INCRETIN-BASED DRUGS AND THE INCIDENCE OF ENDOMETRIAL CANCER AMONG PATIENTS WITH TYPE 2 DIABETES

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ABSTRACT

Background: Incretin-based drugs, which include glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and dipeptidyl peptidase-4 (DPP-4) inhibitors, are second-to third-line antihyperglycemic drugs used to treat type 2 diabetes. Type 2 diabetes is a major risk factor for the development of endometrial cancer. There is novel experimental evidence proposing that incretin-based drugs may attenuate the growth of endometrial cancer cells. Laboratory studies have found that treating human endometrial cells with an incretin-based drug can slow tumour growth rates in a dose-dependent manner. However, there is a paucity of research on the association between the use of incretin-based drugs and the risk of endometrial cancer in the real-world setting.

Objective: The objective of this thesis is to determine whether the use of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and dipeptidyl peptidase-4 (DPP-4) inhibitors, separately, is associated with a decreased risk of endometrial cancer.

Research Design and Methods: Using data from the United Kingdom Clinical Practice Research Datalink linked to the Hospital Episodes Statistics Admitted Patient Care database, Index of Multiple Deprivation and the Office for National Statistics Death Registration Data, we assembled two separate cohorts of female patients with type 2 diabetes. Using sulfonylureas (another second-to third-line drug) as an active-comparator, cohort 1 included those who were newly prescribed GLP-1 RAs or sulfonylureas and cohort 2 included those who were newly prescribed DPP-4 inhibitors or sulfonylureas from January 1, 2007 to December 31, 2020, with follow-up until March 29, 2021. Propensity score fine stratification weighted Cox proportional hazards models were used to estimate adjusted hazard ratios (HRs) and their 95% confidence

intervals (CIs) for incident endometrial cancer. In secondary analyses, we stratified based on drug type within each incretin-based drug, by previous use of the other incretin-based drug before cohort entry and body mass index levels.

Results: Cohort 1 included 9,239 new users of GLP-1 RAs and 80,086 new users of sulfonylureas. The use of GLP-1 RAs was not associated with a decreased risk of endometrial cancer when compared with the use of sulfonylureas (weighted incidence rates 1.26 and 1.41 per 1000 person-years, respectively; HR: 1.11, 95% CI: 0.66-1.88). In secondary analyses, GLP-1 RA drug types generated similar results, except for exenatide, which was associated with an increased risk for endometrial cancer when compared to sulfonylureas (HR: 2.26, 95% CI:1.06-4.82). Cohort 2 included 42,486 new users of DPP-4 inhibitors and 79,353 new users of sulfonylureas. The use of DPP-4 inhibitors was not associated with a decreased risk of endometrial cancer when compared to the use of sulfonylureas (weighted IR 1.38 and 1.38, respectively; HR: 1.00, 95% CI: 0.76-1.32). In secondary analyses, the different DPP-4 inhibitor drug types generated similar results.

Conclusions: The results of this large, population-based study indicate that the overall use of GLP-1 RAs and DPP-4 inhibitors was not associated with a decreased risk of endometrial cancer when compared with the use of sulfonylureas. Interestingly, exenatide, a type of GLP-1 RA was associated with an elevated risk of endometrial cancer when compared with the use of sulfonylureas among females with type 2 diabetes.

RÉSUMÉ

Contexte : Les médicaments à base d'incrétines, incluant les agonistes des récepteurs du peptide-1 de type glucagon (GLP-1 RA) et les inhibiteurs de la dipeptidyl peptidase-4 (DPP-4), représentent des antihyperglycémiants de deuxième à troisième ligne utilisés dans le traitement du diabète de type 2. Ce dernier constitue un facteur de risque majeur pour le développement du cancer de l'endomètre. Des études récentes récentes suggèrent que les médicaments à base d'incrétines pourraient freiner la croissance des cellules cancéreuses endométriales. En laboratoire, le traitement des cellules endométriales humaines avec ces médicaments a montré une réduction de la vitesse de croissance tumorale de manière dose-dépendante. Cependant, les recherches portant sur l'association entre l'utilisation de ces médicaments et le risque de cancer de l'endomètre dans des conditions réelles restent limitées.

Objectif : Cette thèse vise à déterminer si l'utilisation des agonistes des récepteurs du peptide-1 de type glucagon (GLP-1 RA) et des inhibiteurs de la dipeptidyl peptidase-4 (DPP-4), de manière séparée, est associée à une diminution du risque de cancer de l'endomètre.

Conception de la recherche et méthodes : En utilisant les données du Clinical Practice Research Datalink du Royaume-Uni, reliées à la base de données Hospital Episodes Statistics Admitted Patient Care, à l'Index de Déprivation Multiple et aux données de l'Office for National Statistics sur les enregistrements de décès, nous avons constitué deux cohortes distinctes de patientes atteintes de diabète de type 2 ayant récemment reçu une prescription de GLP-1 RA ou de sulfonylurées (cohorte 1) et d'inhibiteurs de DPP-4 ou de sulfonylurées (cohorte 2) entre le 1er janvier 2007 et le 31 décembre 2020, avec un suivi jusqu'au 29 mars 2021. Des modèles de risques proportionnels de Cox, pondérés par une stratification fine des scores de propension, ont

été utilisés pour estimer les ratios de risque ajustés (RR) et leurs intervalles de confiance à 95 % (IC) pour l'apparition d'un cancer de l'endomètre. Dans des analyses secondaires, nous avons stratifié les résultats en fonction du type de médicament au sein de chaque catégorie d'incrétines, de l'utilisation antérieure de l'autre catégorie d'incrétines avant l'entrée dans la cohorte et des niveaux d'indice de masse corporelle.

Résultats : La cohorte 1 comprenait 9 239 nouvelles utilisatrices de GLP-1 RA et 80 086 nouvelles utilisatrices de sulfonylurées. L'utilisation des GLP-1 RA n'était pas associée à une diminution du risque de cancer de l'endomètre comparativement à l'utilisation des sulfonylurées (taux d'incidence pondéré de 1,26 et 1,41 pour 1000 personnes-années, respectivement ; RR : 1,11, IC 95 % : 0,66-1,88). Lors de l'analyse par type de GLP-1 RA dans les analyses secondaires, l'exénatide était associée à un risque accru de cancer de l'endomètre comparativement aux sulfonylurées (RR : 2,26, IC 95 % : 1,06-4,82). La cohorte 2 comprenait 42 486 nouvelles utilisatrices d'inhibiteurs de DPP-4 et 79 353 nouvelles utilisatrices de sulfonylurées. L'utilisation des inhibiteurs de DPP-4 n'était pas associée à une diminution du risque de cancer de l'endomètre comparativement à l'utilisation des sulfonylurées (TDI pondéré de 1,38 pour les deux groupes ; RR : 1,00, IC 95 % : 0,76-1,32).

Conclusions : Les résultats de cette vaste étude populationnelle indiquent que l'utilisation globale des GLP-1 RA et des inhibiteurs de DPP-4 n'est pas associée à une diminution du risque de cancer de l'endomètre comparativement à l'utilisation des sulfonylurées. De manière intéressante, l'exénatide, un type de GLP-1 RA, est associée à un risque accru de cancer de l'endomètre comparativement aux sulfonylurées chez les femmes atteintes de diabète de type 2.

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AUTHOR CONTRIBUTIONS

This thesis consists of a literature review, original research manuscript, discussion of results, and final conclusions. Sonny Rothman and Dr. Laurent Azoulay conceptualized the project, developed the research question and devised the study design. Sonny Rothman, Hui Yin and Dr. Laurent Azoulay contributed to the statistical analysis. Sonny Rothman drafted the thesis and corresponding manuscript. Dr. Oriana Yu and Dr. Michael Pollok both contributed to the interpretation of results and provided expertise on the biological plausibility. All contributing authors reviewed and provided input during the revision process of the manuscript. Dr. Laurent Azoulay acquired the data and supervised the study.

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ACRONYMS

AGI	Alpha-glucosidase inhibitor
AMPK	AMP-activated protein kinase
ASD	Absolute Standardized Difference
ATP	Adenosine Triphosphate
BMI	Body mass index
CPRD	Clinical Practice Research Datalink
DALY	Disability-adjusted-life years
DPP-4	Dipeptidyl peptidase-4
FIGO	The International Federation of Gynecology and Obstetrics
FPG	Fasting plasma glucose
eGFR	Estimated glomerular filtration rate
GI	Gastrointestinal
GIP	Glucose-dependent insulinotropic peptide
GLP-1 RA	Glucagon-like peptide-1 receptor agonist
GLUT4	Glucose transporter-4
GOLD	Gp OnLine Data
HES APC	Hospital Episodes Statistics Admitted Patient Care
HR	Hazard ratio
ICD-10	The International Classification of Diseases, version 10
IGF-1	Insulin-like growth factor-1
IMD	Index of multiple deprivation
IPCW	Inverse probability of censoring weighting
IR	Incidence rate
MACE	Major adverse cardiovascular events
NHS	National Health Service
NSAIDS	Nonsteroidal anti-inflammatory drugs
OGTT	Oral glucose tolerance test

ONS	Office for National Statistics Death Registration Data
PCOS	Polycystic ovarian syndrome
PPAR-γ	Peroxisome proliferators activated receptor gamma
PPV	Positive predictive value
SD	Standard Deviation
SGLT	Sodium-glucose cotransporter-2
SNOMED-CT	Systematized Nomenclature of Medicine – Clinical Terms
SRR	Standardized relative risks
SUR1	Sulfonylurea receptor-1
mTOR	Mammalian target of rapamycin
TZD	Thiazolidinedione
UK	United Kingdom

CHAPTER 1: INTRODUCTION

Type 2 diabetes is a chronic metabolic disease characterized by persistent hyperglycemia due to impaired insulin secretion and insulin resistance in the tissues.[1] It introduces many challenges, including a reduced quality of life, increased risks of microvascular and macrovascular complications, all-cause mortality, major adverse cardiovascular events (MACE) and multiple types of cancer. As of 2021, there were an estimated 530 million individuals living with diabetes globally, with type 2 diabetes accounting for approximately 96% of all diabetes diagnoses.[2] Thus, it is a major public health concern, with the burden of disease continuing to rise.[2,3] Management of the disease relies on behavioural and lifestyle modifications in conjunction with pharmacological treatment. Overall, glycemic control is the main objective of treatment for type 2 diabetes.[4]

There are many pharmacological agents available for the treatment of type 2 diabetes. Incretin-based drugs, which include glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and dipeptidyl peptidase-4 (DPP-4) inhibitors, are a relatively newer class of second-to third-line drugs that have been introduced to the market.[5] GLP-1 RAs effectively lower plasma glucose levels by enhancing the effects of endogenous GLP-1, a hormone that stimulates insulin secretion from the pancreas in response to nutrient ingestion.[6,7] DPP-4 inhibitors work by preventing GLP-1 degradation by the DPP-4 enzyme.[8] Hence, the main effect of DPP-4 inhibitors is an increase of endogenous GLP-1 concentration that leads to a glucose-dependent stimulation of insulin secretion. Incretin-based drugs provide several favourable effects over other antihyperglycemic drugs, including a low risk of hypoglycemia, and GLP-1 RAs ability to induce weight loss and decrease the risk of adverse cardiovascular events.[9] There have been

concerns that their use may increase the risk of certain cancers and conditions; pancreatic cancer and acute pancreatitis were thought to be associated with the use of GLP-1 RAs and DPP-4 inhibitors, but supplemental epidemiological studies have been unable to corroborate these claims.[10–12]

As type 2 diabetes is a major risk factor for the development of endometrial cancer, researchers have begun to investigate potential effects of certain antihyperglycemic drugs on endometrial cancer cells.[13] Moreover, due to the presence of GLP-1 receptors in sites outside the pancreas, such as in the brain, lung, stomach, and endometrium, it has been hypothesized that incretin-based drugs may have pleiotropic properties.[14] Indeed, laboratory studies have suggested that incretin-based drugs can attenuate endometrial cancer cell growth.[14–16] Many cardiovascular outcome trials on incretin-based drugs have been published; endometrial cancer events were not included in these trials. To date, no observational study has been conducted to investigate the effects of GLP-1 RAs on endometrial cancer in a real-world setting.

Considering this lack of observational research, large, real-world studies are needed to investigate whether the use of incretin-based drugs is associated with the incidence of endometrial cancer. This thesis aims to assess whether the use of incretin-based drugs are associated with a decreased risk of endometrial cancer. Given that type 2 diabetes is a major risk factor for endometrial cancer[17] and the growing incidence of type 2 diabetes and endometrial cancer[3,18], such findings may render important clinical implications in the development of treatment plans for women with type 2 diabetes at high risk of endometrial cancer.

CHAPTER 2: LITERATURE REVIEW

The second chapter is a comprehensive literature review comprised of three sections. The first section outlines type 2 diabetes, its epidemiology, risk factors, pathophysiology, diagnosis, clinical management, pharmacological treatments, and association with endometrial cancer. The following section describes endometrial cancer, its epidemiology, pathophysiology, diagnosis, treatment and association with type 2 diabetes. Lastly, the third section describes what is presently known about the association between incretin-based drugs and endometrial cancer. This literature review provides the necessary background knowledge for an enhanced understanding of the context, rationale, biological plausibility and implications of this study.

2.1 TYPE 2 DIABETES

2.1.1 Epidemiology and Risk Factors

Type 2 diabetes is a major public health concern, with the burden of the disease rising worldwide.[3,19] As of 2021, it was reported that there were approximately 530 million individuals living with diabetes worldwide, with type 2 diabetes accounting for an estimated 96% of all diabetes diagnoses.[2] This chronic metabolic disease introduces multifaceted challenges, causing a considerable reduction in an individual's quality of life.[2,4,20] Type 2 diabetes increases risk of all-cause mortality and various comorbidities including microvascular complications such as retinopathy, nephropathy and neuropathy, and macrovascular complications such as myocardial infarction, peripheral vascular disease and stroke.[2–4] The risk of vascular diseases is on average two times greater for individuals with type 2 diabetes than those without.[21] It was reported in 2017 that diabetes is the ninth leading cause of mortality globally and over 1 million deaths per

year are caused by diabetes alone.[3] Policy makers, medical professionals and health researchers are working diligently to halt the rising prevalence of the insulin resistance and type 2 diabetes.[2] Overall, the global, age-standardized prevalence of type 2 diabetes is estimated to be 10.5% in adults aged 20-79 in 2021.[22] The prevalence has increased rapidly over the last decade in all parts of the world;[3] from 1990 to 2021, the global age-standardized prevalence of diabetes increased from 3.2% to 6.1%. Type 2 diabetes is expected to affect more than 640 million people (aged 20-79) by 2040.[23]

The rising prevalence of type 2 diabetes is accompanied by a significant and growing economic burden on individuals, families and healthcare systems.[9,20] In 2021, the high prevalence of the disease resulted in over $960 billion spent in healthcare expenses, globally.[2] Diabetes healthcare is estimated to range from 3.2 to 9.4 times greater than the average per capita healthcare expenditure.[3] According to Diabetes Canada, individuals with diabetes are over 3 times more likely to be hospitalized with cardiovascular disease, 12 times more likely to be hospitalized with end-stage renal disease and almost 20 times more likely to be hospitalized for a non-traumatic limb amputation, compared to the general Canadian population.[24]

There are disparities in diabetes prevalence and outcomes across populations. While the prevalence is steadily increasing in both sexes, men are typically diagnosed with type 2 diabetes at younger ages and at lower BMIs.[25] In 2021, the global, age standardized prevalence of diabetes was slightly higher in males than in females (10.8% and 10.2%, respectively).[22] This ratio varied depending on the socioeconomic status of the geographical location. Low-income and middle-income countries have seen a greater rising incidence of type 2 diabetes, where socioeconomic challenges pose additional barriers to treatment.[1,2] Low-income and middle-income countries have underfunded healthcare systems and are more likely to have residents

living in poverty, consuming poor nutrition and lack sufficient physical activity levels.[2] Within countries, there is a higher prevalence seen among lower-incomes residents. In Canada, the prevalence of diabetes among adults in the lowest income group is 2.1 times that of adults in the highest income group.[26] Additionally, higher prevalence is seen in urban areas compared to rural areas (12.1% and 8.3% respectively.)[22] Although type 2 diabetes is known to affect older individuals with the highest prevalence seen in the 65 and over age group, the prevalence is rising among children and adolescents.[22,27,28] It has been recently reported that over one third of diabetes-related mortality occurs in individuals under the age of 60.[3]

Type 2 diabetes results from an interaction among genetic, environmental and lifestyle risk factors.[20] Obesity, physical inactivity, innutritious or high caloric diets and the ageing population the primary factors contributing to the trends seen in diabetes prevalence.[2,3,21] According to the World Health Organization, almost 90% of type 2 diabetes diagnoses are related to excess body weight.[20] Duration of obesity can be considered an independent risk factor, as it has been established using data from the Nurses' Health Study that there is a 14% increased risk of type 2 diabetes for every additional 2 years of obesity.[29] Smoking is another significant risk factor for the development of type 2 diabetes, as smoking increases the risk of type 2 diabetes by 30%-40% for active smokers compared to non-smokers.[30]

A meta-analysis of prospective studies found that adopting a healthy lifestyle was associated with a substantially lower risk of type 2 diabetes. Unhealthy lifestyle factors considered in these studies included smoking, alcohol intake, physical activity level, diet, obesity and sleep duration and quality. Those with the healthiest lifestyle have a 75% lower risk of incident type 2 diabetes when compared with those with the least healthy lifestyles.[31] Indeed, those with the healthiest lifestyles have a 56% lower risk of all-cause mortality, 49% lower risk

of cardiovascular disease mortality, 31% lower risk of cancer mortality and a 52% lower risk of incident cardiovascular disease.[31] Lastly, the ageing population contributes greatly to the rising prevalence of type 2 diabetes.[22,32] It is predicted that the prevalence of diabetes will increase by 14% by 2045, driven by the ageing of the population.[22]

2.1.2 Pathophysiology

Type 2 diabetes is characterized by elevated blood glucose levels (hyperglycemia) resulting from impaired insulin secretion, tissue insulin resistance, insufficient compensatory insulin secretory response, or a combination thereof.[1,4] In metabolically stable systems, the homoeostasis of glucose in the body is maintained primarily by insulin. Insulin facilitates the uptake of glucose by skeletal muscle, liver and adipose tissue while inhibiting the production of glucose by gluconeogenesis and glycogenolysis in the liver. Insulin is secreted by β-cells of the pancreas when the concentration of blood glucose rises. Additionally, insulin works to inhibit lipolysis in adipose tissue, preventing the release of free fatty acids and promoting triglyceride storage..[1,33–35]

This system becomes impaired when tissues become insulin resistant, eventually causing hyperglycemia. Individuals with type 2 diabetes display impaired insulin-stimulated glucose uptake into muscle and adipose tissue and defective insulin suppression of hepatic glucose output. In early stages of the metabolic disease, decreased insulin sensitivity in the tissues (insulin resistance) triggers β-cell hyperfunction causing high compensatory insulin secretion (hyperinsulinemia) in order to maintain normal glucose levels in the blood.[33,34] These high levels of insulin initially prevent hyperglycemia. Overtime, the increased insulin secretion by the β-cells is unable to counterbalance the decreased sensitivity to insulin in the tissues and maintain

glucose homeostasis. Consequently, β-cell function begins to decline, initiating an insulin deficiency which progressively results in defective homeostatic regulation of systemic glucose.[1,33,34]

The initial insulin resistance in the tissues is marked by an impaired biologic response to insulin stimulation in target tissues, primarily in the liver, skeletal muscles and adipose tissue.[1,34] The etiology of insulin resistance can be genetic, although causes are primarily environmental factors.[36] The main acquired causes of insulin resistance are excessive visceral adiposity, aging, physical inactivity, nutritional imbalance, high-sodium diets, glucose toxicity, certain medications and lipotoxicity from excess free fatty acids.[34]

When there is a deficiency of insulin, and lipolysis in adipose tissues is no longer being appropriately inhibited, high levels of circulating free fatty acids can accumulate, impairing glucose metabolism in the tissue and contributing to lipotoxicity-induced β--cell dysfunction.[1] Excess calories accumulate in non-adipose tissues such as the liver, pancreas and muscle leading to lipotoxicity, a metabolically harmful condition in which excess fat stored in these organ's cells inhibits their typical metabolic functioning. Myocellular lipotoxicity inhibits glucose uptake through glucose transporter 4 (GLUT4) transporter dysfunction, leading to peripheral tissue insulin resistance.[37] Pancreatic liptoxicity inhibits β- cell insulin production, leading to a unsatisfactory level of insulin being produced to counteract the insulin resistance being experienced in the other tissues. Insulin resistance can also occur in the kidneys, brain, small intestine and blood vessels, as they also have insulin receptors.[1] Factors such as ageing, genetics, glucotoxicity, activation of inflammatory pathways and reactive oxygen species can also contribute to the initiation of β-cell dysfunction and eventual failure.[1] These multiple pathophysiological mechanisms, primarily β-cell dysfunction, also lead to a diminished incretin-

effect in the gut, decreasing the insulinotropic actions of endogenous glucose-dependent insulinotropic peptide (GIP) and GLP-1.[38]

Insulin resistance typically precedes the development and diagnosis of type 2 diabetes by, on average, 10 to 15 years, therefore the full progression of the disease should be somewhat preventable by managing insulin resistance.[34] This extended period before full manifestation of type 2 diabetes is due to the complicated and malfunctioning feedback loop between insulin action and insulin secretion, resulting in the β-cell dysfunction in the pancreas.[34]

2.1.3 Diagnosis

Diagnosis of type 2 diabetes relies on specific criteria involving plasma glucose or hemoglobin A1c (HbA1c) levels. Blood glucose levels are assessed using a fasting plasma glucose (FPG) value or a 2-hour plasma glucose (2-h PG) value during a 75 g oral glucose tolerance test (OGTT).[5] FPG is evaluated using a venous blood sample that is drawn after an 8-hour fast. According to the American Diabetes Association, FPG levels of more than 126 mg/dL (7.0 mmol/L) are indicative of type 2 diabetes.[4,39] In the OGTT, a 2-h plasma glucose level is measured before and 2 hours after ingestion of 75 gm of glucose. A plasma glucose level greater than 200 mg/dL (11.1 mmol/L) taken after the 2 hours following ingestion of glucose, is indicative of type 2 diabetes.[39] A hemoglobin A1c (HbA1c) level of 6.5% (48 mmol/L) or higher is consistent with a type 2 diabetes diagnosis.[4,40] The HbA1c test has high specificity, but lower sensitivity than blood glucose tests to diagnose type 2 diabetes.[41] A1c is also measured via blood sample and can be measured at any time of day regardless of recent food intake, making it more convenient than the FPG and OGTT.[4] As the A1c test reflects the average plasma glucose of the previous 8 to 12 weeks, it avoids the issue of variability of glucose values from one day to the

next.[40] HbA1c values are an indirect measure of plasma glucose therefore the correlation between these values and true blood glucose levels is not perfect.[40]

2.1.4 Clinical Management

Effective management of type 2 diabetes is complex and requires a comprehensive approach with many factors to consider. As there are varying degrees of insulin resistance, obesity, β-cell dysfunction, disease progression rate and comorbidities between patients, not every patient's treatment plan will look the same.[4,42] After evaluation of a patient's complete health profile, existing complications, and risk factors, clinicians can tailor an individualized and curated treatment plan. Routine blood glucose monitoring serves as a cornerstone of diabetes management, facilitating ongoing assessment of glycemic control and guiding treatment adjustments as necessary.[43] Clinical management typically begins with setting a target HbA1c value. Management of the disease relies on lifestyle/behavioural modifications in conjunction with pharmacological treatment. Both components ultimately aim to prevent complications and maintain a patient's quality of life.[4]

2.1.4.1 Lifestyle Modifications

Having diabetes strongly influences the daily life of the patient. Lifestyle interventions are fundamental in type 2 diabetes management, often acting as the first line of defense in a patient's treatment plan.[28] For some patients, lifestyle changes can be the most effective intervention for delaying progression and avoiding complications.[23,28] A healthy lifestyle can help prevent the development of type 2 diabetes, as well as diminish the risk for adverse complications such as cardiovascular disease, once a type 2 diabetes diagnosis has been given.[23]

Overall, dietary modifications, increased levels of physical activity, and smoking cessation are central to managing type 2 diabetes and improving clinical outcomes.[4,28]

It has long been established that insulin resistance, lipotoxicity and excessive adiposity are the underlying causes of type 2 diabetes. These causes most often result from excessive caloric intake.[28] Therefore, maintaining a healthy diet, attaining modest weight loss and increasing regular physical activity levels can improve glycemic control, lower blood pressure, reduce the concentration of plasma lipids and reduce the risk of micro- and macrovascular complications associated with type 2 diabetes.[44] These health behaviours are important for long-term diabetes management. A meta-analysis showed that sufficiently intensive lifestyle interventions alone can lead to type 2 diabetes remission.[28] The study claims that a therapeutically dosed whole foods and a plant-based diet is the best intervention to achieve remission. Additionally, substantial caloric restriction has been proven to remove free fatty acids from the pancreas and liver, resulting in restored β- cell insulin production.[45] This effect occurs without substantial weight loss, indicating that it is excess calories and not necessarily excess weight, that is leading to insulin resistance.[28]

Aside from contributing to weight loss, exercise plays an important role in glycemic control. During exercise, there is an increase of glucose uptake into the skeletal muscles.[46] This process is independent from insulin-mediated glucose uptake, but rather contractile activity of the muscles during exercise. Mechanical shifts in the muscle involving the movement of GLUT4, allows glucose to diffuse into the muscle.[46] More, myocellular liptoxicity resulting from excessive caloric intake is reduced with exercise, allowing peripheral muscle tissues to become more responsive to insulin.[28]

2.1.4.2 Pharmacological Treatments

In conjunction with lifestyle interventions, pharmacological therapy assumes significance in the management of type 2 diabetes. A diverse array of medications including oral antihyperglycemic agents, injectable therapies and insulin, are clinically available to optimize blood glucose levels and mitigate the risk of diabetes-related complications.[47] The therapeutic targets of antihyperglycemic drugs are the pathophysiological mechanisms that lead to persistent hyperglycemia. Impaired glucose uptake in skeletal muscle, neurotransmitter dysfunctions, increased lipolysis, increased glucose reabsorption, deficient insulin secretion by the pancreatic β-cells and the reduced incretin effect in the gut (see section 2.1.4.2.2.5) are some of the metabolic and pathophysiological mechanisms that these drugs target.[48] Combination therapies are often required to address multiple pathological defects to achieve proper glycemic control.[35,42,48] Each antihyperglycemic drug has a different clinical profile to consider when determining a patients' pharmacotherapy plan. The determination of antihyperglycemic agents must also consider a range of patient-specific factors such as, age, duration of diabetes, present or potential comorbidities and risk of hypoglycemia.[48,49]

2.1.4.2.1 First-Line Pharmacological Treatments

Metformin is the recommended first-line treatment of type 2 diabetes.[42,50,51] Approved by the Food and Drug Administration in 1994, metformin is the most commonly prescribed antihyperglycemic drug as it is known to be effective as a monotherapy and in combination with other antihyperglycemic agents, generally well-tolerated and has a favourable safety profile.[52] Over the last couple decades, clinical trials and real-world evidence-based studies have been

exploring the safety profile of metformin and results continue to corroborate findings that metformin is a safe and effective treatment for the majority of patients with type 2 diabetes.[52,53]

Metformin belongs to a drug class known as biguanides.[52] Guanidine-based therapies were derived from a plant source and not originally synthesized with specific targets.[52] Metformin is the only biguanide that is still clinically available, as the other medications in this drug class proved to increase risks of lactic acidosis, an outcome that is thought to be infrequent with the use of metformin.[54]

As metformin was not created with specific physiological targets, some of its actions have not been fully elucidated, though there are several known mechanisms through which metformin improves glycemic. Primarily, it's antihyperglycemic effect occurs through supressing glucose production in the liver (hepatic gluconeogenesis). After hepatic uptake, the mitochondria are the primary targets of metformin.[55] Mitochondrial function is disrupted by the inhibition of mitochondrial respiratory-chain complex I, facilitated by the presence of metformin in the liver.[53] This causes decreased cellular energy (Adenosine triphosphate; ATP) production in the liver, resulting in the suppression of the energy-consuming gluconeogenic pathway through the activation of AMP-activated protein kinase (AMPK).[53] AMPK is a protein that plays a role in protecting cellular functioning under energy-restricted conditions.[53] Metformin also leads to the inhibition of glucose production by impairing gluconeogenesis gene expression.[53,53,55]

Furthermore, metformin facilitates increased glucose uptake the peripheral tissues, including the liver, skeletal muscles and adipose tissue, through activation of insulin receptors at these sites.[56] Metformin use has also been shown to increase GLP-1 secretion.[56]

Metformin rarely causes hypoglycemia and is neutral on weight change.[52,53,56] It effectively lowers fasting plasma glucose levels; metformin has been shown to decrease mean

HbA1c by 1.3% compared to a 0.4% increase in a placebo group.[52] Meta-analyses have indicated that metformin is associated with a decreased risk of mortality and myocardial infarction among overweight patients.[52] Moreover, when compared with glipizide, metformin therapy resulted in a 12% risk reduction of major adverse cardiovascular events.[57] Hepatic failure and renal impairment are contraindications for metformin use.

Several side effects have been reported from metformin use. Gastrointestinal (GI) issues (nausea, diarrhea, abdominal discomfort) are relatively common (20-30%) among patients taking metformin.[52] These can be avoided by titrating the dose slowly and assessing tolerability gradually. There are also alternate formulations such as an extended-release tablet, that can subside the GI discomforts. Additionally, malabsorption of B12 is associated with metformin use. Patients are regularly tested for vitamin B12 levels and may require an oral B12 supplement.[52]

2.1.4.2.2 Second- to Third-Line Pharmacological Treatments

As type 2 diabetes is a progressive disease, one pharmacological therapy may not continue to be sufficient for glycemic control. If this is the case, switching to a second- or third-line treatment may be necessary. In addition, introducing a combination therapy with a second- to third-line treatment is customary when HbA1c targets are not being met.[35,47,58,59]

2.1.4.2.2.1 Sulfonylureas

Sulfonylureas, first introduced over 60 years ago, were the first class of oral antidiabetic agents on the market.[60,61] They may be used as a monotherapy, or in combination with other oral or injectable medications.[61] Both alone, and in combination with another oral antidiabetic medication, sulfonylureas have been shown to effectively reduce HbA1c levels by around 1.5%.[62,63] There are three generations of sulfonylureas; first-generation (chlorpropamide, tolazamide, tolbutamide) are rarely prescribed in recent years, as second-(gliclazide, glipizide, glyburide) and third-generation (glimepiride) can be administered at lower loses and less frequently which decreases the risk of adverse reactions.[61,64]

Sulfonylureas are insulinotropic agents, effectively lower plasma blood glucose levels by stimulating insulin secretion. The mechanism through which insulin release is stimulated begins with sulfonylureas binding to sulfonylurea receptor 1 on the β-cells of the pancreatic islets.[61,65] This results in the closure of the ATP-dependent potassium channel leading to an accumulation of potassium ions.[60,65,66] The inner membrane of the cell becomes depolarized, allowing for the influx of extracellular calcium ions which bind to insulin vesicles, promoting insulin release into circulating blood.[66] Sulfonylurea-stimulated insulin secretion is independent of plasma glucose levels, therefore they are associated with a high risk of hypoglycemia.[60,62,65,66] Sulfonylurea receptors (SUR1 receptors) exist in various tissues, therefore they have extra-pancreatic effects such as suppression of glucose output in the liver and lipolysis in adipose tissue.[65]

Sulfonylureas are known to cause weight gain and have been shown to increase risk of MACE.[67,68] A short acting sulfonylurea (e.g. glipizide) is an option for patients who have contraindications to metformin.[69] They are known to be reliable, relatively well-tolerated and affordable, although their hypoglycemia-inducing effect limits their use, especially with the large

variety of other antidiabetic agents currently available.[63,65] Meglitinide use is a contraindication for being prescribed sulfonylureas (see next section).[61,64]

2.1.4.2.2.2 Meglitinides

Meglitinides are class of antidiabetic medications comprised of repaglinide and nateglinide.[64] They are insulinotropic agents that use the same mechanism of action as sulfonylureas; they bind to SUR1 receptors on pancreatic β-cells and act on the potassium-dependent ATPase, thereby leading to the closure of ATP-sensitive potassium channels and consequent secretion of endogenous insulin.[64] Due to their weaker affinity for sulfonylurea receptors, meglitinides have a shorter onset (more rapid insulin secretory response) and a briefer period of action than sulfonylureas.[70,71] Their effects depend on glucose levels, requiring a high blood sugar level to stimulate β-cell insulin secretion. This allows for effective control of post-prandial hyperglycemia, while reducing the risk of hypoglycemia.[70,72] These qualities of meglitinides require that the medication be taken often and before meals. They are effective in combination therapy with metformin or thiazolidinediones.[64,70]

2.1.4.2.2.3 Alpha-Glucosidase Inhibitors

Alpha-glucosidase inhibitors (AGIs) are a class of drugs used to control postprandial hyperglycemia, treat type 2 diabetes and can be used to delay the onset of type 2 diabetes in individuals with impaired glucose tolerance.[73,74] AGIs decrease the rate of absorption of carbohydrates in the intestines, thereby lowering postprandial blood glucose levels. They inhibit alpha-glucoside enzymes, which are responsible for the converting ingested complex

carbohydrates into simple absorbable carbohydrates in the small intestine.[75] The delay in absorption reduces the rise of postprandial blood glucose concentration by approximately 3mmol/L.[73]

This drug class is comprised of acarbose, voglibose and miglitol.[58,76] AGIs need to be present in the gut in order to be effective therefore they are administered orally, typically three times a day with each meal.[73,75] AGIS are not associated with weight gain or hypoglycemia.[75] These drugs are a beneficial option for those at risk of hypoglycemia or lactic acidosis, who are not candidates for metformin or sulfonylureas. They can cause gastrointestinal side effects, which are typically worsened with carbohydrate-heavy diets.[76] Contraindications include conditions which are known to be worsened by excess gas in the gut (e.g. irritable bowel syndrome and gastroesophageal reflux), diabetic ketoacidosis, chronic intestinal disease, inflammatory bowel disease, colonic ulcerations and intestinal obstructions.[73]

2.1.4.2.2.4. Thiazolidinediones

Thiazolidinediones (TZDs) are a class of insulin sensitizers used in the treatment of type 2 diabetes. They control hyperglycemia by reducing hepatic glucose output and insulin resistance in the peripheral tissues including adipose tissue, skeletal muscle and the liver.[77] They enhance insulin sensitivity by activating peroxisome proliferators activated receptor gamma (PPAR-γ), which are receptors that play an important role in glucose and lipid metabolism .[63,78] TZDs bind to the gamma isoform of PPARs leading to modifications in the transcription (transactivation or transrepression) of insulin-responsive genes and genes involved in energy metabolism in peripheral tissues.[63,78] This leads to increased glucose uptake in muscle and fat cells and decreases in hepatic gluconeogenesis.

Rosiglitazone and pioglitazone are the two available TZDs on the market. One study found that rosiglitazone reduces the long term incidence of diabetes by delaying the underlying disease process.[79] TZDs are not associated with hypoglycemia, do not cause weight gain and are inexpensive, but the use of these drugs have been restricted or limited due to safety concerns.[78,80] Troglitazone was withdrawn from the market due to idiosyncratic hepatic reactions causing hepatic failure.[58] Rosiglitazone has been found to be associated with an increased risk of adverse cardiovascular outcomes.[81,82] Pioglitazone has been found to increase risk of bladder cancer.[63,83] Other side effects of TZDs include fluid retention and increased risk of bone fractures.[80]

2.1.4.2.2.5. Incretin-Based Drugs

Incretin effect

Another major contributor to the development and persistence of type 2 diabetes is a reduction of the incretin effect.[84] The incretin effect describes the phenomenon in which ingested glucose elicits a greater insulin release than that of glucose administered intravenously, even when blood glucose concentrations are the same.[84] This physiological effect is mediated by the gut-derived incretin hormones, GIP and GLP-1 which are secreted following nutrient ingestion.[85] GLP-1 is a peptide hormone generated through enzymatic breakdown of proglucagon and is predominantly expressed in the gut, pancreas and hindbrain.[6,84] It is synthesized in and secreted from L-cells in the distal ileum and colon.[6,86] The hormone augments insulin secretion from pancreatic β-cells in a glucose-dependent manner, inhibits glucagon secretion, slows gastric emptying, and promotes satiety. GIP, the other incretin hormone, is secreted by K-cells in the proximal small intestines and promotes insulin secretion in response to glucose.[87] Under hyperglycemic conditions, these hormones contribute to approximately 70% of the postprandial

insulin secretion.[8] Incretin hormones have a short half-life of approximately two to three minutes due to rapid enzymatic degradation by the enzyme DPP-4.[8,9] In individuals with type 2 diabetes, the incretin effect is often reduced or absent due to blunted GLP-1 secretion and a diminished response to GIP.[85] As a result, insulin secretion following nutrient ingestion is impaired, contributing to β-cell dysfunction hyperglycemia.[85,87]

2.1.4.2.2.5.1 GLP-1 RAs

GLP-1 receptor agonists are a class of antihyperglycemic agents utilized for the treatment of type 2 diabetes and obesity. The effects of endogenous GLP-1 are enhanced with the use of GLP-1 RAs, as they are synthetic analogs of the endogenous hormone that can activate the GLP-1 receptor. Unlike endogenous GLP-1, GLP-1 RAs are more resistant to degradation by the DPP-4 enzyme and thus, have longer half-lives. Aside from oral semaglutide tablets, these drugs are administered via subcutaneous injection.

Exenatide was the first GLP-1 RA approved by the FDA in 2005.[88] Since, numerous GLP-1 RAs have been produced and can be classified as either short-acting or long-acting agents.[64] Short-acting receptor agonists are characterized by a rapid, large and intermittent increases in plasma peptide levels, whereas long-acting agents generate a slower, more consistent activation of the GLP-1 receptor.[88] The pharmacokinetic differences between short-acting and long-acting analogues have important implications for the efficacy and tolerability of these medications.[38]

Short-acting GLP-1 receptor agonists (exenatide and lixisenatide) have half-lives of approximately two to five hours and can activate the GLP-1 receptor for up to 6 hours after injection.[88] Modifying the positioning of certain amino acids within the synthesized short-acting

peptide, allows it to be resistant to cleavage by DPP-4.[38,89] Due to their duration of action, recommended dosing intervals are typically before meals - twice daily for exenatide and once daily for lixisenatide.[38,88] Plasma levels of these short-acting compounds rapidly increase following injection, resulting in a substantial delay of gastric emptying, reducing postprandial blood glucose levels by way of slowed glucose absorption into circulation.[90] Thus, short-acting GLP-1 RAs actually exert an insulin-lowering effect in the postprandial state, rather than an insulinotropic effect.[38,91] Additional effects of delayed gastric emptying include supressed appetite and possible nausea. These compounds are associated with an average 1-5 kg reduction in body weight.[38] Short-acting GLP-1 RAs cause a modest reduction on fasting blood glucose levels - plasma concentration the receptor agonists decline in a fasting state, therefore their ability to control glucose and insulin secretion is not as stable as that of long-acting GLP-1 RAs.[38,88,90]

The long-acting GLP-1 RAs (albiglutide, dulaglutide, long-acting release exenatide, liraglutide and oral and injectable semaglutide) provide better glycemic control than short-acting GLP-1 RAs due to their sustained activation of GLP-1 receptors.[89,90] These long-acting compounds are further modified to be resistant to renal filtration, giving them half-lives of 12 hours to several days, with plasma levels remaining elevated between doses.[88,92,93] They do not have a substantial effect on gastric emptying rate therefore they do not lower postprandial glucose concentration as substantially as their short-acting counterparts, however, they do provide better continuous glycemic control, overall. As such, postprandial insulin concentrations are increased with the long-acting compounds, unlike their short-acting counterparts. Like the long-acting compounds, they supress appetite, can induce nausea and are associated with comparable weight loss (2-5 kg).[88] Because these long-acting drugs do not have a substantial

effect on gastric emptying, but do have a comparable effect on weight loss as the short-acting compounds, reductions in body weight induced by GLP-1 is thought to be independent of gastric emptying rate and rather mediated by activity in the hypothalamus, mesolimbic reward system and other areas of the central nervous system.[94]

GLP-1 RAs are highly effective at reducing HbA1c levels (up to 2.0% reduction).[95] As these drug's effects are glucose-dependent, they are not associated with hypoglycemia. They are known to exert cardiovascular protective effects by regulating multiple signaling pathways.[96,97] GLP-1 RAs are contraindicated in patients with certain gastrointestinal diseases, multiple endocrine neoplasia, or kidney failure.[92] Although they have been associated with risk of acute pancreatitis, studies using real-word evidence have found no association between risk of pancreatitis and GLP-1 RA use.[10,11,98–100] Some epidemiological studies have revealed their association with thyroid and pancreatic cancers, although meta analyses of randomized control trials and epidemiological studies have suggested there is no increased risk of these cancers associated with the use of GLP-1 RAs . [12,101,102] GLP-1 RAs have been found to be associated with a decreased risk of prostate cancer.[103,104]

Figure 2-1. GLP-1 receptor agonists actions on peripheral target tissues

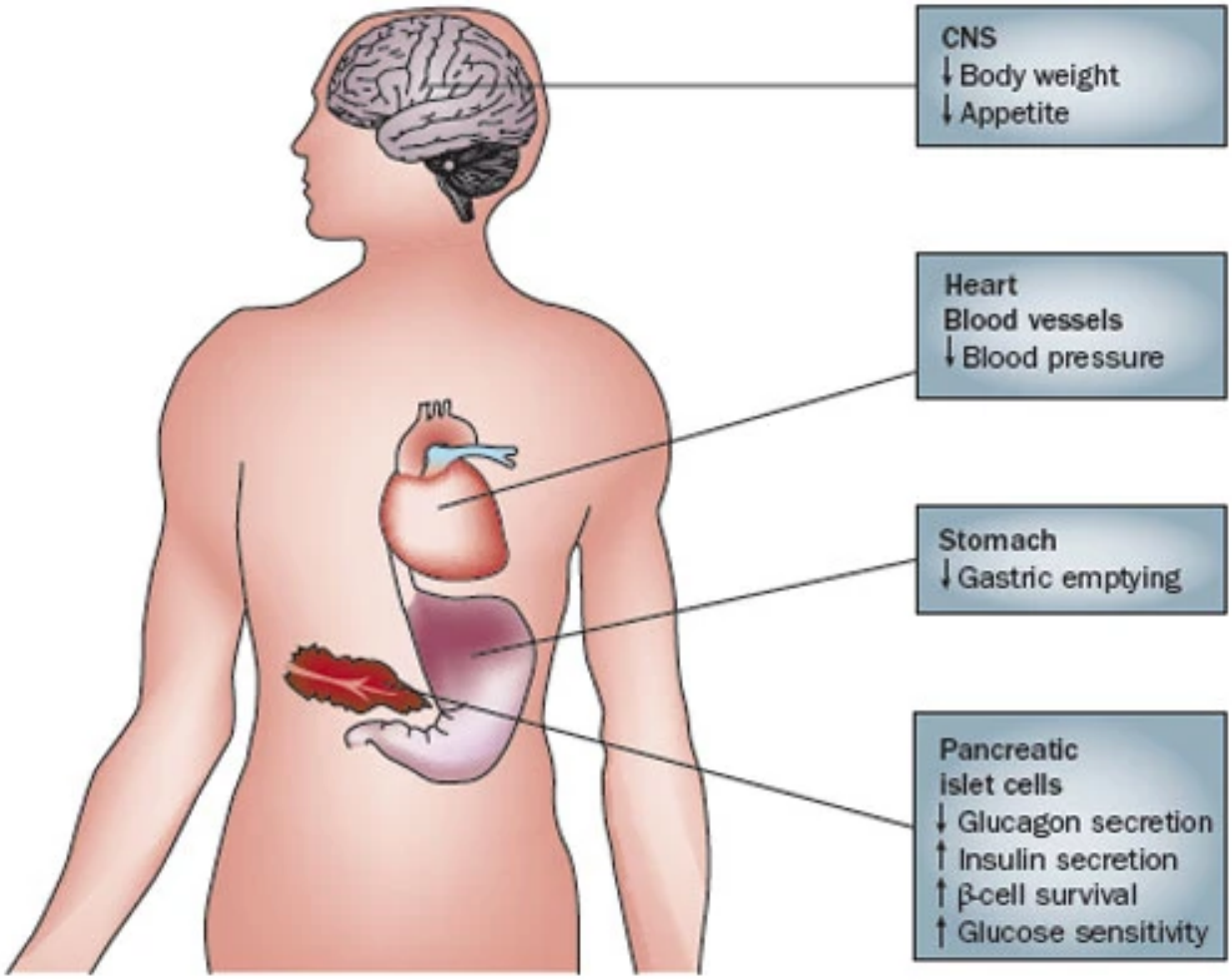

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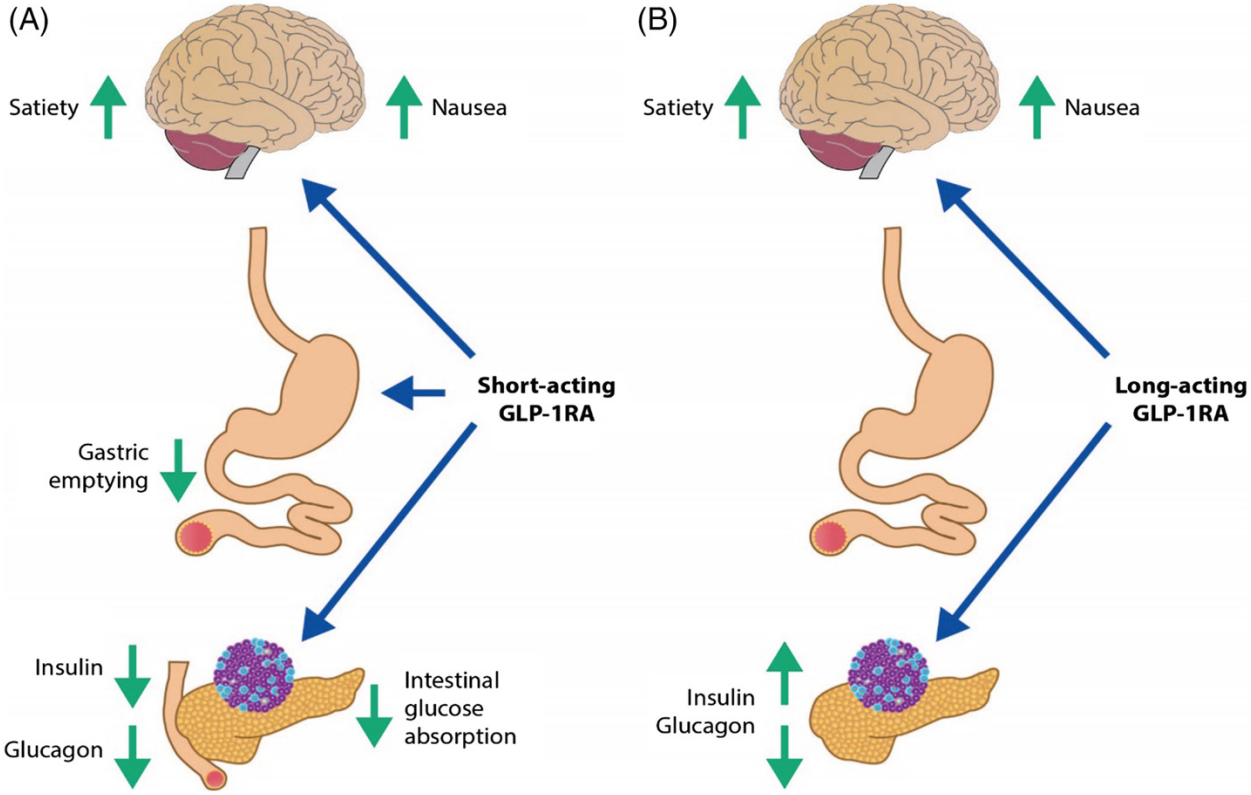
Figure 2-2. Gastric emptying effects of short-acting and long-acting GLP-1 RAs



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2.1.4.2.2.5.2 DPP-4 Inhibitors

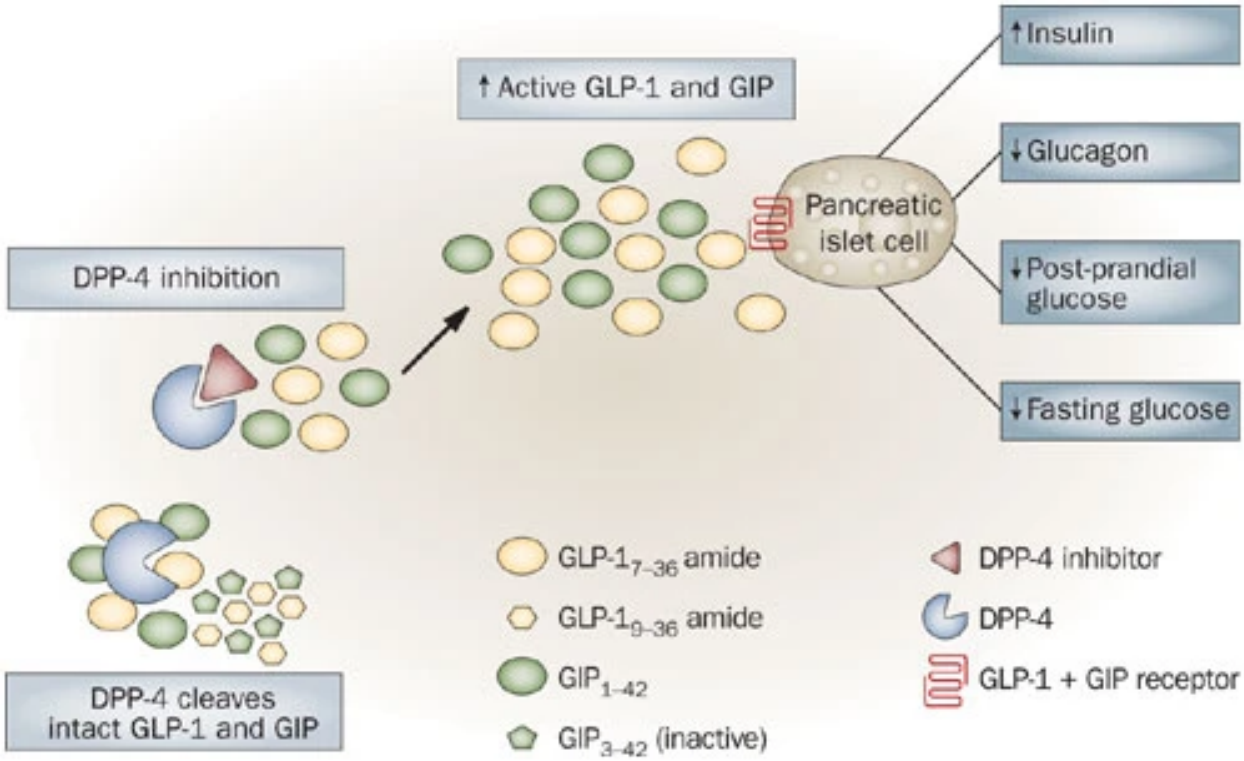
DPP-4 inhibitors are a class of drugs that potentiate the effects endogenous GLP-1 by preventing their degradation by the DPP-4 enzyme.[8] Thus, the main effect of DPP-4 inhibitors is the elevation of endogenous GLP-1 concentration that leads to a glucose-dependent stimulation of insulin secretion and inhibition of glucagon secretion. This insulinotropic mechanism allows for a low intrinsic risk of hypoglycemia. These agents have a high specificity for DPP-4, resulting in an 80-90% inhibition and consequently, up to a 2-3 fold elevation of endogenous, post-prandial GLP-1 concentration.[8] Therefore, they are capable of lowering HbA1c by

approximately 0.5-1%.[8,108] Compared to GLP-1 RAs, DPP-4 inhibitors are not as effective at glycemic control, likely due to GLP-1 RAs ability for sustained activation of GLP-1 receptors.[109,110] DPP-4 inhibitors have a neutral effect on body weight because, unlike GLP-1 RAs, they are not associated with delayed gastric emptying.[8,109]

In 2006, sitagliptin was introduced as the first DPP-4 inhibitor for the treatment of type 2 diabetes.[109] Alogliptin, linagliptin, saxagliptin, vildagliptin were introduced as other agents in this class thereafter (United States and Europe).[108] The various gliptins have comparable efficacy, yet they have differences in their pharmacokinetic and pharmacodynamic properties including, potency, selectivity, oral bioavailability, elimination half-life, potential drug interactions and more.[108]

Multiple cardiovascular outcome trials have been conducted to evaluate the safety of DPP-4 inhibitors. All clinical trials have shown that DPP-4 inhibitors are safe in regards to major adverse cardiac events.[108] Overall. DPP-4 inhibitors are well-tolerated. As with GLP-1 RAs, pancreatic cancer and acute pancreatitis have been reported to be associated with the use of DPP-4 inhibitors, but supplemental studies have been unable to substantiate these claims.[108] Impairments in renal function was suspected to be a contraindication for DPP-4 inhibitor use as most DPP-4 inhibitors are excreted renally, but it has been shown that patients with renal impairment are able to tolerate these agents at lower doses.[108]

Figure 2-3. Mechanism of Action of DPP-4 inhibitors



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2.1.4.2.2.6 SGLT2 Inhibitors

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors selectively inhibit SGLT-2 proteins in the proximal convoluted tubules of the kidneys, supressing renal filtered glucose reabsorption and decreasing the renal threshold for glucose.[111,112] This inhibition facilitates a diuretic effect in which urinary glucose is excreted, resulting in decreased plasma glucose levels and improved glycemic control.[112,113] Approximately 60-100 grams of glucose is excreted in the urine after a therapeutic dose of an SGLT-2 inhibitor.[40] These drug's hypoglycemic effects work independently from insulin-related glycemic control, therefore they do not cause hypoglycemia

and are a suitable treatment for those with limited β-cell function.[111,112] They are administered via oral tablets, dosing depending on the indication.[111] There are currently five SGLT-2 inhibitors on the market in the United States including bexagliflozin, canagliflozin, dapagliflozin, empagliflozin and ertugliflozin.[114] Three of these are currently available in Canada (dapagliflozin, canagliflozin and empagliflozin).[115] Clinical trials have indicated that these drugs decrease HbA1c levels by 0.6-0.9%.[112] Aside from their hypoglycemic effects, they exhibit cardioprotective, lipid-modulating and weight loss effects. Large cardiovascular trials have demonstrated that dapagliflozin and empagliflozin reduce the risk of MACE among patients with type 2 diabetes.[113,116,117] The American Diabetes Association recommends the addition of SGLT-2 inhibitors (dapagliflozin and empagliflozin) in the management of type 2 diabetes for patients at high risk of heart failure or chronic kidney disease (with tolerable estimated glomerular filtration rate; eGFRs).[113,118] Adverse events associated with the use of SGLT-2 inhibitors include genital mycotic infections, urinary tract infections, lower limb amputations, diabetic ketoacidosis and acute kidney injury.[111] Renal function is often assessed before initiating the drug as those with an eGFR less than 30 mL/min/1.73m^2 (and receiving dialysis treatment) are contraindicated for therapy with SGLT-1 inhibitors.[118]

2.1.4.2.3. Last-Line Pharmacological Treatment

Insulin has been available for the treatment of diabetes for a century and remains the most effective treatment for hyperglycemia.[119] It is typically introduced in a patient's pharmacological therapy plan as the last option, when patients are no longer able to maintain glycemic targets with non-insulin treatments.[120] As type 2 diabetes is progressive in nature, many

patients will eventually require insulin therapy.[121] Insulin can lower HbA1c by 0.9-1.5%.[50] Patients with HbA1c levels greater than 10%, often initiate insulin immediately.[50] It is often added on to an existing non-insulin therapy as a combination therapy. Insulin therapy has been shown to reduce the risk of microvascular complications, treat ketoacidosis and increase a patient's quality of life.[120] Exogenous insulin has a neutral effect on cardiovascular outcomes.[50]

Normal insulin secretion involves both a basal level insulin secretion that maintains stable blood glucose levels in fasting states and an incremental postprandial secretion.[119] The feedback mechanism that controls secretion is based on changes in blood glucose levels. Injected exogenous insulin does not feed this feedback loop, therefore blood glucose levels must be measured to guide insulin dosing.[119] There are rapid-acting, intermediate-acting and long-acting exogenous insulins. The first available analogues, rapid-acting insulin analogues, have a quick onset of action, rapidly peak, and have a short duration of action, and thus are typically injected around mealtimes.[50,119] Intermediate-acting insulin analogues provide basal insulin levels that last up to 24 hours.[119,120] These are administered twice daily to achieve adequate basal insulin coverage. Long-acting insulin analogues have a slower onset of action, peaking at 6 hours and lasting 24 hours (can last up to 42 hours).[119] These are also considered a basal insulin.[119] Typically, basal insulins are the first of insulin therapies to be added to existing antihyperglycemic regimens. If glycemic targets are still not met, then a rapid-acting insulin may be added to the regimen.

2.1.5. Association between Type 2 Diabetes and Cancer Incidence

Many epidemiological studies have demonstrated an association between type 2 diabetes and increased risk of various cancers including liver, pancreatic, endometrial, colorectal, breast, and bladder cancers.[122] There are several hypothesized mechanisms linking diabetes with increased risk of cancer, but the complete biological mechanisms behind this association have not been fully elucidated. Type 2 diabetes and cancer share many risk factors such as aging, obesity, poor diet, and physical inactivity which can lead to the development of metabolic abnormalities (i.e., insulin resistance, hyperinsulinemia, increased levels of insulin-like growth factor-1 (IGF-1), increased peptide hormones, and increased activity of pro-inflammatory cytokines).[123] These metabolic abnormalities play a critical role in carcinogenesis in patients with type 2 diabetes, although their contributions are not equal, with adiposity and hyperinsulinemia assuming the highest role.[124] Hyperinsulinemia is often experienced in patients with insulin resistance and has been found to be associated with increased risk of breast, endometrial, ovarian and prostate cancer.[125]. More, antihyperglycemic medications have been shown to modulate cancer risk.[12,104,126] Every specific cancer will have its own distinct pathophysiological pathways that lead to its development and progression, however many factors in these processes are shared within various malignancies.[123] Accordingly, epidemiological evidence shows that type 2 diabetes may be strongly associated with certain cancers but inversely or only moderately associated with others, therefore site-specific cancers rather than overall cancer incidence should be used as the outcome of interest when assessing the association between this diseases.[127]

2.2 Endometrial Cancer

2.2.1 Epidemiology and Risk Factors of Endometrial Cancer

Endometrial cancer is the fourth most common cancer in women, with approximately 417,000 incident diagnoses made globally in 2020.[128,129] It represents the most frequently diagnosed gynecologic cancer worldwide.[128] It was reported that there were approximately 90,000 deaths in 2018 globally, from the disease.[130] Due to a rise in the prevalence of risk factors for endometrial cancer, prominently obesity and an aging population, the incidence has risen by 132% in the last 30 years.[128]

The incidence of endometrial cancer is rising, specifically in high income countries. The highest rate of endometrial cancer is in North America (86.6 per 100,000), followed by eastern (52.5 per 100,000) and then central Europe (21.9 per 100,000).[128,130] The incidence and mortality rate of endometrial cancer in Canada were 35.7 and 5.3 per 100,000 women respectively, in 2017.[131] According to the Canadian Cancer Society, an estimated 8,600 Canadian women will be diagnosed with endometrial cancer in 2024.

Endometrial cancer is primarily diagnosed in postmenopausal women, with the median age at diagnosis being 61 years old.[128,132] It is uncommon in women under the age of 45.[133] The incidence of endometrial cancer is increasing more significantly among Hispanic, Asian and black women. Black women have a higher incidence of advanced, high-grade endometrial cancer at the time of diagnosis and poorer outcomes.[134]

Researchers have calculated and quantified the trends of endometrial cancer burden of disease estimates from 1990-2017.[133] They found that the age-standardized incidence and prevalence rate increased globally by 0.58 and 0.89% per year, respectively. In contrast, the age-

standardized death rate and disability-adjusted-life years (DALY) decreased by 1.19 and 1.21% per year, respectively.[133]

Endometrial cancer is predominantly endocrine-related. The most well-established risk factors of endometrial cancer are obesity, estrogen hormone replacement therapy, oral contraceptives, intrauterine devices, obesity, tamoxifen use, polycystic ovarian syndrome (PCOS), diabetes, radiation to the pelvic region, older age at menopause and a family history of Cowden or Lynch syndrome.[17] A strong association between obesity and endometrial cancer has been well established; a study found that the lifetime risk of endometrial cancer in women with a BMI over 40 kg/m^2 is 10-15%.[135]

2.2.2 Classification and Pathophysiology of Endometrial Cancer

Endometrial cancer originates from the endometrium (uterine corpus), the inner lining of the uterus.[136] This malignancy primarily involves changes in cellular regulation and hormonal influence, primarily involving estrogen. Two main pathways contribute to endometrial carcinogenesis and each one corresponds to a distinct cancer subtype.

Most endometrial cancers are estrogen-dependent endometrial adenocarcinomas (Type I). These are tumours that originate in the gland epithelial cells and account for approximately 80% of all uterine cancers.[136] Type I cancers are associated with an imbalance of estrogen and progesterone (unopposed estrogen) which act as a proliferating factor and tend to lead to endometrial hyperplasia and eventually, cancer. Obesity, insulin resistance, PCOS and estrogen therapy can all increase estrogen levels without adequate counteraction from progesterone, leading to prolonged endometrial stimulation, mitogenesis and increased cancer risk.[128] Type I

endometrial cancers are typically well differentiated, have a better prognosis and are less aggressive.[17]. These cancers commonly involve mutations in *PTEN*, *PAX2*, and *PIK3CA*, resulting in modified cell survival and cell proliferation effects.[128]

Type II endometrial cancers are generally more aggressive, higher grade, more likely to metastasize and exhibit more complex genetic mutations and alterations in tumor suppressor genes, resulting in poor prognosis.[17] These are not estrogen driven malignancies, rather they are driven by genetic instability.[134] Type II includes grade III endometrioid adenocarcinomas, serous clear cell, undifferentiated and carcinosarcomas.[134] These cancers often involve mutations in important tumour suppressors such as *TP53*.[128]

The International Federation of Gynecology and Obstetrics (FIGO) define the stages of endometrial cancer. FIGO staging relates to how far the cancer has spread within and beyond the uterus and influence the corresponding treatment plan. Stage I defines a cancer that is confined to the uterine corpus and ovary and non-aggressive, low-grade endometroid.[137] Surgery alone is typically adequate and no adjuvant treatment (radiation, chemotherapy) is recommended, unless it is a type II endometrial cancer due to high reoccurrence risks.[137] Stage II involves the cancer spreading to the cervical stroma, but remaining within the uterus or an aggressive histological type with myometrial invasion.[137] Stage III describes a cancer that spread beyond the uterus, to nearby tissues. Stage IV describes distant metastasis.[137]

2.2.3 Screening and Diagnosis of Endometrial Cancer

There are currently no standard or routine screening tests for endometrial cancer. According to the American National Cancer Institute, screening tests for endometrial cancer are

currently being studied in clinical trials. Transvaginal ultrasounds can be used to measure endometrial thickness, although there are no studies that have shown that screening by this modality lowers the number of deaths caused by endometrial cancer.[128]

The first sign is of endometrial cancer is often abnormal bleeding, primarily postmenopausal bleeding.[128] However, a study found that an estimated 15% of diagnoses are made pre-menopause, with intermenstrual bleeding being the most predictive clinical presentation.[128] After an initial clinical assessment, a histological examination of a biopsy of endometrial tissue is the main diagnostic test.[128] Endometrial biopsy is a highly sensitive (90%) and specific (100%) diagnostic test.[131,138] Typically, biopsies are only performed following a pelvic exam and transvaginal ultrasound to measure thickness of the endometrial wall due to the invasive nature of tissue sampling. A endometrial thickness of 5mm is considered the normal upper limit for postmenopausal women, therefore any measurement greater than that will indicate further testing.[134] MRI (magnetic resonance imaging) or CT (computed tomography) scans are used for preoperative staging and assessment of endometrial cancer.[134]

2.2.4 Treatment and Prognosis of Endometrial Cancer

Treatment of endometrial cancer varies by cancer-type and stage. The standard treatment involves surgery, with adjuvant procedures and treatments based on cancer aggressiveness and individual patient characteristics.

For localized, early-stage type I endometrial adenocarcinomas, a total hysterectomy with bilateral salpingo-oophorectomy is the standard procedure.[139] This involves the removal of the uterus, cervix fallopian tubes and ovaries.[137] Higher-risk, early-stage type I cancers typically

require radiation therapy as an adjuvant treatment. Advanced stage type I typically requires surgery combined with radiation or chemotherapy, depending on lymph node involvement and metastasis distance.[140] Due to the aggressive and recurring nature of type II endometrial cancers, all stages are typically treated with a more intensive approach. This could involve a total hysterectomy, bilateral salpingo-oophorectomy and lymph node dissections. These are typically accompanied by radiation or chemotherapy, regardless of stage.[134,139]

Hormone therapy (progesterone) may be considered for women with early-stage cancer who want to preserve fertility.[139] The use of hormonal contraceptive or progestin-only therapy have been shown to decrease risk of endometrial cancer.[131] For advanced or recurrent endometrial cancers, targeted therapy such as anti-HER2 (human epidermal growth factor receptor 2) medications and immunotherapy may be considered.[139]

2.2.5 Association Between Type 2 Diabetes and Endometrial Cancer

As previously stated, type 2 diabetes is associated with an increased risk of endometrial cancer.[141] The disease has also been found to increase the mortality of endometrial cancer.[142–144] A systematic review and meta-analysis including 31 studies and comprising 55,475 endometrial cancer patients found a worse cancer-specific survival in individuals with diabetes compared to those without diabetes (HR: 1.15, 95% CI: 1.00-1.32, I^2: 62%) .[143] Additionally, a prospective cohort study that included 533 women diagnosed with endometrial cancer (majority low-grade and early-stage) with a median age and BMI of 66 years and 32 kg/m^2, respectively, found a two-fold increase in overall mortality (HR: 2.07, 95% CI: 1.21-3.55), cancer-specific mortality (HR: 2.15, 95% CI: 1.05-4.39) and recurrence rate (HR: 2.22, 95% CI: 1.08-4.56) compared to

those without type 2 diabetes. Another meta-analysis of prospective cohort studies estimated standardized relative risks (SRR) of incident endometrial cancer and mortality.[145] They found that diabetes was associated with an increased incidence of endometrial cancer (SRR: 1.81, 95% CI: 1.38-2.37, I^2: 95.4%) compared with individuals without diabetes. In this study, diabetes was not associated with endometrial cancer-specific mortality (SRR: 1.23, 95% CI: 0.80-1.90, I^2: 58.2%).[145] Lastly, a meta-analysis comprised of 22 cohort and case-control studies found that diabetes was associated with an increased risk of endometrial cancer (RR: 1.72, 95% CI: 1.48-2.01).[146]

This relationship is primarily explained by insulin resistance and consequent hyperinsulinemia promoting endometrial carcinogenesis and progression through the proliferative and anti-apoptotic effects increased levels of IGF-1 on endometrial cells.[143,147] In addition, mutations or over-expressions of important regulators of glucose metabolism including phosphatase and tensin homologue (PTEN) and phosphatidylinositol 3-kinase (PI3K) are often seen in individuals with endometrial cancer. Loss of *PTEN* and downstream targets in the PI3K/PTEN/Akt pathway alter cell cycle regulation and cell metabolism, and have been shown to initiate endometrial cancer in mice.[147] Accordingly, studies have shown that the PI3K/Akt/mTOR (mammalian target of rapamycin) pathway is altered in up to 93% of endometrial cancer patients.[147]

2.3 Incretin-Based Drugs and Endometrial Cancer

2.3.1 Biological Evidence of the Effect of GLP-1 RAs on Endometrial Cancer Cells

Emerging evidence suggests that incretin-based drugs may have anti-proliferative and pro-apoptotic effects on endometrial cancer cells. A study by Zhang et al., investigated the effects of exenatide (exendin-4) on endometrial cancer using subcutaneous human endometrial cancer cell Ishikawa xenografts in nude mice.[16] They obtained endometrial cancer tissues from 10 patients (45-55 years old) who had received a hysterectomy due to endometrial cancer and the Ishikawa cells were injected into 10 mice; 5 mice were treated with exenatide and 5 mice acted as controls (saline injections). They found that the tumour growth rate was slower in the exenatide group than that in the control group. Exendin-4 weakened cell viability of the Ishikawa cells and promoted a significantly high apoptosis rate. They found that exendin-4 phosphorylates AMPK which results in the reduced phosphorylation of mTOR, promoting apoptosis. They also showed that GLP-1 receptor is abundantly expressed in both endometrial cancer tissue and non-cancerous endometrial tissue and that exenatide elevated serum GLP-1 levels. They postulate that exenatide (exendin-4) inhibits endometrial cancer growth through phosphorylating AMPK mediated by GLP-1 receptor signalling.[16]

Based on the findings from the study discussed above, Kanda et al. conducted a similar in vitro study investigating the pathophysiological role of GLP-1 receptors in endometrial cancer.[14] They treated human Ishikawa endometrial cancer cells with different concentrations of liraglutide. They analysed cell viability, GLP-1 receptor expression and autophagy induction. They found that liraglutide dose-dependently increased GLP-1 receptor expression in Ishikawa cells. They also found reduced cell viability and decreased number of colonies in the cancer cells treated with higher doses of liraglutide compared with control cells indicating that liraglutide

inhibits endometrial cancer cell proliferation in a dose-dependent manner. Additionally, they showed that through GLP-1 receptor signalling, liraglutide stimulated apoptosis and autophagy via the AMPK pathway in a dose-dependent manner. They postulated that GLP-1 receptor expression may be a biomarker of endometrial cancer, that higher GLP-1 receptor expression may be associated with better prognosis, and the use of liraglutide should be considered to target autophagy in endometrial cancer cells as a novel treatment for the disease.[14]

2.3.1.2 Biological Evidence of the Effect of DPP-4 inhibitors on Endometrial Cancer Cells

Biological studies on the association between the use of DPP-4 inhibitors and endometrial cancer are limited. DPP-4 is expressed in numerous cell types including epithelial and glandular cells.[15] There are contradictory results on whether DPP-4 suppresses or promotes malignant activity in cells. Although DPP-4 has been implicated in the initial stages of carcinogenesis and cancer cell proliferation, it has also been reported to act as a tumour suppressor depending on the characteristics of the tumour and cell lines.[15]

A study conducted by Yang et al. described a positive association between DPP-4 expression and cancer cell proliferation. DPP-4 overexpression altered cell morphology which promoted cell proliferation, tumorigenesis and migration (metastasis) in vitro and in vivo. When treated with sitagliptin to inhibit DPP-4, these effects were not observed. Given these results, they state that DPP-4 is a promising therapeutic target for endometrial cancer treatment.

Moreover, it has been found that expression of DPP-4 is downregulated in endometrial adenocarcinomas.[148] Khin et al. found that DPP-4 is expressed in normal endometrial glandular cells but in endometrial cancer cells, DPP-4 becomes more downregulated with increasing

histological grade of cancer. Additionally, DPP-4 expression was inversely correlated with the degree of tumour differentiation. These findings indicate that level of DPP-4 activity has a positive association with tumour grading levels.

2.4 Knowledge Gaps

There is compelling biological evidence that the use of incretin-based drugs may decrease the risk of endometrial cancer. As laboratory studies have found GLP-1 receptor expression in endometrial tissue and dose-dependent antiproliferative and apoptotic effects of incretin-based drugs on endometrial cancer cells, it can be hypothesized that the use of incretin-based drugs would be associated with a decreased risk of endometrial cancer. However, no observational studies have been conducted to help fill this gap in knowledge. Thus, the goal of this thesis is to assess whether the use of incretin-based drugs (GLP-1 RAs and DPP-4 inhibitors, separately) is associated with a decreased incidence of endometrial cancer among women with type 2 diabetes.

CHAPTER 3: OBJECTIVES AND HYPOTHESES

3.1 OBJECTIVE

The primary objective of this thesis is to determine whether the use of GLP-1 RAs and DPP-4 inhibitors separately, is associated with a decreased risk of endometrial cancer among patients with type 2 diabetes when compared with sulfonylureas.

3.1.1 Secondary Objectives

The secondary objectives of this thesis include the investigation of:

(1) whether the association varies with drug type within each class of incretin-based drug (drug-specific effect);

(2) whether there is effect measure modification by BMI level (i.e., <30 kg/m2, ≥30 kg/m2);

(3) whether there is effect measure modification by previous use of the *other* incretin-based drug before cohort entry (i.e., yes/no).

3.2 HYPOTHESES

The primary hypothesis is that the use of incretin-based drugs is associated with a lower incidence of endometrial cancer when compared with the use of sulfonylureas among women with type 2 diabetes.

3.2.1. Secondary Hypotheses

(1) The association will not vary among different drug types (no drug-specific effect);

(2) The association will vary at different levels of BMI;

(3) The association will vary with previous use of the other incretin-based drug.

CHAPTER 4: METHODOLOGY

The methodology for this thesis is briefly detailed in the manuscript found in Chapter 5. This chapter will give a comprehensive description of the methodology used in this thesis study, including details that were not fully elaborated on in the manuscript due to word count restrictions given by the journal. Specifically, this chapter will give a thorough description of the data source, justification for the selection of the active comparator, construction of the study cohorts, exposure definition, potential confounders, propensity score fine stratification, and inverse probability of censoring weighting.

4.1 Data Source

4.1.1 Clinical Practice Research Datalink

This study was conducted using data from the CPRD, a primary care database containing anonymized electronic health record data collated from general practice patients in the United Kingdom (UK). These data have been collected from roughly 60 million patients across England, Wales, Scotland and Northern Ireland; The CPRD is largely representative of the UK population with over 98% of the English population registered at a General Practice, as there is no charge to visit a general practitioner in these regions. General practitioners oversee and manage all non-emergent primary care and referrals to secondary care, as needed.[149] Secondary care providers transfer all health information, including diagnoses, back to the general practitioner.[149]

The CPRD consists of two separate datasets: GP OnLine Data (GOLD) and Aurum. GOLD data is contributed from practices that use EMIS Web® patient management software

and Aurum data is contributed from practices that use Vision ® software. While GOLD has been collecting data for over 30 years, Aurum was introduced in 2017. Together, they include approximately 60 million patients from roughly 2000 general practices.

Each patient has a unique National Health Service (NHS) number that is recorded in a computer system with all corresponding health record data.[149] The CPRD collects this data on a monthly basis from all general practices who have agreed at a practice level to provide data. Within the practice, patients can opt out of data sharing.[149] Willing patients are included in the data set from their initial visit until their final visit, with a reported median follow-up time of 9.4 years.[149]

Demographics, diagnoses, symptoms, signs, prescriptions, referrals, immunisations, lifestyle and behavioural factors (e.g., smoking status) and diagnostic testing is all recorded.[149] Diagnoses and procedures are recorded using the Read and Systematized Nomenclature of Medicine – Clinical Terms (SNOMED-CT) classification system, and prescription data is recorded using a British National Formulary code from their drug dictionary and a product name.[149,150]

Studies have assessed the validity and completeness of cancer diagnoses recorded in the CPRD.[151–153] A validity studied found that endometrial cancer was well-recorded in the CPRD, with a high positive predictive value (PPV); 100% of endometrial cancer cases identified between 2004-2012 in a stratified random sample were confirmed by clinical review of patient profiles.[151] As general practitioners provide and oversee the long-term care of patients with type 2 diabetes rather than specialists, diabetes is also well-recorded in the CPRD with a PPV of 99% in the Aurum dataset.[154]

4.1.2 CPRD Linkage

The CPRD is linked to a range of patient-level data sources including secondary care, disease registries and death registration records.[150] This thesis study utilized linkage to the Hospital Episodes Statistics Admitted Patient Care database (HES APC), the Office for National Statistics Death Registration Data (ONS) and the Index of Multiple Deprivation (IMD). The HES APC database contains all admissions to, or attendances to NHS health care providers. An HES record contains information about an individual patient admitted to an NHS hospital including diagnoses, operations, procedures, specialists seen, demographics, and administrative information (e.g., hospital admission and discharge dates).[155] The International Classification of Diseases, version 10 (ICD-10) is used to code diagnostic data in the HES APC. A hospital admission includes any secondary care that requires a hospital bed, whether it be an emergent or planned admission.[156] It has been established through past analyses that linking to the HES APC allows for a more robust and accurate analysis and mitigates misclassification bias.[157]

The ONS contains death registration data including date and location. Although an validity study showed that mortality was well-recorded in the CPRD (PPV: 98.2%)[158], linking to the death registry provides more accurate information on date of death for censoring and rate calculation purposes.

IMD is a dataset containing composite measures of relative deprivation across each area of the UK. Measurements of deprivation are defined slightly differently by each area, though the primary themes include: education, income, employment, health, crime, barriers to housing and the living environment.[159]

4.2 Active Comparator Group

Sulfonylureas were used as the active comparator in this study because they are a drug that is typically prescribed at a similar disease stage as incretin-based drugs and have no association with an altered risk of endometrial cancer.[160–162] Sulfonylureas have been used for over half a century and continue to be a widely used in the treatment of type 2 diabetes, thus offering a high number of patients potentially eligible for inclusion in the comparison group.

Using SGLT-2 inhibitors as an active comparator would restrict the cohort to patients who initiated the study drugs after 2013, as this was the year they entered the market in the UK. This would generate an underpowered study, as fewer patients would be included in the cohort and follow-up would be very limited. Metformin and insulin were deemed unsuitable active comparators as they are antihyperglycemic drugs that are used at different disease stages than incretin-based drugs and therefore would introduce confounding by indication. TZDs are used at a similar disease stage as incretin-based drugs, however their use is less prevalent due to adverse clinical side effects. Following consideration of these factors, sulfonylureas appeared to be the most suitable active comparator.

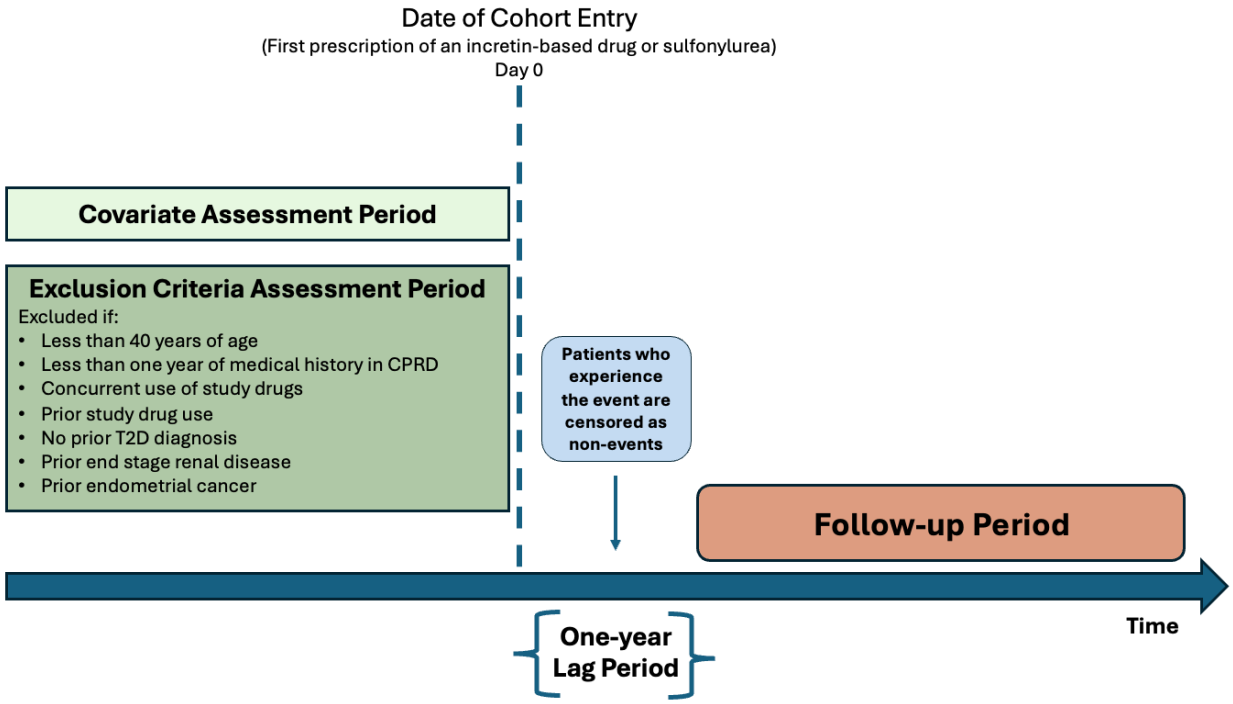
4.3 Cohort Formation

We assembled a separate cohort for each incretin-based drug class to allow us to analyze GLP-1-RAs and DPP-4 inhibitors against an active comparator, separately. The first cohort consisted of female initiators of a GLP-1 RA (albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide, and subcutaneous semaglutide) or a sulfonylurea (chlorpropamide, glibenclamide, gliborunide, gliclazide, glimepiride, glipizide, gliquidone and tolbutamide)

between January 1, 2007 (the year that incretin-based drugs became available in the UK) and December 31, 2020. The second cohort consisted of female initiators of a DPP-4 inhibitor (alogliptin, linagliptin, saxagliptin, sitagliptin, and vildagliptin) or a sulfonylurea between January 1, 2007, and December 31, 2020. The date of cohort entry was the first prescription of the incretin-based drug of interest (GLP-1 RA of DPP-4 inhibitor, depending on the analysis) or sulfonylurea during the study period.

To enter the cohort, a patient needed to have at least one year of medical history in the CPRD before cohort entry as a means to ascertain that they were a new user (washout period) and assess patient covariates (baseline period). To adhere to our new-user cohort design, patients that were prescribed an incretin-based drug or sulfonylurea at any time before cohort entry were excluded. Additional exclusion criteria included: age less than 40 (as endometrial cancer is rarely diagnosed in that age group), concurrent use of the study drugs at cohort entry (incretin-based drug and sulfonylurea prescription), end-stage renal disease (contraindication to sulfonylurea use), previous diagnosis of endometrial cancer, and those who did not have a type 2 diabetes diagnosis. A cohort formation timeline is illustrated in **Figure 4-3** below.

Figure 4-4. Study cohort of female patients who initiated treatment with incretin-based drugs or sulfonylureas



4.4 Exposure Definition

An on-treatment exposure definition was used, in that patients were followed while continuously exposed to the drug. Continuous exposure was defined by overlapping consecutive prescriptions with a one-year grace period, utilized to account for residual effects of the drug and diagnostic delays associated with endometrial cancer. Additionally, a one-year lag period was used to account for cancer latency (as early events are unlikely associated with the exposure) and to reduce detection bias, given that patients might be monitored more closely after initiating a new treatment. Therefore, those diagnosed with endometrial cancer during the one-year lag period were censored as non-events. Using this exposure definition, patients were considered exposed to the study drug starting one year after cohort entry until an incident diagnosis of

endometrial cancer, death from any cause, one year after switching or discontinuing treatment, or until the end of the study period (March 29, 2021), whichever occurred first.

4.5 Outcome Definition

The primary outcome was defined as an incident diagnosis of endometrial cancer recorded in either the CPRD or HES APC. Using HES APC helped identify events not recorded in the CPRD, thereby maximizing the sensitivity of the outcome definition. **Tables 4-1, 4-2 and 4-3** below provide the Read codes used to define endometrial cancer in the GOLD and Aurum databases and the HES APC (ICD-10 codes).

Table 4-1. Aurum Read codes for endometrial cancer

Read Code	Read Term
B430200	Malignant neoplasm of endometrium of corpus uteri
B40..00	Malignant neoplasm of uterus, part unspecified
B43..00	Malignant neoplasm of body of uterus
B43z.00	Malignant neoplasm of body of uterus NOS
B430.00	Malignant neoplasm of corpus uteri, excluding isthmus
B430z00	Malignant neoplasm of corpus uteri NOS
B430211	Malignant neoplasm of endometrium
B43y.00	Malignant neoplasm of other site of uterine body
B432.00	Malignant neoplasm of overlapping lesion of corpus uteri
B430300	Malignant neoplasm of myometrium of corpus uteri
B431.00	Malignant neoplasm of isthmus of uterine body
B431000	Malignant neoplasm of lower uterine segment
B430100	Malignant neoplasm of fundus of corpus uteri
B430000	Malignant neoplasm of cornu of corpus uteri
B431z00	Malignant neoplasm of isthmus of uterine body NOS
BB5j.00	[M]Endometrioid adenomas and carcinomas
BB5j200	[M]Endometrioid carcinoma
BBL0.00	[M]Endometrial stromal sarcoma
BB5j500	[M]Endometrioid adenofibroma, malignant

Table 4-2. GOLD Read codes for endometrial cancer

Read Code	Read Term
BB5j.00	[M]Endometrioid adenomas and carcinomas
B430100	Malignant neoplasm of fundus of corpus uteri
BB5j200	[M]Endometrioid carcinoma
BB5j500	[M]Endometrioid adenofibroma, malignant
B43..00	Malignant neoplasm of body of uterus
B40..00	Malignant neoplasm of uterus, part unspecified
B430.00	Malignant neoplasm of corpus uteri, excluding isthmus
B430000	Malignant neoplasm of cornu of corpus uteri
B430200	Malignant neoplasm of endometrium of corpus uteri
B430211	Malignant neoplasm of endometrium
B430300	Malignant neoplasm of myometrium of corpus uteri
B430z00	Malignant neoplasm of corpus uteri NOS
B431.00	Malignant neoplasm of isthmus of uterine body
B431000	Malignant neoplasm of lower uterine segment
B431z00	Malignant neoplasm of isthmus of uterine body NOS
B432.00	Malignant neoplasm of overlapping lesion of corpus uteri
B43y.00	Malignant neoplasm of other site of uterine body
B43z.00	Malignant neoplasm of body of uterus NOS

Table 4-3. ICD-10 codes for endometrial cancer

Read Code	Read Term
C54.3	Malignant neoplasm of fundas uteri
C54	Malignant neoplasm of corpus uteri
C54.1	Endometrium
C55	Malignant neoplasm of uterus, part unspecified
C54.9	Corpus uteri, unspecified
C54.0	Isthmus uteri
C54.8	Overlapping lesion of corpus uteri
Z90.710	Acquired absence of both cervix and uterus

4.6 Potential Confounders

This study considered 31 potential confounders that were selected based on a review of scientific literature and clinical knowledge. Demographic and lifestyle variables that were measured at or before cohort entry include: age, BMI, smoking status (ever, never, unknown), alcohol related disorders, IMD, and year of cohort entry. Variables related with diabetes severity were also considered, as type 2 diabetes is associated with an increased incidence of endometrial cancer. These included: glycosylated hemoglobin (HbA1c; last measure before cohort entry), duration of diabetes (years; date of the first of either an HbA1c $\geq$ 6.5%, a diagnosis, or prescription for an anti-hyperglycemic drug), presence of macrovascular (peripheral vascular disease, stroke, myocardial infarction; assessed ever before cohort entry) and microvascular complications (retinopathy, neuropathy; assessed ever before cohort entry) and type of antidiabetic drugs used (alpha-glucosidase inhibitors, insulin, meglitinides, metformin, TZDs, SGLT-2 inhibitors, and DPP-4i or GLP-1 RA, depending on the cohort analysis; non-mutually exclusive categories, assessed in the year before cohort entry).

Variables strongly associated to the incidence of endometrial cancer were also considered including tamoxifen use, hormone replacement therapy, intrauterine devices, endometrial fibroids, oral contraceptives, and PCOS (see section 2.2). Additionally, other medications proposed to modulate the risk of endometrial cancer were also considered including nonsteroidal anti-inflammatory drugs (NSAIDS),[163] aspirin,[164] and statins[165,166] (measured any time before cohort entry). Lastly, previous cancer diagnoses were considered, as this may encourage greater contact with the healthcare system and propensity for screening for other cancers, such as endometrial. A summary of all covariates considered with their definitions, variable types, and time of assessment are outlined in **Table 4-4** below.

Table 4-4. Summary of covariates

Covariate	Variable Type	Definition	Time of Assessment
Demographic/lifestyle variables			
Age	Continuous	Cohort entry year minus birth year	Cohort entry
BMI	Categorical	<30 kg/m2, ≥30 kg/m2, unknown	Last measure before cohort entry
Smoking Status	Categorical	Ever, never, unknown	Cohort entry
Alcohol-related disorders	Binary	Present/absent	Ever before cohort entry
Index of Multiple Deprivation	Categorical	1 = least deprived, 5 = most deprived	Cohort entry
Year of cohort entry	Categorical	Cohort entry year	Cohort entry
Diabetes-related variables			
Hemoglobin A1c	Categorical	≤7.0%, 7.1%-8.0%, >8.0%, unknown	Last measure before cohort entry
Duration of diabetes	Continuous	Date of the first of either an HbA1c ≥6.5%, a diagnosis of type 2 diabetes, or prescription for an antidiabetic drug to the date of cohort entry	Cohort entry
Peripheral vascular disease	Binary	Present/absent	Ever before cohort entry
Stroke	Binary	Present/absent	Ever before cohort entry
Myocardial infarction	Binary	Present/absent	Ever before cohort entry
Renal disease	Binary	Present/absent	Ever before cohort entry
Retinopathy	Binary	Present/absent	Ever before cohort entry
Neuropathy	Binary	Present/absent	Ever before cohort entry
Type of antidiabetic drugs			
Alpha-glucosidase inhibitors	Binary	Present/absent	Year before cohort entry
Insulin	Binary	Present/absent	Year before cohort entry
Meglitinides	Binary	Present/absent	Year before cohort entry
Metformin	Binary	Present/absent	Year before cohort entry
Thiazolidinediones	Binary	Present/absent	Year before cohort entry
SGLT-2 inhibitors	Binary	Present/absent	Year before cohort entry
DPP-4 inhibitors (cohort 1)	Binary	Present/absent	Year before cohort entry
GLP-1 RAs (cohort 2)	Binary	Present/absent	Year before cohort entry
Endometrial cancer risk factors			
Tamoxifen	Binary	Present/absent	Ever before cohort entry
Hormone replacement therapy	Binary	Present/absent	Ever before cohort entry
Intrauterine devices	Binary	Present/absent	Ever before cohort entry

Endometrial fibroids	Binary	Present/absent	Ever before cohort entry
Oral contraceptives	Binary	Present/absent	Ever before cohort entry
PCOS	Binary	Present/absent	Ever before cohort entry
Other prescription drugs			
NSAIDS, n (%)	Binary	Present/absent	Ever before cohort entry
Aspirin, n (%)	Binary	Present/absent	Ever before cohort entry
Statins, n (%)	Binary	Present/absent	Ever before cohort entry
Previous cancer diagnosis	Binary	Present/absent	Ever before cohort entry

4.7 Statistical Analysis

4.7.1 Propensity Score Fine Stratification

Propensity score analysis is statistical method used when estimating treatment effects to balance exposure groups, generally using observed data. Propensity score methods allow us to account for systematic differences in baseline characteristics between exposed and unexposed subjects when estimating a treatment effect on outcomes in a study.[167] A propensity score gives a subject's predicted probability of being exposed or assigned to a treatment conditional on their baseline characteristics, defined in 1983 by Rosenbaum and Rubin.[167,168] These scores are typically calculated using logistic regression.[169] There are multiple methods based on propensity scores used in observational studies including matching, stratification, adjustment, and weighting.[169] All methods are used to help achieve exchangeability between exposed and unexposed groups with respect to measured confounders, thus adjusting for confounding.

Propensity score weighting is best suited for studies when the prevalence of exposure is expected to be low because it allows for the retention of most subjects in the analysis, thus maximizing statistical power.[170] We expected low prevalence in the incretin-based drug groups, as they are a relatively recent addition to anti-hyperglycemic drugs on the market. Therefore, propensity score fine stratification weighting was used to adjust for confounding in this study. This method uses many fine strata with a corresponding weight that represents membership within the stratum. With this, a distribution of measured confounders among groups is generated and used to make the unexposed group more similar to the exposed group with respect to this distribution. Therefore, the estimated effect that is calculated is the average treatment effect among the exposed population.[170]

In this study, we used multivariate logistic regression to calculate propensity scores of treatment with a GLP-1 RA or DPP-4 inhibitor versus a sulfonylurea. Using the propensity score distribution, 50 strata of the incretin-based drug users were created, and non-overlapping regions of the distribution were trimmed to balance the groups as precisely as possible. In each stratum, a weight of 1 was given to each incretin-based drug user and sulfonylurea users were reweighted to create a proportional comparator group to the number of exposed patients in each strata.

4.7.2 Inverse probability of censoring weighting

Inverse probability of censoring weighting (IPCW) is a statistical method that is used to account for potential informative censoring from censoring mechanisms such as treatment discontinuation, treatment switching, mortality, and administrative censoring. In time-to-event analyses, it is assumed that the reason for which a patient is censored is independent of the outcome. However, a covariate might be associated to the censoring mechanism which can induce informative censoring, a form of selection bias. In other words, a certain characteristic might influence the timing and probability that a patient will be lost to follow-up.[171] That characteristic might heavily skew the "survival distribution", or in this case, a patient's possibility of experiencing the outcome. IPCW accounts for the mechanism of censoring by adjusting parameter estimates based on conditional probabilities of staying in the study (uncensored) for each patient throughout follow-up.[171,172] This method corrects for informative censoring by reweighting subjects based on their censoring status; more weight is allocated to patients who are not censored thereby reducing the likelihood that censoring was associated with certain unbalanced cohort covariates, leading to an overestimated or underestimate effect

estimate.[171] In this study, this method was utilized in a sensitivity analysis to assess whether censoring for death by any cause induced a biased result.

CHAPTER 5: MANUSCRIPT

This chapter presents a manuscript on the association between the use of incretin-based drugs and the risk of endometrial cancer using the methods detailed in Chapter 4. First, the Background section presents the context and rationale for the study. Second, the Research Design and Methods section briefly details the data sources, study population, process for constructing the cohorts, exposure definition, potential confounders, and statistical analysis. Following, is the Results section which includes descriptive characteristics of the cohorts and results from the primary, secondary, and sensitivity analyses. Finally, the Discussion section provides a summary of the main findings, an overview of prior experimental research on the topic, and strengths and limitations of the study. This manuscript is currently under consideration for publication in *Drug Safety* and has been formatted accordingly.

Incretin-based drugs and the incidence of endometrial cancer among people with type 2 diabetes

Incretin-based drugs and risk of endometrial cancer

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5.1 ABSTRACT

Introduction: The use of incretin-based drugs may be associated with a decreased risk of endometrial cancer among women with type 2 diabetes.

Methods: Using data from the UK Clinical Practice Research Datalink and linked databases, two new-user active comparator cohorts of women with type 2 diabetes who initiated GLP-1 RAs or sulfonylureas (cohort 1) and DPP-4 inhibitors or sulfonylureas (cohort 2) were assembled. Propensity score fine stratification weighted Cox proportional hazards models were fitted to estimate adjusted hazard ratios and 95% confidence intervals for incident endometrial cancer.

Results: Cohort 1 included 9,239 new users of GLP-1 RAs and 80,086 new users of sulfonylureas. GLP-1 RAs were not associated with a decreased risk of endometrial cancer when compared with sulfonylureas (HR: 1.11, 95% CI: 0.66-1.88). When analyzed by drug type, exenatide was associated with an elevated risk when compared to sulfonylureas (HR: 2.26, 95% CI:1.06-4.82). Cohort 2 included 42,486 new users of DPP-4 inhibitors and 79,353 new users of sulfonylureas. DPP-4 inhibitors were not associated with a decreased risk of endometrial cancer compared with sulfonylureas (HR: 1.00, 95% CI: 0.76-1.32).

Conclusions: In this large population-based study, the use of GLP-1 RAs and DPP-4 inhibitors was not associated with a decreased risk of endometrial cancer when compared with the use of sulfonylureas among women with type 2 diabetes.

Key points

- Laboratory studies have suggested that incretin-based drugs can attenuate endometrial cancer cell growth; however, no observational study has been conducted to investigate these effects in a real-world setting.
- The overall use of glucagon-like peptide 1 receptor agonists (GLP-1 RAs) and (dipeptidyl peptidase-4) DPP-4 inhibitors was not associated with a decreased risk of endometrial cancer when compared with the use of sulfonylureas among women with type 2 diabetes.
- The use of exenatide, a type of GLP-1 RA, was associated with an elevated risk of endometrial cancer.

5.2 INTRODUCTION

Incretin-based drugs, which include glucagon-like peptide 1 receptor agonists (GLP-1 RAs) and dipeptidyl peptidase-4 (DPP-4) inhibitors, are second-to third-line drugs used to treat type 2 diabetes [1]. Although incretin-based drugs have several benefits over other antihyperglycemic drugs, such as their ability to lower hemoglobin A1c levels and reduce risk of hypoglycemia, and GLP-1 RAs ability to induce weight loss and lower the risk of cardiovascular events, there are concerns that their use may increase the risk of certain cancers [2,3]. Due to the presence of GLP-1 receptors in sites outside the pancreas, such as in the brain, lung, stomach, and endometrium, it has been hypothesized that incretin-based drugs may have pleiotropic properties [4]. Indeed, laboratory studies have suggested that incretin-based drugs can attenuate endometrial cancer cell growth [4,5]. To date, however, no observational study has been conducted to investigate the effects of GLP-1 RAs on endometrial cancer in the real-world setting.

Given that type 2 diabetes is a risk factor for endometrial cancer [6] and the lack of real-world studies on the chemopreventative effects of incretin-based drugs on the incidence of endometrial cancer, the objective of this study was to determine whether the use of GLP-1 RAs and DPP-4 inhibitors separately, is associated with a decreased risk of endometrial cancer among women with type 2 diabetes when compared with sulfonylureas.

5.3 Research Design and Methods

5.3.1 Data Sources

This population-based cohort study was conducted using the GOLD and AURUM databases of the Clinical Practice Research Datalink (CPRD) linked to the Hospital Episodes Statistics Admitted Patient Care database (HES APC), and the Office for National Statistics Death Registration Data (ONS). The CPRD is a United Kingdom (UK) primary care database containing anonymized electronic health record data from roughly 60 million patients collected over the past 30 years. The CPRD is largely representative of the UK population [7]. Demographics, diagnoses, prescriptions, symptoms, laboratory tests, health-related behaviours (e.g. smoking status) and referrals to secondary care are all well recorded in the CPRD [8]. Diagnoses and procedures are recorded using Read code and Systematized Nomenclature of Medicine (SNOMED) Clinical Terms classification system. The British National Formulary is used for recording prescriptions using a coded drug dictionary [8].

The HES APC database encompasses all admission, visits, discharge dates, specialists seen and procedures for each linked patient with a hospitalization record at English National health Service healthcare providers. Diagnoses are recorded using the International Classification of Diseases version 10 (ICD-10) codes and procedure data is coded using the UK Office of Population, Census, and Surveys classification [9]. The study protocol was approved by the CPRD's Research Data Governance (Protocol 23_003631) and by the McGill University ethics committee.

5.3.2 Study Population

We used an active-comparator, new-user cohort design to assemble two separate cohorts of women with type 2 diabetes: (1) initiators of GLP-1 RAs (albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide, and subcutaneous semaglutide) versus initiators of sulfonylureas (chlorpropamide, glibenclamide, gliborunide, gliclazide, glimepiride, glipizide, gliquidone and tolbutamide) and (2) initiators of DPP-4 inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin, and vildagliptin) versus initiators of sulfonylureas, between January 1, 2007 and December 31, 2020, with follow-up until March 29, 2021. Sulfonylureas were chosen as an active comparator as they are typically prescribed at a similar disease stage as incretin-based drugs and shown to have no association with the incidence of endometrial cancer [10–12]. The date of cohort entry was the first prescription of either an incretin-based drug or a sulfonylurea during the study period. We excluded participants who were less than 40 years old at the first prescription as endometrial cancer is rarely diagnosed in that age group, had prior use of the study drugs ever before cohort entry, concurrent use of the study drugs at cohort entry, had less than one year of medical history in the CPRD before cohort entry, those who did not have a diagnosis of type 2 diabetes ever before cohort entry and those diagnosed with end-stage renal disease, or endometrial cancer ever before cohort entry.

5.3.3 Exposure Definition

An on-treatment exposure definition was used in which participants were followed while continuously exposed to the study drugs. Continuous exposure was measured by overlapping consecutive prescriptions and using a one-year grace period (to account for residual effects of the drugs and diagnostic delays) to bridge non-overlapping prescriptions. Thus, participants were

followed while they were continuously exposed to drugs under investigation from cohort entry and until an incident diagnosis of endometrial cancer, or censored upon a hysterectomy, death from any cause, one year after discontinuing or switching treatment, or end of the study period (March 29, 2021), whichever occurred first. Endometrial cancer events occurring in the first year of follow-up were censored as non-events to account for latency (as early events are unlikely associated with the exposure) and reduce the risk of detection bias (i.e., there may be more frequent contact with the healthcare system in the weeks to months after drug initiation).

5.3.4 Outcome Definition

The primary outcome was defined as an incident diagnosis of endometrial cancer recorded either in CPRD or HES APC. Endometrial cancer was shown to be well-recorded in the CPRD with a positive predictive value of 100; validation study showed that 100% of endometrial cancer cases identified between 2004-2012 in the CPRD were confirmed by clinical review of patient profiles [13]. Using HES APC helped identify events not recorded in the CPRD, thereby maximizing the sensitivity of the outcome definition.

5.3.5 Potential Confounders

We considered important potential confounders and known risk factors of the outcome, all measured at or before cohort entry. They included age, alcohol-related disorders (alcoholism, cirrhosis, alcoholic hepatitis, hepatic failure), body mass index (BMI), smoking status, and index of multiple deprivation (a measure of socioeconomic status) [6,14–17]. As type 2 diabetes is associated with the risk of endometrial cancer, variables related to the severity of diabetes were also considered including glycated hemoglobin A1C (HbA1c; last measure before cohort entry), duration of diabetes (defined by the date of the first of either an HbA1c ≥6.5%, a diagnosis of

type 2 diabetes, or prescription for an antidiabetic drug), other types of antidiabetic drugs prescribed ever before cohort entry (alpha-glucosidase inhibitors, insulin, meglitinides, metformin, sodium-glucose cotransporter-2 inhibitors, thiazolidinedione), previous use of incretin-based drugs (DPP-4 inhibitors in cohort 1, and GLP-1 RAs in cohort 2), macrovascular complications (peripheral vascular disease, ischemic stroke, myocardial infarction; assessed ever before cohort entry), and microvascular complications (nephropathy, retinopathy, neuropathy; assessed ever before cohort entry) [11,14,16–19]. We also considered prescription drugs associated with endometrial cancer incidence, including non-steroidal anti-inflammatory drugs, aspirin, statins and tamoxifen [14,15,19]. Hormone replacement therapy, intrauterine devices, endometrial fibroids, oral contraceptives and polycystic ovarian syndrome (PCOS) were also considered as these factors may affect the risk of endometrial cancer [15,20]. Additionally, we considered previous cancer diagnoses and year of cohort entry.

5.3.6 Statistical Analysis

Propensity score fine stratification weighting was used to control for confounding. This method gives an estimate of the average effect of the treatment on the treated (ATT) [21]. Multivariable logistic regression was used to calculate the predicted probability (propensity score) of being treated with either a GLP-1 RA or DPP-4 inhibitor versus a sulfonylurea, based on the previously listed covariates. Using the propensity score distribution, 50 strata of the incretin-based drug users were created. Non-overlapping regions of the distribution were trimmed to balance the groups as precisely as possible. In each stratum, a weight of 1 was given to each incretin-based drug user and sulfonylurea users were reweighted to create a proportional comparator group to the number of exposed participants in the strata. This method is suitable

when exposure prevalence is expected to be low, as it allows for the number of participants retained in the analysis to be maximized [22,23].

Crude and weighted endometrial cancer incidence rates with their corresponding 95% confidence intervals (CI) based on the Poisson distribution were calculated. Weighted Cox proportional hazards models were used to estimate hazard ratios (HRs) and their corresponding 95% CIs. Weighted Kaplan-Meier (KM) curves were constructed to display the cumulative incidence of endometrial cancer for each exposure group during follow-up time.

Secondary Analyses

Three secondary analyses were performed. First, we stratified based on drug type within each incretin-based drug to determine if there was a drug-type specific effect (i.e., exenatide). Second, given that high BMI is a strong risk factor for endometrial cancer, we stratified by BMI level (i.e., <30 kg/m^2, ≥ 30 kg/m^2) [24]. Third, we assessed whether previous use of the *other* incretin-based drug before cohort entry (i.e., yes/no) modified the HR by adding an interaction term between these groups and exposure in the outcome model.

Sensitivity Analyses

Three sensitivity analyses were conducted to evaluate potential bias in our findings. First, we altered the length of both the lag period and grace period to assess outcome and exposure misclassification, respectively. To do so, we reduced the periods to six months and extended them to 18 and 24 months to capture different cancer latency periods. Second, we used inverse-probability-of-censoring weighting (IPCW) to account for potential informative censoring.

Finally, we restricted the outcome to those recorded in HES APC to assess outcome misclassification, as the HES APC events may be more specific in ascertaining the outcome.

5.4 RESULTS

5.4.1 GLP-1 RAs vs Sulfonylureas

The first cohort included 9239 new users of GLP-1 RAs and 80,086 new users of sulfonylureas (**eFigure 1**). GLP-1 RA users were followed for a median (Q1, Q3) of 1.8 years (1.1, 3.3) and the sulfonylurea users for a median of 2.7 years (1.3, 5.5), including the lag period. During the 242,388 person-years of follow-up, there were 354 incident cases of endometrial cancer, yielding a crude incidence rate (95% CI) of 1.46 (1.31-1.62) per 1000 person-years.

Table 5-1 presents the characteristics of GLP-1 RA and sulfonylurea users before and after propensity score weighting. Before weighting, GLP-1 RA users were younger and more likely to be obese, have smoked, have more severe diabetes, have an intrauterine device, have endometrial fibroids, have PCOS and have been previously diagnosed with cancer. After weighting, the exposure groups were well balanced across all covariates aside from previous use of DPP-4 inhibitors with a standardized difference of 0.12, therefore this variable was included in the outcome model for additional adjustment.

Table 5-2 presents the results of the primary and first of secondary analyses. The use of GLP-1 RAs was not associated with a decreased risk of endometrial cancer when compared to the use of sulfonylureas (1.41 vs. 1.26 per 1000 person-years; HR: 1.11, 95% CI: 0.66-1.88). The cumulative incidence curves diverged and crossed within the first year of follow-up and subsequently crossed at around 2.5 years and 3.5 years (**eFigure 3**). In secondary analyses, exenatide was associated with an increased risk for endometrial cancer when compared to sulfonylureas (HR: 2.26, 95% CI:1.06-4.82), while null effects were observed for the other GLP-1 RAs (**Table 5-2**).

Assessing previous use of the other incretin-based drug did not modify the association between GLP-1 RA users who had previously used DPP-4 inhibitors and risk of endometrial cancer in cohort 1 (**eTable1**). Similarly, stratifying BMI groups (<30 kg/m^2 and ≥ 30 kg/m^2) did not alter the association between GLP-1 RAs and endometrial cancer (**eTable 2**).

Overall, our findings from sensitivity analyses were consistent with the primary analysis. Altering the grace and lag periods to 6-month, 18-month and 24-month periods did not modify the association between GLP-1 RA users and endometrial cancer (**eTable 3**). Most participants' loss to follow-up among the GLP-1 RA users was due to administrative censoring (56.4), followed by drug switching or discontinuation (40.6%). When weighted using IPCW, the GLP-1 RA gave null results. Restricting to HES data alone did not alter the association between either GLP-1 RA and endometrial cancer.

5.4.2 DPP-4 Inhibitors vs. Sulfonylureas

The second cohort included 42,486 new users of DPP-4 inhibitors and 79,353 new users of sulfonylureas (**eFigure 2**). DPP-4 inhibitor users were followed for a median (Q1, Q3) of 2.01 years (1.21, 3.49) and the sulfonylurea users for a median of 2.54 years (1.29, 4.84), including the lag period. During the 272,179 person-years of follow-up, there were 385 incident cases of endometrial cancer, yielding a crude incidence rate (95% CI) of 1.41 (1.28, 1.56) per 1000 person-years.

Before propensity score weighting, DPP-4 inhibitor users were more obese and more likely to have smoked, have an intrauterine device, have endometrial fibroids, take oral contraceptives, have PCOS, been previously diagnosed with cancer and have a higher prevalence

of microvascular complications. After propensity score weighting, the exposure groups were well balanced across all covariates (**Table 5-3**).

Table 5-4 presents the results of the primary and first of the secondary analyses. The use of DPP-4 inhibitors was not associated with a decreased risk of endometrial cancer when compared to the use of sulfonylureas (1.38 vs. 1.38 per 1000 person-years; HR: 1.00, 95% CI: 0.76, 1.32). The cumulative incidence curves diverge after around 4 months of follow-up and converged after about 26 months of follow-up (**eFigure 4**). In the secondary analyses, there were no events in the DPP-4 inhibitor group among participants who previously used GLP-1 RAs (**eTable 1**). Stratifying BMI groups (<30 kg/m^2 and ≥ 30 kg/m^2) did not alter the association between DPP-4 inhibitors and endometrial cancer (**eTable 2**).

In the sensitivity analyses, altering the grace and lag periods to 6-month, 18-month and 24-month periods did not modify the association between, DPP-4 inhibitor users and endometrial cancer (**eTable 3**). The main reason for loss to follow-up in the DPP-4 inhibitor group was administrative censoring (50.4%). When weighted using IPCW, DPP-4 inhibitor users gave null results. Restricting to HES data alone did not alter the association between DPP-4 inhibitors and endometrial cancer.

5.5 DISCUSSION

In this large population-based cohort study, the use of GLP-1 RAs and DPP-4 inhibitors was not associated with a decreased incidence of endometrial cancer when compared with the use of sulfonylureas in women with type 2 diabetes. Results from the sensitivity analyses were consistent with those of the primary analyses.

Based on prior observations that GLP-1 RAs can inhibit the growth of tumour cells in the breast, prostate and colon and that the GLP-1 receptor is, in fact, expressed in endometrial tissue, an in vitro investigation was conducted on the effect of GLP-1 RAs on endometrial cancer cells [4]. This study, using human Ishikawa endometrial cancer cells, revealed that GLP-1 RAs – specifically liraglutide –inhibited cell growth in a dose-dependent manner. It was concluded that higher GLP-1 expression may be associated with better prognosis in women with endometrial cancer due to its antiproliferative effects on endometrial cells [4]. Similarly, in a laboratory study using human endometrial cancer cell Ishikawa xenografts in nude mice, tumour growth rates were slower in those treated with the GLP-1 RA exenatide, than in controls. The study revealed that exenatide promotes the attenuation of tumour growth by acting on AMPK signalling pathways that inhibit the phosphorylation of mTOR as the mechanism of action [25]. To date, there are no observational studies using real-world evidence to substantiate these pre-clinical findings in humans. This observational study using real-world evidence found contrasting results to in vitro study results.

As exenatide was the GLP-1 RA used in the experimental study, for secondary analyses we stratified by type of GLP-1 RA to determine if different agents had varying associations with the outcome. Exenatide was found to be associated with an increased risk for endometrial cancer when compared to sulfonylureas (HR: 2.26, 95% CI:1.06, 4.82). Therefore, associated risk could

be incretin-based drug-type specific. These results do not follow expectations based on the laboratory studies. Future studies on the association between exenatide, specifically and endometrial cancer should be conducted.

This study has several strengths. First, the use of the CPRD was shown to be highly representative of the UK population and contains high-quality and regularly updated data, including BMI and HbA1c records [13,26]. Second, by restricting to new users of the drugs, we avoided prevalent user bias which could have distorted our results [27]. Third, we used propensity score fine stratification weighting to balance our exposure groups. This is a suitable method when we expect the exposure prevalence to be low (i.e. less participants in the incretin-based drugs groups compared to the sulfonylurea comparator groups) as it allows for the retention of more participants in the analysis.[4,5] Fourth, sulfonylureas were chosen as the active comparator, a drug class typically prescribed at a similar disease stage as incretin-based drugs and shown have no association with risk of endometrial cancer which mitigates confounding by indication [1]. Finally, our sensitivity analyses addressed various sources of bias and reassuringly proved to be consistent with our primary findings. We considered cancer latency and mitigated detection bias by altering our grace and lag periods and used IPCW analysis to account for informative censoring.

This study has some limitations. First, as with all observational research, residual confounding by unmeasured variables remains possible. However, it is expected that any unmeasured variables were evenly distributed between the exposure groups. Second, outcome misclassification remains possible despite attempting to mitigate this by linking and restricting to HES data, as it is not a cancer registry. This misclassification would bias our results toward the null due to missed outcomes, underestimating the risk of endometrial cancer. Additionally, if

outcomes were missed, this would cause a loss of power, creating wider confidence intervals that would be more likely to encompass the null. Third, restricting inclusion to new users limited long-term follow-up. Finally, as prescriptions recorded in the CPRD are those written by general practitioners and not those dispensed, there is potential exposure misclassification existent in this data [26,28]. However, it is unlikely that any exposure misclassification would be differentially distributed between exposure groups, deeming potential misclassification nondifferential.

The results of this study indicate that the use of incretin-based drugs is not associated with a reduced risk of endometrial cancer when compared to sulfonylureas. With the prevalence of obesity and endometrial cancer increasing rapidly over the last several decades, [29] additional studies are needed to corroborate these findings. These findings may help guide treatment plans for women with type 2 diabetes at high risk of developing endometrial cancer.

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Competing interests: LA received speaking and consulting fees from Pfizer and Roche for work unrelated to this project; other authors declare that they have no competing interests or relationships that could have appeared to influence the submitted work.

Data availability: This study is based on data from the Clinical Practice Research Datalink obtained under license from the UK Medicines and Healthcare products Regulatory Agency. The data are provided by patients and collected by the UK National Health Service as part of their care and support. The interpretation and conclusions contained in this study are those of the author/s alone. Because electronic health records are classified as "sensitive data" by the UK Data Protection Act, information governance restrictions (to protect patient confidentiality) prevent data sharing via public deposition. Data are available with approval through the individual constituent entities controlling access to the data. Specifically, the primary care data can be requested via application to the Clinical Practice Research Datalink (https://www.cprd.com).

Ethics approval: The study protocol was approved by the Research Data Governance of the CPRD (Protocol 23_003631) and by the McGill University ethics committee.

Consent to publish: Not applicable.

Code availability: Codes may be made privately available upon reasonable request to the corresponding author.

Consent to participate: Not applicable.

Author Contributions: S.R., L.A. and H.Y., were involved in the conception, design, conduct of study, analysis and interpretation of the results. O.Y. and M.P were involved in the design, analysis, and interpretation of the results. S.R. wrote the manuscript. All authors edited, reviewed, approved the final version of the manuscript, and are accountable for its accuracy. L.A. acquired the data and supervised the study.

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5.7 TABLES

Table 5-1. Baseline Characteristics of the GLP-1 RA and Sulfonylurea Exposure Groups Before and After Propensity Score Weighting

	Before Weighting			After Weighting		
Characteristics	**GLP-1 RA**	**Sulfonylureas**	**ASD**	**GLP-1 RA**	**Sulfonylureas**	**ASD**
Total	9239	80,086		9239	80,086	
Age, years, mean (SD)	56.2 (9.4)	62.4 (11.7)	0.58	56.2 (9.4)	56.1 (9.5)	0.01
Alcohol related disorders, n (%)	447 (4.8)	3,574 (4.5)	0.02	447 (4.8)	4,180 (5.2)	0.02
BMI, kg/m^2, n (%)						
Unknown	220 (2.4)	1,626 (2.0)	0.02	220 (2.4)	2,084 (2.6)	0.01
<30	603 (6.5)	27,436 (34.3)	0.73	603 (6.5)	5,131 (6.4)	0.00
≥ 30	8,416 (91.1)	51,024 (63.7)	0.69	8,416 (91.1)	72,871 (91.0)	0.00
Smoking Status, n (%)						
Unknown	31 (0.3)	236 (0.3)	0.01	31 (0.3)	337 (0.4)	0.01
Never	2,230 (24.1)	22,498 (28.1)	0.09	2,230 (24.1)	18,978 (23.7)	0.01
Ever	6,978 (75.5)	57,352 (71.6)	0.09	6,978 (75.5)	60,771 (75.9)	0.01
Index of multiple deprivation, n(%)						
0	S[a]	42 (0.1)	0.01	S[a]	34 (0.0)	0.01
1	S[a]	11,961 (14.9)	0.01	S[a]	11,353 (14.2)	0.01
2	1,542 (16.7)	13,986 (17.5)	0.02	1,542 (16.7)	13,576 (17.0)	0.01
3	1,711 (18.5)	15,450 (19.3)	0.02	1,711 (18.5)	14,765 (18.4)	0.00
4	2,022 (21.9)	18,224 (22.8)	0.02	2,022 (21.9)	17,702 (22.1)	0.01
5	2,615 (28.3)	20,423 (25.5)	0.06	2,615 (28.3)	22,657 (28.3)	0.00
Hemoglobin A1c, n (%)						
Unknown	56 (0.6)	2,372 (3.0)	0.18	56 (0.6)	484 (0.6)	0.00
≤7%	1,026 (11.1)	8,721 (10.9)	0.01	1,026 (11.1)	9,690 (12.1)	0.03
7.1-8.0%	2,095 (22.7)	22,080 (27.6)	0.11	2,095 (22.7)	17,601 (22.0)	0.02
>8.0%	6,062 (65.6)	46,913 (58.6)	0.15	6,062 (65.6)	52,311 (65.3)	0.01
Duration of diabetes, years, mean(SD)	8.5 (6.8)	5.6 (5.3)	0.47	8.5 (6.8)	8.0 (6.3)	0.07
Type of antidiabetic drugs, n(%)						
Alpha-glucosidase inhibitors	29 (0.3)	96 (0.1)	0.04	29 (0.3)	228 (0.3)	0.01
Insulin	2,237 (24.2)	2,096 (2.6)	0.67	2,237 (24.2)	16,737 (20.9)	0.08
Meglitinides	88 (1.0)	353 (0.4)	0.06	88 (1.0)	979 (1.2)	0.03
Metformin	8,205 (88.8)	69,663 (87.0)	0.06	8,205 (88.8)	72,005 (89.9)	0.04
Thiazolidinediones	754 (8.2)	5,084 (6.3)	0.07	754 (8.2)	7,384 (9.2)	0.04
SGLT-2 inhibitors	2,084 (22.6)	1,939 (2.4)	0.64	2,084 (22.6)	18,101 (22.6)	0.00
DPP-4 inhibitors	3,305 (35.8)	11,044 (13.8)	0.53	3,305 (35.8)	33,251 (41.5)	0.12
Peripheral vascular disease, n(%)	657 (7.1)	5,144 (6.4)	0.03	657 (7.1)	5,334 (6.7)	0.02
Stroke, n(%)	343 (3.7)	3,917 (4.9)	0.06	343 (3.7)	3,026 (3.8)	0.00
Myocardial infarction, n(%)	359 (3.9)	3,423 (4.3)	0.02	359 (3.9)	2,980 (3.7)	0.01
Renal disease, n(%)	1,229 (13.3)	14,587 (18.2)	0.14	1,229 (13.3)	10,310 (12.9)	0.01
Retinopathy, n(%)	2,846 (30.8)	17,582 (22.0)	0.20	2,846 (30.8)	23,414 (29.2)	0.03
Neuropathy, n(%)	2,158 (23.4)	15,492 (19.3)	0.10	2,158 (23.4)	17,942 (22.4)	0.02
NSAIDS, n(%)	7,182 (77.7)	58,743 (73.3)	0.10	7,182 (77.7)	62,391 (77.9)	0.00
Asprin, n (%)	3,305 (35.8)	32,705 (40.8)	0.10	3,305 (35.8)	27,938 (34.9)	0.02
Statins, n (%)	7,465 (80.8)	62,920 (78.6)	0.06	7,465 (80.8)	64,225 (80.2)	0.02
Tamoxifen, n(%)	111 (1.2)	1,739 (2.2)	0.08	111 (1.2)	936 (1.2)	0.00

Hormone replacement therapy, n (%)	3,017 (32.7)	24,388 (30.5)	0.05	3,017 (32.7)	26,372 (32.9)	0.01
Intrauterine devices, n(%)	1,069 (11.6)	4,651 (5.8)	0.21	1,069 (11.6)	9,504 (11.9)	0.01
Endometrial Fibroids, n (%)	716 (7.7)	4,750 (5.9)	0.07	716 (7.7)	6,361 (7.9)	0.01
Oral Contraceptives, n(%)	3,120 (33.8)	14,749 (18.4)	0.36	3,120 (33.8)	27,456 (34.3)	0.01
PCOS, n (%)	836 (9.0)	2,448 (3.1)	0.25	836 (9.0)	7,262 (9.1)	0.00
Previous Cancer Diagnosis, n(%)	1,958 (21.2)	15,069 (18.8)	0.06	1,958 (21.2)	17,403 (21.7)	0.01
Year of cohort entry, n (%)						
2007	25 (0.3)	3,593 (4.5)	0.28	25 (0.3)	220 (0.3)	0.00
2008	167 (1.8)	6,421 (8.0)	0.29	167 (1.8)	1,211 (1.5)	0.02
2009	363 (3.9)	7,405 (9.2)	0.22	363 (3.9)	2,722 (3.4)	0.03
2010	508 (5.5)	7,448 (9.3)	0.15	508 (5.5)	4,109 (5.1)	0.02
2011	479 (5.2)	7,334 (9.2)	0.15	479 (5.2)	3,835 (4.8)	0.02
2012	633 (6.9)	6,897 (8.6)	0.07	633 (6.9)	5,566 (7.0)	0.00
2013	508 (5.5)	6,794 (8.5)	0.12	508 (5.5)	4,136 (5.2)	0.01
2014	476 (5.2)	5,913 (7.4)	0.09	476 (5.2)	3,939 (4.9)	0.01
2015	614 (6.6)	6,207 (7.8)	0.04	614 (6.6)	5,399 (6.7)	0.00
2016	645 (7.0)	5,179 (6.5)	0.02	645 (7.0)	5,685 (7.1)	0.00
2017	869 (9.4)	4,752 (5.9)	0.13	869 (9.4)	7,812 (9.8)	0.01
2018	1,013 (11.0)	4,415 (5.5)	0.20	1,013 (11.0)	9,436 (11.8)	0.03
2019	1,469 (15.9)	4,186 (5.2)	0.35	1,469 (15.9)	12,902 (16.1)	0.01
2020	1,470 (15.9)	3,542 (4.4)	0.39	1,470 (15.9)	13,113 (16.4)	0.01

Abbreviations: ASD, absolute standardized difference; BMI, body mass index; DPP-4, dipeptidyl peptidase 4; GLP-1 RA, glucagon-like peptide 1 receptor agonist; PCOS, Polycystic Ovarian Syndrome; NSAIDS, Non-steroidal anti-inflammatory drugs; SD, standard deviation; SGLT-2, sodium-glucose cotransporter-2

Table 5-2. Hazard Ratios for Endometrial Cancer Comparing GLP-1 RAs with Sulfonylureas

Exposure	No. of participants	Events	Person-years	Crude IR *	Weighted IR (95% CI) *	Crude HR (95% CI)	Weighted HR (95% CI) †
Overall							
Sulfonylureas	80,086	333	227,478	1.46	1.26 (1.07-1.47)	1.00 [Reference]	1.00 [Reference]
GLP-1 RAs	9239	21	14,910	1.41	1.41 (0.87-2.15)	0.97 (0.62-1.51)	1.11 (0.66-1.88) §
GLP-1 RA Type							
Sulfonylureas	23,784	40	28,127	1.42	1.44 (0.94-2.11)	1.00 [Reference]	1.00 [Reference]
Dulaglutide	2532	S[a]	2190	-	-	-	-
Sulfonylureas	77,860	345	234,416	1.47	1.27 (1.13-1.43)	1.00 [Reference]	1.00 [Reference]
Exenatide	1784	10	3369	2.97	2.97 (1.42-5.46)	2.01 (1.07-3.78)	2.26 (1.06-4.82)
Sulfonylureas	65,804	251	171,791	1.46	1.26 (1.08-1.46)	1.00 [Reference]	1.00 [Reference]
Liraglutide	3333	7	6551	1.07	1.07 (0.43-2.20)	0.72 (0.34-1.52)	0.83 (0.38-1.84)
Sulfonylureas	32,319	90	62,417	1.44	1.06 (0.83-1.35)	1.00 [Reference]	1.00 [Reference]
Lixisenatide	529	S[a]	S[a]	1.08	1.08 (0.03-6.02)	0.74 (0.10-5.34)	1.04 (0.14-7.73)
Sulfonylureas	6851	S[a]	1973	1.01	0.74 (0.02-4.06)	1.00 [Reference]	1.00 [Reference]
Semaglutide	1046	S[a]	S[a]	-	-	-	-

Abbreviations: CI, confidence interval; DPP-4, dipeptidyl peptidase 4; GLP-1 RAs, glucagon-like peptide 1 receptor agonists; HR, hazard ratio; IR, incidence rate.

***** Per 1000 person-years.

† The models were weighted using propensity score fine stratification.

§ Additionally adjusted for prior use of DPP-4 inhibitor.

[a] Suppressed: Numbers fewer than five are not displayed, as per confidentiality policies of the CPRD.

Table 5-3. Baseline Characteristics of the DPP-4 Inhibitor and Sulfonylurea Exposure Groups Before and After Propensity Score Weighting

	Before Weighting			After Weighting		
Characteristics	**DPP-4i**	**Sulfonylureas**	**ASD**	**DPP-4i**	**Sulfonylureas**	**ASD**
Total	42,486	80,040		42,486	79,353	
Age, years, mean (SD)	63.9 (12.7)	64.3 (12.8)	0.03	63.9 (12.7)	63.4 (12.6)	0.04
Alcohol related disorders, n (%)	2011 (4.7)	3222 (4.1)	0.03	2,011 (4.7)	3,779 (4.8)	0.00
BMI, kg/m^2, n (%)						
Unknown	535 (1.3)	1665 (2.1)	0.07	535 (1.3)	1,028 (1.3)	0.00
<30	13,979 (32.9)	32,665 (41.2)	0.17	13,979 (32.9)	25,233 (31.8)	0.02
≥30	27,972 (65.8)	45,023 (56.7)	0.19	27,972 (65.8)	53,093 (66.9)	0.02
Smoking Status, n (%)						
Unknown	81 (0.2)	247 (0.3)	0.02	81 (0.2)	190 (0.2)	0.01
Never	11,734 (27.6)	23,309 (29.4)	0.04	11,734 (27.6)	21,989 (27.7)	0.00
Ever	30,671 (72.2)	55,797 (70.3)	0.04	30,671 (72.2)	57,174 (72.0)	0.00
Index of multiple deprivation, n(%)						
0	28 (0.1)	43 (0.1)	0.00	28 (0.1)	53 (0.1)	0.00
1	6,320 (14.9)	12,245 (15.4)	0.02	6,320 (14.9)	11,575 (14.6)	0.01
2	7,303 (17.2)	14,108 (17.8)	0.02	7,303 (17.2)	13,485 (17.0)	0.01
3	8,086 (19.0)	15,508 (19.5)	0.01	8,086 (19.0)	15,021 (18.9)	0.00
4	9,609 (22.6)	17,910 (22.6)	0.00	9,609 (22.6)	18,119 (22.8)	0.01
5	11,140 (26.2)	19,539 (24.6)	0.04	11,140 (26.2)	21,101 (26.6)	0.01
Hemoglobin A1c, n (%)						
Unknown	296 (0.7)	3,676 (4.6)	0.25	296 (0.7)	569 (0.7)	0.00
≤ 7%	5,476 (12.9)	9,537 (12.0)	0.03	5,476 (12.9)	10,108 (12.7)	0.00
7.1-8.0%	15,399 (36.2)	22,504 (28.4)	0.17	15,399 (36.2)	27,353 (34.5)	0.04
>8.0%	21,315 (50.2)	43,636 (55.0)	0.10	21,315 (50.2)	41,322 (52.1)	0.04
Duration of diabetes, years, mean(SD)	7.1 (6.0)	5.2 (5.2)	0.35	7.1 (6.0)	7.0 (6.0)	0.02
Type of antidiabetic drugs, n(%)						
Alpha-glucosidase inhibitors	45 (0.1)	87 (0.1)	0.00	45 (0.1)	67 (0.1)	0.01
Insulin	2,392 (5.6)	1,943 (2.4)	0.16	2,392 (5.6)	4,334 (5.5)	0.01
Meglitinides	260 (0.6)	282 (0.4)	0.04	260 (0.6)	540 (0.7)	0.01
Metformin	37,888 (89.2)	66,610 (83.9)	0.15	37,888 (89.2)	71,387 (90.0)	0.03
SGLT-2 inhibitors	2,032 (4.8)	883 (1.1)	0.22	2,032 (4.8)	3,678 (4.6)	0.01
Thiazolidinediones	2,632 (6.2)	4,734 (6.0)	0.01	2,632 (6.2)	5,285 (6.7)	0.02
GLP-1 receptor agonists	533 (1.3)	701 (0.9)	0.04	533 (1.3)	1,193 (1.5)	0.02
Peripheral vascular disease, n(%)	3,086 (7.3)	5,265 (6.6)	0.02	3,086 (7.3)	5,639 (7.1)	0.01
Stroke, n(%)	2,312 (5.4)	4,573 (5.8)	0.01	2,312 (5.4)	4,200 (5.3)	0.01
Myocardial infarction, n(%)	2,009 (4.7)	3,956 (5.0)	0.01	2,009 (4.7)	3,635 (4.6)	0.01
Renal disease, n(%)	9,173 (21.6)	16,203 (20.4)	0.03	9,173 (21.6)	16,235 (20.5)	0.03
Retinopathy, n(%)	11,372 (26.8)	16,126 (20.3)	0.15	11,372 (26.8)	20,838 (26.3)	0.01
Neuropathy, n(%)	8,822 (20.8)	14,641 (18.5)	0.06	8,822 (20.8)	16,458 (20.7)	0.00
NSAIDS, n(%)	31,685 (74.6)	56,913 (71.7)	0.06	31,685 (74.6)	59,170 (74.6)	0.00
Aspirin, n (%)	16,574 (39.0)	34,113 (43.0)	0.08	16,574 (39.0)	30,702 (38.7)	0.01
Statins, n (%)	35,158 (82.8)	60,901 (76.7)	0.15	35,158 (82.8)	65,502 (82.5)	0.01
Tamoxifen, n(%)	888 (2.1)	1,898 (2.4)	0.02	888 (2.1)	1,605 (2.0)	0.00
Hormone replacement therapy, n (%)	13,433 (31.6)	22,555 (28.4)	0.07	13,433 (31.6)	25,012 (31.5)	0.00
Intrauterine Devices, n(%)	2,711 (6.4)	4,050 (5.1)	0.05	2,711 (6.4)	5,236 (6.6)	0.01
Endometrial Fibroids, n (%)	2,743 (6.5)	4,308 (5.4)	0.04	2,743 (6.5)	5,141 (6.5)	0.00

Oral Contraceptives, n(%)	8,566 (20.2)	12,869 (16.2)	0.10	8,566 (20.2)	16,526 (20.8)	0.02
PCOS, n (%)	1,695 (4.0)	2,076 (2.6)	0.08	1,695 (4.0)	3,323 (4.2)	0.01
Previous Cancer Diagnosis, n(%)	9,553 (22.5)	14,567 (18.4)	0.10	9,553 (22.5)	17,478 (22.0)	0.01
Year of cohort entry, n (%)						
2007	117 (0.3)	6,902 (8.7)	0.42	117 (0.3)	525 (0.7)	0.06
2008	447 (1.1)	8,195 (10.3)	0.41	447 (1.1)	773 (1.0)	0.01
2009	1,177 (2.8)	8,483 (10.7)	0.32	1,177 (2.8)	1,966 (2.5)	0.02
2010	2,384 (5.6)	7,938 (10.0)	0.16	2,384 (5.6)	4,370 (5.5)	0.00
2011	2,341 (5.5)	7,367 (9.3)	0.14	2,341 (5.5)	4,369 (5.5)	0.00
2012	2,518 (5.9)	6,661 (8.4)	0.10	2,518 (5.9)	4,757 (6.0)	0.00
2013	2,564 (6.0)	6,461 (8.1)	0.08	2,564 (6.0)	4,823 (6.1)	0.00
2014	2,898 (6.8)	5,435 (6.8)	0.00	2,898 (6.8)	5,469 (6.9)	0.00
2015	3,771 (8.9)	5,535 (7.0)	0.07	3,771 (8.9)	7,155 (9.0)	0.00
2016	4,553 (10.7)	4,276 (5.4)	0.20	4,553 (10.7)	8,728 (11.0)	0.01
2017	4,949 (11.6)	3,657 (4.6)	0.26	4,949 (11.6)	9,504 (12.0)	0.01
2018	5,340 (12.6)	3,145 (4.0)	0.32	5,340 (12.6)	9,844 (12.4)	0.00
2019	5,290 (12.5)	2,854 (3.6)	0.33	5,290 (12.5)	9,520 (12.0)	0.01
2020	4,137 (9.7)	2,444 (3.1)	0.27	4,137 (9.7)	7,550 (9.5)	0.01

Abbreviations: ASD, absolute standardized difference; BMI, body mass index; DPP-4, dipeptidyl peptidase 4; GLP-1 RA, glucagon-like peptide 1 receptor agonist; PCOS, Polycystic Ovarian Syndrome; NSAIDS, Non-steroidal anti-inflammatory drugs; SD, standard deviation; SGLT-2, sodium-glucose cotransporter-2

Table 5-4. Hazard Ratios for Endometrial Cancer Comparing DPP-4 Inhibitors with Sulfonylureas

Exposure	No. of participants	Events	Person-years	Crude IR *	Weighted IR (95% CI) *	Crude HR (95% CI)	Weighted HR (95% CI) †
Overall							
Sulfonylureas	79,353	284	198,880	1.43	1.38 (1.18-1.59)	1.00 [Reference]	1.00 [Reference]
DPP-4 I	42,486	101	73,299	1.38	1.38 (1.12-1.67)	0.98 (0.78-1.23)	1.00 (0.76-1.32)
DPP-4 I Type							
Sulfonylureas	26,623	51	38,542	1.32	1.73 (1.26-2.32)	1.00 [Reference]	1.00 [Reference]
Alogliptin	7368	11	7832	1.40	1.40 (0.70-2.51)	1.01 (0.53-1.95)	0.81 (0.39-1.69)
Sulfonylureas	46,773	125	90,811	1.38	1.58 (1.26-1.94)	1.00 [Reference]	1.00 [Reference]
Linagliptin	10,288	23	13,266	1.73	1.73 (1.10-2.60)	1.22 (0.78-1.91)	1.11 (0.64-1.91)
Sulfonylureas	63,708	205	143,358	1.43	1.31 (1.13-1.51)	1.00 [Reference]	1.00 [Reference]
Saxagliptin	2573	7	4947	1.41	1.41 (0.57-2.92)	0.98 (0.46-2.08)	1.06 (0.49-2.28)
Sulfonylureas	79,680	285	199,926	1.43	1.33 (1.15-1.52)	1.00 [Reference]	1.00 [Reference]
Sitagliptin	21,056	46	39,208	1.17	1.17 (0.86-1.56)	0.84 (0.61-1.15)	0.88 (0.63-1.24)
Sulfonylureas	75,941	273	187,939	1.45	1.46 (1.31-1.63)	1.00 [Reference]	1.00 [Reference]
Vildagliptin	1173	S[a]	2987	S[a]	S[a]	0.69 (0.22-2.16)	0.69 (0.22-2.15)

Abbreviations: CI, confidence interval; DPP-4 I, dipeptidyl peptidase 4 inhibitor; GLP-1 RAs, glucagon-like peptide 1 receptor agonists; HR, hazard ratio; IR, incidence rate.

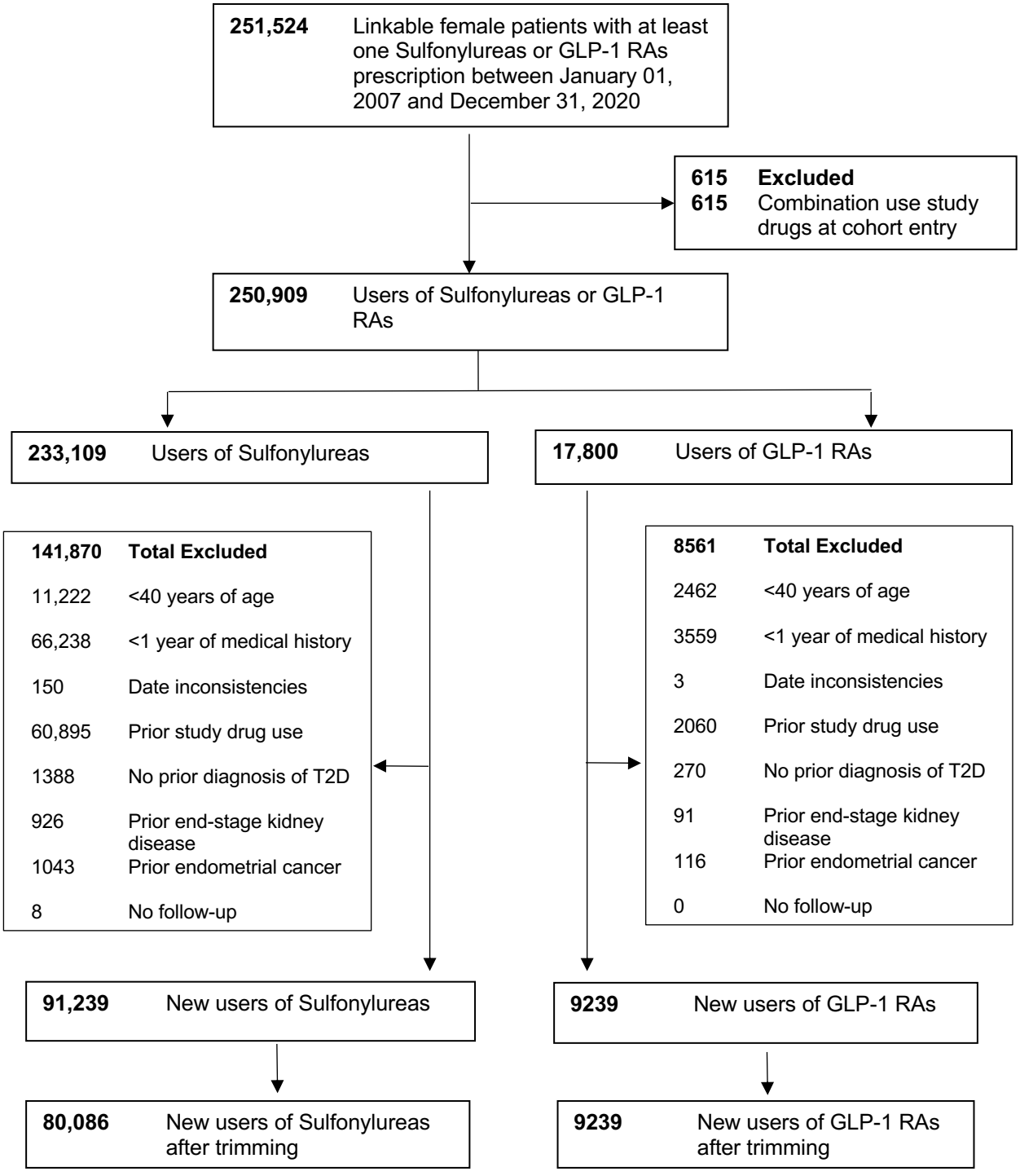
***** Per 1000 person-years.

† The models were weighted using propensity score fine stratification.

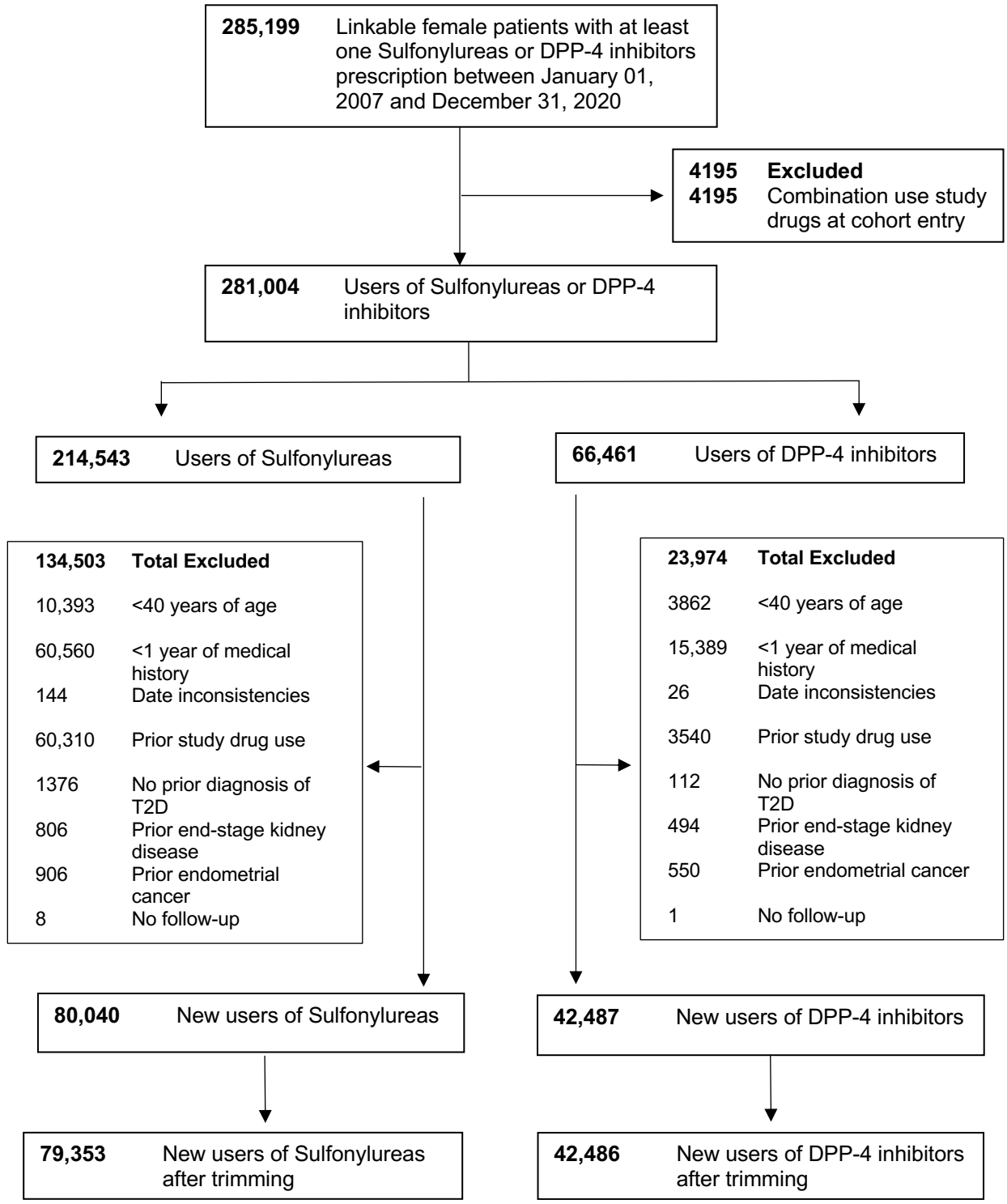
[a] Suppressed: Numbers fewer than five are not displayed, as per confidentiality policies of the CPRD.

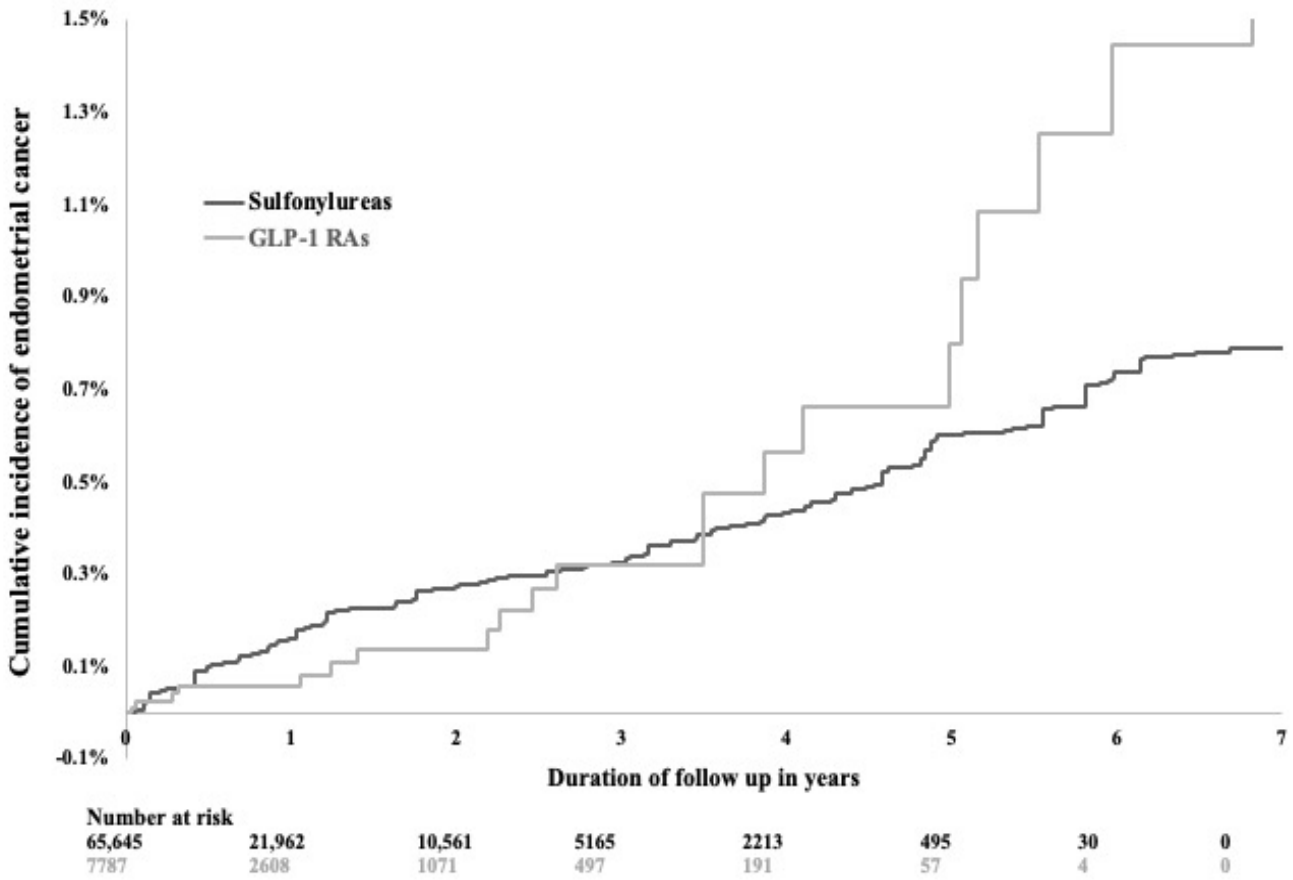
5.8 Supplementary Online Figures and Tables

eFigure 1. Flow diagram of Study Inclusion for Cohort 1 (GLP-1 RA vs. Sulfonylureas)

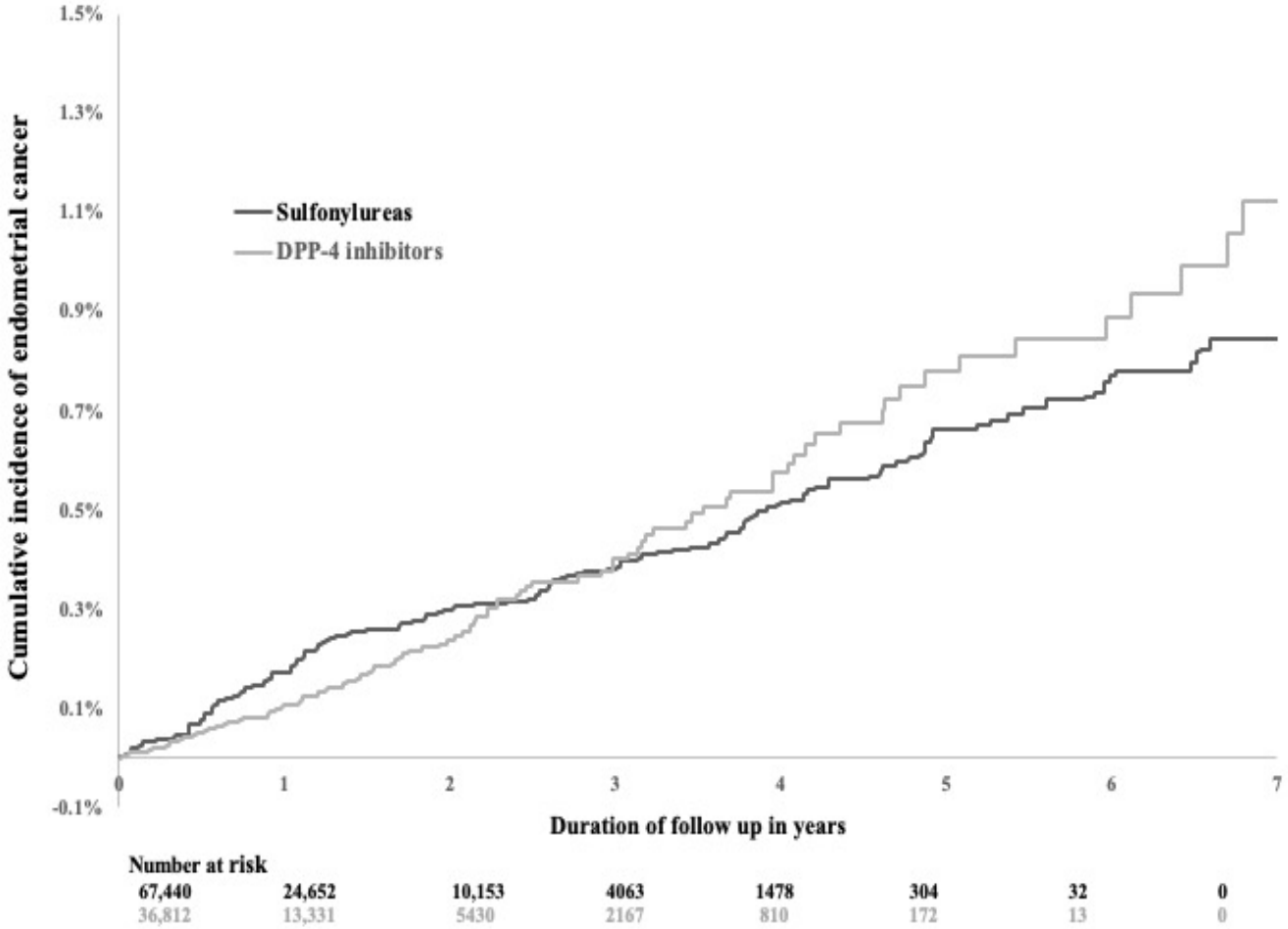


eFigure 2. Flow diagram of Study Inclusion for Cohort 2 (DPP-4 Inhibitors vs. Sulfonylureas)





eFigure 3. Weighted cumulative incidence curves of endometrial cancer for GLP-1 RAs vs. sulfonylureas



eFigure 4. Weighted cumulative incidence curves of endometrial cancer for DPP-4 inhibitors vs. sulfonylureas

eTable 1. Hazard Ratios for Endometrial Cancer Comparing GLP-1 RAs and DPP-4 Inhibitors with Sulfonylureas (Interaction with previous use of the other incretin-based drug)

Exposure	Without use of the other incretin-based drug	With use of the other incretin-based drug
Cohort1		
Sulfonylureas	1.00 [Reference]	1.00 [Reference]
GLP-1 RAs	1.24 (0.67-2.31)	0.84 (0.31-2.28)
		p-interaction=0.52
Cohort2*		
Sulfonylureas	1.00 [Reference]	1.00 [Reference]
DPP-4 inhibitors	1.00 (0.76-1.32)	-
		p-interaction<.0001

Abbreviations: DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1.
The models were weighted using propensity score fine stratification.
*No event generated in the exposed group among patients with use of other incretin-based drug.

eTable 2. Hazard Ratios for Endometrial Cancer Comparing GLP-1 RAs and DPP-4 Inhibitors with Sulfonylureas (Interaction with BMI)

Exposure	BMI<30	BMI≥30
Cohort1*		
Sulfonylureas	1.00 [Reference]	1.00 [Reference]
GLP-1 RAs	-	1.03 (0.60-1.79)
		p-interaction<.0001
Cohort2		
Sulfonylureas	1.00 [Reference]	1.00 [Reference]
DPP-4 inhibitors	1.06 (0.56-2.00)	0.98 (0.72-1.33)
		p-interaction=0.42

Abbreviations: DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1.
The models were weighted using propensity score fine stratification. Patients with unknown BMI were included in the analysis, but results were not presented in the table.
No event were generated in the exposed group among patients with BMI < 30.

eTable 3. Hazard Ratios for Endometrial Cancer Comparing GLP-1 RAs and DPP-4 Inhibitors with Sulfonylureas (Vary lag/grac period)

Exposure	No. of patient	Events	Person-years	Crude incidence	Weighted incidence rate	Crude HR (95% CI)	Weighted HR (95% CI) [†]
Cohort1							
6-month lag/grace period							
Sulfonylureas	80,086	331	225,746	1.47	1.21 (1.04-1.42)	1.00 [Reference]	1.00 [Reference]
GLP-1 RAs	9239	23	15,626	1.47	1.47 (0.93-2.21)	0.99 (0.65-1.51)	1.21 (0.73-1.98)
18-month lag/grace period							
Sulfonylureas	80,086	311	217,985	1.43	1.08 (0.90-1.28)	1.00 [Reference]	1.00 [Reference]
GLP-1 RAs	9239	21	13,646	1.54	1.54 (0.95-2.35)	1.10 (0.71-1.72)	1.44 (0.89-2.35)
24-month lag/grace period							
Sulfonylureas	80,086	291	205,772	1.41	1.24 (1.03-1.47)	1.00 [Reference]	1.00 [Reference]
GLP-1 RAs	9239	23	12,351	1.86	1.86 (1.18-2.79)	1.35 (0.88-2.07)	1.56 (0.92-2.64)
Cohort2							
6-month lag/grace period							
Sulfonylureas	79,353	289	197,239	1.47	1.43 (1.24-1.64)	1.00 [Reference]	1.00 [Reference]
DPP-4 inhibitors	42,486	106	79,092	1.34	1.34 (1.10-1.62)	0.92 (0.74-1.15)	0.94 (0.72-1.23)
18-month lag/grace							
Sulfonylureas	79,353	269	191,705	1.40	1.32 (1.13-1.54)	1.00 [Reference]	1.00 [Reference]
DPP-4 inhibitors	42,486	93	66,190	1.41	1.41 (1.13-1.72)	1.01 (0.80-1.29)	1.06 (0.80-1.40)
24-month lag/grace period							
Sulfonylureas	79,353	251	182,415	1.38	1.15 (0.96-1.37)	1.00 [Reference]	1.00 [Reference]
DPP-4 inhibitors	42,486	84	58,935	1.43	1.43 (1.14-1.76)	1.06 (0.82-1.36)	1.24 (0.93-1.65)

Abbreviations: HR, hazard ratio; CI, confidence interval; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1.

***** Per 1000 person-years.

[†] The models were weighted using propensity score fine stratification.

[§] Additionally adjusted for prior use of DPP-4.

CHAPTER 6: DISCUSSION

6.1 Summary of Findings

This thesis explored the real-world evidence for the association between incretin-based drugs and endometrial cancer in females with type 2 diabetes. Based on scientific literature that indicated a potential chemoprotective effect of incretin-based drugs on the development of endometrial cancer in the laboratory setting, a protective association was hypothesized in this study. The manuscript of this thesis consisted of a large, population-based cohort study using data from the UK CPRD. This study found that the overall use of GLP-1 RAs and DPP-4 inhibitors, separately, were not associated with a decreased risk of endometrial cancer when compared to the use of sulfonylureas. In secondary analyses, assessing this association by type of incretin-based drug showed that exenatide (a GLP-1 RA) was associated with a significant, over two-fold increased risk of endometrial cancer, while all other GLP-1 RA and DPP-4 inhibitor types generated results that were consistent with the primary analysis. The results from the primary analysis remained consistent across all three sensitivity analyses that assessed potential sources of bias. The strengths and limitations of the methodology used in this study were discussed in the manuscript (see Section 5.5).

6.2 Implication of Results

Given that GLP-1 receptors are widely expressed in extra-pancreatic tissues, various *in vitro* and *in vivo* studies have been conducted to investigate the pleiotropic effects of GLP-1 analogs and DPP-4 inhibitors.[14–16] The biological evidence in the scientific literature that

suggests a protective effect of both incretin-based drug types against endometrial cancer, provided the basis for this study.[14,16] The results from these studies were postulated to have clinically relevant implications in the prevention and/or treatment of various pathologies, although no real-world evidence has corroborated these findings. Therefore, to our knowledge, this cohort study was the first to explore this potential protective effect on endometrial cancer in the real-world setting. The results of this study differ from initial expectations, revealing a null association between the use of incretin-based drugs and incident risk of endometrial cancer. The data did not support our hypothesis, inviting further consideration of the mechanistic effects of these drugs and the study design that was used.

Interestingly, all HRs generated in the primary and secondary analyses were insignificant with confidence intervals encompassing the null — aside from exenatide, which showed over a two-fold greater risk of the outcome. This unexpected finding mandates further exploration of possible explanations. Firstly, the possibility that this result could be a type 1 error should not be excluded. As there were only 10 events in this comparison, this could be a chance finding. However, this unexpected result could also be a true estimate for various reasons. Exenatide was the first GLP-1 RA introduced to the UK market, which allows for longer follow-up for the exenatide and sulfonylurea groups and thus, more likely to detect latent events. In addition, exenatide differs from other GLP-1 RAs in its glycemic control, effect on weight loss, and dosing and formulation. Compared to other GLP-1 RAs included in this study, exenatide use has been reported to result in less weight loss and glycemic reduction.[106,173] Exenatide is a synthetic exendin-4 molecule with 53% homology to human GLP-1 RA.[174] Since its discovery, the other GLP-1 RAs have been developed to be more homologous to endogenous GLP-1 by modifying amino acid positioning.[6] It is administered in the smallest doses compared to other

GLP-1 RAs due to its strong biological activity and potency.[6] Exenatide is the only exendin 4-based agent used in this study, and therefore a different effect seen by this drug could be due to its structural difference or potency. Furthermore, as endometrial cancer is driven by excess adiposity, the mechanism by which GLP-1 RAs are thought to reduce the risk of endometrial cancer may be mediated by weight loss. As exenatide does not typically cause as substantial of a weight reduction as other GLP-1 RAs do,[175] this could account for the higher number of events seen in the exenatide group. Future studies, with larger sample sizes, will be needed to investigate the effects of the individual GLP-1 RAs on the incidence of endometrial cancer.

6.3 Future Directions for Research

As this was the first observational study on the topic, additional real-world evidence-based research is needed to corroborate the findings that the use of incretin-based drugs are not associated with a decreased risk of endometrial cancer and the potentially harmful effect of exenatide on endometrial cancer risk. Both epidemiological and mechanistic studies are needed to supplement and substantiate these findings while addressing the limitations of the current study.

This thesis was prompted by biological evidence of the potential beneficial effects of incretin-based drugs on endometrial cancer (see Section 2.3.1.2). It is necessary to consider that these studies were performed on endometrial cancer cells. The mechanisms that govern the chemoprevention of endometrial cancer versus the attenuation of existing endometrial tumours may be distinct. Therefore, anticarcinogenic effects may only exist regarding the proliferation and viability of existing tumours, rather than the prevention of endometrial tumours altogether. Future research should consider conducting a similar study, but this time among patients

diagnosed with endometrial cancer to assess whether incretin-based drugs have an effect on prognostic outcomes. Indeed, while incretin-based drugs may not reduce the risk of endometrial cancer, it is theoretically possible that they may be useful in improving outcomes in patients with endometrial cancer.

As previously discussed, given that obesity and hyperglycemia are major contributors to the development of endometrial cancer, the association between incretin-based drugs and endometrial cancer may be mediated by weight loss or lowered HbA1c. Future research should assess this association among patients at different BMI and glycemic levels while considering change in BMI and HbA1c using a time-varying analysis through mediation analyses.

CHAPTER 7: CONCLUSIONS

Incretin-based drugs, which include GLP-1 RAs and DPP-4 inhibitors, have greatly contributed to the management of type 2 diabetes. These drugs effectively lower blood glucose levels with a low risk of hypoglycemia or weight gain and have favourable clinical profiles. As GLP-1 receptors are expressed in many tissues throughout the body, beneficial pleiotropic effects of the incretin-based drugs have begun to be investigated.

Biological evidence in scientific literature has suggested antiproliferative effects of incretin-based drugs on endometrial cancer cells. Based on these findings, this thesis hypothesized that incretin-based drugs would be associated with a decreased risk of endometrial cancer. To our knowledge, the study described in this thesis is the first to investigate the effects of GLP-1 RAs and DPP-4 inhibitors on the incidence of endometrial cancer in a real-world setting. The results indicate that the use of GLP-1 RAs and DPP-4 inhibitors, separately, is not associated with a decreased risk of endometrial cancer. In fact, exenatide, a GLP-1 RA, was found to be associated with a two-fold increased risk of endometrial cancer. The divergence from expectations underscores the need for further investigation on this association. Future research should also be directed towards investigating whether the use of incretin-based drugs can improve outcomes in patients with endometrial cancer and whether this association is mediated by weight loss or improved glycemic control.

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