Incretin-Based Drugs and the Incidence of Prostate Cancer Among Patients with Type 2 Diabetes

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ABSTRACT

Background: The incretin-based drugs, glucagon-like peptide 1 receptor agonists (GLP-1 RAs) and dipeptidyl peptidase-4 (DPP-4) inhibitors are second- to third-line anti-hyperglycemic drugs that have favourable clinical profiles. There is some evidence from laboratory studies and randomized controlled trials that GLP-1 RAs and DPP-4 inhibitors may have chemopreventive effects on prostate cells and decrease the risk of prostate cancer. However, there is a paucity of research on the association between the use of incretin-based drugs and the risk of prostate cancer in the real-world setting.

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

Methods: Using the United Kingdom (UK) Clinical Practice Research Datalink (CPRD), two new-user, active comparator cohorts of male patients with type 2 diabetes who initiated treatment with an incretin-based drug or sulfonylurea between January 1, 2007 and July 31, 2019, were assembled. Patients were considered exposed from the date of the first prescription until the end of the follow-up period, regardless of treatment discontinuation or crossover to one of the other study drugs. Cox proportional hazards models, weighted using propensity score fine stratification, were fitted to estimate adjusted hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) of incident prostate cancer, separately for GLP-1 RAs and DPP-4 inhibitors. Secondary analyses assessed whether the association varied with cumulative duration of use, whether there was a drug-specific effect, and whether there was effect measure modification by age, body mass index (BMI), and smoking status. Furthermore, several sensitivity analyses were conducted to assess different sources of bias.

Results: In the first cohort, which included 5063 initiators of GLP-1 RAs and 112,955 initiators of sulfonylureas, GLP-1 RAs were associated with a decreased risk of prostate cancer when compared with sulfonylureas (incidence rates: 156.4 vs. 232.0 per 100,000 person-years, respectively; HR: 0.65, 95% CI: 0.43-0.99) after a median follow-up of 5.0 years. In the second cohort, which included 53,529 initiators of DPP-4 inhibitors and 114,417 initiators of sulfonylureas, DPP-4 inhibitors were also associated with a decreased risk of prostate cancer when compared with sulfonylureas (incidence rates: 316.2 vs. 350.5 events per 100,000 person-years, respectively; HR: 0.90, CI: 0.81-1.00), after a median follow-up of 4.2 years. The association did not vary with cumulative duration of use, and there was no drug-specific effect or effect measure modification by age, BMI, and smoking status.

Conclusions: The results of this large population-based cohort study indicate that the use of GLP-1 RAs and DPP-4 inhibitors, separately, may decrease the risk of prostate cancer among patients with type 2 diabetes, when compared with the use of sulfonylureas. While future studies, including randomized controlled trials, are needed to corroborate these findings, this study supports the hypothesis that the incretin-based drugs may have pleiotropic chemopreventive effects on the prostate.

RÉSUMÉ

Contexte: Les médicaments agissants sur les incrétines, spécifiquement les analogues du glucagon-like-peptide-1 (les RA du GLP-1) et les inhibiteurs de la dipeptidyl peptidase-4 (DPP-4), sont des antihyperglycémiants du deuxième à la troisième ligne qui ont des profils cliniques favorables. Il y a des études de laboratoire et des essais contrôlés randomisés qui ont providés des preuves que les RA du GLP-1 et les inhibiteurs DPP-4 peuvent avoir des effets chimiopréventif sur les cellules prostatiques et peuvent diminuer le risque de cancer de la prostate. Néanmoins, il y a une pénurie de recherche sur l'association entre l'utilisation des médicaments agissants sur les incrétines et le risque de cancer de la prostate au cadre du monde réel.

Objectif: L'objectif de cette thèse c'est de déterminer si, séparément, l'utilisation des RA du GLP-1 et des DPP-4 inhibiteurs, par rapport aux sulfonylurées, sont associés avec un risqué diminué de cancer de la prostate parmi les patients avec le diabète du type 2.

Méthodes: Utilisant le Lien de Données sur la Recherche en Pratique Clinique/Clinical Practice Research Datalink (CPRD) du Royaume-Uni, deux nouveaux-utilisateurs ont été assemblés, les cohortes comparatrices actives de patients masculins avec le diabète de type 2 qui ont commencés un traitement avec un médicament agissants sur les incrétines ou une sulfonylurée depuis le 1 janvier, 2007 jusqu'au 31 juillet de l'année 2019. Les patients ont été considérés comme exposés aux médicaments à partir de la date de la première prescription jusqu'à la fin de la période de suivi, quel que soit de l'arrêt du traitement ou du passage à l'un des autres médicaments durant l'étude. Les modèles à proportionnels de Cox, pondérés à l'aide d'une stratification fine du score de propension, ont été conformés pour estimer les rapports de risque (RR) ajustés et les intervalles de confiance (IC) à 95% correspondants aux incidents du cancer de

la prostate, séparément pour les RA du GLP-1 et les inhibiteurs de la DPP-4. Les analyses secondaires déterminent si l'association varie avec la durée cumulée d'utilisation, précisément s'il y a un effet spécifique au médicament et s'il y a une modification de la mesure de l'effet en fonction de l'âge, de l'indice de masse corporelle (IMC) ou du statut tabagique. De plus, diverses analyses de sensibilité ont été menée pour évaluer les diffèrent origines de biais.

Résultats: Dans la première cohorte, comprenant 5 063 initiateurs des RA du GLP-1 et 112 955 initiateurs de sulfonylurées, les RA du GLP-1 étaient associés à une diminution du risque de cancer de la prostate par rapport aux sulfonylurées (taux d'incidence : 156.4 contre 232.0 pour 100 000 années-de-personnes, respectivement; RR : 0.65, IC 95% : 0.43-0.99) après un médian d'un suivi de 5.0 ans. Dans la deuxième cohorte, comprenant 53 529 initiateurs d'inhibiteurs de la DPP-4 et 114 417 initiateurs de sulfonylurées, les inhibiteurs de la DPP-4 étaient également associés à une diminution de risque de cancer de la prostate par rapport aux sulfonylurées (taux d'incidence : 316.2 v. 350.5 événements pour 100 000 années-de-personnes, respectivement ; RR : 0.90, IC 95% : 0.81-1.00), après un médian d'un suivi de 4.2 ans. L'association ne variait pas avec la durée cumulée d'utilisation, et il n'y avait pas d'effet spécifique au médicament et s'il y a une modification de la mesure de l'effet en fonction de l'âge, de l'indice de masse corporelle (IMC) ou du statut tabagique.

Conclusions: Les résultats de cette grande étude de cohorte basée sur la population indiquent que l'utilisation des RA du GLP-1 et des inhibiteurs de la DPP-4, séparément, peuvent réduire le risque de cancer de la prostate chez les patients d'atteints de diabète de type 2, par rapport à l'utilisation de la sulfonylurée. Tandis que des études complémentaires, incluent les essais contrôlés randomises, se nécessites pour corroborer ces résultats de recherches, cette étude

soutient l’hypothèse que les médicaments agissants sur les incrétines peuvent avoir des effets chimiopréventifs pléiotropies pour la prostate.

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CONTRIBUTION OF AUTHORS

Sally Lu developed the research question and study design with guidance from Dr. Laurent Azoulay, her supervisor. Sally Lu drafted the thesis and corresponding manuscript. Sally Lu, Hui Yin and Dr. Laurent Azoulay contributed to the statistical analyses. Dr. Oriana Yu (diabetologist) contributed to the methods and interpretation of the results, as well as provided expertise on the biological plausibility. All contributing authors critically revised the manuscript for intellectual content and provided input during the revision process. Dr. Laurent Azoulay acquired the data, supervised the study and is the guarantor.

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ABBREVIATIONS

ADT	androgen deprivation therapy
AMPK	AMP-activated protein kinase
BMI	body mass index
CI	confidence interval
CPRD	Clinical Practice Research Datalink
CRPC	castration-resistant prostate cancer
DHT	dihydrotestosterone
DPP-4	dipeptidyl peptidase-4
FDA	Food and Drug Administration
FPG	fasting plasma glucose
GIP	glucose-dependent insulinotropic polypeptide
GLP-1 RA	glucagon-like peptide 1 receptor agonist
GOLD	Gp OnLine Data
HbA1c	glycosylated hemoglobin A1c
HR	hazard ratio
LEADER	Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results
LHRH	luteinizing hormone-releasing hormone
MACE	major adverse cardiovascular events
NHS	National Health Service
OGTT	oral glucose tolerance test
PSA	prostate specific antigen
SAVOR-TIMI	Saxagliptin Assessment of Vascular Outcomes Recorded in

	Patients with Diabetes Mellitus – Thrombolysis in Myocardial Infarction
SGLT-2	sodium-glucose cotransporter-2
SNOMED-CT	Systematized Nomenclature of Medicine – Clinical Terms
TZD	thiazolidinedione
UK	United Kingdom
US	United States

Chapter 1: Introduction

Type 2 diabetes is a chronic metabolic disease characterized by persistent hyperglycemia[1] that has numerous negative consequences such as reduced quality of life,[2] microvascular and macrovascular complications,[3] and increased risks of all-cause mortality[4] and several types of cancers.[5] It is a global health concern as it is estimated that 537 million people worldwide were living with diabetes in 2021, with type 2 diabetes accounting for over 90% of cases.[6,7] In Canada alone, over 3.7 million people have been diagnosed with diabetes as of 2020.[8] Given that persistent hyperglycemia can cause long-term damage and dysfunction to various organs, glycemic control is paramount in the treatment of type 2 diabetes.[1]

Many pharmacological treatments are available on the market for lowering blood glucose levels. The incretin-based drugs, which include glucagon-like peptide 1 receptor agonists (GLP-1 RAs) and dipeptidyl peptidase-4 (DPP-4) inhibitors, are a newer class of second- to third-line drugs introduced in the past decade.[9] These drugs work by augmenting the effects of GLP-1, a gut-derived hormone that stimulates pancreatic insulin release, thereby lowering plasma glucose levels.[10] Whereas GLP-1 RAs mimic endogenous GLP-1, DPP-4 inhibitors prolong their duration of action by inhibiting the enzyme responsible for their degradation.[11] Although there were initial concerns that the incretin-based drugs may be associated with an increased risk of pancreatitis and pancreatic cancer, these concerns were not corroborated in subsequent large epidemiologic studies.[12,13] Moreover, the incretin-based drugs have several advantages over other anti-hyperglycemic drugs, which include their favourable effects on body weight and decreased propensity to induce hypoglycemic events.[14] Furthermore, large cardiovascular outcome trials have associated certain GLP-1 RAs with decreased risks of major adverse

cardiovascular events (MACE),[15-18] whereas DPP-4 inhibitors were shown to have neutral cardiovascular effects.[19-22]

In addition to their known clinical benefits, there has been emerging biologic evidence from laboratory studies suggesting that GLP-1 RAs may reduce the growth of prostate cancer cells, although the evidence is mixed for DPP-4 inhibitors.[23-28] Currently, there is a paucity of research on the association between the use of incretin-based drugs and the incidence of prostate cancer in humans. Although numerous cardiovascular outcome trials on the incretin-based drugs have been published, only two of them have reported on prostate cancer events.[15,21] In the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial, the imbalance in prostate cancer events favoured liraglutide (a GLP-1 RA).[15,29] On the other hand, in the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus – Thrombolysis in Myocardial Infarction (SAVOR-TIMI) 53 trial, there was no notable imbalance in events between saxagliptin (a DPP-4 inhibitor) and placebo.[21,30] These cardiovascular outcome trials, however, were not designed nor powered to ascertain prostate cancer incidence. To date, two observational studies have been published on this topic.[31,32] The first study reported a decreased risk of prostate cancer with the use of sitagliptin (a DPP-4 inhibitor),[31] although this inverse association may have been exaggerated by the presence of immortal time bias.[33] The second study found no association between the use of incretin-based drugs and prostate cancer.[32] However, this study did not specifically investigate prostate cancer as an outcome and did not consider important potential confounders related to prostate cancer. Furthermore, it combined GLP-1 RAs and DPP-4 inhibitors into a single exposure, assuming that their individual effects would be similar. This may not be the case as these two drug classes have different mechanisms of action and systemic effects.

Given the limitations of the small number of existing studies and the increasing use of incretin-based drugs, large real-world studies are needed to investigate whether the use of incretin-based drugs is associated with a decreased risk of prostate cancer. As prostate cancer is one of the most common cancers among males worldwide, such findings may have important clinical implications for guiding the treatment of those at increased risk of prostate cancer.

Chapter 2: Literature Review

The following chapter is divided into three sections. The first section provides an overview of type 2 diabetes, detailing its epidemiology, pathophysiology, diagnosis, clinical management, and its association with overall cancer incidence. The second section provides an overview of prostate cancer, detailing its epidemiology, pathophysiology, screening and diagnosis, treatment, and its association with type 2 diabetes. Finally, the third section outlines what is currently known in the scientific literature about the association between incretin-based drugs and prostate cancer.

2.1 Type 2 Diabetes

2.1.1 Epidemiology and Risk Factors of Type 2 Diabetes

Type 2 diabetes is a major public health concern worldwide. This chronic metabolic disease reduces the quality of life and functional capacities of individuals,[2] and increases the risks of all-cause mortality,[4] end-stage renal disease, and non-traumatic lower limb amputations.[8] Moreover, it is associated with comorbidities[34] and microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (myocardial infarction, peripheral vascular disease, stroke) complications.[3] While type 2 diabetes increases the risk of cardiovascular disease in men and women, women with type 2 diabetes have a 25-50% greater excess risk of experiencing an incident cardiovascular event compared to men with type 2 diabetes.[35]

The prevalence of diabetes has increased in every country since 1980,[36] and the International Diabetes Federation estimates that approximately 537 million people globally (prevalence of 11%) were living with diabetes in 2021, with type 2 diabetes accounting for over 90% of cases.[6,7] This number is projected to rise to 783 million by 2045.[6] There are sex

differences in the incidence of type 2 diabetes throughout the life course. In youth, the incidence is higher in females, while it is higher in males during midlife.[35] In 2021, the global prevalence of diabetes in men aged 20-79 years was slightly higher than that in women of the same age group (10.8% vs. 10.2%);[6] 17.7 million more men than women were living with diabetes.[6] Diabetes prevalence varies depending on geographical region, with the majority of patients living in urban (12.1%) compared to rural (8.3%) areas, and in high-income (11.1%) compared to low-income (5.5%) countries.[6,7] In Canada alone, with an incidence rate of approximately 200,400 new cases per year,[37] over 3.7 million people have been diagnosed with diabetes (prevalence of 10%) as of 2020, directly costing the health care system $3.8 billion.[8] Global direct costs of diabetes have increased by 316% over the past 15 years, reaching $966 billion in 2021, with costs expected to continue to increase.[6]

Increased levels of obesity, physical inactivity, and energy-dense diets globally, as well as the ageing of the human population, are the main factors that have contributed to the rising prevalence and burden of type 2 diabetes.[7,38] Excessive adiposity, assessed by body mass index (BMI) or waist circumference,[39] is the strongest risk factor for type 2 diabetes.[3] The Nurses' Health Study found that 61% of type 2 diabetes cases were attributable to being overweight, as defined as a BMI of ≥25 kg/m^2.[40] Furthermore, duration of obesity is also an independent risk factor for type 2 diabetes, given that there is a 14% increased risk for every 2 extra years of obesity.[41] Physical inactivity is another key risk factor. While sedentary behaviours, such as extended television watching, increase the risk,[42] aerobic and resistance exercises are beneficial for the prevention of type 2 diabetes.[43] Additionally, cigarette smoking is also an important independent risk factor for the development of type 2 diabetes. Compared to non-smokers, current smokers have a 45% increased risk of developing the disease.[44] Canada has a high rate of

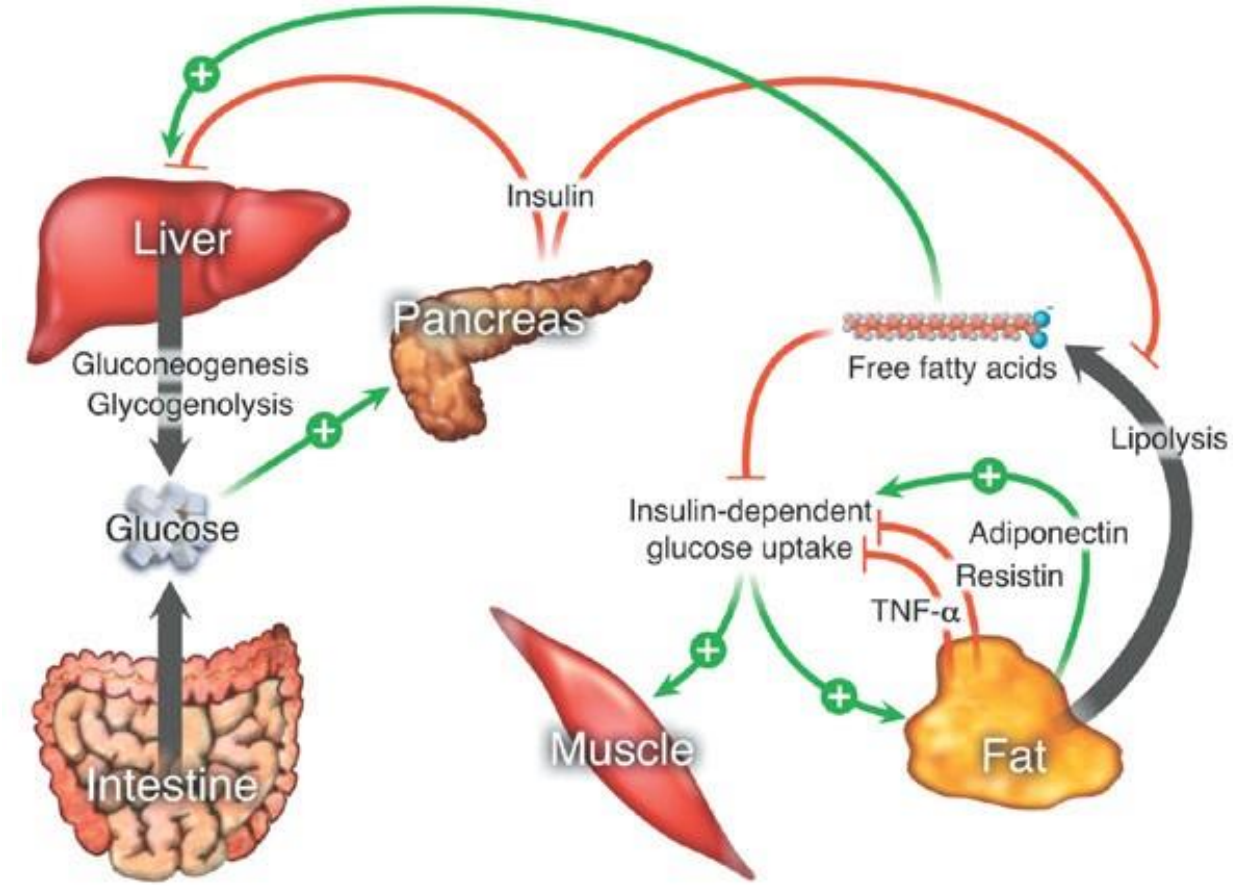
these modifiable risk factors, which is contributing to its increasing prevalence of type 2 diabetes; of the adult population, 36.3% and 26.8% are overweight and obese, respectively, 45.4% are physically inactive, and 16.2% are current cigarette smokers.[8] Age is a significant non-modifiable risk factor. While the incidence of type 2 diabetes is low for those under 30 years of age, it increases quickly and continuously with aging.[45] It is projected that the global prevalence of diabetes will increase by 16% by 2045 due to the ageing of the population.[6]

2.1.2 Pathophysiology of Type 2 Diabetes

Type 2 diabetes is characterized by insulin resistance (decreased insulin sensitivity in target tissues), deficient insulin secretion, or a combination of the two, resulting in persistent hyperglycemia.[38] It is a highly complex disease with multiple levels of dysfunction contributing to its manifestation and progression. Given that excessive adiposity and obesity are the strongest risk factors for type 2 diabetes,[3] the majority of patients are overweight or obese.[1] The adipose tissues in obese individuals secrete increased levels of non-esterified fatty acids, glycerol, hormones, pro-inflammatory cytokines and other factors that can lead to the development of insulin resistance in target tissues such as the liver, skeletal muscle, and adipose tissues themselves.[46] **Figure 1** illustrates the actions of insulin. Under insulin-sensitive conditions, insulin promotes glucose uptake in skeletal muscle and adipose tissue, and inhibits gluconeogenesis and glycogenolysis in the liver, preventing further glucose release.[47] Furthermore, it also inhibits lipolysis in adipose tissue, preventing the release of free fatty acids, which can promote insulin resistance in skeletal muscle and impair glucose metabolism in the liver.[47] When the target tissues become insulin-resistant, these processes are impaired, leading to hyperglycemia. Although the liver and skeletal muscle are the tissues primarily responsible for

postprandial (after meal) glucose disposal, insulin resistance can also occur in the kidneys, gastrointestinal tract, vasculature, and brain.[3] Insulin resistance usually occurs many years before a diagnosis of type 2 diabetes is made. This is because the disease usually does not manifest in the form of persistent hyperglycemia until there is pancreatic β-cell dysfunction and/or failure, when the cells are no longer able to secrete enough insulin to counterbalance the insulin resistance.[3] There is initial hyperinsulinemia when insulin resistance first occurs, as the β-cells augment insulin release to overcompensate for the loss of insulin-signalling.[48] This, however, places stress on the β-cells and ultimately leads to their failure; blood glucose concentrations increase as insulin secretion is progressively reduced.[3,48] Other factors such as ageing, genetic abnormalities, lipotoxicity, glucotoxicity, reactive oxygen species, and activation of inflammatory pathways, can also contribute to β-cell dysfunction and failure.[3]

Figure 1. Insulin signalling in target tissues



Reprinted with permission from Nature Medicine[47]

2.1.3 Diagnosis of Type 2 Diabetes

A diagnosis of type 2 diabetes can be made based on blood glucose levels or glycosylated hemoglobin A1c (HbA1c) values. Blood glucose levels can be assessed with a fasting plasma glucose (FPG) value or the oral glucose tolerance test (OGTT). For the FPG value, a blood sample is taken after the patient fasts for at least 8 hours. Values ≥126 mg/dL (7.0 mmol/L) are indicative of type 2 diabetes.[49] The OGTT is performed by having the patient ingest 75 grams of glucose after fasting for at least 8 hours. A blood sample is taken 2 hours later, with values ≥200 mg/dL (11.1 mmol/L) indicating type 2 diabetes.[49] HbA1c values indicate a patient's average

blood glucose level over the past 8-12 weeks,[50] and are also assessed with a blood sample. No fasting is required, however, and values ≥6.5% (48 mmol/mol) are indicative of type 2 diabetes.[49] Although HbA1c values are more convenient by not requiring fasting and are more stable against daily fluctuations due to stress, diet, and illness, they are an indirect measure and the correlation between these values and actual average blood glucose is not perfect.[49] In diagnosing type 2 diabetes, when there is disagreement between the blood glucose level (obtained by FPG or OGTT) and the HbA1c value in an individual, the blood glucose level is generally more accurate.[51]

2.1.4 Clinical Management of Type 2 Diabetes

The management of type 2 diabetes is multifaceted and aims to control hyperglycemia and prevent microvascular and macrovascular complications. Managing type 2 diabetes begins with establishing a target HbA1c value. Clinical guidelines recommend patients to aim for a target HbA1c of ≤7.0%, as this value is associated with reduced risks of microvascular complications.[52] Type 2 diabetes patients represent a heterogeneous group, with variability in degrees of insulin resistance,[53] β-cell dysfunction,[53] and disease progression and complications[54] between patients. Thus, treatment plans are individualized after careful consideration of an individual's health profile, disease severity, and needs. Managing type 2 diabetes generally involves two components: lifestyle modifications and pharmacological treatments.

2.1.4.1 Lifestyle Modifications

Excessive adiposity and obesity, states associated with lipotoxicity and insulin resistance,[3] are major problems in patients with type 2 diabetes.[1] Weight gain is also associated

with ageing and certain anti-hyperglycemic medications,[9] and thus, reaching and maintaining a healthy weight through lifestyle modifications such as diet and exercise, is an important component in all treatment plans for type 2 diabetes. Modest but sustained weight loss (5-10% of body weight) in overweight and obese patients with type 2 diabetes has many beneficial effects including reduced insulin resistance resulting in improved glycemic control and plasma lipid levels,[55,56] reduced blood pressure,[55] and improvements in cardiovascular disease risk factors.[57] Weight loss has also been shown to result in the discontinuation of anti-hyperglycemic medications and even remission of type 2 diabetes.[58] In the Look Action for Health in Diabetes trial, patients who were randomized to receive the intensive lifestyle intervention lost significantly more weight and were more likely to experience remission of type 2 diabetes after one year compared to patients who received standard care.[58] Bariatric surgery, which allows patients to lose up to 25% of their body weight, has also been shown to be effective for improving glycemic control and achieving remission in patients with type 2 diabetes.[59]

Besides promoting weight loss, exercise has other beneficial effects on glycemic control and blood glucose levels.[60] Glucose uptake into skeletal muscle is acutely increased during a bout of exercise and up to 24 hours afterwards.[61] This effect is distinct from insulin-mediated glucose uptake and is facilitated by the contractile activity of muscles during exercise. Muscle contractions stimulate the translocation of glucose transporter type 4's to the sarcolemma and T-tubules of muscle fibres, allowing glucose to diffuse into the muscle.[61] Furthermore, exercise also improves whole-body insulin sensitivity both acutely and long-term,[60] independent of changes in body composition due to weight loss.[62]

2.1.4.2 Pharmacological Treatments

Given that persistent hyperglycemia, the hallmark of type 2 diabetes, can cause long-term damage and dysfunction to various organs[1] and contributes to the development of microvascular and macrovascular complications,[63] glycemic control is paramount in the treatment of type 2 diabetes. Many pathophysiological mechanisms work in isolation or in tandem to cause persistent hyperglycemia;[64] they include impaired glucose uptake in skeletal muscle, the liver, and adipose tissue, deficient insulin secretion by the pancreatic β-cells, increased glucagon secretion by the pancreatic α-cells, increased hepatic glucose production, neurotransmitter dysfunction and insulin resistance in the brain, increased lipolysis, increased glucose reabsorption by the kidneys, and diminished incretin effect in the gut.[48,64] These mechanisms are the therapeutic targets of the wide array of anti-hyperglycemic medications that are available. As most drugs do not address multiple pathological defects, more than one drug (i.e., combination therapy) is often required for effective glycemic control, depending on the severity of the diabetes.[3] Many factors are considered when choosing an anti-hyperglycemic medication including efficacy, cost, potential side effects, weight gain, comorbidities, risk of hypoglycemia, and patient preferences.[64]

2.1.4.2.1 First-Line Treatment

Metformin (dimethylbiguanide) is the most commonly prescribed anti-hyperglycemic medication[65] and is the first-line oral therapy of choice according to many guidelines.[9,14,66] It was first introduced in Canada in 1972[67] and belongs to a drug class known as the biguanides. Metformin is the only remaining biguanide on the market as phenformin and buformin were

withdrawn due to excessive risks of lactic acidosis,[68] an adverse event that is rare with metformin.[69]

Metformin lowers blood glucose by supressing hepatic glucose production. It accumulates in the liver and impairs mitochondrial function by inhibiting mitochondrial respiratory-chain complex 1. The resulting decrease in energy production activates AMP-activated protein kinase (AMPK) and suppresses gluconeogenesis.[70] Metformin also improves insulin sensitivity and hepatic glucose uptake by enhancing the activation of insulin receptors.[71] Furthermore, recent research suggests that metformin also stimulates the release of GLP-1 from intestinal L-cells[72,73] and increases the expression of GLP-1 receptors on pancreatic β-cells[73] (see Section 2.1.4.2.2.5 Incretin-Based Drugs). Unless it is contraindicated, metformin is selected as the initial pharmacologic treatment, along with lifestyle modifications, in the majority of people newly diagnosed with type 2 diabetes for many reasons. It effectively lowers fasting blood glucose levels and reduces HbA1c by approximately 1.0%,[9] it does not cause hypoglycemia or weight gain, and it is inexpensive.[14] Furthermore, results from the United Kingdom Prospective Diabetes Study indicate that metformin is associated with a decreased risk of myocardial infarctions and death from any cause in overweight patients.[74] Although metformin is associated with gastrointestinal side effects (bloating, abdominal discomfort, diarrhea), these can be mitigated by starting at a reduced dosage and gradually increasing over the span of several weeks.[14] Vitamin B12 deficiency is another possible side effect of metformin.[14] It is contraindicated in patients with hepatic failure and moderate to severe renal impairment.[9] In the event of contraindications or intolerance to metformin, another anti-hyperglycemic medication can be chosen based on individual patient needs and the characteristics of the other medication options.

2.1.4.2.2 Second- to Third-Line Treatments

Given the progressive nature of type 2 diabetes, blood glucose levels will often continue to rise over time, and many patients will not be able to maintain glycemic targets in the long term with monotherapy alone.[9,14,75,76] When glycemic targets are no longer maintained with the current pharmacotherapy regimen, the addition of another medication (i.e., second to third-line treatments) is required.

2.1.4.2.2.1 Sulfonylureas

Sulfonylureas are a class of drugs that lower blood glucose levels by augmenting insulin secretion. They bind to the sulfonylurea receptors on pancreatic β-cells and block ATP-dependent potassium channels, which ultimately leads to local plasma membrane depolarization and exocytosis of insulin granules.[77] Because this mechanism of insulin secretion is independent of glucose levels, the use of sulfonylureas is associated with an increased risk of hypoglycemia.[9,14,77] Sulfonylureas can also cause weight gain[9,14] and may increase the risk of adverse cardiovascular events.[78,79] As their mechanism of action depends on patients having functional β-cells, the efficacy of sulfonylureas may decrease over time as β-cells fail with the progression of type 2 diabetes and these drugs do not have protective effects on β-cell function.[3,76,80] Sulfonylureas have high efficacy and can lower HbA1c by 0.7-1.3%.[9] Although sulfonylureas primarily act on the pancreas, they also have some beneficial extra-pancreatic effects; they inhibit glucose output by the liver and lipolysis in adipose tissue.[64,77]

Sulfonylureas can be divided into first- (chlorpropamide, tolazamide, tolbutamide), second- (gliclazide, glipizide, glibenclamide (glyburide)), and third-generation (glimepiride) drugs.[80] The first-generation sulfonylureas have largely been replaced by the newer second- and

third-generation drugs since they are more potent (i.e., administered at lower doses and with less frequency) and have reduced risks of adverse reactions.[80] While chlorpropamide and tolbutamide are still available in Canada, they are rarely prescribed.[9] Sulfonylureas have been prescribed for more than 50 years,[81] and even after the approval of several new drugs, they remain one of the most prescribed second- to third-line anti-hyperglycemic medications.[82]

2.1.4.2.2.2 Meglitinides

Meglitinides (repaglinide and nateglinide) are a class of non-sulfonylurea secretagogues. They share the same mechanism of action as sulfonylureas and stimulate insulin secretion after binding to the sulfonylurea receptors on pancreatic β-cells.[64] Meglitinides have a weaker affinity for the sulfonylurea receptor and thus, have a shorter onset of action and shorter half-life compared to sulfonylureas.[64] Furthermore, meglitinides are less effective than sulfonylureas as higher blood glucose levels are required before they can stimulate insulin secretion.[64] The risk of hypoglycemia, however, is lower with the use of meglitinides compared to sulfonylureas.[38] Meglitinides can lower HbA1c levels by 0.7-1.1%[9] and are also associated with weight gain.[9] These drugs are usually taken 15-30 minutes before a meal to decrease the postprandial rise in blood glucose.[81] Although meglitinides are not commonly prescribed,[83] they are a good option for patients who eat irregularly and require short-acting, meal-related insulin secretion.[38,64]

2.1.4.2.2.3 Alpha-Glucosidase Inhibitors

Alpha-glucosidase inhibitors (acarbose, voglibose, and miglitol) are a class of drugs that lower postprandial blood glucose levels by decreasing the rate of absorption of carbohydrates in the intestine.[3] These drugs inhibit alpha-glucosidase enzymes, which are responsible for the

degradation and absorption of carbohydrates from meals, in the brush-border membrane of the small intestine.[84] Glucose absorption is delayed, which also results in increased glucose delivery to the ileum, where it can stimulate GLP-1 secretion[85] (see Section 2.1.4.2.2.5 Incretin-Based Drugs). Because glucose enters the circulation at a decreased rate, postprandial plasma insulin levels are decreased with the use of alpha-glucosidase inhibitors.[84,85] These drugs need to be present in the gut in order to be effective and thus, are taken three times per day, before each meal.[85] Alpha-glucosidase inhibitors can cause gastrointestinal side effects (flatulence, abdominal distension, borborygmus and diarrhoea),[84] but are not associated with weight gain nor hypoglycemia,[9] and can reduce HbA1c by 0.7-0.8%.[9]

2.1.4.2.2.4 Thiazolidinediones

Thiazolidinediones (TZDs) are a class of insulin sensitizers that reduce insulin resistance in target organs such as adipose tissue, skeletal muscle, and the liver.[38,86] These drugs bind to and activate the gamma isoform of peroxisome proliferator-activated receptors, located in the nuclei of cells, which ultimately leads to alterations in the transcription of insulin-responsive genes and genes involved in energy balance.[86] TZDs are not associated with hypoglycemia but can cause weight gain.[9] Although they have high efficacy and can lower HbA1c by 0.8-0.9%,[9] TZDs are a controversial class associated with safety concerns. Troglitazone, the first TZD approved for clinical use in 1997, was withdrawn from the market in 2000 after it was found to cause liver injury and failure.[81] Rosiglitazone, approved in 1999, was found to be associated with an increased risk of cardiovascular events,[87,88] which led to the United States (US) Food and Drug Administration (FDA) restricting its use.[81] Pioglitazone, also approved in 1999, was found to be associated with an increased risk of bladder cancer.[81,89,90] Due to these safety concerns, the use of

TZDs is limited and has declined over the years.[82] Furthermore, TZDs can cause edema and is associated with an increased risk of fractures.[9]

2.1.4.2.2.5 Incretin-Based Drugs

The Incretin System

A reduction in the incretin effect is another notable mechanism of dysfunction that contributes to hyperglycemia in type 2 diabetes. The incretin effect refers to the phenomenon whereby glucose ingested orally elicits a stronger insulin release than glucose administered intravenously, even when they cause the same elevation in blood glucose concentrations.[91] This effect is due to the incretin hormones, glucose-dependent insulinotropic polypeptide (GIP) and GLP-1, which are released by the gastrointestinal tract within minutes after the ingestion of nutrients (e.g., glucose). These incretin hormones stimulate pancreatic β-cells to release insulin in a glucose-dependent manner[92] and account for 50-70% of the total insulin secretion after an oral glucose load.[64,92] The half-lives for these hormones is very short as they are quickly hydrolyzed by the enzyme, DPP-4.[93] In patients with type 2 diabetes, the incretin effect is markedly reduced or completely absent.[94] Specifically, the insulinotropic (i.e., insulin-secreting) effect of GIP, which mediates a large proportion of the incretin effect in healthy individuals, [95,96] is lost in patients.[97] Although the role of GLP-1 in the incretin effect is more minor in comparison to that of GIP, patients remain responsive to its effects[97] and augmenting the actions of GLP-1 with the incretin-based drugs (GLP-1 RAs and DPP-4 inhibitors) reduces blood glucose levels and improves glycemic control.[98] The incretin-based drugs act on the incretin system to help restore glucose homeostasis.

GLP-1 RAs

GLP-1 is an endogenous 30-amino acid peptide hormone synthesized and secreted by intestinal L-cells.[99] After it enters the circulation, it is quickly degraded by DPP-4 within 2-3 minutes.[100] Besides its insulinotropic effects on the pancreas, GLP-1 offers other therapeutic advantages that GIP does not, including suppressing glucagon secretion and hepatic gluconeogenesis, improving insulin sensitivity, delaying gastric emptying, and reducing appetite and food intake, promoting weight loss.[101] **Figure 2a** illustrates some of the effects of endogenous GLP-1. These effects are enhanced with the use of GLP-1 RAs, a class of drugs that are structurally similar to endogenous GLP-1 and activate the GLP-1 receptor. Unlike endogenous GLP-1, however, they are more resistant to degradation by DPP-4 and have longer half-lives.[100] These drugs are administered subcutaneously (with the exception of oral semaglutide)[102] and can be divided into short-acting compounds and long-acting compounds.[100]

The short-acting GLP-1 RAs (exenatide and lixisenatide) activate GLP-1 receptors intermittently.[100] By making modifications to the N-terminals, these short-acting compounds are synthesized to be resistant to DPP-4 degradation.[103] As a result, they have half-lives of 2-4 hours and can activate the GLP-1 receptor for up to 6 hours after injection.[100] Because these short-acting compounds are usually injected before a meal (exenatide: twice daily, before breakfast and dinner; lixisenatide: once daily, before breakfast), they mainly contribute to lowering postprandial blood glucose levels. **Figure 2b** illustrates the effects of short-acting GLP-1 RAs. After administration, plasma levels of these short-acting compounds rapidly increase which significantly delays gastric emptying and consequently, decreases the rate of glucose absorption into the circulation.[100] Because glucose enters the circulation more slowly, insulin secretion is actually decreased in the postprandial state with the short-acting compounds.[100] These short-

acting compounds also suppress appetite but induce nausea as well. In the fasting state, plasma levels of the short-acting compounds have usually returned to near-baseline levels. Consequently, their contribution to fasting insulin secretion and glucose control is not as notable as that of the long-acting GLP-1 RAs.[104]

The long-acting GLP-1 RAs (albiglutide, dulaglutide, exenatide long-acting release, liraglutide,[100] and oral and injectable semaglutide[102]) provide sustained activation of the GLP-1 receptors. Unlike the short-acting compounds, these long-acting compounds are further modified to be resistant to renal filtration.[105] Consequently, they have half-lives of 12 hours to several days and their plasma levels remain elevated between doses.[100] **Figure 2c** illustrates the effects of long-acting GLP-1 RAs. The effects of the long-acting compounds differ slightly from their short-acting counterparts. Unlike the short-acting compounds, the long-acting compounds do not delay gastric emptying with long term use[106] and accordingly, they do not decrease postprandial blood glucose levels as effectively as the short-acting compounds.[104] The long-acting compounds, however, provide better glycemic control overall, as they increase plasma insulin levels in the fasting[104,107] and postprandial states.[107] Like the short-acting compounds, they also suppress appetite and can induce nausea as well.

GLP-1 RAs are associated with weight loss, with comparable reductions in body weight achieved with short-acting (1-5kg) and long-acting compounds (2-5kg).[100,104,108] As such, it is hypothesized that the weight reducing effects of GLP-1 are mainly due to its actions on the hypothalamus and central nervous system, rather than its effects on gastric emptying.[109] These drugs have high efficacy and can reduce HbA1c by 1.0%.[9] Nausea is the most common side effect associated with the use of GLP-1 RAs, but it tends to dissipate after 4-8 weeks of use.[100] Given the glucose-dependent nature of GLP-1, GLP-1 RAs are not associated with

hypoglycemia, unlike sulfonylureas and insulin therapy.[9] Furthermore, many GLP-1 RAs (liraglutide, injectable semaglutide, dulaglutide, albiglutide) have been shown to be cardioprotective and decrease the risk of MACE in large cardiovascular outcome trials.[15-18] **Table 1** summarizes the key details and results from the cardiovascular outcome trials conducted on GLP-1 RAs. Although there were initial concerns with pancreatitis and pancreatic cancer, no increased risk was found in large epidemiological studies[12,13] and in post-hoc analyses of the cardiovascular outcome trials.[110] GLP-1 RAs are contraindicated in patients with renal failure.[64]

Figure 2. Effects of endogenous GLP-1, short-acting GLP-1 receptor agonists, and long-acting GLP-1 receptor agonists

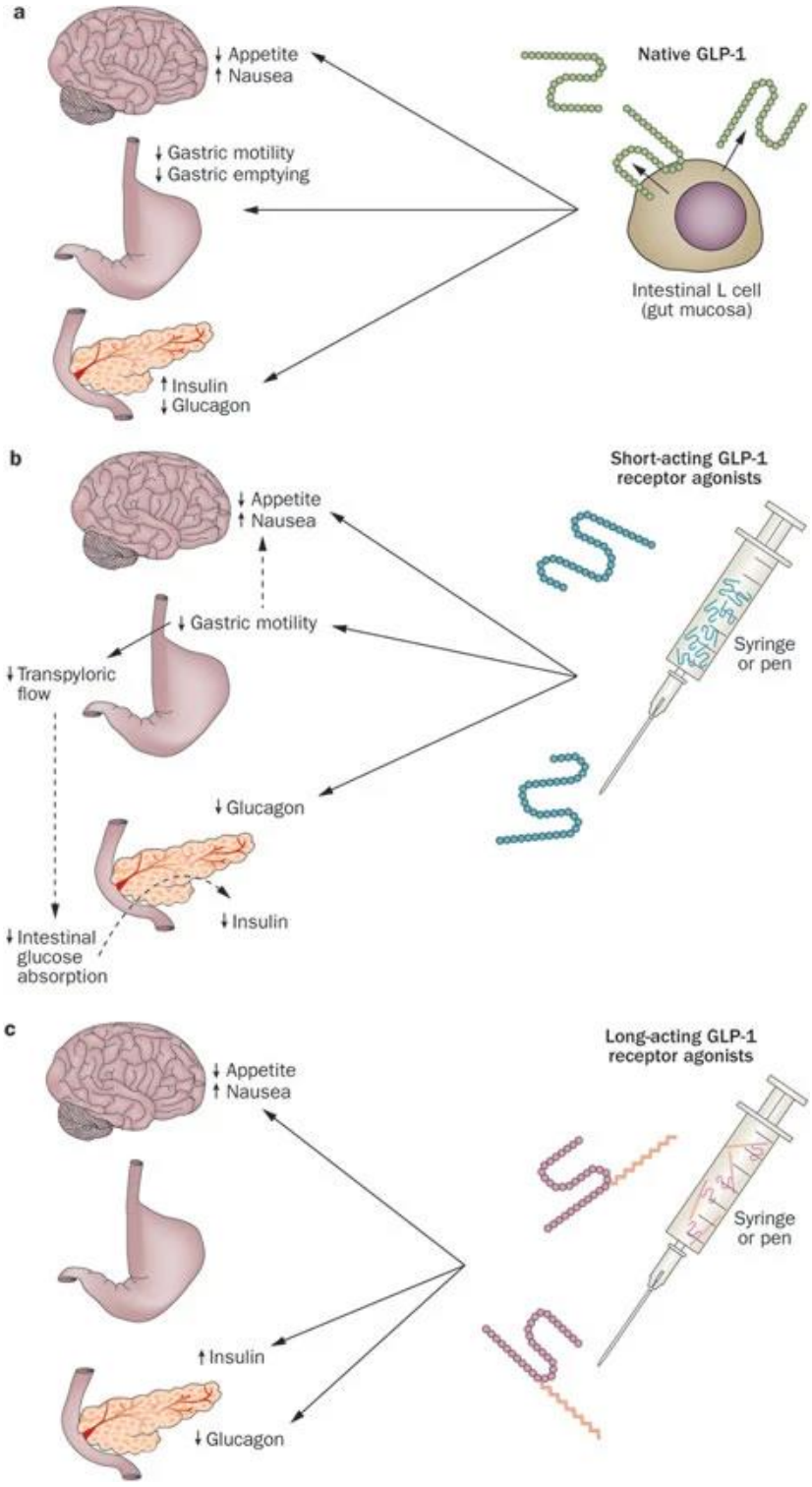


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Table 1. Summary of key details and results from cardiovascular outcome trials conducted on GLP-1 RAs

Study	Completion Date	Participants	Molecule (dose, n)	Comparator (n)	Median Follow-up (years)	Clinical Outcomes (HR [95% CI] vs. comparator)			
						MACE	CV Mortality	Fatal/non-fatal MI	Fatal/non-fatal stroke
LEADER[15]	December 2015	9340	Liraglutide (1.8 mg, n = 4668)	Placebo (n = 4672)	3.8	0.87 (0.78-0.97)	0.78 (0.66-0.93)	0.86 (0.73-1.00)	0.86 (0.71-1.06)
ELIXA[111]	February 2015	6068	Lixisenatide (20 μg, n = 3034)	Placebo (n = 3034)	2.1	1.02 (0.89-1.17)	0.98 (0.78-1.22)	1.03 (0.87-1.22)	1.12 (0.79–1.58)
SUSTAIN-6[16]	March 2016	3297	Semaglutide (0.5 or 1.0 mg, n = 1648)	Placebo (n = 1649)	2.1	0.74 (0.58-0.95)	0.98 (0.65-1.48)	0.74 (0.51-1.08)[a]	0.61 (0.38-0.99)[a]
EXSCEL[112]	April 2017	14,752	Extended-release exenatide (2 mg, n = 7356)	Placebo (n = 7396)	3.2	0.91 (0.83-1.00)	0.88 (0.76-1.02)	0.97 (0.85-1.10)	0.85 (0.70-1.03)
HARMONY[18]	March 2018	9463	Albiglutide (30 mg, n = 4731)	Placebo (n = 4732)	1.6	0.78 (0.68-0.90)	0.93 (0.73-1.19)	0.75 (0.61-0.90)	0.86 (0.66-1.14)
REWIND[17]	August 2018	9901	Dulaglutide (1.5 mg, n = 4949)	Placebo (n = 4952)	5.4	0.88 (0.79-0.99)	0.91 (0.78-1.06)	0.96 (0.79-1.15)	0.76 (0.62-0.94)
PIONEER-6[113]	September 2018	3183	Oral semaglutide (14 mg, n = 1591)	Placebo (n = 1592)	1.3	0.79 (0.57-1.11)	0.49 (0.27-0.92)	1.18 (0.73-1.90)[a]	0.74 (0.35-1.57)[a]

Abbreviations: MACE, major adverse cardiovascular events; CV, cardiovascular; MI, myocardial infarction

[a] Non-fatal events only

DPP-4 Inhibitors

DPP-4 inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin, and vildagliptin) are a class of drugs that augment the effects of endogenous GLP-1 by preventing their degradation by DPP-4.[114] **Figure 3** illustrates the mechanism of action of DPP-4 inhibitors. By blocking DPP-4, DPP-4 inhibitors can increase the levels of endogenous GLP-1 to the upper limit of its normal physiological range.[11] Thus, postprandial levels of biologically active GLP-1 are increased, resulting in increased insulin and decreased glucagon secretion.[115] Unlike GLP-1 RAs, DPP-4 inhibitors are not associated with delayed gastric emptying and weight loss,[11] and do not cause nausea either. As well, compared to long-acting GLP-1 RAs, DPP-4 inhibitors are not as effective at glycemic control, likely because the GLP-1 RAs are able to provide more sustained activation of the GLP-1 receptors.[11] DPP-4 inhibitors can reduce HbA1c by 0.5-0.7%, are not associated with hypoglycemia and are weight neutral.[9] Cardiovascular outcome trials have shown that they are also non-inferior with respect to MACE compared to placebo and standard care (i.e., other pharmacological treatments for the management of diabetes);[19-22] in the CAROLINA trial for linagliptin, glimepiride (a sulfonylurea) was used instead of placebo.[116] Saxagliptin, however, is associated with an increased risk of hospitalization for heart failure.[21] **Table 2** summarizes the key details and results from the cardiovascular outcome trials conducted on DPP-4 inhibitors. As with the GLP-1 RAs, there were initial concerns with pancreatitis and pancreatic cancer, but these concerns were not substantiated in later studies.[12,13] Patients with renal impairment are able to take DPP-4 inhibitors at reduced dosages.[14]

Figure 3. The mechanism of action of DPP-4 inhibitors

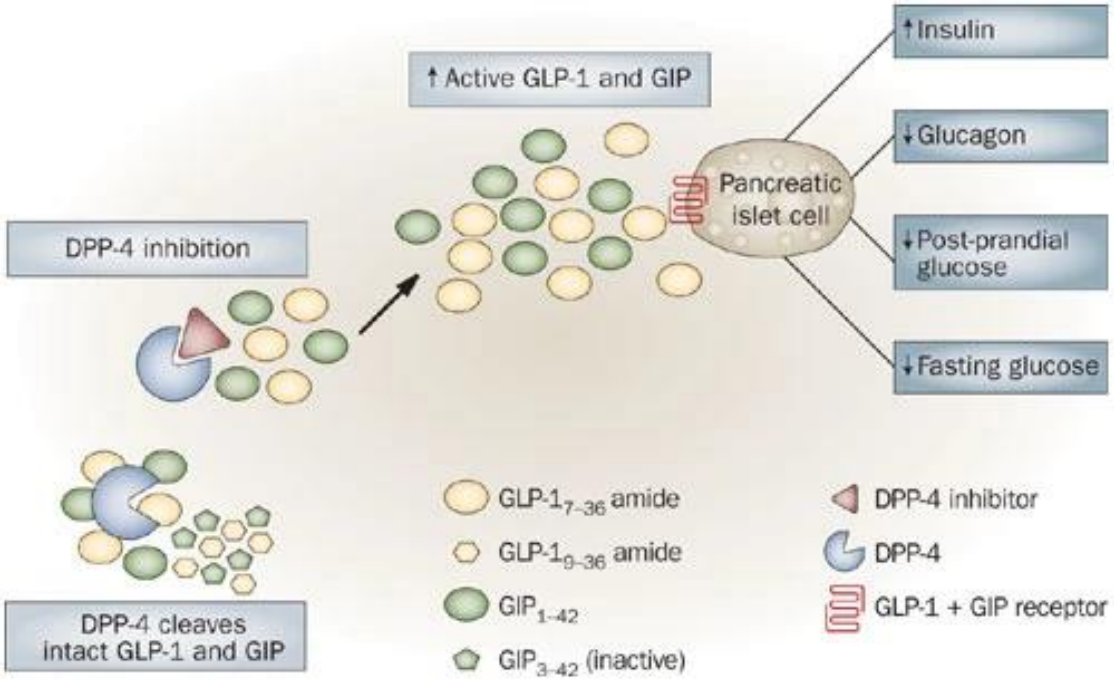

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Table 2. Summary of key details and results from cardiovascular outcome trials conducted on DPP-4 inhibitors

Study	Completion Date	Participants	Molecule (dose, n)	Comparator (n)	Median Follow-up (years)	Clinical Outcomes (HR [95% CI] vs. comparator)			
						MACE	CV Mortality	Fatal/non-fatal MI	Fatal/non-fatal stroke
EXAMINE[20]	June 2013	5380	Alogliptin (25, 12.5 or 6.25 mg, n = 2701)	Placebo (n = 2679)	1.5	0.96 (UL: 1.16)	0.79 (0.60-1.04)	1.08 (0.88-1.33)[a]	0.91 (0.55-1.50)[a]
SAVOR-TIMI 53[21]	May 2013	16,492	Saxagliptin (5 or 2.5 mg, n = 8280)	Placebo (n = 8212)	2.1	1.00 (0.89-1.12)	1.03 (0.87-1.22)	0.95 (0.80-1.12)	1.11 (0.88-1.39)
TECOS[22]	March 2015	14,671	Sitagliptin (100 or 50 mg, n = 7332)	Placebo (n = 7339)	3.0	0.98 (0.89-1.08)	1.03 (0.89-1.19)	0.95 (0.81-1.11)	0.97 (0.79-1.19)
CARMELINA[19]	January 2018	6979	Linagliptin (5 mg, n = 3494)	Placebo (n = 3485)	2.2	1.02 (0.89-1.17)	0.96 (0.81-1.14)	1.12 (0.90-1.40)	0.91 (0.67-1.23)
CAROLINA[116]	August 2018	6033	Linagliptin (5 mg, n = 3023)	Glimepiride (n = 3010)	6.3	0.98 (0.84-1.14)	1.00 (0.81-1.24)	1.03 (0.82-1.29)	0.86 (0.66-1.12)

Abbreviations: MACE, major adverse cardiovascular events; CV, cardiovascular; MI, myocardial infarction; UL, upper limit

[a] non-fatal events only

2.1.4.2.2.6 SGLT-2 Inhibitors

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors (canagliflozin, dapagliflozin, and empagliflozin) are the newest class of anti-hyperglycemic medications that first entered the market in 2013.[64,117] These drugs work by inhibiting SGLT-2 in the proximal convoluted tubules of the kidneys, which prevents the reabsorption of glucose and results in urinary glucose excretion.[118] Blood glucose levels decrease and glycemic control is improved with the excretion of glucose.[118] Because their mechanism of action is independent of insulin, SGLT-2 inhibitors are a good treatment option for patients in advanced stages of type 2 diabetes with limited β-cell function.[64] These drugs have intermediate efficacy[14] and can lower HbA1c by 0.4-0.7%.[9] Their efficacy may be decreased in patients with renal impairment given that SGLT-2 inhibitors depend on normal glomerular-tubular function.[118] SGLT-2 inhibitors are not associated with hypoglycemia and can cause weight loss.[9] Furthermore, SGLT-2 inhibitors have been shown to be cardioprotective and decrease the risk of MACE (empagliflozin and canagliflozin)[119,120] and cardiovascular death (empagliflozin)[119] in large cardiovascular outcome trials. The use of SGLT-2 inhibitors, however, is associated with an increased risk of genital mycotic and urinary tract infections, fractures, and lower extremity amputations.[9]

2.1.4.2.3 Last-Line Treatment

In terms of glycemic control, insulin is the most effective treatment[38] and can lower HbA1c by 0.9-1.2% or more.[9] In the traditional step-wise approach of treating type 2 diabetes, anti-hyperglycemic drugs are introduced one at a time with insulin being added as the final 'step' when patients are no longer able to maintain glycemic targets with non-insulin treatments.[121] Due to the progressive nature of type 2 diabetes, many patients will eventually require insulin[14] and it

is usually initiated 10-15 years after diagnosis.[121] In patients with metabolic decompensation (i.e., marked hyperglycemia, ketosis, or unintentional weight loss) and/or HbA1c ≥10%, insulin is often initiated immediately.[9,64] Although insulin therapy has been shown to reduce the risk of microvascular complications,[122] and improve treatment satisfaction and quality of life[123] in type 2 diabetes, many patients are hesitant to initiate it due to psychological reluctance and fears of hypoglycemia, weight gain, and self-injection with needles.[121]

In general, adding a basal insulin to the current pharmacological regimen is the first step in insulin therapy.[64] These are long- or intermediate-acting insulin analogues that provide basal insulin levels over a 24-hour period.[9,124] If glycemic targets are still not met after the introduction of a basal insulin, then a bolus insulin may be added to the regimen.[9] Bolus insulins are short- or rapid-acting insulin analogues that are administered before meals to help control postprandial blood glucose levels.[9] Insulin regimens are tailored to the specific needs of each individual patient and thus, the mode of administration (continuous subcutaneous infusion vs. injections), the number of injections per day, and the timing of the injections may vary between patients.[9]

To conclude, there are numerous anti-hyperglycemic medications available on the market, each with their own unique clinical profile. **Table 3** below summarizes the route of administration, primary mechanism of action, HbA1c reduction, and main advantages and disadvantages for each anti-hyperglycemic drug class.

Table 3. Summary of the different anti-hyperglycemic drug classes

Drug Class	Year of Introduction to the Market	Route of Administration	Primary Mechanism(s) of Action	HbA1c Reduction (%)	Advantages	Disadvantages
First-line treatment						
Metformin	1970s in Europe and 1995 in the U.S.[125]	Oral	Suppressing hepatic glucose production, reducing insulin resistance	1.0	Effective at lowering HbA1c, no hypoglycemia or weight gain, inexpensive	May cause gastrointestinal side effects and vitamin B12 deficiency
Second-to-third line treatments						
Sulfonylureas	1956 in Germany for tolbutamide, the first sulfonylurea; 1984 in the U.S. (when glipizide and glyburide became available)[81]	Oral	Stimulating insulin secretion by the pancreatic β-cells	0.7-1.3	Effective at lowering HbA1c	Risk of hypoglycemia and weight gain, associated with increased risk of adverse cardiovascular events
Meglitinides	1997 in the U.S. (repaglinide)[126]	Oral	Stimulating insulin secretion by the pancreatic β-cells	0.7-1.1	Lower risk of hypoglycemia than sulfonylureas	Less effective at glycemic control than sulfonylureas, weight gain
Alpha-glucosidase inhibitors	1995 in the U.S. (acarbose)[127]	Oral	Delaying glucose absorption in the small intestine	0.7-0.8	No hypoglycemia or weight gain	May cause gastrointestinal side effects, needs to be taken before each meal
Thiazolidinediones	1996 in the U.S. (troglitazone);[127] 2000 in Europe (pioglitazone)[128]	Oral	Reducing insulin resistance	0.8-0.9	Effective at lowering HbA1c, no hypoglycemia	Associated with various safety concerns (liver injury and failure, cardiovascular events, bladder cancer) and increased risks of edema and fractures, weight gain

GLP-1 RAs	2005 in the U.S.[127] and 2006 in Europe[129] (exenatide)	Injectable (except for oral semaglutide)	Stimulating insulin secretion by the pancreatic β-cells (glucose dependent)	1.0	Effective at lowering HbA1c, no hypoglycemia, weight loss, associated with decreased risk of MACE	May cause nausea, administered through injections (except for oral semaglutide)
DPP-4 inhibitors	2006 in the U.S.[129] and 2007 in Europe[130] (sitagliptin)	Oral	Increasing levels of biologically active GLP-1	0.5-0.7	No hypoglycemia or weight gain, no nausea, does not increase risk of MACE	Less effective at glycemic control, saxagliptin is associated with increased risk of hospitalization for heart failure
SGLT-2 inhibitors	2013 in the U.S.[127] and Europe[131] (canagliflozin)	Oral	Preventing the reabsorption of glucose in the kidneys, resulting in urinary glucose excretion	0.4-0.7	No hypoglycemia, weight loss, associated with decreased risk of MACE	Less effective at glycemic control, associated with increased risks of genital mycotic and urinary tract infections, fractures, and lower extremity amputations
Last-line treatment						
Insulin	1923 in the U.S.[127] and Europe[132]	Injectable	Increasing insulin levels	0.9-1.2 or more	Most effective treatment for glycemic control, reduces the risk of microvascular complications	Risk of hypoglycemia and weight gain, administered through injections

2.1.5 Association Between Type 2 Diabetes and Cancer Incidence

There is substantial epidemiological evidence that type 2 diabetes is associated with the incidence of several types of cancers. The scientific literature indicates that type 2 diabetes is associated with an increased risk of liver, pancreatic, endometrial, colon, rectal, breast, and bladder cancers.[5] Several mechanisms have been hypothesized as to how type 2 diabetes may mediate the neoplastic process of many types of cancers.[5] The most compelling explanations involve insulin, which can promote the proliferation of tumors. Due to insulin resistance, many patients experience hyperinsulinemia in the beginning stages of type 2 diabetes.[133] Receptors for insulin and insulin-like growth factor 1 are expressed by most cancer cells and signalling through these receptors can provide protection from apoptosis and promote proliferation, invasion, and metastasis for these cancer cells.[5] Interestingly, the risk of prostate cancer is decreased in men with type 2 diabetes.[5] One hypothesis is that this is due to reduced circulating testosterone levels in men with type 2 diabetes (see Section 2.2.5 Association Between Type 2 Diabetes and Prostate Cancer).[5]

Given that both type 2 diabetes and cancer are complex and heterogeneous diseases, characterizing their relationship is not straightforward. When assessing the association between type 2 diabetes and cancer incidence, overall cancer incidence as a composite endpoint should not be used as this will mask specific patterns associated with site-specific cancers.[134,135] Type 2 diabetes may be strongly associated with certain cancers but only moderately or even inversely associated with others.[135] However, given the rarity of many site-specific cancers, individual cohort studies may not be well-powered to ascertain the risk associated with type 2 diabetes.[134] To further complicate matters, many anti-hyperglycemic drugs have been shown to modulate

cancer risk in patients with type 2 diabetes.[134] The following section will focus on prostate cancer, the outcome of interest for this thesis.

2.2 Prostate Cancer

2.2.1 Epidemiology and Risk Factors of Prostate Cancer

Prostate cancer is the second most diagnosed cancer (after lung cancer) in men globally.[136] In 2018, there were 1,276,106 incident cases (7.1% of all cancers in men) and 358,989 prostate cancer-related deaths (3.8% of all cancer-related deaths in men)[137] worldwide. In Canada, prostate cancer is the most common cancer in men[138,139] and it is estimated that there will be 24,600 incident cases in 2022, representing 20% of all incident cancer cases in Canadian men in 2022.[140] According to the Canadian Cancer Society, 1 in 7 men will be diagnosed with prostate cancer in his lifetime and 1 in 29 will die from it.[138] However, given that prostate cancer is oftentimes slow-progressing and can be effectively managed with proper treatment, prostate cancer has a 95% five-year survival rate in Canada.[138] Indeed, many older men are unaware they have prostate cancer.[138] In a systematic review of 29 autopsy studies from 1948 to 2013 from over 20 countries, undiagnosed prostate cancer was found in all populations. Furthermore, the mean prevalence of undiagnosed prostate cancer was estimated to be 59% (95% CI: 48-71%) for the >79 years age group.[141]

The most well-established risk factors for prostate cancer are advanced age, ethnicity, and family history.[136] Prostate cancer is the most diagnosed cancer among elderly men as its risk increases with age. In men under 50 years of age, prostate cancer is uncommon, only occurring in 1 in 350. This incidence rate increases to 1 in 52 for men aged 50 to 59 years.[136] The incidence rate of prostate cancer is highest for men aged 75-79 years.[142] Compared to White men, African-

American men have a higher risk of developing prostate cancer.[143] Furthermore, they are more likely to develop more aggressive forms of the disease[144] and the disease at a younger age.[143] Family history is also a significant risk factor as an individual's risk of prostate cancer is 2-2.5 times greater if they have a first-degree relative who had prostate cancer.[145] As well, it is estimated that approximately 20% of prostate cancer patients have a family history of it.[136]

2.2.2 Pathophysiology of Prostate Cancer

The prostate gland is one of the male accessory organs of reproduction, located directly below the bladder and surrounding the urethra.[146] Its primary function is to produce and secrete fluids that form a component of ejaculate and help to maintain sperm viability.[146] There are four anatomic zones of the prostate: the peripheral, central, transition, and fibromuscular zones.[146] The peripheral zone is the largest, comprising >70% of the gland, and contributes the most to normal prostate function. It is also the site where neoplasms most commonly develop, as 80% of prostate cancers originate in this zone.[147] 95% of prostate cancers are adenocarcinomas, tumors that originate in gland epithelial cells.[148]

The mechanisms involved in prostate cancer initiation are not fully elucidated.[149] However, it is believed that genes and genetic mutations accumulated throughout a patient's lifetime are strong drivers of the initiation of prostate cancer.[147] For instance, atypical activation of *nkx3.1*, *FOXA1*, and *AR*, genes involved in the development and maturation of the prostate, have been implicated in the promotion of prostate cancer.[149] As well, genome wide association studies have identified 100 single nucleotide polymorphisms that are associated with the initiation of prostate cancer.[150] The progression of prostate cancer is highly dependent on signalling by the androgen receptor,[149] a nuclear transcription factor that alters gene

transcriptional processes after it binds to its ligands.[151] The androgen receptor is activated by the androgens, testosterone and dihydrotestosterone (DHT), although DHT has a much greater affinity for the androgen receptor.[151] 80-90% of prostate cancers are initially responsive to androgens and can be treated with therapies aimed at reducing circulating androgen levels.[152] However, 10-20% of prostate cancers will progress to castration-resistant prostate cancer (CRPC) where there is reactivation of the androgen receptor independent of androgens.[153]

2.2.3 Screening and Diagnosis of Prostate Cancer

Screening for prostate cancer involves taking measurements of prostate specific antigen (PSA), a serine protease produced by the prostate that is usually elevated in men with prostate cancer.[154] PSA values between 0 to 4.0 ng/mL are considered normal, while values >4.0 ng/mL may need follow-up, depending on a number of patient characteristics such as age, ethnicity, family history of prostate cancer, height, and BMI.[146] PSA testing for prostate cancer was introduced in Canada in 1993 and its importance was underscored in 2001.[138] However, using PSA levels as a screening method is not perfect as PSA levels naturally fluctuate with age and furthermore, a number of conditions besides prostate cancer, such as benign prostatic hyperplasia, prostatitis, urinary tract infections, and trauma, can lead to elevated PSA levels.[138,146] Consequently, widespread PSA testing has resulted in the overdiagnosis and overtreatment of low-grade prostate cancers that do not lead to symptoms or death.[155] In 2014, the Canadian Task Force on Preventive Health Care advised against PSA testing for healthy men of all ages.[138,155] Another method for prostate cancer screening is the digital rectal exam, a physical exam where the prostate is palpated in order to examine gland enlargement, texture, and stiffness.[147] This test has limitations, however, as only the posterior surface of the prostate can be

palpated.[146] If PSA values are rising or abnormally elevated without explanation and/or results from the digital rectal exam are suspicious, a diagnosis of prostate cancer can be made following histologic examination of prostate tissue from a biopsy.[146]

2.2.4 Treatment of Prostate Cancer

Many factors are considered before a treatment option is chosen, including disease progression, tumor characteristics, patient age, health status, comorbidities, and potential side effects of treatment.[146] Patients with localized (organ-confined), low-risk prostate cancer are not expected to gain any benefit from local treatment unless they have a life expectancy of ≥10 years, given the slow progressing nature and low risk of metastasis of this type of cancer.[147] Thus, active surveillance, an alternative to definitive therapy, may be suitable for patients with a <10-year life expectancy, low PSA levels, and early-stage disease.[146] Active surveillance involves monitoring the patient over time with repeat PSA tests, digital rectal exams, and prostate biopsies.[156] Definitive treatment is deferred with this strategy, which avoids unnecessary overtreatment and any potential adverse side effects.[156] Understandably, however, many patients are not comfortable with the idea of leaving cancer untreated.[156]

For patients with higher-risk localized prostate cancer and a life expectancy of >10 years, definitive treatment options include radical prostatectomy, external beam radiation therapy, brachytherapy, and cryotherapy. With a radical prostatectomy, the prostate gland and seminal vesicles are removed in their entirety.[146] External beam radiation therapy targets prostate cancer with a curative dose of radiation, and treatment plans are made based on the risk level of an individual patient's prostate cancer.[146] Depending on the risk level, radiation therapy may be administered to the seminal vesicles as well, and alongside androgen deprivation therapy

(ADT).[146] As well, radiation therapy may also be administered after a radical prostatectomy if there are suspicious pathological results.[146] Brachytherapy is a form of radiation therapy where sources of radiation are placed inside the body near the cancer site, and it can be administered alone or in conjunction with external beam radiation therapy.[146] Finally, cryotherapy is a surgical procedure where the prostate is frozen. It is a suitable option for patients with localized high-risk cancer and a contraindication for radical prostatectomy.[146,157]

For advanced and metastatic prostate cancer, ADT is a treatment option. ADT reduces circulating levels of androgens, which drive the progression of prostate cancer. This can be accomplished surgically with an orchiectomy (removal of the testes), or chemically with the use of luteinizing hormone-releasing hormone (LHRH) agonists and oral anti-androgens.[146] There is disagreement regarding when ADT should be initiated in asymptomatic patients and whether it should be given continuously or intermittently.[146] Although ADT is effective initially, it may eventually fail as the disease progresses to CRPC.[153] Despite this, LHRH agonists are oftentimes continued as some cancer cells remain responsive to them.[146] Treatment options for CRPC include secondary hormone therapy with other anti-androgen drugs (e.g., androgen receptor antagonists), steroids, and chemotherapy.[146]

2.2.5 Association Between Type 2 Diabetes and Prostate Cancer

As previously mentioned, although type 2 diabetes is associated with increased risks of several types of cancers, it has been found to be associated with a decreased risk of prostate cancer.[5] In the Health Professionals Follow-up Study, which followed a cohort of 51,520 American men aged 40 to 75 years at baseline from 1986-2004, an inverse relationship between type 2 diabetes and risk of prostate cancer was observed.[158] The risk of prostate cancer was 17%

decreased in men with type 2 diabetes compared to men without (hazard ratio (HR): 0.83, 95% confidence interval (CI): 0.74-0.94).[158] This inverse association was observed both before and after the introduction of PSA screening, although the reduction in risk was slightly greater in the time period before PSA screening.[158] Furthermore, a temporal relationship was observed between the two diseases; the longer the duration of diabetes, the greater the reduction in the risk of prostate cancer.[158] A subsequent meta-analysis that included 45 observational studies has corroborated the inverse relationship between type 2 diabetes and risk of prostate cancer (risk ratio: 0.86, 95% CI: 0.80–0.92).[159]

One biological mechanism that has been hypothesized to explain this inverse association involves testosterone, a hormone that is critical for the development of prostate cancer. Testosterone levels may be decreased in men with type 2 diabetes, creating an environment that is not conducive for the growth of prostate cancer.[158] One study found reduced total testosterone levels in 43% of men with type 2 diabetes, and reduced free testosterone levels in 57%.[160] As well, as the duration of diabetes increases, the testosterone to sex hormone binding globulin ratio decreases, resulting in reduced levels of bioavailable testosterone.[161] However, circulating testosterone levels have not been consistently associated with an increased risk of prostate cancer.[162-164]

To further complicate matters, prostate cancer patients with type 2 diabetes have worse prognoses than patients without diabetes.[165] In an observational study that followed a cohort of male patients newly diagnosed with non-metastatic prostate cancer, patients with pre-existing type 2 diabetes had a 23% increased risk of prostate cancer mortality (HR: 1.23, 95% CI: 1.04-1.46).[165] It is hypothesized that since type 2 diabetes is associated with lower PSA levels,[166] the detection of prostate cancer may be delayed until the disease has progressed to later, higher-

grade stages, resulting in worse prognoses. Thus, differences in PSA levels between diabetics and non-diabetics may also have a role in the inverse association between type 2 diabetes and risk of prostate cancer.[167] Further research is required to elucidate the mechanisms by which type 2 diabetes is inversely associated with prostate cancer incidence.

2.3 Incretin-Based Drugs and Prostate Cancer

There is emerging evidence from laboratory and clinical studies that suggests that incretin-based drugs may have chemopreventive effects on prostate cells. This section outlines what is currently known about the association between incretin-based drugs and prostate cancer in the scientific literature.

2.3.1 Biological Evidence of the Effect of the Incretin-Based Drugs on Prostate Cancer Cells

2.3.1.1 GLP-1 RAs

Signalling through the GLP-1 receptor has been shown to affect the proliferation of prostate cancer. In a study by Nomiyama et al., exendin-4, a GLP-1 RA, was shown to reduce the proliferation of prostate cancer cells *in vitro* by activating GLP-1 receptors, resulting in the inhibition of the ERK-MAPK signalling pathway.[24] In this study, androgen-sensitive (LNCap and ALVA-41) and androgen-independent (PC3 and DU145) prostate cancer cell lines were treated with exendin-4. Following treatment, cells from LNCap, PC3, and DU145 exhibited significantly decreased proliferation, with the greatest effect observed in the LNCap cells, a prostate cancer cell line with high expression of GLP-1 receptors. In contrast, exendin-4 did not affect the proliferation of cells from ALVA-41, a cell line with no expression of GLP-1 receptors. As well, the anti-proliferative effects of exendin-4 were abolished in the presence of

exendin(9-39), a GLP-1 receptor antagonist, and when GLP-1 receptors were knocked down with small interfering RNA.[24] Furthermore, the suppressive effects of exendin-4 were observed *in vivo* as well. When LNCap cells were transplanted into athymic mice, treatment with exendin-4 inhibited prostate cancer growth.[24]

In a subsequent study, Shigeoka et al. showed that forcing the expression of the GLP-1 receptor can also inhibit the proliferation of prostate cancer *in vitro* and *in vivo*.[23] In this study, GLP-1 receptors were overexpressed in ALVA-41, a prostate cancer cell line with negligible endogenous expression of GLP-1 receptors, using a lentiviral vector. Activation of these overexpressed GLP-1 receptors resulted in reduced proliferation of the prostate cancer cells by inhibiting cell cycle progression.[23] When the ALVA-41 cells with forcefully expressed GLP-1 receptors were implanted into athymic mice, treatment with exendin-4 was able to reduce the growth of the cells.[23]

2.3.1.2 DPP-4 Inhibitors

Biological studies on the association between DPP-4 inhibitors and prostate cancer are less conclusive. There appears to be a complex relationship between the DPP-4 enzyme and the proliferation of prostate cancer. In a study by Lu et al., the expression of DPP-4 was found to be increased in prostate cancer tissues when compared to non-neoplastic tissues, suggesting that DPP-4 may be a potential target for prostate cancer treatment.[25] In line with this hypothesis, when DPP-4 was blocked in an *in vitro* study, the invasiveness of 1-LN prostate cancer cells was reduced.[26] On the other hand, other studies suggest that the inhibition of DPP-4 promotes progression to more severe forms of prostate cancer.[27,28] In an *in vivo* study, treatment with sitagliptin, a DPP-4 inhibitor, following castration accelerated the progression of prostate cancer

xenographs in male mice to androgen-independent prostate cancer.[27] As well, in another *in vitro* study, DPP-4 activity was observed to have suppressive effects on the metastatic potential of prostate cancer,[28] suggesting the use of DPP-4 inhibitors to have pro-neoplastic effects.

2.3.2 Prostate Cancer Events in Cardiovascular Outcome Trials

Due to some controversy regarding the cardiovascular safety of rosiglitazone, a TZD, in 2008, all new anti-hyperglycemic drugs are required by the FDA to be evaluated on cardiovascular outcomes at the time of approval.[9] The cardiovascular outcome trials are randomized, placebo-controlled trials designed to assess cardiovascular risk with the use of these new drugs. The majority of participants for these trials have pre-existing type 2 diabetes and clinical cardiovascular disease or multiple cardiovascular risk factors.[9]

2.3.2.1 GLP-1 RAs

Although many cardiovascular outcome trials have been completed for GLP-1 RAs,[15-18,111-113] only the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial has reported on prostate cancer events.[15] The LEADER study was a double-blind, 1:1 randomized trial designed to assess the long-term safety of liraglutide with respect to cardiovascular outcomes. In this study, 9340 participants with type 2 diabetes and high cardiovascular risk were randomized to receive either 1.8 mg (or the maximum tolerated dose) of liraglutide or matched placebo once daily in addition to standard care. The primary outcome was a composite of the first occurrence of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke. Neoplasms was one of the prespecified exploratory

outcomes. After a median follow-up of 3.8 years, the imbalance in prostate cancer events favoured liraglutide (26 vs. 47 events, HR: 0.54, 95% CI: 0.34-0.88).[29]

2.3.2.2 DPP-4 Inhibitors

Five cardiovascular outcome trials have been completed for DPP-4 inhibitors,[19-22,116] although only the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus – Thrombolysis in Myocardial Infarction (SAVOR-TIMI) 53 trial has reported on prostate cancer events.[21] The SAVOR-TIMI 53 study was a double-blind, 1:1 randomized trial designed to evaluate the long-term safety of saxagliptin with respect to cardiovascular outcomes. In this study, 16,492 type 2 diabetes patients at risk of cardiovascular events were randomized to receive either 5 mg (or 2.5 mg in patients with renal impairment) of saxagliptin or matched placebo once daily. Again, the primary outcome was a composite of cardiovascular death, non-fatal myocardial infarction, or non-fatal ischemic stroke. There was no notable imbalance in prostate cancer events between the saxagliptin and placebo groups (43 vs. 41 events, HR: 1.04, 95% CI: 0.68-1.60) after a median follow-up of 2.1 years.[30]

2.3.3 Observational Studies on the Association Between the Incretin-Based Drugs and Prostate Cancer

To date, there are only two observational studies that have assessed the association between incretin-based drugs and the risk of prostate cancer.[31,32] A 2017 retrospective cohort study by Tseng investigated the association between the use of sitagliptin, a DPP-4 inhibitor, and the incidence of prostate cancer in male patients with type 2 diabetes using Taiwan's National Health Insurance reimbursement database.[31] This study followed 37,924 ever-users of sitagliptin

and 426,276 never-users, and found that the risk of prostate cancer was 39% decreased with ever-use of sitagliptin compared with never-use (HR: 0.63, 95% CI: 0.49, 0.76). This strong protective effect, however, may have been inflated by immortal time bias.[33] This type of bias was likely introduced through the hierarchical exposure definition that was used; ever-users of sitagliptin were identified first and the remaining eligible participants were classified as never-users. By assigning exposure in this manner, the ever-users were given a survival advantage as they needed to survive long enough without the event in order to become a user. On the other hand, never-users could experience the event soon after they initiated treatment.

Another retrospective cohort study conducted in 2018 by Karp et al. primarily investigated whether the use of incretin-based drugs was associated with an increased risk of all cancers (except for non-melanoma skin cancer) in type 2 diabetes patients using the United Kingdom (UK) Clinical Practice Research Datalink (CPRD) and Hospital Episode Statistics.[32] The primary analysis found that the use of incretin-based drugs (GLP-1 RAs and DPP-4 inhibitors combined) compared to the use of sulfonylureas, was not associated with an increased risk of cancer, whether an intention-to-treat (HR: 0.97, 95% CI: 0.90-1.05) or per-protocol (HR: 0.90, 95% CI: 0.81-1.00) analysis was used. In a secondary analysis that stratified by the class of incretin-based drug, the risk of cancer was also not increased when GLP-1 RAs were compared to sulfonylureas nor when DPP-4 inhibitors were compared to sulfonylureas. In another secondary analysis that used prostate cancer as the outcome, the use of incretin-based drugs (GLP-1 RAs and DPP-4 inhibitors combined) compared to the use of sulfonylureas generated risk estimates that were below the null value of 1.00. However, the confidence intervals were wide and included the null value. This was the case whether an intention-to-treat (HR: 0.87, 95% CI: 0.70-1.08) or per-protocol (HR: 0.73, 95% CI: 0.52-1.01) analysis was used. This secondary

analysis, however, did not investigate the individual effects of GLP-1 RAs or DPP-4 inhibitors on the risk of prostate cancer. Combining them into a single exposure may have diluted any notable protective or harmful effects of one of the classes. Furthermore, this study did not specifically investigate prostate cancer as an outcome and did not account for important potential confounders such as lower urinary tract symptoms, drugs associated with prostate cancer incidence (e.g., 5-α reductase inhibitors), and PSA test measurements.

2.3.4 Knowledge Gaps

There is compelling biological evidence in the scientific literature that the incretin-based drugs may decrease the risk of prostate cancer. Regarding the biological evidence, however, it is important to note that the aforementioned laboratory studies assessed the effects of GLP-1 RAs and DPP-4 inhibitors on the proliferation of existing tumors, which might be distinct from their effects on the development of new tumors. There is a paucity of evidence in humans and what is available has limitations. The cardiovascular outcome trials were not designed nor powered to ascertain prostate cancer incidence and are limited by their relatively small sample sizes (6003 and 11,037 male patients for LEADER and SAVOR-TIMI 53, respectively) and short median durations of follow-up (3.8 and 2.1 years for LEADER and SAVOR-TIMI 53, respectively). Currently, there are only two observational studies that have assessed the association between incretin-based drugs and risk of prostate cancer. The first study is limited by immortal time bias, while the second study did not investigate the individual effects of GLP-1 RAs and DPP-4 inhibitors, did not specifically investigate prostate cancer as an outcome, and did not account for important potential confounders related to prostate cancer. Given the limitations of the previous studies, 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 prostate cancer in men with type 2 diabetes. The following chapters will describe the objectives, methodology, and results of this research project.

Chapter 3: Objectives and Hypotheses

3.1 Objective

The primary objective of this thesis is to determine whether the use of incretin-based drugs (GLP-1 RAs and DPP-4 inhibitors, separately), when compared with the use of sulfonylureas, is associated with a decreased incidence of prostate cancer among men with type 2 diabetes.

3.1.1 Secondary Objectives

This thesis has 3 secondary objectives:

1. To determine whether the association varies with cumulative duration of use;
2. To determine whether there is a drug-specific effect (GLP-1 RAs: albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, oral semaglutide, and semaglutide; DPP-4 inhibitors: alogliptin, linagliptin, saxagliptin, sitagliptin, and vildagliptin) on the incidence of prostate cancer;
3. To determine whether there is effect measure modification by age (<75 vs. ≥75 years), BMI (<30 kg/m² vs. ≥ 30.0 kg/m²), and smoking status (ever vs. never).

3.2 Hypothesis

The primary hypothesis is that there is an inverse association between the use of incretin-based drugs (GLP-1 RAs and DPP-4 inhibitors, separately) and the incidence of prostate cancer, when compared with the use of sulfonylureas, among men with type 2 diabetes.

3.2.1 Secondary Hypotheses

1. The association varies with cumulative duration of use;

2. There is no drug-specific effect on the incidence of prostate cancer;

3. There is no effect measure modification by age, BMI, and smoking.

Chapter 4: Methodology

The methodology for this thesis study is detailed in the manuscript in Chapter 5. This chapter will elaborate on aspects of the methodology that were not explained in great detail in the manuscript due to word limitations. Specifically, more details on the data source, rationale behind the choice of the active comparator, construction of the study cohorts, exposure definition, potential confounders, and rationale for the use of propensity score fine stratification will be provided in this chapter.

4.1 Data Source

This thesis study was conducted using data from the UK CPRD, a primary care database that contains anonymized medical records of patients from general practices in the UK.[168] The primary care setting in the UK is conducive for the collection of longitudinal health information. Given that patients are not charged for visits to the general practitioner under the National Health Service (NHS), over 98% of UK's population is registered with a general practitioner.[168] When non-emergency medical issues arise, general practitioners are the first point of contact for patients.[168] If the medical issue cannot be managed by primary care, then patients are referred to secondary care teams who relay information, including diagnoses, back to general practitioners about their patients.[168] Information from participating general practices is collated by the CPRD on a monthly basis, and patients are included in the dataset from their initial until their final visit.[168]

The CPRD consists of the Gp OnLine Data (GOLD) and Aurum datasets. Participating general practices contribute data to either GOLD or Aurum depending on the patient management software that is used. For the past 30 years, the GOLD dataset has been collecting

information from practices that use Vision® software.[169] In 2017, CPRD Aurum was introduced, which collects data from practices that use EMIS Web® software.[169] Together, CPRD GOLD and Aurum include approximately 60 million patients from nearly 2000 general practices, making the CPRD one of the largest databases of longitudinal medical records from general practices in the world.[168,169]

The CPRD is suitable for health-related research as it is broadly representative of the UK population with respect to age, sex, and ethnicity, and records information on demographics, diagnoses, symptoms, laboratory tests, prescriptions, lifestyle factors (e.g., smoking status, alcohol consumption), and referrals to secondary care.[168] Prescription details are recorded using a coded drug dictionary based on the British National Formulary, while medical diagnoses and procedures are recorded using the Read and Systematized Nomenclature of Medicine – Clinical Terms (SNOMED-CT) classification systems.[168,169] Read codes are a clinical vocabulary system that was widely used by general practices in the UK until 2018, when NHS England required all healthcare providers to switch to the SNOMED-CT system for recording electronic patient data.[170] The SNOMED-CT system is regarded as the most comprehensive and precise medical terminology system and it has been widely adopted across the world.[170]

The validity of cancer diagnoses recorded in the CPRD has been confirmed by several studies.[171-174] Indeed, the recording of prostate cancer, the outcome of interest for this thesis study, in the CPRD has high completeness and overlap with Hospital Episode Statistics and the National Cancer Data Repository.[171] In the UK, general practitioners and not specialists, are primarily responsible for the long-term care of patients with type 2 diabetes and renewing their prescriptions.[175,176] As such, diabetes is also well-recorded in the CPRD, with a positive predictive value that exceeds 90%.[177] Furthermore, it is estimated that over 95% of prescriptions

written by general practitioners are recorded in the CPRD.[178] Thus, the CPRD is an appropriate and valuable data source for investigating the association between incretin-based drugs and prostate cancer.

4.2 Active Comparator Group

Sulfonylureas were selected as the active comparator group because they represent an alternative second- to third-line anti-hyperglycemic drug class that is used at a similar disease stage as the incretin-based drugs. Furthermore, they have not been previously associated with prostate cancer incidence.[179,180] Metformin and insulin were not suitable comparator groups as they are used in early and advanced stages of type 2 diabetes, respectively, and thus, their use could introduce confounding by indication. Although TZDs are another second- to third-line drug class, they are used infrequently due to associations with adverse events. The newest anti-hyperglycemic drug class, SGLT-2 inhibitors, were also not selected as the comparator group. Using SGLT-2 inhibitors would restrict the cohort to patients initiating the study drugs after 2013, the year SGLT-2 inhibitors entered the UK market. This would decrease the number of patients included in the study and thus, the statistical power. In comparison, sulfonylureas have been used for the past 50 years and remain one of the most prescribed second- to third-line anti-hyperglycemic drugs,[82] providing a large sample of patients for the comparison group.

4.3 Study Cohort and Exclusion Criteria

A separate cohort was constructed for each incretin-based drug class as GLP-1 RAs and DPP-4 inhibitors were analyzed separately. The study cohorts consisted of male patients who initiated treatment with an incretin-based drug (GLP-1 RAs: albiglutide, dulaglutide, exenatide,

liraglutide, lixisenatide, oral semaglutide, and semaglutide; DPP-4 inhibitors: alogliptin, linagliptin, saxagliptin, sitagliptin, and vildagliptin) or sulfonylurea (glibenclamide, gliclazide, glimepiride, glipizide, and tolbutamide) between January 1, 2007 (the year the first incretin-based drug entered the UK market) and July 31, 2019. Cohort entry was defined as the date of the first prescription of the incretin-based drug class of interest (GLP-1 RA or DPP-4 inhibitor, depending on the analysis) or a sulfonylurea during the study period, whichever came first.

Figure 4 below illustrates how the cohorts were constructed. As described in the manuscript, all patients were required to have at least one year of medical history in the CPRD before cohort entry as this served as the minimum washout period to identify new users and have an adequate baseline period for assessing patient covariates. As a new-user cohort design was implemented, patients previously prescribed an incretin-based drug under investigation or a sulfonylurea at any time before cohort entry were excluded. This included patients previously prescribed DPP-4 inhibitors in the GLP-1 RA vs. sulfonylurea cohort and patients previously prescribed GLP-1 RAs in the DPP-4 inhibitor vs. sulfonylurea cohort. Additional exclusion criteria included age below 40 (prostate cancer is rare in this age category), previous diagnosis of prostate cancer (Read codes provided in **Table 4**), use of the 3 mg/0.5 mL formulation of liraglutide (indicated for weight loss), concomitant prescription of an incretin-based drug and sulfonylurea at cohort entry, and end-stage kidney disease or dialysis (contraindications to receiving sulfonylureas). Furthermore, as illustrated by **Figure 4**, a one-year lag period was imposed before patients were considered exposed to the study drugs. This was necessary for cancer latency purposes and to reduce detection bias, given that patients may be more likely to be monitored after initiating a new treatment. Thus, patients diagnosed with prostate cancer and

those who left the cohort for other reasons during the one-year lag period were also excluded from the cohort.

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

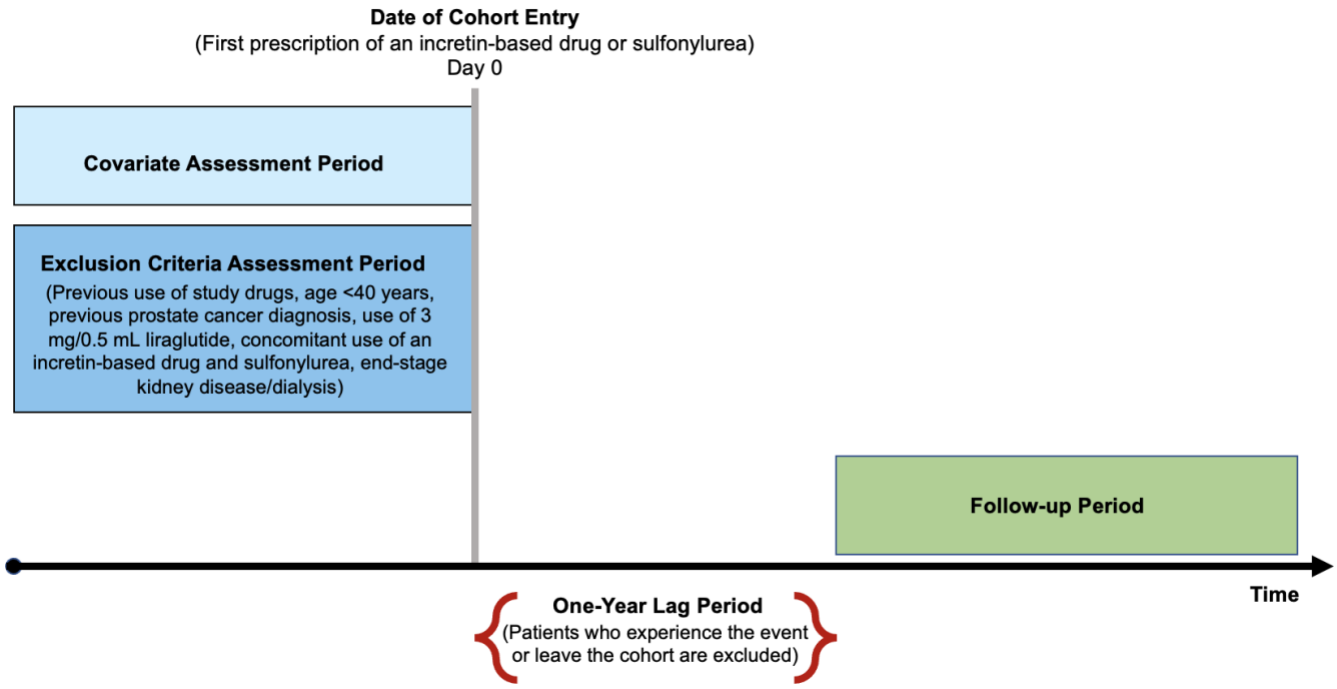

Table 4. Read codes for prostate cancer

Read Code	Read Term
B46..00	Malignant neoplasm of prostate
B834.00	Carcinoma in situ of prostate
4M0..00	Gleason grading of prostate cancer
4M01.00	Gleason prostate grade 5-7 (medium)
B915.00	Neoplasm of uncertain behaviour of prostate
4M00.00	Gleason prostate grade 2-4 (low)
4M02.00	Gleason prostate grade 8-10 (high)
B834000	Malignant neoplasm of prostate

4.4 Exposure Definition

For the primary analysis, an exposure definition analogous to an intention-to-treat approach was used. For this exposure definition, patients were considered exposed to the study drugs starting one year after cohort entry until an incident diagnosis of prostate cancer, death from any cause, end of registration with the general practice, or end of the study period (July 31, 2020), whichever occurred first. This was regardless of treatment discontinuation or crossover to one of the other drugs under investigation. This exposure definition is suitable in the context of cancer pathogenesis. With this approach, it is assumed that the drugs have an irreversible effect on the outcome, and thus, the effects of the drugs would persist even after treatment discontinuation.

In a sensitivity analysis to assess the robustness of the results from the primary analysis, the analysis was repeated using an on-treatment exposure definition in the context that the effects of the drugs may indeed be reversible. With this exposure definition, patients were censored on treatment discontinuation and switching or crossing over to the other study drugs after a one-year grace period. The one-year grace period was used to account for the residual effects of the drugs after discontinuation and diagnostic delays associated with prostate cancer.

4.5 Potential Confounders

This study considered 28 potential confounders. Demographic/lifestyle variables, all measured at or before cohort entry, that were considered include: age, alcohol-related disorders (alcoholism, cirrhosis, alcoholic hepatitis, hepatic failure), BMI, smoking status (current, past, never, unknown), and year of cohort entry.

As type 2 diabetes is inversely associated with the incidence of prostate cancer,[158] variables related to diabetes severity were considered. These included glycosylated hemoglobin (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 anti-hyperglycemic drug), type of anti-hyperglycemic drugs used (metformin, SGLT-2 inhibitors, TZDs, meglitinides, alpha-glucosidase inhibitors, and insulin; entered as non-mutually exclusive categories and assessed in the year before cohort entry), and presence of macrovascular (peripheral arteriopathy, ischemic stroke, myocardial infarction; assessed ever before cohort entry) and microvascular complications (nephropathy, retinopathy, neuropathy; assessed ever before cohort entry).

Other health-related variables were considered as well. This included previous cancer diagnoses as a previous cancer diagnosis may lead patients to screen for other cancers, such as that of the prostate. Previous diagnoses of non-melanoma skin cancer were excluded from this definition as these are very common and non-life threatening. Lower urinary tract symptoms (defined as either a diagnosis for benign prostatic hyperplasia or prostatitis) were considered as men with this condition are more likely to undergo screening for prostate cancer.[181] Finally, previous PSA test measurements and prescriptions for drugs previously associated with prostate cancer incidence, including non-steroidal anti-inflammatory drugs,[182] aspirin,[183] statins,[184] 5-alpha reductase inhibitors (finasteride, dutasteride),[185] and calcium channel blockers,[186,187] all measured at any time before cohort entry, were considered. Although testosterone replacement therapy has not been associated with prostate cancer incidence,[188,189] men on this treatment are more closely monitored for prostate cancer per treatment guidelines,[190] and thus, it was considered as well. **Table 5** below presents a summary of the covariates that were considered,

along with their definitions, variable types, and assessment periods. These covariates were used with propensity score fine stratification, a method for confounding control discussed in the next section.

Table 5. Summary of covariates

Covariate	Variable Type	Definition	Covariate Assessment Period
Demographic/lifestyle variables			
Age	Continuous	Cohort entry year minus birth year	Cohort entry
BMI	Categorical	<30 kg/m², ≥30 kg/m², unknown	Cohort entry
Smoking status	Categorical	Ever, never, unknown	Cohort entry
Alcohol-related disorders	Binary	Present/absent (alcoholism, cirrhosis, alcoholic hepatitis, hepatic failure)	Ever before cohort entry
Year of cohort entry	Continuous	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	Defined by the date of the first of either an HbA1c ≥6.5%, a diagnosis of type 2 diabetes, or prescription for an anti-hyperglycemic 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
Anti-hyperglycemic drugs			
Metformin	Binary	Present/absent	Year before cohort entry
Thiazolidinediones	Binary	Present/absent	Year before cohort entry
Meglitinides	Binary	Present/absent	Year before cohort entry
Alpha-glucosidase inhibitors	Binary	Present/absent	Year before cohort entry
SGLT-2 inhibitors	Binary	Present/absent	Year before cohort entry
Insulin	Binary	Present/absent	Year before cohort entry
Other health-related variables			
Previous cancer diagnoses	Binary	Present/absent	Ever before cohort entry
Lower urinary tract symptoms	Binary	Present/absent (a diagnosis for benign	Ever before cohort entry

		prostatic hyperplasia or prostatitis)	
Previous PSA test measurements	Binary	Present/absent	Ever before cohort entry
Other prescription drugs			
Non-steroidal anti-inflammatory drugs	Binary	Present/absent	Ever before cohort entry
Aspirin	Binary	Present/absent	Ever before cohort entry
Statins	Binary	Present/absent	Ever before cohort entry
5-alpha reductase inhibitors	Binary	Present/absent	Ever before cohort entry
Calcium channel blockers	Binary	Present/absent	Ever before cohort entry
Testosterone replacement therapy	Binary	Present/absent	Ever before cohort entry

4.6 Propensity Score Fine Stratification

The formal definition of a propensity score is an individual's predicted probability of being exposed to a particular treatment given their characteristics, and it is often calculated using logistic regression with observed data.[191] Methods based on propensity scores (matching, stratification, adjustment as a covariate, and weighting) can be used in observational studies to adjust for confounding by helping to achieve exchangeability between the treated and untreated groups with respect to measured (but not unmeasured) confounders.[191] Propensity score matching is a commonly used method for confounding adjustment where each treated individual is matched to one or more untreated individual(s) with a similar propensity score.[192] A prespecified caliper width is used to decide whether or not individuals are matched. With this method, however, unmatched individuals are discarded, which reduces the statistical power of the study.[191] This is the reason propensity score matching was only used in a sensitivity analysis for this thesis study (see Section 5.3 Research Design and Methods), and not in the main analyses. Propensity score-based weighting methods on the other hand, allow for the retention of most individuals in the analysis. Propensity score fine stratification is one such method and is suitable when the prevalence of the exposure is expected to be low,[193] such as that of the incretin-based drugs, which are relatively new to the market. As such, it was used to adjust for confounding in this study. However, propensity score fine stratification is still a suitable method when the numbers in the exposure groups are similar.[191]

Propensity score fine stratification aims to make the untreated group more similar to the treated group with respect to the distribution of measured confounders and thus, the estimand generated is the average treatment effect among the treated population. With this method, the propensity scores are not used to calculate the weights directly, an advantage over inverse

probability of treatment weighting (another weighting method) which often results in extreme weights.[191] Rather, the propensity scores are used to create many fine strata and weighting is done to account for stratum membership.[191] For this study, after using multivariable logistic regression to calculate the propensity scores of treatment with a GLP-1 RA or DPP-4 inhibitor versus a sulfonylurea, patients in non-overlapping regions of the propensity score distributions were trimmed. Fifty strata based on the distribution of the incretin-based drug users (GLP-1 RA or DPP-4 inhibitor users, depending on the analysis) were then created. In each stratum, a weight of 1 was given to the incretin-based drug users (i.e., treated group) while the sulfonylurea users (i.e., untreated group) were reweighted to be proportional to the number of incretin-based drug users in the stratum.[193]

Chapter 5: Manuscript: Incretin-Based Drugs and the Incidence of Prostate Cancer Among Patients with Type 2 Diabetes

This chapter presents a manuscript on the association between the use of incretin-based drugs and the risk of prostate cancer. First, the Background section presents the context and rationale for the study. Second, the Research Design and Methods section details the data source, construction of the cohorts, exposure definition, potential confounders, and statistical analysis. The Results section is followed, 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, comparisons with other studies on the topic in the scientific literature, and strengths and limitations of the study. This manuscript was published in *Epidemiology* (July 2022 – Volume 33 – Issue 4 – p. 563-571).

Incretin-Based Drugs and the Incidence of Prostate Cancer Among Patients with Type 2 Diabetes

Original Research Article

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5.1 Abstract

Background: There is some evidence that glucagon-like peptide 1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors have chemopreventive effects on prostate cancer cells, but real-world evidence for this possible effect is lacking. Thus, the objective of this study was to estimate whether use of GLP-1 receptor agonists and DPP-4 inhibitors, separately, is associated with a decreased risk of prostate cancer among patients with type 2 diabetes.

Methods: We assembled two new-user, active comparator cohorts using the United Kingdom Clinical Practice Research Datalink (2007 to 2019). The first cohort included 5063 initiators of GLP-1 receptor agonists and 112,955 of sulfonylureas. The second cohort included 53,529 initiators of DPP-4 inhibitors and 114,417 of sulfonylureas. We fit Cox proportional hazards models to estimate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for prostate cancer. We weighted the models using propensity score fine stratification, which considered over 50 potential confounders.

Results: GLP-1 receptor agonists were associated with a decreased risk of prostate cancer when compared with sulfonylureas (incidence rates: 156.4 vs. 232.0 per 100,000 person–years, respectively; HR: 0.65, 95% CI: 0.43, 0.99). DPP-4 inhibitors were also associated with a decreased risk of prostate cancer when compared with sulfonylureas (incidence rates: 316.2 vs. 350.5 events per 100,000 person–years, respectively; HR: 0.90, CI: 0.81, 1.00).

Conclusions: The results of this study are consistent with the hypothesis that the use of GLP-1 receptor agonists and DPP-4 inhibitors, separately, may decrease the risk of prostate cancer when compared with the use of sulfonylureas.

5.2 Background

Dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptidase (GLP-1) receptor agonists are second- to third-line drugs commonly used to treat type 2 diabetes (1). In addition to their known clinical benefits, there is some laboratory evidence that these incretin-based drugs may reduce the growth of prostate cancer cells (2-7). *In vitro* and *in vivo* studies found GLP-1 receptor agonists to have anti-proliferative effects on prostate cancer cells by inhibiting the ERK-MAPK signaling pathway (3). DPP-4 inhibitors may also reduce the growth of prostate cancer, although the biological evidence is mixed (4-7).

To date, however, the evidence in humans is limited. Indeed, only two incretin-based drug cardiovascular outcome trials reported on prostate cancer events (8,9). In the LEADER trial, the GLP-1 receptor agonist liraglutide was associated with decreased risk of prostate cancer when compared to placebo (26 vs. 47 events, hazard ratio [HR]: 0.54, 95% confidence interval [CI]: 0.34, 0.88) (8,10). In the SAVOR-TIMI 53 trial, the DPP-4 inhibitor saxagliptin was not associated with a decreased risk of prostate cancer (43 vs. 41 events, HR: 1.04, 95% CI: 0.68, 1.60) (9,11). These trials, however, were not designed to ascertain cancer incidence and were limited by their relatively small sample sizes and short median durations of follow-up (9340 and 16,492 patients; 3.8 and 2.1 years, for LEADER and SAVOR-TIMI 53, respectively). To our knowledge, the only observational study on the topic reported a decreased risk of prostate cancer with sitagliptin, a DPP-4 inhibitor (HR: 0.63, 95% CI: 0.49, 0.76) (12). However, this inverse association may have been due to immortal time bias (13).

Given the uncertainties related to the chemopreventive effects of incretin-based drugs on the development of prostate cancer, we conducted a large population-based cohort study to

estimate whether the use of GLP-1 receptor agonists and DPP-4 inhibitors, separately, decreases the incidence of prostate cancer among men with type 2 diabetes.

5.3 Research Design and Methods

Data Source

We conducted this population-based cohort study using the GOLD and Aurum databases of the Clinical Practice Research Datalink (CPRD), a primary care database from the United Kingdom (UK) with approximately 60 million patients from nearly 2000 general practices (14). The CPRD is broadly representative of the UK population (14) and records information on demographics, diagnoses, symptoms, laboratory tests, prescriptions, lifestyle factors (e.g., smoking status, alcohol consumption), and referrals to secondary care, making it a rich source of health-related data for research purposes (14). Medical diagnoses and procedures are recorded using the Read code and SNOMED-CT classification system, which have been shown to produce high-quality and valid data (15-17). Furthermore, several studies have confirmed the validity of cancer diagnoses recorded in the CPRD (18-21), with prostate cancer recording shown to have high completeness and overlap with Hospital Episode Statistics and the National Cancer Data Repository (18). A coded drug dictionary based on the *British National Formulary* is used for recording prescription details (14).

The study protocol was approved by the CPRD's Research Data Governance (Protocol 21_000526) and by the Research Ethics Board of the Jewish General Hospital, Montreal, Canada.

Study Population

We used a new-user, active-comparator study design that included initiators of GLP-1 receptor agonists (albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, oral semaglutide, and semaglutide) and DPP-4 inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin, and

vildagliptin) and initiators of sulfonylureas (glibenclamide, gliclazide, glimepiride, glipizide, and tolbutamide). We chose sulfonylureas as the comparator group because they are used at a similar disease stage as incretin-based drugs (thus should reduce confounding by indication) (22) and were shown to have neutral effects on the incidence of prostate cancer (23,24).

We identified all patients assigned male at birth prescribed incretin-based drugs or sulfonylureas between 1 January 2007 (the year the first incretin-based drug entered the UK market) and 31 July 2019. Separate cohorts were constructed for each incretin-based drug class, and thus GLP-1 receptor agonists and DPP-4 inhibitors were analyzed separately. The cohort entry date was the first prescription of the incretin-based drug class of interest or a sulfonylurea during the study period. We excluded patients under 40 years of age and those prescribed an incretin-based drug and sulfonylurea concomitantly at cohort entry. All patients were required to have at least 1 year of medical history in the CPRD before cohort entry; this served as a minimum washout period to identify new users and have an adequate baseline period for assessing patient covariates. We excluded patients previously prescribed sulfonylureas or incretin-based drugs under investigation at any time before cohort entry. This included patients previously prescribed DPP-4 inhibitors in the GLP-1 RA vs. sulfonylurea cohort and patients previously prescribed GLP-1 receptor agonists in the DPP-4 inhibitor vs. sulfonylurea cohort. We also excluded patients prescribed GLP-1 receptor agonists for the treatment of obesity, patients previously diagnosed with prostate cancer at any time before cohort entry, and patients with end-stage kidney disease or undergoing dialysis as these are contraindications to receiving sulfonylureas. Finally, all patients were required to have at least 1 year of follow-up (i.e., lag period). This was necessary for cancer latency purposes and to reduce detection bias, given that patients may be more likely to be monitored after initiating a new treatment. Thus, we excluded

from the cohorts, patients diagnosed with prostate cancer and those who left the cohort for other reasons during the one-year lag period.

Exposure Definition

We followed patients starting 1 year after cohort entry until an incident diagnosis of prostate cancer, death from any cause, end of registration with the general practice, or end of the study period (July 31, 2020), whichever occurred first. Patients were considered exposed to the study drugs until the end of the follow-up period, regardless of treatment discontinuation or crossover to one of the other drugs under investigation (analogous to an intention-to-treat approach.)

Potential Confounders

We considered the following potential confounders, all measured at or before cohort entry: age, alcohol-related disorders (alcoholism, cirrhosis, alcoholic hepatitis, hepatic failure), body mass index, and smoking status (current, past, never, unknown). As type 2 diabetes is inversely associated with the incidence of prostate cancer (25), we considered variables related to diabetes severity. These included glycated hemoglobin (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), type of antidiabetic drugs used (metformin, SGLT-2 inhibitors, thiazolidinediones, meglitinides, alpha-glucosidase inhibitors, and insulin; entered as non-mutually exclusive categories and assessed in the year before cohort entry), and presence of macrovascular (peripheral arteriopathy, ischemic stroke, myocardial infarction; assessed ever before cohort entry) and microvascular complications

(nephropathy, retinopathy, neuropathy; assessed ever before cohort entry). We also considered any previous cancer diagnoses (other than nonmelanoma skin cancer), lower urinary tract symptoms (defined as either a diagnosis for benign prostatic hyperplasia or prostatitis), and prescriptions for drugs previously associated with prostate cancer incidence, including non-steroidal anti-inflammatory drugs (NSAIDs), aspirin, statins, 5-α reductase inhibitors (finasteride or dutasteride), calcium channel blockers, and testosterone replacement therapy, all measured at any time before cohort entry. Finally, we considered previous prostate-specific antigen (PSA) test measurements and year of cohort entry.

Statistical Analysis

We used propensity score fine stratification for confounding control. This method is suitable when exposure prevalence is expected to be low (i.e., smaller numbers in the incretin-based drug groups than the sulfonylurea groups). It allows efficiency and the number of patients retained in the analysis to be optimized (26). Multivariable logistic regression was used to calculate the predicted probability of being prescribed a GLP-1 receptor agonist or DPP-4 inhibitor versus a sulfonylurea, conditional on the covariates listed above. We trimmed patients in non-overlapping regions of the propensity score distributions and created 50 strata based on the distribution of the incretin-based drug users. In each stratum, we gave a weight of 1 to incretin-based drug users, while sulfonylurea users were reweighted to be proportional to the number of exposed patients in the stratum (26). Following propensity score weighting, standardized differences were calculated to assess covariate balance between the exposure groups with values less than 0.10 indicating good balance.

For each exposure group, we calculated crude incidence rates of prostate cancer with 95% CIs based on the Poisson distribution. We fit weighted Cox proportional hazards models to estimate adjusted HRs and their corresponding 95% CIs, using robust variance estimators, of prostate cancer associated with use of incretin-based drugs compared with use of sulfonylureas. Additionally, we constructed weighted Kaplan-Meier curves for each exposure group to plot the cumulative incidence of prostate cancer during the follow-up period.

Secondary Analyses

We conducted three secondary analyses. First, we assessed whether the association varied with cumulative duration of use, defined in a time-varying fashion as the sum of the durations associated with each prescription from cohort entry until the risk set date (i.e., time of the event); this was modeled as a continuous variable using restricted cubic spline models that produced a smooth risk function over time (27). Second, we assessed whether there was a drug-specific effect by stratifying on individual incretin-based drug molecules. Finally, we assessed whether age (<75 vs. ≥75 years, the age at which the incidence of prostate cancer is the highest in the UK), BMI (<30 kg/m² vs. ≥ 30.0 kg/m²), and smoking (ever vs. never) were effect modifiers of the association by including an interaction term between these variables and exposure in the outcome model.

Sensitivity Analyses

We performed five sensitivity analyses to assess the robustness of our results. First, we extended the length of the lag period to 18 and 24 months to evaluate different cancer latency periods. Second, we conducted two analyses to assess the impact of possible differential

screening opportunities between the exposure groups (i.e., potential detection bias). In the first analysis, we generated HRs among patients with and without a PSA test in the year before cohort entry. We determined this by including an interaction term between the exposure and PSA testing in the outcome model. In the second analysis, we used inverse-probability of screening weighting with PSA measurements, serving as a proxy for screening, assessed in one-year intervals during the follow-up period (28). This analysis balanced the exposure groups based on the probability of undergoing PSA screenings during the follow-up period. Third, given that some incretin-based drugs, such as GLP-1 receptor agonists, have been associated with a decreased risk of major adverse cardiovascular events (8,29-31), we repeated the analyses using inverse-probability of censoring weighting to account for potential differential mortality and administrative censoring between the exposure groups. Fourth, to assess the impact of treatment discontinuation and switching or crossing over to one of the other study drugs during the follow-up period, we repeated the analyses using an on-treatment exposure definition using a one-year grace period between non-overlapping consecutive prescriptions and censoring patients on treatment discontinuation and switching or crossing over to the other study drugs. Finally, we repeated the analysis by matching incretin-based drug users to sulfonylurea users on propensity score in a 1:1 ratio using nearest-neighbor matching and a caliper of 0.05. We conducted all analyses with SAS, version 9.4 (SAS Institute, Inc., Cary, North Carolina), and R, version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

5.4 Results

GLP-1 receptor agonists vs. Sulfonylureas

The first cohort included 5063 new users of GLP-1 receptor agonists and 112,955 new users of sulfonylureas (we trimmed one GLP-1 receptor agonist user and 2265 sulfonylurea users from the cohort due to non-overlapping propensity score distributions; **eFigure 1**). We followed the GLP-1 receptor agonist users for a median (Q1, Q3) of 3.6 (1.4, 7.0) years and the sulfonylurea users for a median of 5.0 (2.4, 5.0) years. During the follow-up period, 2769 (54.7%) GLP-1 receptor agonist users and 67,667 (59.9%) sulfonylurea users discontinued treatment or crossed over to the other study drug. During 626,680 person–years of follow-up, there were 2191 incident prostate cancer events, yielding a crude incidence rate (95% CI) of 349.6 (335.1, 364.6) per 100,000 person–years. Before propensity score weighting, GLP-1 receptor agonist users were younger, more likely to be obese, had elevated HbA1c levels, had a longer duration of diabetes, and had a higher prevalence of microvascular complications of diabetes compared with sulfonylurea users (**Table 6**). After propensity score weighting, the exposure groups were well balanced across all covariates, except for diabetes duration and HbA1c, with standardized differences equal to 0.10. As a result, these variables were included in the outcome models.

The results of the primary analysis are presented in **Table 7**. The use of GLP-1 receptor agonists was associated with a decreased risk of prostate cancer when compared with the use of sulfonylureas (incidence rates: 156.4 vs. 232.0 events per 100,000 person–years, respectively; HR: 0.65, 95% CI: 0.43, 0.99). The cumulative incidence curves diverged after around 30 months of use (**Figure 5**).

DPP-4 Inhibitors vs. Sulfonylureas

The second cohort included 53,529 new users of DPP-4 inhibitors and 114,417 new users of sulfonylureas (we trimmed two DPP-4 inhibitor users and 803 sulfonylurea users from the cohort due to non-overlapping propensity score distributions; **eFigure 2**). We followed the DPP-4 inhibitor users for a median (Q1, Q3) of 2.9 (1.3, 5.5) years and the sulfonylurea users for a median of 5.0 (2.4, 8.1) years. A total of 24,761 (46.3%) DPP-4 inhibitor users and 67,891 (59.3%) sulfonylurea users discontinued treatment or crossed over to the other study drug during the follow-up period. Overall, this cohort generated 802,922 person–years of follow-up, during which time there were 2819 incident prostate cancer events, yielding a crude incidence rate (95% CI) of 351.1 (338.3, 364.3) per 100,000 person–years. Before propensity score weighting, DPP-4 inhibitor users were more likely to be obese, more likely to have had diabetes for a longer period, more likely to be on certain prescription drugs, and had a higher prevalence of retinopathy compared with sulfonylurea users (**Table 8**). After propensity score weighting, the exposure groups were well balanced across all covariates.

Table 7 presents the results of the primary analysis. Overall, the use of DPP-4 inhibitors was associated with a decreased risk of prostate cancer compared with the use of sulfonylureas (incidence rates: 316.2 vs. 350.5 events per 100,000 person–years, respectively; HR: 0.90, CI: 0.81, 1.00). The cumulative incidence curves diverged after around 20 months of follow-up (**Figure 6**).

Secondary Analyses

In the restricted cubic splines, 2-year cumulative durations of use were associated with a decreased risk of prostate cancer for both GLP-1 receptor agonists and DPP-4 inhibitors

(**eFigures 3** and **4**). When we assessed drug-specific effects, exenatide (HR: 0.54, 95% CI: 0.30, 0.95) and saxagliptin (HR: 0.74, 95% CI: 0.57, 0.98) generated the lowest HRs, although their CIs overlapped with others in the same drug class (**eTables 1** and **2**). Finally, age, BMI, and smoking did not notably modify the associations for both GLP-1 receptor agonists and DPP-4 inhibitors (**eTables 3-5**).

Sensitivity Analyses

The results of the sensitivity analyses are presented in detail in **eTables 6-13**. Overall, the sensitivity analyses generated findings consistent with the primary analysis, although the inverse-probability of censoring weighting analysis led to an attenuation of the point estimates in both cohorts (**eTable 7**). The results of the detection bias analyses are presented in **eTables 8** and **9**. A PSA test in the year before cohort entry did not modify the association between incretin-based drugs and prostate cancer. During the follow-up period, PSA testing rates were higher in sulfonylurea users than in GLP-1 receptor agonist users (10.2%, 95% CI: 10.1, 10.3 per year vs. 9.3%, 95% CI: 8.9, 9.7 per year, respectively). In contrast, PSA testing rates were similar between DPP-4 inhibitor and sulfonylurea users (10.5%, 95% CI: 10.4, 10.7 per year vs. 10.2%, 95% CI: 10.1, 10.3) per year, respectively). Overall, similar HRs were generated in the inverse-probability of PSA screening analysis. The results of the propensity score-matched analysis are presented in **eTables 11-13**. After propensity score matching, there was good balance across all covariates except for calendar year in both cohorts and prior use of SGLT-2 inhibitors in the GLP-1 receptor agonists vs. sulfonylureas cohort. These covariates were additionally adjusted for in the outcome model. Overall, the use of GLP-1 receptor agonists was associated with a

decreased risk of prostate cancer in the propensity score-matched analysis (HR: 0.58, 95% CI: 0.37, 0.92) as was use of DPP-4 inhibitors (HR: 0.88, 95% CI: 0.78, 0.98).

5.5 Discussion

In this large population-based cohort study, the use of GLP-1 receptor agonists and DPP-4 inhibitors, separately, were associated with a decreased risk of prostate cancer, compared with the use of sulfonylureas. The cumulative incidence curves diverged after around 30 months of use for the GLP-1 receptor agonist cohort and after 20 months for the DPP-4 inhibitor cohort. Overall, the results from the sensitivity analyses were consistent with those of the primary analyses.

The GLP-1 receptor has been shown to be related to prostate cancer progression. Indeed, forced expression of this receptor was observed to reduce the proliferation of prostate cancer cells by inhibiting cell cycle progression (2). Furthermore, in *in vitro* and *in vivo* models of prostate cancer, treatment with GLP-1 receptor agonists reduced the progression of the disease by activating GLP-1 receptors, resulting in inhibition of the ERK-MAPK signaling pathway (3). The available clinical evidence, including our study, supports a protective effect of GLP-1 receptor agonists against prostate cancer. In the LEADER trial of liraglutide, the imbalance in prostate cancer events favored liraglutide (26 vs. 47 events, HR: 0.54, 95% CI: 0.34, 0.88) (8,10). This trial, however, was not designed or powered to ascertain prostate cancer incidence (relatively small sample size of 6003 male patients with a short median duration of follow-up of 3.8 years). Our study, specifically designed to assess prostate cancer incidence, also estimated a protective, albeit smaller, effect of GLP-1 receptor agonists.

The current literature on the relationship between DPP-4 inhibitors and prostate cancer remains uncertain and mixed. The biological evidence shows a complex relationship between the DPP-4 enzyme and the progression of prostate cancer. DPP-4 expression was found to be increased in prostate cancer tissues when compared to non-neoplastic tissues, suggesting DPP-4

to be a potential target for prostate cancer treatment (4). Indeed, in an *in vitro* study, blockage of DPP-4 resulted in reduced invasiveness of prostate cancer cells (5). Other studies, however, suggest that inhibiting DPP-4 promotes progression to more severe forms of prostate cancer (6,7). It is important to note that in contrast to the aforementioned biological studies, our study focused on the effect of incretin-based drugs on cancer development, which might differ from their effects on the proliferation of existing tumors. The clinical evidence is similarly mixed. In the SAVOR-TIMI 53 trial, there was no notable imbalance in events between the saxagliptin and placebo groups (43 vs. 41 events, HR: 1.04, 95% CI: 0.68, 1.60) (9,11). However, this RCT was limited by its relatively small sample size (11,037 male patients) and short median duration of follow-up (2.1 years). The only observational study on the topic, to our knowledge, found that ever use of sitagliptin was associated with a strong decreased risk of prostate cancer incidence compared with never use (HR: 0.63, 95% CI: 0.49, 0.76) (12). However, this protective effect may have been inflated by immortal time bias (13), which was introduced by the method of classifying the exposure during the follow-up period. The authors used a hierarchical exposure definition in which ever-users of sitagliptin were identified first and the remainder of the eligible participants were classified as never-users. Selecting ever- vs. never-users in this manner conferred the ever-users a survival advantage; ever-users needed to survive long enough without the event in order to become a user, while never-users could experience the event soon after treatment initiation. We avoided immortal time bias by not using a hierarchical exposure definition and assigned exposure based on which drug the patient was exposed to first, either an incretin-based drug or sulfonylurea during the study period. Our study addressed the limitations of the previous clinical studies and found a protective, albeit smaller association with DPP-4 inhibitors.

This study has several strengths. First, the cohorts were constructed using the CPRD, a database shown to be representative of the UK population (14) and with high-quality data (18-21). Second, the assembled cohorts were restricted to new users, eliminating prevalent user bias (32). Third, confounding by indication was reduced by using sulfonylureas as the active comparator, a drug class used at a similar disease stage as incretin-based drugs (22). Furthermore, sulfonylureas have neutral effects on prostate cancer incidence. Lastly, our results were consistent across different sensitivity analyses that addressed different sources of bias. Although the inverse-probability of censoring weighting analysis attenuated the point estimates for both cohorts, it is noteworthy that the CIs generated by this sensitivity analysis are wider and overlap with those from the primary analysis.

Our study has some limitations. First, as with all observational studies, residual confounding by unknown or unmeasured variables, such as family history of prostate cancer and race/ethnicity, is possible. However, it is unlikely that these missing variables were differentially distributed between the exposure groups. Moreover, the propensity score fine stratification model included over 50 covariates, with several likely to be associated with these missing variables, thereby reducing this potential bias (26). Time-dependent confounding is also a possibility given that covariates were measured at baseline and follow-up extended up to 13 years for some patients. Second, exposure misclassification is possible as the prescriptions recorded in the CPRD are written by general practitioners and not those dispensed or taken as intended. Any exposure misclassification, however, is expected to be non-differential between the different exposure groups. Furthermore, while the CPRD records prescriptions written by general practitioners and not specialists, general practitioners are primarily responsible for the long-term care of patients with type 2 diabetes and renewing medications in the UK (33,34).

Finally, while prostate cancer is well-recorded in the CPRD (18,35), it was not possible to stratify the analyses on tumor grade or stage as this information is not available in the database. Future studies should investigate whether incretin-based drugs have impact on these important disease parameters.

In summary, the results of this study are consistent with the hypothesis that use of GLP-1 receptor agonists and DPP-4 inhibitors, separately, is associated with a decreased risk of prostate cancer when compared with the use of sulfonylureas. As prostate cancer is one of the most common cancers among males worldwide (36,37), additional studies are needed to corroborate our findings. These may have important clinical implications for guiding the treatment of those at increased risk for prostate cancer.

5.6 References

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5.7 Figures and Tables

FIGURE LEGENDS

Figure 5: Weighted cumulative incidence curves of prostate cancer for GLP-1 RAs vs. sulfonylureas

Footnote: GLP-1 RA, glucagon-like peptide 1 receptor agonist; Log-rank p-value=0.19

Figure 6: Weighted cumulative incidence curves of prostate cancer for DPP-4 inhibitors vs. sulfonylureas

Footnote: DPP-4, dipeptidyl peptidase-4; Log-rank p-value=0.048

Figure 5. Weighted cumulative incidence curves of prostate cancer for GLP-1 RAs vs. sulfonylureas

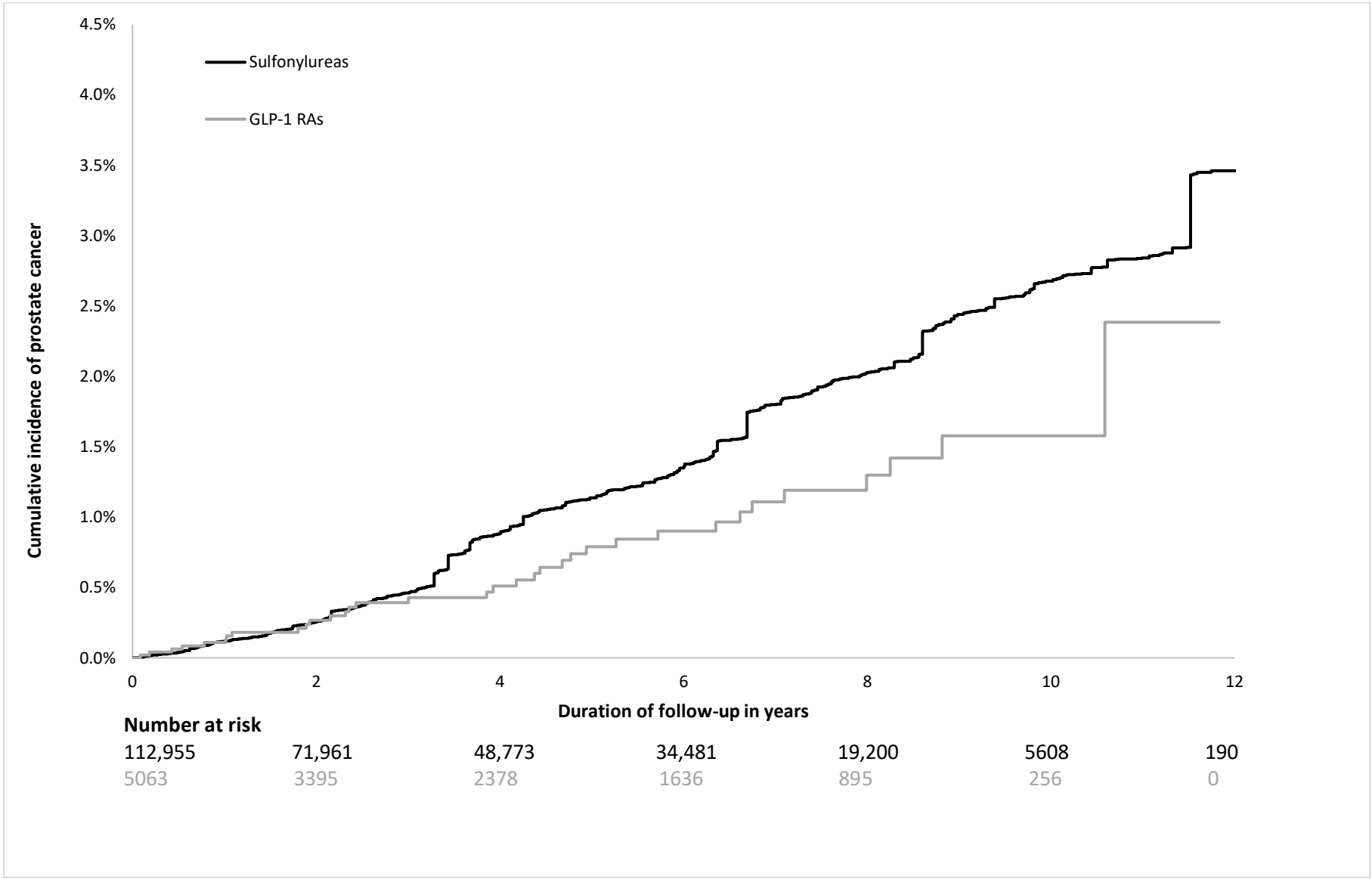


Figure 6. Weighted cumulative incidence curves of prostate cancer for DPP-4 inhibitors vs. sulfonylureas

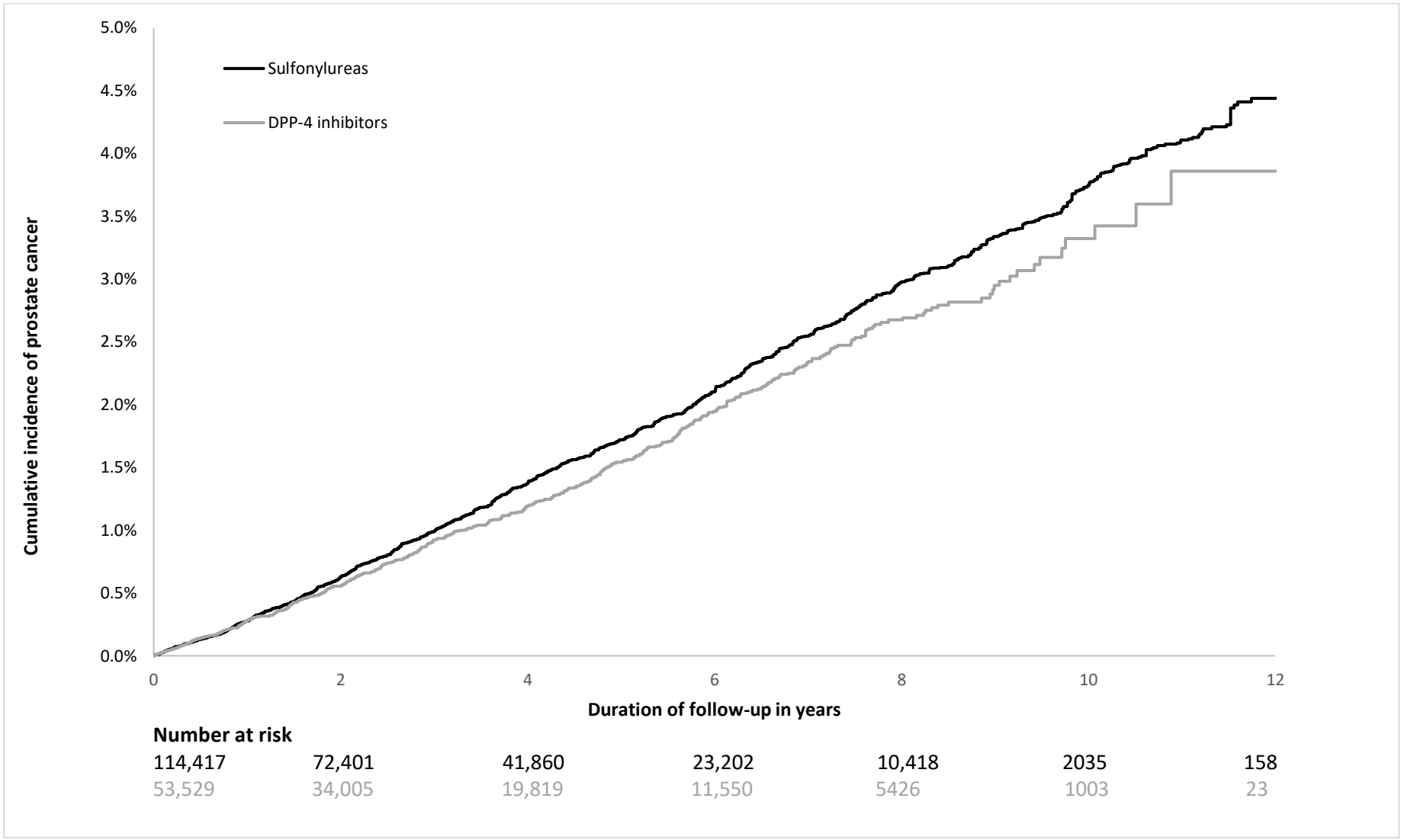


Table 6. Baseline Characteristics of the GLP-1 RA and Sulfonylurea Exposure Groups Before and After Propensity Score Weighting

Characteristics	Before Weighting			After Weighting		
	GLP-1 RA	Sulfonylureas	ASD	GLP-1 RA	Sulfonylureas	ASD
Total	5063	112,955		5063	112,955	
Age, years, mean (SD)	56.5 (9.0)	61.4 (11.2)	0.47	56.5 (9.0)	56.2 (9.0)	0.03
Alcohol-related disorders, n (%)	393 (7.8)	9,581 (8.5)	0.03	393 (7.8)	9,409 (8.3)	0.02
Body mass index, n (%)						
<30 kg/m²	314 (6.2)	54,039 (48)	1.06	314 (6.2)	7,550 (6.7)	0.02
≥30 kg/m²	4,620 (91)	56,948 (50)	1.01	4,620 (91)	101,172 (90)	0.06
Unknown	129 (2.5)	1,968 (1.7)	0.06	129 (2.5)	4,233 (3.7)	0.07
Smoking status, n (%)						
Ever	4,146 (82)	94,282 (84)	0.04	4,146 (82)	93,322 (83)	0.02
Never	S[a]	18,547 (16)	0.04	S[a]	19,592 (17)	0.02
Unknown	S[a]	126 (0.1)	0.03	S[a]	41 (0.0)	0.00
Hemoglobin A1c, n (%)						
≤7.0%	652 (13)	9,780 (8.7)	0.14	652 (13)	18,583 (17)	0.10
7.1%-8.0%	1,025 (20)	27,853 (25)	0.11	1,025 (20)	22,008 (20)	0.02
>8.0%	3,293 (65)	68,336 (61)	0.09	3,293 (65)	69,741 (62)	0.07
Unknown	93 (1.8)	6,986 (6.2)	0.22	93 (1.8)	2,623 (2.3)	0.03
Duration of diabetes, years, mean (SD)	8.0 (6.6)	4.5 (4.3)	0.62	8.0 (6.6)	7.3 (6.5)	0.10
Type of antidiabetic drugs, n (%)						
Metformin	4,602 (91)	96,329 (85)	0.17	4,602 (91)	103,543 (92)	0.03
Thiazolidinediones	832 (16)	8,494 (7.5)	0.28	832 (16)	20,721 (18)	0.05
Meglitinides	71 (1.4)	411 (0.4)	0.11	71 (1.4)	2,145 (1.9)	0.04
Alpha-glucosidase inhibitors	24 (0.5)	129 (0.1)	0.07	24 (0.5)	704 (0.6)	0.02
SGLT-2 inhibitors	528 (10)	727 (0.6)	0.44	528 (10)	12,509 (11)	0.02
Insulin	1,947 (39)	2,107 (1.9)	1.02	1,947 (39)	41,783 (37)	0.03
Peripheral vascular disease, n (%)	547 (11)	7,802 (6.9)	0.14	547 (11)	11,818 (11)	0.01
Stroke, n (%)	185 (3.7)	5,614 (5.0)	0.06	185 (3.7)	4,021 (3.6)	0.01
Myocardial infarction, n (%)	549 (11)	10,961 (9.7)	0.04	549 (11)	11,811 (11)	0.01
Renal disease, n (%)	588 (12)	14,338 (13)	0.03	588 (12)	12,195 (11)	0.03
Retinopathy, n (%)	1,755 (35)	22,250 (20)	0.34	1,755 (35)	34,470 (31)	0.09
Neuropathy, n (%)	1,245 (25)	18,975 (17)	0.19	1,245 (25)	23,896 (21)	0.08
Cancer, n (%)	184 (3.6)	5,914 (5.2)	0.08	184 (3.6)	4,163 (3.7)	0.00
Lower urinary tract symptoms, n (%)	186 (3.7)	5,224 (4.6)	0.05	186 (3.7)	4,220 (3.7)	0.00
Non-steroidal anti-inflammatory drugs, n (%)	3,577 (71)	76,172 (67)	0.07	3,577 (71)	79,468 (70)	0.01

Aspirin, n (%)	2,580 (51)	53,679 (48)	0.07	2,580 (51)	55,746 (49)	0.03
Statins, n (%)	4,406 (87)	89,107 (79)	0.22	4,406 (87)	96,744 (86)	0.04
5-α reductase inhibitors, n (%)	122 (2.4)	4,420 (3.9)	0.09	122 (2.4)	2,832 (2.5)	0.01
Calcium channel blockers, n (%)	2,347 (46)	41,929 (37)	0.19	2,347 (46)	50,686 (45)	0.03
Testosterone replacement therapy, n (%)	176 (3.5)	1,239 (1.1)	0.16	176 (3.5)	3,241 (2.9)	0.03
Prostate-specific antigen testing, n (%)	468 (9.2)	13,594 (12)	0.09	468 (9.2)	9,782 (8.7)	0.02
Year of cohort entry, n (%)						
2007	34 (0.7)	9,454 (8.4)	0.38	34 (0.7)	900 (0.8)	0.01
2008	235 (4.6)	12,084 (11)	0.23	235 (4.6)	5,307 (4.7)	0.00
2009	447 (8.8)	13,073 (12)	0.09	447 (8.8)	9,633 (8.5)	0.01
2010	579 (11)	12,457 (11)	0.01	579 (11)	12,930 (11)	0.00
2011	446 (8.8)	10,919 (9.7)	0.03	446 (8.8)	9,700 (8.6)	0.01
2012	516 (10)	10,280 (9.1)	0.04	516 (10)	10,570 (9.4)	0.03
2013	363 (7.2)	9,395 (8.3)	0.04	363 (7.2)	6,866 (6.1)	0.04
2014	277 (5.5)	8,049 (7.1)	0.07	277 (5.5)	5,911 (5.2)	0.01
2015	346 (6.8)	7,860 (7.0)	0.00	346 (6.8)	7,731 (6.8)	0.00
2016	385 (7.6)	6,369 (5.6)	0.08	385 (7.6)	8,622 (7.6)	0.00
2017	427 (8.4)	5,525 (4.9)	0.14	427 (8.4)	9,763 (8.6)	0.01
2018	559 (11)	4,749 (4.2)	0.26	559 (11)	12,946 (12)	0.01
2019	449 (8.9)	2,741 (2.4)	0.28	449 (8.9)	12,075 (11)	0.06

Abbreviations: ASD, absolute standardized difference; DPP-4, dipeptidyl peptidase 4; GLP-1 RA, glucagon-like peptide 1 receptor agonist; SD, standard deviation; SGLT-2, sodium-glucose cotransporter-2.

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

Table 7. Hazard Ratios for Prostate Cancer Comparing GLP-1 RAs and DPP-4 Inhibitors with Sulfonylureas

Exposure	No. of patients	Events	Person-years	Weighted incidence rate (95% CI) [a]	Crude HR	Weighted HR (95% CI) [b]
GLP-1 RAs vs. Sulfonylureas						
Sulfonylureas	112,955	2157	604,934	232.0 (218.3-246.3)	1.00	1.00 [Reference]
GLP-1 RAs	5063	34	21,746	156.4 (108.3-218.5)	0.44	0.65 (0.43, 0.99)
DPP-4 Inhibitors vs. Sulfonylureas						
Sulfonylureas	114,417	2208	609,680	350.5 (332.5-369.2)	1.00	1.00 [Reference]
DPP-4 inhibitors	53,529	611	193,242	316.2 (291.6-342.3)	0.90	0.90 (0.81, 1.00)

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

[a] Per 100,000 person-years.

[b] The models were weighted using propensity score fine stratification. The model was additionally adjusted for duration of diabetes and HbA1c for the GLP-1 RA vs. sulfonylurea comparison.

Table 8. Baseline Characteristics of the DPP-4 Inhibitor and Sulfonylurea Exposure Groups Before and After Propensity Score Weighting

Characteristics	Before Weighting			After Weighting		
	DPP-4 Inhibitors	Sulfonylureas	ASD	DPP-4 Inhibitors	Sulfonylureas	ASD
Total	53,529	114,417		53,529	114,417	
Age, years, mean (SD)	62.0 (11.2)	61.7 (11.5)	0.02	62.0 (11.2)	61.7 (11.2)	0.03
Alcohol-related disorders, n (%)	4,640 (8.7)	9,589 (8.4)	0.01	4,640 (8.7)	9,995 (8.7)	0.00
Body mass index, n (%)						
<30 kg/m²	20,703 (39)	55,703 (49)	0.20	20,703 (39)	43,240 (38)	0.02
≥30 kg/m²	32,325 (60)	56,840 (50)	0.22	32,325 (60)	70,051 (61)	0.02
Unknown	501 (0.9)	1,874 (1.6)	0.06	501 (0.9)	1,127 (1.0)	0.00
Smoking status, n (%)						
Ever	44,083 (82)	95,546 (84)	0.03	44,083 (82)	93,985 (82)	0.01
Never	9,426 (18)	18,747 (16)	0.03	9,426 (18)	20,383 (18)	0.01
Unknown	20 (0.0)	124 (0.1)	0.03	20 (0.0)	49 (0.0)	0.00
Hemoglobin A1c, n (%)						
≤7.0%	4,676 (8.7)	9,979 (8.7)	0.00	4,676 (8.7)	10,118 (8.8)	0.00
7.1%-8.0%	18,117 (34)	28,488 (25)	0.20	18,117 (34)	36,977 (32)	0.03
>8.0%	30,254 (57)	69,207 (61)	0.08	30,254 (57)	66,254 (58)	0.03
Unknown	482 (0.9)	6,743 (5.9)	0.28	482 (0.9)	1,067 (0.9)	0.00
Duration of diabetes, years, mean (SD)	6.2 (4.9)	4.5 (4.4)	0.36	6.2 (4.9)	6.1 (5.0)	0.01
Type of antidiabetic drugs, n (%)						
Metformin	50,138 (94)	97,311 (85)	0.28	50,138 (94)	107,707 (94)	0.02
Thiazolidinediones	4,640 (8.7)	8,524 (7.4)	0.04	4,640 (8.7)	10,423 (9.1)	0.02
Meglitinides	351 (0.7)	412 (0.4)	0.04	351 (0.7)	834 (0.7)	0.01
Alpha-glucosidase inhibitors	55 (0.1)	129 (0.1)	0.00	55 (0.1)	120 (0.1)	0.00
SGLT-2 inhibitors	1,646 (3.1)	727 (0.6)	0.18	1,646 (3.1)	3,388 (3.0)	0.01
Insulin	2,013 (3.8)	2,106 (1.8)	0.12	2,013 (3.8)	4,314 (3.8)	0.00
Peripheral vascular disease, n (%)	4,093 (7.6)	7,957 (7.0)	0.03	4,093 (7.6)	8,499 (7.4)	0.01
Stroke, n (%)	2,697 (5.0)	5,904 (5.2)	0.01	2,697 (5.0)	5,764 (5.0)	0.00
Myocardial infarction, n (%)	5,051 (9.4)	11,280 (9.9)	0.01	5,051 (9.4)	10,851 (9.5)	0.00
Renal disease, n (%)	7,284 (14)	15,035 (13)	0.01	7,284 (14)	15,102 (13)	0.01
Retinopathy, n (%)	14,038 (26)	22,537 (20)	0.16	14,038 (26)	29,560 (26)	0.01
Neuropathy, n (%)	10,222 (19)	19,294 (17)	0.06	10,222 (19)	21,696 (19)	0.00
Cancer, n (%)	2,942 (5.5)	6,079 (5.3)	0.01	2,942 (5.5)	6,179 (5.4)	0.00
Lower urinary tract symptoms, n (%)	2,633 (4.9)	5,407 (4.7)	0.01	2,633 (4.9)	5,505 (4.8)	0.00
Non-steroidal anti-inflammatory drugs, n (%)	38,108 (71)	77,107 (67)	0.08	38,108 (71)	81,416 (71)	0.00

Aspirin, n (%)	24,179 (45)	54,834 (48)	0.06	24,179 (45)	51,727 (45)	0.00
Statins, n (%)	46,149 (86)	90,253 (79)	0.19	46,149 (86)	98,628 (86)	0.00
5-α reductase inhibitors, n (%)	2,487 (4.6)	4,617 (4.0)	0.03	2,487 (4.6)	5,202 (4.5)	0.00
Calcium channel blockers, n (%)	22,196 (42)	42,628 (37)	0.09	22,196 (42)	47,224 (41)	0.00
Testosterone replacement therapy, n (%)	881 (1.6)	1,237 (1.1)	0.05	881 (1.6)	1,919 (1.7)	0.00
Prostate-specific antigen testing, n (%)	6,835 (13)	13,859 (12)	0.02	6,835 (13)	14,564 (13)	0.00
Year of cohort entry, n (%)						
2007	185 (0.3)	10,062 (8.8)	0.41	185 (0.3)	781 (0.7)	0.05
2008	752 (1.4)	12,377 (11)	0.40	752 (1.4)	1,431 (1.3)	0.01
2009	1,863 (3.5)	13,193 (12)	0.31	1,863 (3.5)	3,708 (3.2)	0.01
2010	3,921 (7.3)	12,563 (11)	0.13	3,921 (7.3)	8,393 (7.3)	0.00
2011	3,627 (6.8)	11,001 (9.6)	0.10	3,627 (6.8)	7,825 (6.8)	0.00
2012	3,967 (7.4)	10,323 (9.0)	0.06	3,967 (7.4)	8,711 (7.6)	0.01
2013	4,115 (7.7)	9,457 (8.3)	0.02	4,115 (7.7)	8,985 (7.9)	0.01
2014	4,261 (8.0)	8,114 (7.1)	0.03	4,261 (8.0)	9,312 (8.1)	0.01
2015	5,462 (10)	7,893 (6.9)	0.12	5,462 (10)	11,938 (10)	0.01
2016	6,578 (12)	6,394 (5.6)	0.24	6,578 (12)	14,114 (12)	0.00
2017	6,957 (13)	5,536 (4.8)	0.29	6,957 (13)	14,814 (13)	0.00
2018	7,477 (14)	4,761 (4.2)	0.35	7,477 (14)	15,437 (14)	0.01
2019	4,364 (8.2)	2,743 (2.4)	0.26	4,364 (8.2)	8,967 (7.8)	0.01

Abbreviations: ASD, absolute standardized difference; DPP-4, dipeptidyl peptidase 4; GLP-1 RA, glucagon-like peptide 1 receptor agonist; SD, standard deviation; SGLT-2, sodium-glucose cotransporter-2

5.8 Supplementary Online Content

eFigure 1: Study flow chart illustrating the process for assembling the study cohort of men initiating sulfonylureas or GLP-1 RAs in the United Kingdom Clinical Practice Research Datalink between 2007 and 2020. GLP-1 RA, glucagon-like peptide 1 receptor agonist.

eFigure 2: Study flow chart illustrating the process for assembling the study cohort of men initiating sulfonylureas or DPP-4 inhibitors in the United Kingdom Clinical Practice Research Datalink between 2007 and 2020. DPP, dipeptidyl peptidase.

eFigure 3: Smooth restricted cubic spline curve of adjusted hazard ratio of prostate cancer as a function of cumulative duration of GLP-1 RAs use in years, United Kingdom, 2007-2020. GLP-1 RA, glucagon-like peptide 1 receptor agonist.

eFigure 4: Smooth restricted cubic spline curve of adjusted hazard ratio of prostate cancer as a function of cumulative duration of DPP-4 inhibitors use in years, United Kingdom, 2007-2020. DPP, dipeptidyl peptidase.

eTable 1. Hazard Ratios for Prostate Cancer Comparing GLP-1 RA Molecules with Sulfonylurea

eTable 2. Hazard Ratios for Prostate Cancer Comparing DPP-4 Inhibitors Molecules with Sulfonylurea

eTable 3. Hazard Ratios for Prostate Cancer Comparing Incretins with Sulfonylurea (Interaction with Age)

eTable 4. Hazard Ratios for Prostate Cancer Comparing Incretins with Sulfonylurea (Interaction with body mass index)

eTable 5. Hazard Ratios for Prostate Cancer Comparing Incretins with Sulfonylurea (Interaction with smoking)

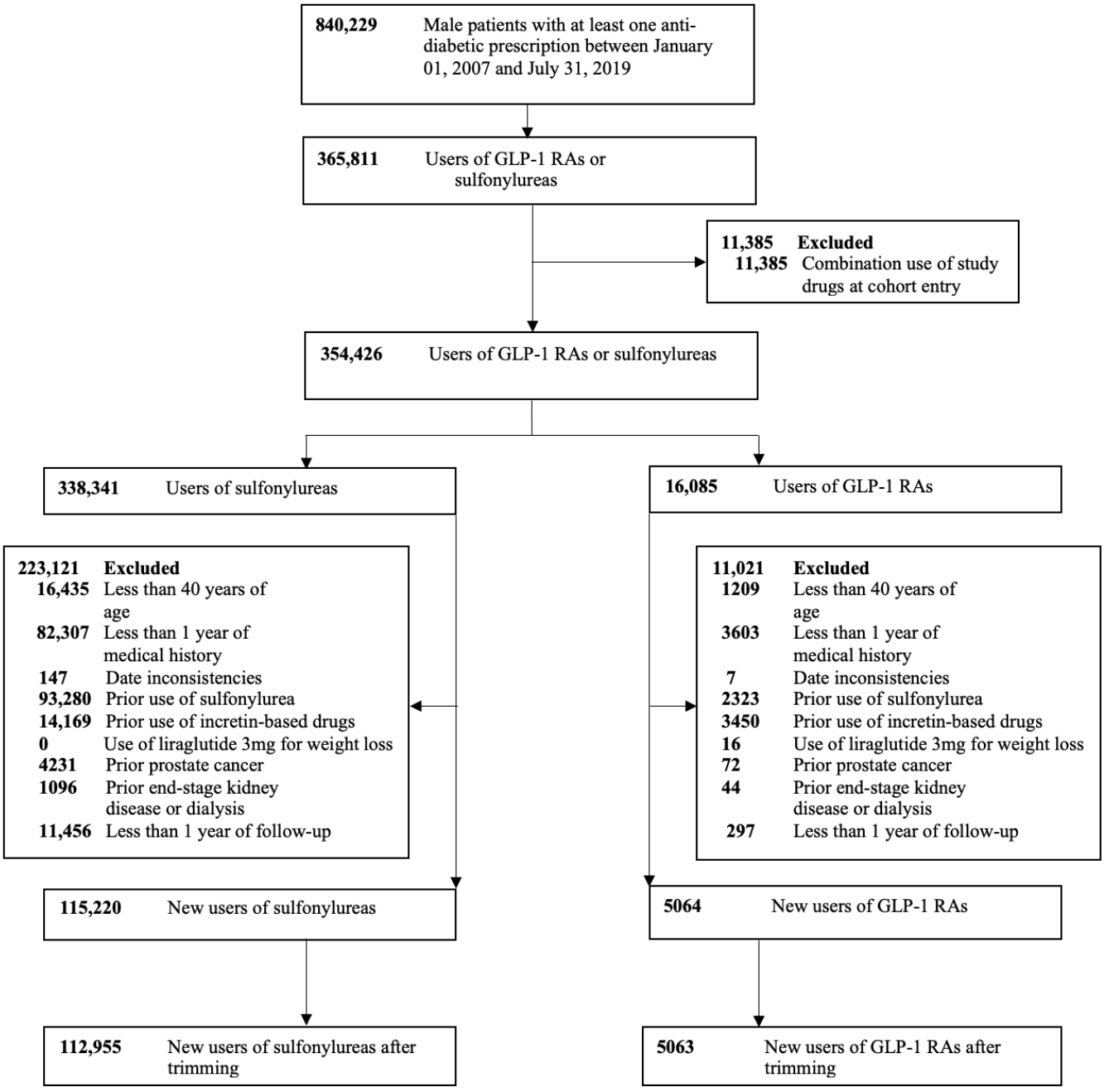
eTable 6. Hazard Ratios for Prostate Cancer Comparing Incretins with Sulfonylurea (Varying lag period)

eTable 7. Hazard Ratios for Prostate Cancer Comparing Incretins with Sulfonylurea (Inverse probability of censoring weighting)

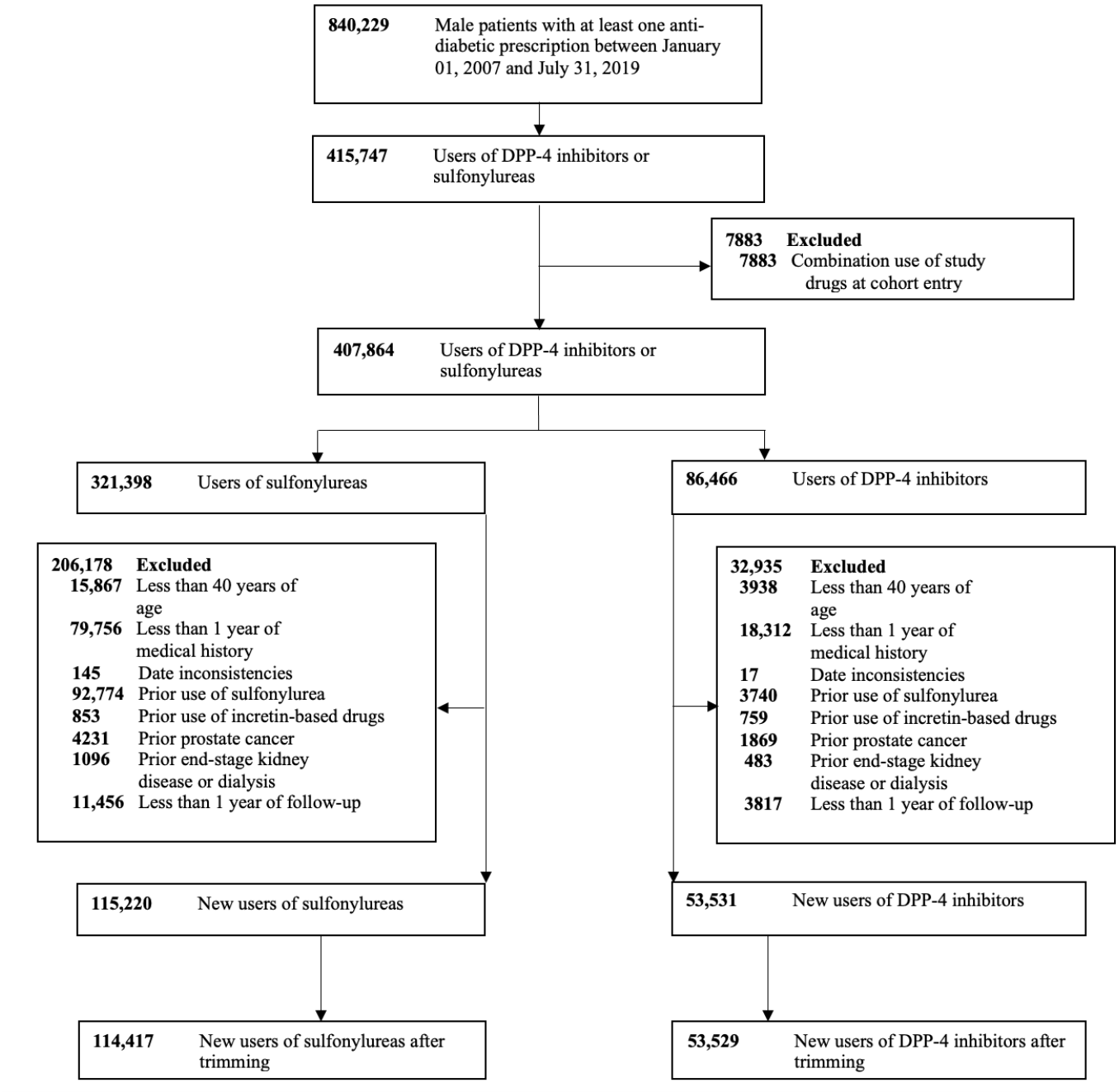
eTable 8. Hazard Ratios for Prostate Cancer Comparing Incretins with Sulfonylurea (Interaction with PSA in the year before cohort entry)

eTable 9. Hazard Ratios for Prostate Cancer Comparing Incretins with Sulfonylurea (Inverse probability of screening weighting)

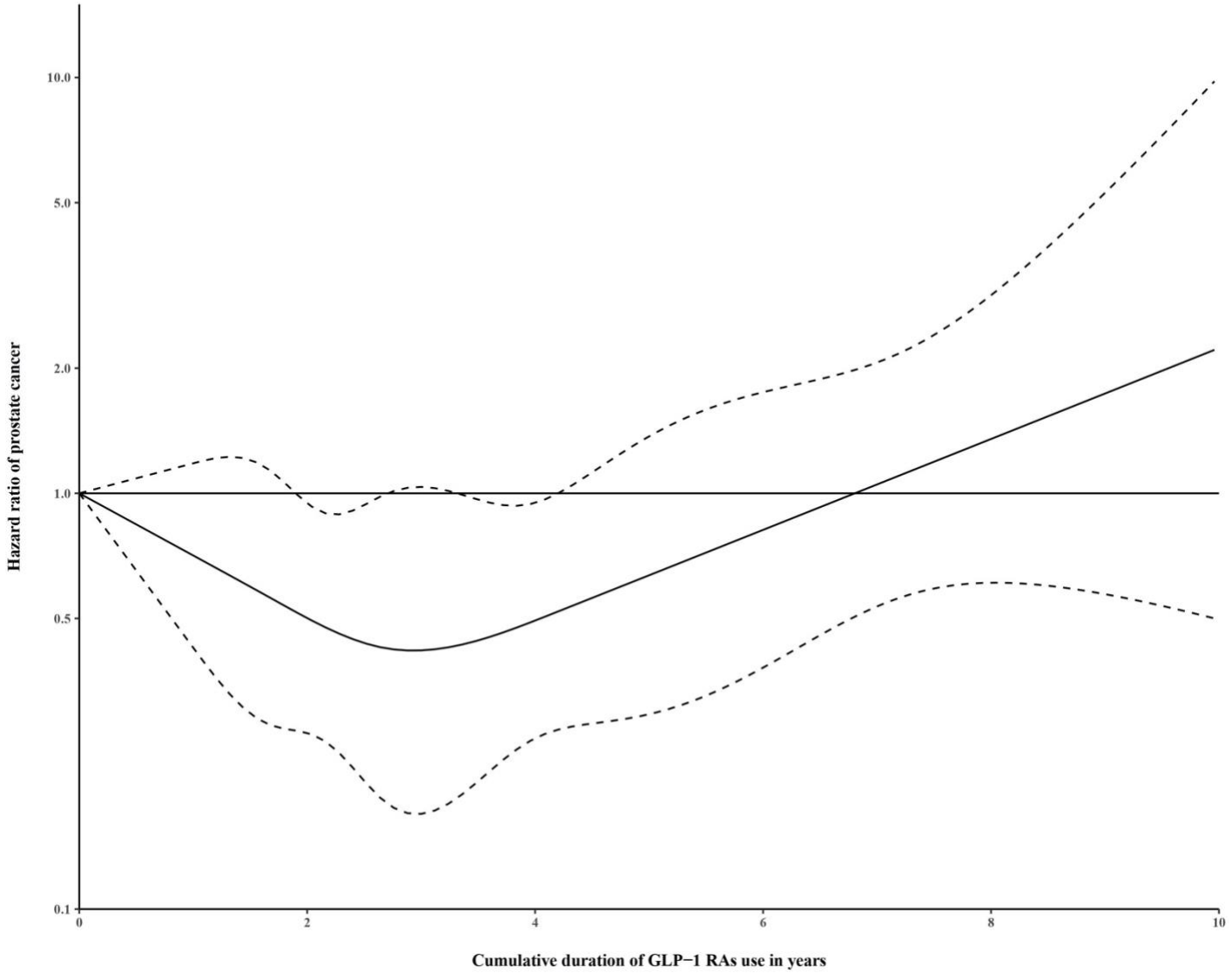
eFigure 1. Study flow chart illustrating the process for assembling the study cohort of men initiating sulfonylureas or GLP-1 RAs in the United Kingdom Clinical Practice Research Datalink between 2007 and 2020. GLP-1 RA, glucagon-like peptide 1 receptor agonist.



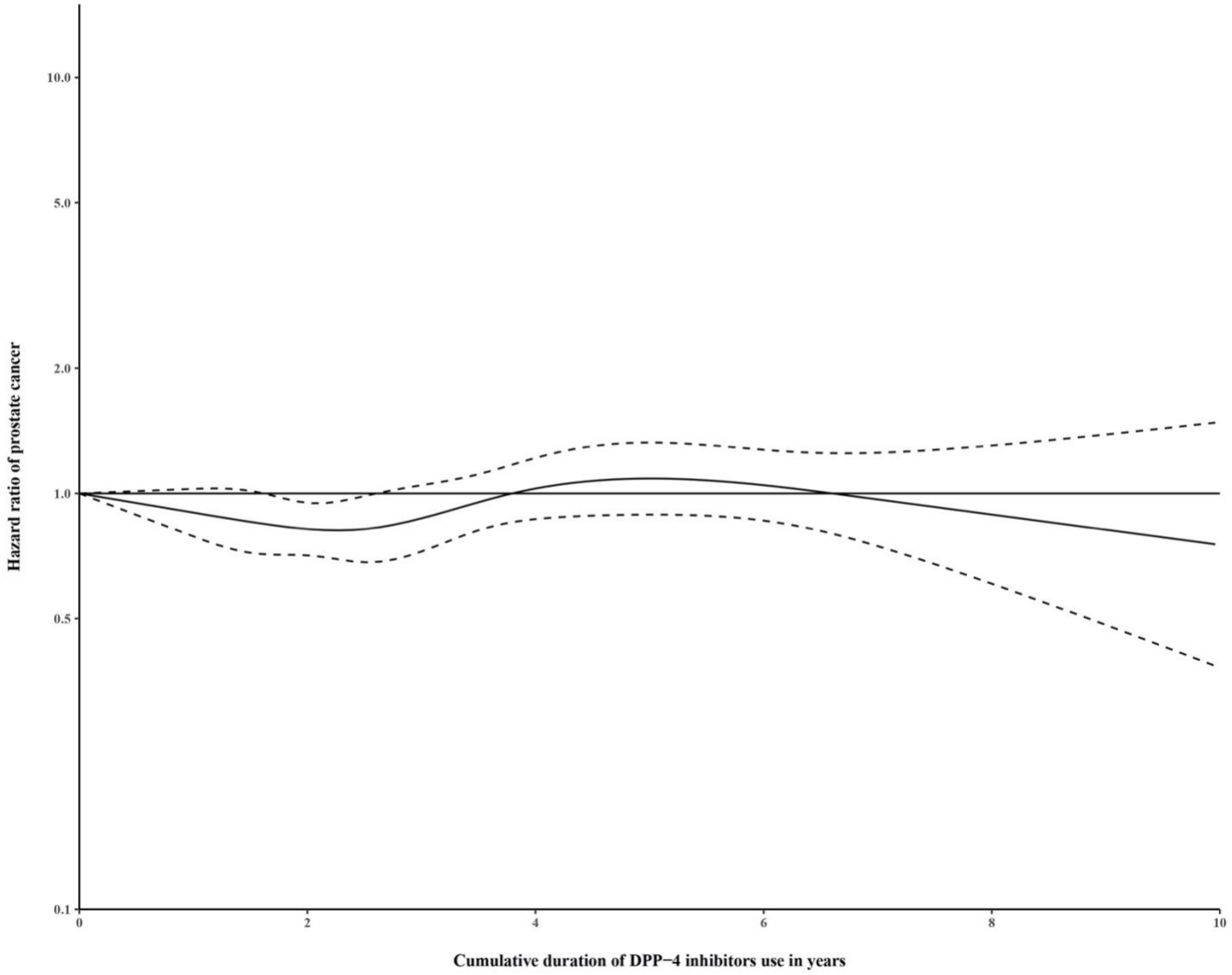
eFigure 2. Study flow chart illustrating the process for assembling the study cohort of men initiating sulfonylureas or DPP-4 inhibitors in the United Kingdom Clinical Practice Research Datalink between 2007 and 2020. DPP, dipeptidyl peptidase.



eFigure 3. Smooth restricted cubic spline curve of adjusted hazard ratio of prostate cancer as a function of cumulative duration of GLP-1 RAs use in years, United Kingdom, 2007-2020. GLP-1 RA, glucagon-like peptide 1 receptor agonist.



eFigure 4. Smooth restricted cubic spline curve of adjusted hazard ratio of prostate cancer as a function of cumulative duration of DPP-4 inhibitors use in years, United Kingdom, 2007-2020. DPP, dipeptidyl peptidase.



eTable 1. Hazard Ratios for Prostate Cancer Comparing GLP-1 RA Molecules with Sulfonylurea

Exposure	No. of patients	Events	Person-years	Weighted incidence rate (95% CI) *	Crude HR	Weighted HR (95% CI) †
GLP-1 RA molecule [c]						
Sulfonylureas	18,689	74	35,667	101.8 (65.5, 151.0)	1.00	1.00 [Reference]
Dulaglutide	835	S*	S*	94.5 (2.4, 526.0)	0.45	0.95 (0.13, 7.11)
Sulfonylureas	113,611	2201	610,174	251.7 (239.8, 264.1)	1.00	1.00 [Reference]
Exenatide	1637	14	10,148	138.0 (75.4, 231.5)	0.38	0.54 (0.30, 0.95)
Sulfonylureas	82,481	1280	390,732	235.5 (219.6, 252.3)	1.00	1.00 [Reference]
Liraglutide	2253	18	9681	185.9 (110.2, 293.8)	0.57	0.77 (0.45, 1.32)
Sulfonylureas	31,647	276	104,023	206.9 (180.2, 236.6)	1.00	1.00 [Reference]
Lixisenatide	244	S*	S*	118.8 (3.01, 661.9)	0.45	0.58 (0.07, 4.55)
Sulfonylureas	2141	0	649			
Semaglutide	84	0	13			

Abbreviations: HR, hazard ratio; CI, confidence interval; GLP-1 RAs, glucagon-like peptide 1 receptor agonists

***** Per 100,000 person-years.

* Suppressed: Numbers fewer than five are not displayed, as per confidentiality policies of the Clinical Practice Research Datalink.

† The models were weighted using propensity score fine stratification. Separate PS analyses were conducted for each comparison. The model was additionally adjusted for duration of diabetes and HbA1c. There were no albiglutide users in the cohort.

eTable 2. Hazard Ratios for Prostate Cancer Comparing DPP-4 Inhibitors Molecules with Sulfonylurea

Exposure	No. of patients	Events	Person-years	Weighted Incidence rate (95% CI) *	Crude HR	Weighted HR (95% CI) †
DPP-4 inhibitor molecule [c]						
Sulfonylureas	34,205	285	90,813	294.7 (251.8, 342.8)	1.00	1.00 [Reference]
Alogliptin	7569	45	12,531	359.1 (261.9, 480.5)	1.18	1.22 (0.85, 1.75)
Sulfonylureas	65,074	879	255,305	398.3 (367.6, 431.0)	1.00	1.00 [Reference]
Linagliptin	10,362	85	24,880	341.6 (272.9, 422.4)	1.01	0.86 (0.67, 1.09)
Sulfonylureas	88,375	1475	413,884	360.4 (341.5, 380.1)	1.00	1.00 [Reference]
Saxagliptin	4630	54	20,109	268.5 (201.7, 350.4)	0.76	0.74 (0.57, 0.98)
Sulfonylureas	114,554	2210	610,836	339.0 (322.7, 356.0)	1.00	1.00 [Reference]
Sitagliptin	29,168	385	123,933	310.7 (280.4, 343.3)	0.88	0.91 (0.81, 1.03)
Sulfonylureas	110,778	2097	583,321	371.8 (357.5, 386.5)	1.00	1.00 [Reference]
Vildagliptin	1771	41	11,728	349.6 (250.9, 474.3)	0.96	0.94 (0.69, 1.29)

Abbreviations: HR, hazard ratio; CI, confidence interval; DPP, dipeptidyl peptidase.

***** Per 100,000 person-years.

† The models were weighted using propensity score fine stratification. Separate PS analyses were conducted for each comparison.

eTable 3. Hazard Ratios for Prostate Cancer Comparing Incretins with Sulfonylurea (Interaction with Age)

Exposure	< 75 years of age	≥ 75 years of age
GLP-1 RAs vs. sulfonylureas		
Sulfonylureas	1.00 [Reference]	1.00 [Reference]
GLP-1 RAs	0.69 (0.45, 1.04)	-
DPP-4 inhibitors vs. sulfonylureas		
Sulfonylureas	1.00 [Reference]	1.00 [Reference]
DPP-4 inhibitors	0.89 (0.79, 1.00)	0.99 (0.80, 1.24)

Abbreviations: DPP, dipeptidyl peptidase; GLP-1 RAs, glucagon-like peptide-1 receptor agonists

The models were weighted using propensity score fine stratification. The model was additionally adjusted for duration of diabetes and HbA1c for the GLP-1 RAs and sulfonylurea comparison.

The HR for GLP-1 RA users for the ≥75 years of age stratum was not estimable as this exposure group did not generate enough events.

The coefficient and CI for the cross-product term of the interaction between exposure and age ≥ 75 is 0.11 (-0.14-0.36) for the DPP-4 inhibitors vs. sulfonylureas comparison.

eTable 4. Hazard Ratios for Prostate Cancer Comparing Incretins with Sulfonylurea (Interaction with body mass index)

Exposure	BMI < 30 kg/m²	BMI ≥ 30.0 kg/m²
GLP-1 RAs vs. sulfonylureas		
Sulfonylureas	1.00 [Reference]	1.00 [Reference]
GLP-1 RAs	0.66 (0.16, 2.69)	0.66 (0.43, 1.01)
DPP-4 inhibitors vs. sulfonylureas		
Sulfonylureas	1.00 [Reference]	1.00 [Reference]
DPP-4 inhibitors	0.96 (0.83, 1.12)	0.86 (0.75, 0.99)

Abbreviations: DPP, dipeptidyl peptidase; GLP-1 RAs, glucagon-like peptide-1 receptor agonists

The models were weighted using propensity score fine stratification. The model was additionally adjusted for duration of diabetes and HbA1c for the GLP-1 RAs and sulfonylurea comparison.

The unknown BMI stratum was considered in the model, but not presented in the table. The HR for GLP-1 RA users for the unknown BMI stratum was not estimable as this exposure group did not generate enough events.

The coefficient and CI for the cross-product term of the interaction between exposure and BMI < 30 kg/m² and exposure and BMI ≥ 30.0 kg/m² is 0.53 (-1.50, 2.57) and 0.43 (-1.60, 2.46), respectively for the DPP-4 inhibitors vs. sulfonylureas comparison.

eTable 5. Hazard Ratios for Prostate Cancer Comparing Incretins with Sulfonylurea (Interaction with smoking)

Exposure	Never smoker	Ever smoker
GLP-1 RAs vs. sulfonylureas		
Sulfonylureas	1.00 [Reference]	1.00 [Reference]
GLP-1 RAs	0.85 (0.33, 2.16)	0.63 (0.40, 0.99)
DPP-4 inhibitors vs. sulfonylureas		
Sulfonylureas	1.00 [Reference]	1.00 [Reference]
DPP-4 inhibitors	0.86 (0.65, 1.13)	0.91 (0.81, 1.01)

Abbreviations: DPP, dipeptidyl peptidase; GLP-1 RAs, glucagon-like peptide-1 receptor agonists

The models were weighted using propensity score fine stratification. The model was additionally adjusted for duration of diabetes and HbA1c for the GLP-1 RAs vs. sulfonylurea comparison.

The unknown smoking stratum was considered in the model, but not presented in the table.

The coefficient and CI for the cross-product term of the interaction between exposure and never smoker and exposure and ever smoker is -0.25 (-1.93, 1.43) and -0.54 (-1.99, 0.92), respectively for the GLP-1 RAs vs. sulfonylureas comparison.

The coefficient and CI for the cross-product term of the interaction between exposure and never smoker and exposure and ever smoker is -0.15 (-0.85, 0.54) and -0.09 (-0.74, 0.55), respectively for the DPP-4 inhibitors vs. sulfonylureas comparison.

eTable 6. Hazard Ratios for Prostate Cancer Comparing Incretins with Sulfonylurea (Varying lag period)

Exposure	No. of patients	Events	Person-years	Weighted incidence rate (95% CI) *	Crude HR	Weighted HR (95% CI) †
GLP-1 RAs vs. sulfonylureas						
18-month lag period						
Sulfonylureas	106,379	2000	550,342	251.7 (237.2, 266.9)	1.00	1.00 [Reference]
GLP-1 RAs	4521	31	19,453	159.4 (108.3, 226.2)	0.44	0.61 (0.39, 0.96)
24-month lag period						
Sulfonylureas	94,671	1660	464,632	261.5 (245.7, 278.1)	1.00	1.00 [Reference]
GLP-1 RAs	4117	29	17,324	167.4 (112.1, 240.4)	0.47	0.62 (0.39, 0.99)
DPP-4 inhibitors vs. sulfonylureas						
18-month lag period						
Sulfonylureas	107,934	2049	556,447	358.3 (339.4, 378.1)	1.00	1.00 [Reference]
DPP-4 inhibitors	48,246	540	168,828	319.9 (293.4, 348.0)	0.89	0.89 (0.80, 0.99)
24-month lag period						
Sulfonylureas	102,073	1886	504,743	368.9 (348.7, 390.0)	1.00	1.00 [Reference]
DPP-4 inhibitors	43,626	479	146,202	327.6 (298.9, 358.3)	0.90	0.89 (0.79, 0.99)

Abbreviations: CI, confidence interval; DPP-4, dipeptidyl peptidase 4; GLP-1 RAs, glucagon-like peptide 1 receptor agonists; HR, hazard ratio.
* Per 100,000 person-years.
† The models were weighted using propensity score fine stratification. The model was additionally adjusted for duration of diabetes and HbA1c for the GLP-1 RAs and sulfonylurea comparison.

eTable 7. Hazard Ratios for Prostate Cancer Comparing Incretins with Sulfonylurea (Inverse probability of censoring weighting)

Exposure	Events	Person-years	Weighted incidence rate (95% CI) *	Crude HR	Weighted HR (95% CI) †
GLP-1 RAs vs. sulfonylureas					
Sulfonylureas	2157	663,337	129.3 (120.4, 138.6)	1.00	1.00 [Reference]
GLP-1 RAs	34	24,401	116.3 (79.5, 164.2)	0.43	0.83 (0.50, 1.38)
DPP-4 inhibitors vs. sulfonylureas					
Sulfonylureas	2208	668,843	203.7 (192.2, 215.7)	1.00	1.00 [Reference]
DPP-4 inhibitors	611	221,393	190.2 (174.1, 207.4)	0.85	0.94 (0.83, 1.06)

Abbreviations: CI, confidence interval; DPP-4, dipeptidyl peptidase 4; GLP-1 RAs, glucagon-like peptide 1 receptor agonists; HR, hazard ratio.
* Per 100,000 person-years.
† The models were weighted using propensity score fine stratification and inverse probability of censoring weighting. The model was additionally adjusted for duration of diabetes and HbA1c for the GLP-1 RAs and sulfonylurea comparison.

eTable 8. Hazard Ratios for Prostate Cancer Comparing Incretins with Sulfonylurea (Interaction with PSA in the year before cohort entry)

Exposure	Without prior PSA	With prior PSA
GLP-1 RAs vs. sulfonylureas		
Sulfonylureas	1.00 [Reference]	1.00 [Reference]
GLP-1 RAs	0.63 (0.40, 0.99)	0.75 (0.29, 1.92)
DPP-4 inhibitors vs. sulfonylureas		
Sulfonylureas	1.00 [Reference]	1.00 [Reference]
DPP-4 inhibitors	0.90 (0.80, 1.00)	0.91 (0.70, 1.17)

Abbreviations: DPP, dipeptidyl peptidase; GLP-1 RAs, glucagon-like peptide-1 receptor agonists

The models were weighted using propensity score fine stratification. The model was additionally adjusted for duration of diabetes and HbA1c for the GLP-1 RAs and sulfonylurea comparison.

The coefficient and CI for the cross-product term of the interaction between exposure and prior PSA is 0.17 (-0.86, 1.20) for the GLP-1 RAs vs. sulfonylureas comparison.

The coefficient and CI for the cross-product term of the interaction between exposure and prior PSA is 0.01 (-0.27, 0.29) for the DPP-4 inhibitors vs. sulfonylureas comparison.

eTable 9. Hazard Ratios for Prostate Cancer Comparing Incretins with Sulfonylurea (Inverse probability of screening weighting)

Exposure	Events	Person-years	Weighted incidence rate (95% CI) *	Crude HR	Weighted HR (95% CI) †
GLP-1 RAs vs. sulfonylureas					
Sulfonylureas	2157	663,337	407.2 (390.1, 424.8)	1.00	1.00 [Reference]
GLP-1 RAs	34	24,401	269.1 (207.9, 342.6)	0.43	0.63 (0.39, 1.04)
DPP-4 inhibitors vs. sulfonylureas					
Sulfonylureas	2208	668,843	601.1 (579.0, 623.8)	1.00	1.00 [Reference]
DPP-4 inhibitors	611	221,393	527.4 (497.6, 558.5)	0.85	0.88 (0.78, 0.99)

Abbreviations: CI, confidence interval; DPP-4, dipeptidyl peptidase 4; GLP-1 RAs, glucagon-like peptide 1 receptor agonists; HR, hazard ratio.
* Per 100,000 person-years.
† The models were weighted using propensity score fine stratification and inverse probability of screening weighting. The model was additionally adjusted for duration of diabetes and HbA1c for the GLP-1 RAs and sulfonylurea comparison.

eTable 10. Hazard Ratios for Prostate Cancer Comparing Incretins with Sulfonylurea (On-treatment exposure definition)

Exposure	No. of patients	Events	Person-years	Weighted incidence rate (95% CI) *	Crude HR	Weighted HR (95% CI) †
GLP-1 RAs vs. sulfonylureas						
Sulfonylureas	112,955	1221	329,400	243.3 (223.2, 264.6)	1.00	1.00 [Reference]
GLP-1 RAs	5063	18	10,591	170.0 (100.7, 268.6)	0.48	0.61 (0.33, 1.12)
DPP-4 inhibitors vs. sulfonylureas						
Sulfonylureas	114,417	1262	334,925	371.0 (347.1, 396.2)	1.00	1.00 [Reference]
DPP-4 inhibitors	53,529	356	111,024	320.7 (288.2, 355.8)	0.89	0.87 (0.76, 0.996)

Abbreviations: CI, confidence interval; DPP-4, dipeptidyl peptidase 4; GLP-1 RAs, glucagon-like peptide 1 receptor agonists; HR, hazard ratio.
* Per 100,000 person-years.
† The models were weighted using propensity score fine stratification. The model was additionally adjusted for duration of diabetes and HbA1c for the GLP-1 RAs and sulfonylurea comparison.

eTable 11. Baseline Characteristics of the Matched Sulfonylurea and GLP-1 RAs Exposure Groups

Characteristics	Sulfonylurea	GLP-1 RAs	Standardized Difference
Total	3988	3988	
Age, years, mean (SD)	56.7 (9.1)	56.4 (9.2)	0.03
Alcohol-related disorders, n (%)	314 (7.9)	314 (7.9)	0.00
Body mass index, mean (SD)			
BMI < 30 kg/m², n (%)	302 (7.6)	317 (7.9)	0.01
BMI ≥ 30.0 kg/m², n (%)	3,573 (90)	3,547 (89)	0.02
Unknown	113 (2.8)	124 (3.1)	0.02
Smoking status, n (%)			
Ever	3,299 (83)	3,291 (83)	0.01
Never	687 (17)	697 (18)	0.01
Unknown	S*	0 (0.0)	-
Hemoglobin A1c, n (%)			
≤7.0%	541 (14)	560 (14)	0.01
7.1%-8.0%	837 (21)	859 (22)	0.01
>8.0%	2,520 (63)	2,475 (62)	0.02
Unknown	90 (2.3)	94 (2.4)	0.01
Duration of diabetes in years, mean (SD)	6.7 (5.8)	6.6 (5.7)	0.03
Type of antidiabetic drugs, n (%)			
Metformin	3,652 (92)	3,672 (92)	0.02
Thiazolidinedione	754 (19)	737 (19)	0.01
Meglitinides	61 (1.5)	56 (1.4)	0.01
Alpha-glucosidase inhibitors	20 (0.5)	19 (0.5)	0.00
SGLT-2 inhibitors	237 (5.9)	361 (9.1)	0.12
Insulin	1,036 (26)	896 (23)	0.08
Peripheral vascular disease, n (%)	363 (9.1)	352 (8.8)	0.01
Stroke, n (%)	147 (3.7)	140 (3.5)	0.01
Myocardial infarction, n (%)	421 (11)	373 (9.4)	0.04
Renal disease, n (%)	439 (11)	396 (9.9)	0.04
Retinopathy, n (%)	1,168 (29)	1,121 (28)	0.03
Neuropathy, n (%)	864 (22)	815 (20)	0.03
Cancer, n (%)	159 (4.0)	146 (3.7)	0.02
Lower urinary tract symptoms, n (%)	149 (3.7)	144 (3.6)	0.01
Non-steroidal anti-inflammatory drugs, n (%)	2,837 (71)	2,801 (70)	0.02
Aspirin	1,999 (50)	1,923 (48)	0.04
Statins, n (%)	3,409 (86)	3,399 (85)	0.01
5-α reductase inhibitors, n (%)	106 (2.7)	91 (2.3)	0.02
Calcium channel blockers, n (%)	1,787 (45)	1,767 (44)	0.01
Testosterone replacement therapy, n (%)	117 (2.9)	132 (3.3)	0.02
Prostate-specific antigen testing, n (%)	362 (9.1)	368 (9.2)	0.01
Year of cohort entry, n (%)			
2007	34 (0.9)	38 (1.0)	0.01
2008	235 (5.9)	202 (5.1)	0.04

2009	447 (11)	358 (9.0)	0.07
2010	578 (15)	448 (11)	0.10
2011	426 (11)	362 (9.1)	0.05
2012	380 (9.5)	375 (9.4)	0.00
2013	253 (6.3)	300 (7.5)	0.05
2014	211 (5.3)	208 (5.2)	0.00
2015	268 (6.7)	295 (7.4)	0.03
2016	272 (6.8)	311 (7.8)	0.04
2017	300 (7.5)	357 (9.0)	0.05
2018	325 (8.1)	405 (10)	0.07
2019	259 (6.5)	329 (8.2)	0.07

Abbreviations: SD, standard deviation; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT, sodium-glucose transport protein.

* Suppressed: Numbers fewer than five are not displayed, as per confidentiality policies of the Clinical Practice Research Datalink.

eTable 12. Baseline Characteristics of the Matched Sulfonylurea and DPP-4 inhibitors Exposure Groups

Characteristics	Sulfonylurea	DPP-4 inhibitors	Standardized Difference
Total	44,118	44,118	
Age, years, mean (SD)	61.7 (11.2)	61.6 (11.3)	0.00
Alcohol-related disorders, n (%)	3,728 (8.5)	3,915 (8.9)	0.02
Body mass index, mean (SD)			
BMI < 30 kg/m², n (%)	17,164 (39)	17,949 (41)	0.04
BMI ≥ 30.0 kg/m², n (%)	26,512 (60)	25,743 (58)	0.04
Unknown	442 (1.0)	426 (1.0)	0.00
Smoking status, n (%)			
Ever	36,408 (83)	36,401 (83)	0.00
Never	7,690 (17)	7,699 (18)	0.00
Unknown	20 (0.0)	18 (0.0)	0.00
Hemoglobin A1c, n (%)			
≤7.0%	3,855 (8.7)	3,882 (8.8)	0.00
7.1%-8.0%	14,235 (32)	13,215 (30)	0.05
>8.0%	25,549 (58)	26,590 (60)	0.05
Unknown	479 (1.1)	431 (1.0)	0.01
Duration of diabetes in years, mean (SD)	5.9 (4.8)	5.6 (4.7)	0.05
Type of antidiabetic drugs, n (%)			
Metformin	41,003 (93)	41,122 (93)	0.01
Thiazolidinedione	4,397 (10)	3,688 (8.4)	0.06
Meglitinides	322 (0.7)	248 (0.6)	0.02
Alpha-glucosidase inhibitors	50 (0.1)	43 (0.1)	0.00
SGLT-2 inhibitors	777 (1.8)	713 (1.6)	0.01
Insulin	1,644 (3.7)	1,220 (2.8)	0.05
Peripheral vascular disease, n (%)	3,304 (7.5)	3,177 (7.2)	0.01
Stroke, n (%)	2,192 (5.0)	2,232 (5.1)	0.00
Myocardial infarction, n (%)	4,170 (9.5)	4,133 (9.4)	0.00
Renal disease, n (%)	5,923 (13)	5,646 (13)	0.02
Retinopathy, n (%)	11,313 (26)	10,902 (25)	0.02
Neuropathy, n (%)	8,615 (20)	8,063 (18)	0.03
Cancer, n (%)	2,365 (5.4)	2,426 (5.5)	0.01
Lower urinary tract symptoms, n (%)	2,078 (4.7)	2,089 (4.7)	0.00
Non-steroidal anti-inflammatory drugs, n (%)	31,142 (71)	31,104 (71)	0.00
Aspirin	20,438 (46)	20,047 (45)	0.02
Statins, n (%)	37,691 (85)	37,396 (85)	0.02
5-α reductase inhibitors, n (%)	1,921 (4.4)	1,962 (4.4)	0.00
Calcium channel blockers, n (%)	17,881 (41)	17,668 (40)	0.01
Testosterone replacement therapy, n (%)	694 (1.6)	637 (1.4)	0.01
Prostate-specific antigen testing, n (%)	5,469 (12)	5,550 (13)	0.01
Year of cohort entry, n (%)			
2007	185 (0.4)	149 (0.3)	0.01
2008	752 (1.7)	707 (1.6)	0.01

2009	1,863 (4.2)	1,870 (4.2)	0.00
2010	3,921 (8.9)	3,910 (8.9)	0.00
2011	3,627 (8.2)	3,569 (8.1)	0.00
2012	3,967 (9.0)	3,905 (8.9)	0.00
2013	4,115 (9.3)	4,039 (9.2)	0.01
2014	4,261 (9.7)	4,229 (9.6)	0.00
2015	5,462 (12)	5,127 (12)	0.02
2016	6,578 (15)	5,115 (12)	0.10
2017	6,889 (16)	4,767 (11)	0.14
2018	1,922 (4.4)	4,248 (9.6)	0.21
2019	576 (1.3)	2,483 (5.6)	0.24

Abbreviations: SD, standard deviation; SGLT, sodium-glucose transport protein; DPP, dipeptidyl peptidase

eTable 13. Hazard Ratios for Prostate Cancer Comparing Incretins with Sulfonylurea (PS matching)

Exposure	No. of patients	Events	Person-years	Incidence rate (95% CI) [a]	HR (95% CI) [b]
GLP-1 RAs vs. sulfonylureas					
Sulfonylurea	3988	48	17,251	278.2 (205.2, 368.9)	1.00 [Reference]
GLP-1 RAs	3988	31	19,005	163.1 (110.8, 231.5)	0.58 (0.37, 0.92)
DPP-4 inhibitors vs. sulfonylureas					
Sulfonylurea	44,118	627	173,000	362.4 (334.6, 391.9)	1.00 [Reference]
DPP-4 inhibitors	44,118	592	186,333	317.7 (292.6, 344.4)	0.88 (0.78, 0.98)

Abbreviations: HR, hazard ratio; CI, confidence interval; DPP, dipeptidyl peptidase; SGLT, sodium-glucose transport protein

[a] Per 100,000 person-years.

[b] Patients were matched on propensity score. The models were further adjusted for year of cohort entry and prior use of SGLT-2 inhibitors.

5.9 Supplemental Digital Content

Key SAS codes for the creation of the cohorts, propensity score construction, and statistical procedures related to the generation of the results accompanied this manuscript as supplemental digital content.

```
/* GOLD patients */

data goldpatient;
merge bridge(in=a keep=gold_pracid rename=(gold_pracid=practice)) practice
patient(where=(acceptable=1 and male ne .));
by practice;
if not a;
format start end date9.; start=max(crd+365,uts+365,'01jan2007'd);
end=min(lcd,dod,tod,'31jul2020'd);
keep id practice start end yob male acceptable dod toreason tod lcd aurum;
run;

/* The data set "goldpatient" contains basic patient demographics and
registration details */

/* AURUM patients */

data aupt;
set auad20r1.patient1 auad20r2.patient1 auad20r3.patient1;
run;

data aupr;
set auad20r1.practice1 auad20r2.practice1 auad20r3.practice1;
run;

/*
check if practices were repeated
proc sort data=aupr;by practice;run;
data one;
set aupr;
by practice;
if practice=lag(practice) and (region ne lag(region) or lcd ne lag(lcd));
run;
No repetition. Delete dupliates
*/

proc sort data=aupr nodupkey;by practice;run;

proc sql;
create table aupatient as
select p.*,pr.lcd,max(regstart+365,'01jan2007'd) as start
format=date9.,min(lcd,cprd_dod,regend,'31jul2020'd) as end format=date9.
from aupt as p,aupr as pr
where p.practice=pr.practice and acceptable=1 and male ne .
order by id;
quit;

/* The data set "aupatient" contains basic patient demographics and
registration details */

/*Create a cohort of GLP-1/SULFO users and identify the cohort entry*/

/*identify patients' first GLP-1/SULFO in GOLD. The data set "ad20.anti_gold"
contains patients' full information on antidiabetic drugs prescriptions. */
```

```
proc sql;
 create table anti_gold as
 select a.id, min(a.date) as entry format=date9.
 from ad20.anti_gold as a,goldpatient as p
 where a.id=p.id  and a.classification in (2,10,12,9,16)  and p.male = 1 and
 '01jan2007'd <= date <='31jul2019'd group by a.id
 order by id;
quit;

 /*identify patients' first GLP-1/SULFO in AURUM. The data set
 "ad20.anti_aurum" contains patients' full information on antidiabetic drugs
 prescriptions. */

proc sql;
 create table anti_aurum as
 select input(a.id,20.) as id, min(a.date) as entry format=date9.
 from ad20.anti_aurum as a,aupatient as p
 where a.id=p.id and a.classification in (2,10,12,9,16) and p.male = 1 and
 '01jan2007'd <= date <= '31jul2019'd
 group by a.id
 order by id;
 quit;


 data cohort1;
 set anti_gold anti_aurum(in=c);
 by id;
 aurum=c;
 run;


 /*create exposure groups and exclude combination use*/

 /*The data set "co.antidiabetic_2020" and "covau.antidiabetic_2020" contains
 antidiabetic drugs details including their prodcut name,
 clssification, etc*/

proc sql;
 create table a1 as
 select a.*,co.productname
 from ad20.anti_gold as a,co.antidiabetic_2020 as co
 where a.prodcode=co.prodcode;

 create table a2 as
 select a.*,co.productname
 from ad20.anti_aurum as a,covau.antidiabetic_2020 as co
 where a.prodcodeid=co.prodcodeid;
quit;

 data anti;
 length productname $110.;
 set a1(keep=id date classification productname in=a) a2(keep=id date
 classification productname rename=(id=patid) in=b);
 if a then do;id=id; aurum=0;end;
 else if b then do;id=input(patid,20.);aurum=1;end;
```

```
run;

proc sql;
 create table combo1 as
 select c.id,c.aurum,c.entry,a.classification
 from anti as a, cohort1 as c
 where a.id=c.id and a.date=c.entry and a.aurum=c.aurum
 order by id,aurum;
quit;

 data combo;
 set combo1;
 by id aurum;
 retain dpp sulfo glp;
 if first.aurum then do;dpp=0;sulfo=0;glp=0;end;
 if classification in (7,13,15) then dpp=1;
 if classification in (2,10,12) then sulfo=1;
 if classification in (9,16) then glp=1;
 if last.aurum;
 run;

 /*proc freq data=combo;tables glp sulfo;run;*/

 data cohort2 comboex;
 merge combo cohort1;
 by id aurum;
 if glp=1 then exposure=1;
 else if sulfo=1 then exposure=0;
 if dpp+sulfo+glp>=2 then output comboex;
 else output cohort2;
 run;
```

```
/*propensity score model*/

proc logistic data=cohort descending;
effect age_spline=spline(age /
naturalcubic
                                        basis=tpf(noint) knotmethod=Rangefractions(0.05
                                    0.275 0.50
0.725 0.95));
effect dmdur_spline=spline(dmdur / naturalcubic
                                        basis=tpf(noint) knotmethod=Rangefractions(0.05
                                    0.275 0.50
0.725 0.95));
class smoking(ref='1')  hba1cgrp(ref='1') year(ref='2016') obesity(ref='1')
/param=ref;
model exposure=age_spline dmdur_spline alcohol smoking obesity hba1cgrp
renal neuropathy retinopathy mi stroke pvd     cancer luts nsaids statins
acetyl ccb alpha trt psa met_t0 tzd_t0 meg_t0 alpha_t0 insulin_t0 sglt_t0
year/rl; output out=ps_1 prob=ps;
run;

/*Generate Hazard Ratio for GLP-1 RAs vs SULFO comparison*/

data one;
merge ad20.cohort_prostate_glp ad20.ps_prostate_glp(keep=id psweight
dmdur hba1cgrp in=a);
by
id;
if a;
time=end-entry-365+1;
run;

/*Crude HR*/

proc phreg data=one;
class
exposure(ref='0')/param=ref;
model       time*event(0)       =
exposure/rl; run;

/*Weighted HR*/

proc phreg data=one covs;
class exposure(ref='0')
hba1cgrp(ref='1')/param=ref; model time*event(0) =
exposure dmdur hba1cgrp/rl; weight psweight;
run;

/*K-M curve*/

proc lifetest data=km outsurv=test cs=none conftype=linear
method=km plots=survival(atrisk=0 to 14 by 2);
time time*event(0);
strata exposure
/test=logrank; weight
psweight;
run;
```

Chapter 6: Discussion

6.1 Summary of Findings

The goal of this thesis study was to determine whether the use of GLP-1 RAs and DPP-4 inhibitors, separately, was associated with a decreased risk of prostate cancer among patients with type 2 diabetes. This study was prompted by biological and clinical evidence in the scientific literature that indicated a potential chemopreventive benefit of the incretin-based drugs on the development of prostate cancer. The large, population-based cohort study that was conducted for this thesis using the UK CPRD found that the use of GLP-1 RAs and DPP-4 inhibitors, separately, were associated with a decreased risk of prostate cancer when compared to the use of sulfonylureas. In the secondary analyses, two-year cumulative durations of use were associated with a decreased risk of prostate cancer for both GLP-1 RAs and DPP-4 inhibitors. While exenatide (a GLP-1 RA) and saxagliptin (a DPP-4 inhibitor) generated the lowest HRs in their respective drug classes, their CIs were wide and overlapped with others in the same drug class. Furthermore, there was no evidence of effect measure modification by age, BMI, or smoking for either drug classes. Finally, the results from the primary analysis remained consistent across several sensitivity analyses that examined various sources of bias.

6.2 Implication of Results

After the incretin-based drugs were introduced to the market, there were initial safety concerns regarding pancreatic-related events.[194-198] In an analysis of the US FDA's adverse event reporting system database, the use of exenatide (a GLP-1 RA) or sitagliptin (a DPP-4 inhibitor), compared to the use of other anti-hyperglycemic medications, was associated with a 6-fold increase in the reported event rate of pancreatitis.[194] Furthermore, compared to users of other

anti-hyperglycemic medications, users of exenatide had a 2.9-fold increase in the reported event rate of pancreatic cancer while users of sitagliptin had a 2.7-fold increase.[194] These pancreatic-related concerns, however, have not been corroborated in subsequent large epidemiologic studies as no increased risk of pancreatitis[12] nor pancreatic cancer[13] was observed with the use of the incretin-based drugs. Based on evidence from animal studies, there has also been concerns that the incretin-based drugs, GLP-1 RAs in particular, may be associated with the development of medullary thyroid cancer.[199] In rodents, GLP-1 receptors are expressed on the calcitonin-secreting C-cells of the thyroid and long-term exposure to liraglutide (a GLP-1 RA) was shown to induce C-cell hyperplasia and tumor formation.[199] However, GLP-1 receptors are not as abundantly expressed on the C-cells of humans and non-human primates, and long-term exposure to liraglutide was not shown to cause C-cell hyperplasia in monkeys.[199] Given the biological differences between the rodent and human thyroid, the FDA concluded that the risk of medullary thyroid cancer associated with the use of GLP-1 RAs in humans is low.[200]

With these initial safety concerns assuaged, there has been recent interest in the beneficial pleiotropic effects (the actions of a drug besides the ones it was specifically designed for[201]) of the incretin-based drugs beyond glycemic control. Although endogenous GLP-1 is known for its glucose-dependent, insulinotropic effects on the pancreas, its receptors are also widely expressed in tissues outside of the pancreas such as the brain, heart, kidneys, lungs, and liver.[202] As such, numerous *in vitro* and *in vivo* studies have shown that GLP-1 and its analogs have a plethora of beneficial physiological effects beyond glucose homeostasis in many different tissues.[100,203] For example, under experimental conditions, GLP-1 activity has been shown to stimulate neurite outgrowth,[204] attenuate neural degeneration,[204] improve cardiac function,[205] protect against myocardial damage,[206] enhance vasodilation,[207] improve kidney function,[208-213] and reduce

hepatic steatosis.[214,215] Evidence from biological studies provide the basis for further investigating whether the incretin-based drugs, designed to augment GLP-1 activity, may have clinically relevant pleiotropic effects in the prevention and/or treatment of various diseases in humans. This is especially true for the GLP-1 RAs as they are able to provide more sustained activation of the GLP-1 receptors compared to the DPP-4 inhibitors.[11] Evidence from clinical trials in humans have shown that treatment with GLP-1 RAs can promote weight loss,[216] reduce blood pressure[217,218] and plasma lipid levels,[104] protect against MACE,[15-18] improve lung function,[219] reduce liver fat content,[220] and improve kidney outcomes.[221] With respect to DPP-4 inhibitors, clinical trials have also found these drugs to reduce blood pressure[222] and plasma lipid levels,[223] and improve kidney outcomes.[224]

There is biological evidence in the scientific literature for a beneficial effect of the incretin-based drugs in the prevention of prostate cancer.[23-26] This thesis study was prompted by this information, and the results of the study provide real-world evidence for a potential pleiotropic benefit and novel application of GLP-1 RAs and DPP-4 inhibitors in the chemoprevention of prostate cancer. Pharmacoepidemiologic studies such as the one described in this thesis are important for investigating unintended clinically relevant effects of drugs in real-world populations. Randomized controlled trials are expensive to conduct and for rare outcomes like cancer, large sample sizes and extended follow-up periods are required. Furthermore, they may not be ethical to conduct if the existing scientific evidence for a clinically relevant effect is weak. Given that prostate cancer is one of the most common cancers among males worldwide, the results of this and future studies on the topic may have important implications in guiding the treatment of those at increased risk for prostate cancer.

6.3 Future Directions for Research

Further research corroborating the results from this thesis study is required before the incretin-based drugs can be definitively established as chemopreventive agents for prostate cancer. The results from this and future epidemiological studies on the topic may provide a precedent for conducting randomized controlled trials investigating whether the use of the incretin-based drugs decreases the risk of incident prostate cancer. Similar randomized controlled trials have been conducted in the past, as two trials have studied the use of 5-alpha reductase inhibitors on the prevention of prostate cancer.[225,226] In the Prostate Cancer Prevention Trial, 18,882 men aged 55 years or older with a normal digital rectal examination and a PSA level of ≥3.0 ng/mL, were randomized to receive 5 mg of finasteride daily or placebo.[225] After 7 years of follow-up, finasteride was found to decrease the risk of incident prostate cancer by 24.8%.[225] Similar results were observed in the Reduction by Dutasteride of Prostate Cancer Events trial. In this trial, 8231 men aged 50-75 years, with a PSA level of 2.5-10.0 ng/mL and one negative prostate biopsy within 6 months before enrollment, were randomized to receive 0.5 mg of dutasteride daily or placebo.[226] After 4 years of follow-up, dutasteride was found to decrease the risk of incident prostate cancer by 22.8%.[226] Given the well-tolerability of the incretin-based drugs,[114] similar trials can be conducted to more definitively ascertain whether these drugs can prevent prostate cancer in both diabetic and non-diabetic patient populations.

While the incretin-based drugs may decrease the risk of developing prostate cancer, it is unknown whether this protective effect will translate into reduced prostate cancer mortality as the mechanisms that control the chemoprevention of prostate cancer may be distinct from the ones that govern the attenuation of existing prostate tumors. Thus, another direction of research is to investigate whether the use of the incretin-based drugs after prostate cancer diagnosis can

lead to improved cancer outcomes in patients. Another avenue of future research is to investigate whether the use of the incretin-based drugs is associated with a decreased incidence of other malignancies. Recent biological research suggests that the incretin-based based drugs, GLP-1 RAs in particular, may reduce the growth of certain gynecological cancers such as those of the endometrium[227] and ovaries.[228] To date, the chemopreventive effects of the incretin-based drugs on the development of these cancers are uncertain as no studies have investigated these questions. Given that endometrial and ovarian cancers are common malignancies among women,[229] with over 400,000 and 300,000 new cases in 2020,[230] respectively, these questions are worth further investigation.

Chapter 7: Conclusion

Since their introduction to the market, the use of the incretin-based drugs, which include GLP-1 RAs and DPP-4 inhibitors, has increased and revolutionized the management of type 2 diabetes. These drugs have favourable clinical profiles as they effectively lower blood glucose levels without causing hypoglycemia or weight gain, and are generally well-tolerated. After some initial safety concerns were found to be unsubstantiated, there has been recent interest in the beneficial pleiotropic effects of the incretin-based drugs beyond glycemic control.

The study detailed in this thesis is the first observational study to investigate the individual effects of GLP-1 RAs and DPP-4 inhibitors on the incidence of prostate cancer in the real-world setting. The results indicate that the use of GLP-1 RAs and DPP-4 inhibitors, separately, may decrease the risk of prostate cancer in patients with type 2 diabetes. Before these drugs can be used as novel chemopreventive agents for prostate cancer, more observational studies and clinical trials on the topic in patients with and without type 2 diabetes are required. Future research should also be directed towards investigating whether the use of the incretin-based drugs after diagnosis can improve prostate cancer outcomes and whether these drugs are associated with a reduced risk of other malignancies, such as endometrial and ovarian cancers.

Chapter 8: References

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