferreira 2013 ESRD 0 64 5 65 0.09 [0.01 , 1.67]
RE Model for All Studies 0.24 [0.03 , 1.94]
I-squared = 52 %
0.05
0.25
1.00
4.00
16.00
Relative Risk

Appendix 3.A Complete list of baseline covariates adjusted for in the regression model

Age at initiation of second-line agent	Sex
Index of deprivation (socioeconomic indicator)	HbA1c
Smoking status	CKD stage
BMI	Systolic blood pressure
Number of physician visits during the year prior to second-line therapy initiation	Charlson comorbidity index
History of cardiovascular disease	Duration of treated diabetes
Use of the following agents in the year prior to second-line therapy initiation: statins, NSAIDs, calcium channel blockers, beta blockers, anticoagulants, antiplatelets, and agents that at on the renin-angiotensin system	Duration of metformin overlap

Appendix 3.B Summary of Cardiovascular Events (n=4650)

	MACE	STROKE	MI	CVD
SU	385	237	143	60
DPP4i	33	21	8	NR
GLP1ra	NR	NR	NR	NR
Insulin	22	14	14	10
TZD	33	27	9	6
Other	7	NR	NR	NR
TOTAL	**480**	**299**	**174**	**76**

* NR = not reportable

Appendix 3.C Adjusted Cox model subgroup analysis for Major Adverse Cardiovascular Events (MACE) in patients using 2nd-line DPP4i compared to 2nd-line SU

Group	Events (n)	Events: SU (n)	Events: DPP4i (n)	Patients (n)	Adjusted HR [95% CI]	p-value (interaction)
AGE						0.18
<65	68	43	9	1068	1.49 [0.82-2.71]	
≥65	413	342	24	3582	0.94 [0.26-3.35]	
SEX						0.0008*
male	227	187	8	2107	1.61 [0.29-8.95]	
female	254	198	25	2543	5.80 [2.21-15.2]	
eGFR						0.80
<45	114	99	5	790	0.97 [0.28-3.30]	
45-60	367	286	28	3860	1.09 [0.77-1.53]	

*p-value <0.001
DPP4i=dipeptidyl-peptidase-4 inhibitor, SU=sulfonylurea

Appendix 3.D Adjusted Cox model subgroup analysis for Myocardial Infarction (MI) in patients using 2nd-line DPP4i compared to 2nd-line SU

Group	Events (n)	Events: SU (n)	Events: DPP4i (n)	Patients (n)	Adjusted HR [95% CI]	p-value (interaction)
AGE						0.07
<65	24	13	NR	1068	1.5 [0.54-4.15]	
≥65	153	130	5	3582	O.45 [0.05-4.50]	
SEX						0.13
male	105	87	NR	2107	1.09 [0.47-25.27]	
female	72	56	5	2543	2.92 [0.45-19.02]	
eGFR						0.42
<45	39	34	NR	790	1.14 [0.11-11.36]	
45-60	138	109	7	3860	0.60 [0.29-1.22]	

* NR = not reportable
DPP4i=dipeptidyl-peptidase-4 inhibitor, SU=sulfonylurea

Appendix 3.E Adjusted Cox model subgroup analysis for Stroke Events in patients using 2nd-line DPP4i compared to 2nd-line SU

Group	Events (n)	Events: SU (n)	Events: DPP4i (n)	Patients (n)	Adjusted HR [95% CI]	p-value (interaction)
AGE						0.85
<65	45	29	NR	1068	1.04 [0.44-2.48]	
≥65	259	208	17	3582	0.95 [0.15-5.95]	
SEX						0.009*
male	129	105	NR	2107	1.48 [0.10-21.4]	
female	175	132	18	2543	7.62 [1.79-32.4]	
eGFR						0.85
<45	72	59	NR	790	1.06 [0.22-5.03]	
45-60	232	178	17	3860	0.96 [0.61-1.51]	

*p-value <0.0. NR = not reportable
DPP4i=dipeptidyl-peptidase-4 inhibitor, SU=sulfonylurea

Appendix 3.F Adjusted Cox model subgroup analysis for Cardiovascular Death (CVD) in patients using 2nd-line DPP4i compared to 2nd-line SU

Group	Events (n)	Events: SU (n)	Events: DPP4i (n)	Patients (n)	Adjusted HR [95% CI]	p-value (interaction)
AGE						1.0
<65	10	6	NR	1068	<0.001 [0.00-Inf]	
≥65	66	54	NR	3582	<0.001 [0.00-Inf]	
SEX						1.0
male	44	35	NR	2107	<0.001 [0.00-Inf]	
female	32	25	NR	2543	<0.001 [0.00-Inf]	
eGFR						1.0
<45	23	19	NR	790	<0.001 [0.00-Inf]	
45-60	53	41	NR	3860	<0.001 [0.00-Inf]	

DPP4i=dipeptidyl-peptidase-4 inhibitor, SU=sulfonylurea