**LAY SUMMARY**

SGLT2 inhibitors (SGLT2s) and GLP1 analogues (GLP1s) are prescription medications proven to reduce the risk of heart failure, kidney failure, stroke, heart attack, and death in patients with type 2 diabetes. However, these medications are not being prescribed to patients on the scale one might expect, considering their impressive benefits. Particularly, the use of SGLT2s in hospitalized patients is often restricted, owing in part to one rare side effect of the medication: diabetic ketoacidosis, known as DKA. Our goal is to study the use of SGLT2s and GLP1s in hospitals to better understand [1] what factors are related to the decision to either prescribe or not prescribe an SGLT2 or GLP1, [2] the risk of DKA when a hospitalized patient is given an SGLT2, [3] the short- and long-term consequences when a patient who may benefit from an SGLT2 or GLP1 does not receive one, and [4] whether the rare outcome of DKA from use of an SGLT2 is attributable to a genetic variant. The aim of this work is to better understand how to optimize these medications to provide real benefits to patients while still protecting those who are most vulnerable from any serious side effects.

**STATEMENT OF OBJECTIVES AND SPECIFIC AIMS**

**OBJECTIVE:** To understand the risks and benefits of newer diabetes medications when used in routine care, including in the inpatient setting. We need strategies to ensure patients are receiving medications that have real benefits for them, especially high-risk, vulnerable populations who, owing to inherent biases in medical practice, can be excluded from these therapies. Further, we need to educate providers and patients about the degree of risk so that this risk does not have undue power in clinical decision-making.

**SPECIFIC AIMS:**

[1] To identify how often patients are prescribed sodium glucose co-transporter 2 (SGLT2) inhibitors or glucagon like peptide-1 (GLP1) analogues during hospitalization, and to quantify (using logistic regression) whether this is driven by patient-level, physician-level, or hospital-level characteristics.

[2] To calculate the risk of diabetic ketoacidosis (DKA) in patients who are prescribed an SGLT2 inhibitor during hospitalization compared to patients who are prescribed another second-line diabetes medication.

[3] To calculate the in-hospital (e.g., hypoglycemia) and long-term (e.g., heart failure hospitalization, cardiovascular event) consequences of not receiving an SGLT2 inhibitor or GLP1 analogue, using data from Ontario and Denmark.

[4] To identify if genetic variants are associated with SGLT2i-associated DKA, through a Genome Wide Association Study (GWAS).

**WHY HAS THIS NOT ALREADY BEEN DONE?**

The first three objectives remain unaddressed because most available healthcare databases in North America, Europe, and Asia lack detailed data from a patient’s hospitalization. One of the few large in-hospital databases is the General Medicine Inpatient Initiative (GEMINI) database. GEMINI is Canada’s largest hospital data and analytics network, and in 2022 it grew to include over 1.8 million hospitalizations. Fralick (PI) is a core GEMINI investigator, and Razak and Verma (co-investigators) are the founders of GEMINI. The fourth objective has simply not been undertaken by researchers because SGLT2 inhibitors are a relatively new class of medications, and widespread agreement that they can cause DKA did not exist until 2019.

**HYPOTHESES:**

[1] SGLT2 inhibitors and GLP1 analogues are rarely prescribed during hospitalization or at discharge from hospital, and patient-level characteristics indicative of highest cardiovascular risk (e.g., known coronary artery disease) are likely weak predictors of who is prescribed an SGLT2 inhibitor or GLP1 analogue, compared to physician- or hospital-level characteristics. Understanding what drives prescribing can help inform future knowledge translation studies.

[2] The risk of DKA from SGLT2 inhibitor use in hospital is low, especially compared to the potential benefits of these medications.

[3] When SGLT2 inhibitors and GLP1 analogues are not prescribed in hospital, patients are more likely to receive a medication with no proven cardiovascular benefits (e.g., sulfonylurea) which places them at higher risk of both in-hospital harm (e.g., hypoglycemia) and long-term harm (e.g., heart failure).

[4] Genetic variants may identify patients at highest risk of SGLT2i-associated DKA.

**STATEMENT OF RELEVANCE**

Sodium glucose co-transporter 2 (SGLT2) inhibitors and glucagon like peptide-1 (GLP1) analogues are the most effective classes of medications for adults with type 2 diabetes mellitus (T2DM). These medications have the potential to improve the quality of life for the ~1.4 million Ontarians living with diabetes, and to reduce the economic and healthcare resource burdens associated with diabetes-related complications. Yet the uptake of these medications has been slow, particularly in the inpatient setting, where use of SGLT2 inhibitors can be restricted by hospital-level policies. Such policies, coupled with prescribing inertia and lack of familiarity with these newer medications, have led to patients receiving alternate medications (e.g., sulfonylureas, insulin) that lack established cardiovascular benefits and carry well-established harms like hypoglycemia and weight gain. Important opportunities are being missed: starting a new medication during a patient’s hospitalization has been shown to improve long-term adherence, and in-hospital initiation of a new medication allows the patient to be closely monitored for potential adverse events. We anticipate this research will result in evidence-based findings to inform policymaking, shared decision-making, and knowledge translation efforts, to increase the uptake of these medications in patients for whom the benefits outweigh the risks. Potential impacts for Ontarians include better health outcomes for hospitalized patients; increased equity in uptake among high-risk, vulnerable populations who are excluded from these medications despite standing to benefit most; and improved long-term adherence to these highly beneficial medications. The work with our colleagues in Denmark serves to strengthen our study’s findings and benefit both parties through exchange of ideas and insights into different approaches to healthcare advancement. Pharmacogenomics is an innovative approach to filling the knowledge gap of why a small subset of patients will experience the life-threatening side-effect of SGLT2i-associated DKA. The focus of our submission at this time is adults with T2DM, but the heart failure and renal failure benefits of SGLT2 inhibitors have recently been confirmed in large-scale, double-blind, randomized trials among adults who do *not* have T2DM1–5; similarly, recent trials have shown that some of the benefits of GLP1 analogues extend to adults with increased body mass index who do not have diabetes.6,7 Our research will lay the groundwork for future studies in the safety and effectiveness of these medications, which will be important as their use is expanded to a larger population.

**STATEMENT ON EDI AND SEX- AND GENDER-BASED ANALYSIS +**

T2DM disproportionately affects Indigenous peoples and racial and ethnic minority groups, and among patients with T2DM, these groups have a higher burden of related complications, including cardiovascular disease, chronic kidney disease, and hypoglycaemia.8–13 Novel diabetes medications like SGLT2 inhibitors and GLP1 analogues have been proven to mitigate these complications; consequently, slow uptake of these medications disproportionately affects vulnerable, high-risk groups, exacerbating already-existing inequities. These disparities are of particular concern because diabetes is one of the most common chronic conditions: in North America, 10% of the population has diabetes, and the lifetime risk of developing diabetes is approximately 30% by age 65.14–17

Despite being among those who stand to benefit most from use of these medications, Indigenous peoples and racial and ethnic minority groups are less likely to receive them. One study of outpatients in the US identified that the following patient-level characteristics were associated with lower odds of receiving an SGLT2 inhibitor: female sex, non-white race, and lower socioeconomic status.18 A second study focused on GLP1 analogues, identifying that Asian, Black, and Hispanic patients, and those with lower socioeconomic status, were less likely to receive treatment with a GLP1 analogue.19 Another study found racial/ethnic disparities in the initiation of newer diabetes medications independent of socioeconomic factors.8 Racial disparities in prescribing persist even after adjusting for trends by income, education, and insurance20—which indicates that while certain policy-level solutions like comprehensive insurance coverage and increased access to specialists may help, there is persistent racism and bias in care delivery.

Age and frailty are other equity domains that require examination, particularly considering the higher burden of T2DM among older adults. A recent study in Alberta found older age was associated with lower odds of filling an SGLT2 inhibitor prescription.21 Further, existing frailty-specific guidelines on SGLT2 inhibitor and GLP1 analogue prescribing are based on fixed assumptions that categorize frail older people as one homogeneous group; however, this can be misleading.22 A recent secondary analysis of a large clinical trial of dapagliflozin (an SGLT2 inhibitor) identified that benefits pertained to older adults regardless of frailty status; in fact, larger absolute benefits were observed in patients with a higher level of frailty.23

One notable limitation of the available literature to date is the focus on patient-level characteristics; methodical description of physician-level (e.g., sex, years in practice, subspeciality) or hospital-level characteristics (e.g., prescribing policies at the place where the patient received care) is lacking. Our proposed research would help to fill this gap by widening the scope to include those characteristics (made possible by the data available through the recent GEMINI-ICES linkage). Clarity on predictors will be essential when designing subsequent knowledge translation studies. Evidence-based outreach and knowledge translation direct to stakeholders (i.e., patients, physicians, hospital administrators) will be required to combat the racism, bias, and clinical inertia that is limiting the uptake of these extremely beneficial medications in vulnerable populations. Our proposed research can help to inform clearer guidance and pathways to achieve more equitable prescribing of these novel diabetes medications.

**CONSIDERATIONS IN THE PROPOSED RESEARCH**

**SEX- AND GENDER-BASED ANALYSIS:**

**Objectives 1, 2, 3:** Data on sex are available for both patients and providers in our proposed data sets. We consider sex as a biological component with chromosomal, cellular, and molecular differences. Primary and secondary outcomes will include analyses stratified by sex, allowing us to quantify any sex-specific differences in the study’s outcomes. Gender encompasses socio-cultural, environmental, and behavioural factors that determine self-identity. Unfortunately, our proposed data sets (GEMINI, ICES, and the Nationwide Danish Data Repository) lack self-reported gender for patients or providers.

**Objective 4:** Cases and controls will be matched on sex. Information on sex will be available for all patients through one of (i) electronic medical record (inpatient-sourced cases and controls) or (ii) patient data in the Canadian Longitudinal Study on Aging (CLSA) dataset (supplementary controls, as needed).

**EQUITY CONSIDERATIONS BEYOND SEX AND GENDER:**

**Objectives 1, 2, 3:** Patient-level equity domains will include individual-level sociodemographic characteristics, including age, frailty, disability, insurance status (presence of OHIP), and neighborhood-level characteristics including income quintile and percentage visible minority. Neighborhood-level variables will be linked to GEMINI at the level of the dissemination area using PCCF+ postal code linkage from Statistics Canada’s 2016 census data24,25; this approach has been applied in prior GEMINI publications.26 Our prior work has validated an approach to identify patients with a disability (PPV > 80%, specificity 100%).26 We will also implement a previously validated hospital frailty risk score [in-press]. A complete overview of the GBA+ analysis plan for Objectives 1, 2, and 3 can be found in Appendix A, Table 1.

**Objective 4:** In addition to sex, cases and controls will be matched on genetic ancestry. Information on genetic ancestry will be available for all patients through one of (i) self-reported ancestry (inpatient-sourced cases and controls) or (ii) patient data in the Canadian Longitudinal Study on Aging (CLSA) dataset (supplementary controls, as needed).

**EDI PRACTICES ON THE RESEARCH TEAM**

Our research team is based out of academic/research institutions in large metropolitan cities in Canada, and includes a partnership with a rural, underserviced area. Our EDI context is best captured by a recent report from the Canadian Association of University Teachers and Universities Canada that highlights persistent inequalities faced by women, LGBTQ2S+ individuals, Indigenous people, people with disabilities, and racialized minorities.27 For example, women make up just over half the population but hold only 40% of full-time university faculty positions in Canada. Indigenous peoples account for 3.8% of the total workforce, but only 1.4% of university professors. Black people comprise 3.1% of the total workforce, but only 2% of university teachers. Further, the field Life Sciences is characterized by a lack of diversity from underrepresented groups.

Different perspectives and cognitive diversity on our team are integral to the creativity, productivity, debate, problem-solving, and communication skills that will enable this project to produce excellent research. Both MF and the Lunenfeld-Tanenbaum Research Institute are committed to Equity, Diversity and Inclusion in their research teams. The Tri-Agency Institutional Program Secretariat (TIPS) requirements and practices guide for best practices will be followed. Dr. Fralick’s current 17-person research team is balanced from a gender standpoint and represents a diverse range of Canadians. Further, we strive to develop EDI literacy in our team members and foster EDI on the team through the practices outlined here.

**PRACTICE:** Unbiased Hiring Training for the NPI and all team members involved in the hiring process, to be facilitated by the institutions involved and/or federally available modules.

**Relevance:** EDI begins with the leadership of the research team. The NPI and all team members involved with the hiring process must be able to recognize and actively counter their biases.

**Approach:** Both an institutional-level course in Bias-Free Hiring and the Canada Research Chair Unconscious Bias Training Module will be made available to all team members. Completion of one of the courses, prior to any hiring activities, will be mandatory for all team members participating in the hiring process. Two additional processes to support the equitable recruitment and assessment of all candidates: (i) The use of non-gendered, inclusive, unbiased language in all job postings; and (ii) The use of a pre-established, standardized set of assessments for all candidates. Team members involved in the hiring process will subject each candidate to the same standardized interview questions, developed by the team, and subsequent assessment of suitability will be based on the answers to these standardized questions.

**Measurability:** Certification of completion of the course is to be documented by the NPI and kept on record as part of the project file.

**PRACTICE:** Mentoring for all junior team members, particularly for graduate students, research trainees, and early career researchers.

**Relevance:** All research benefits from a diversity of perspectives, including sharing perspectives and learning opportunities through mentorship. Additionally, mentorship provides the opportunity for less-established researchers to get a firmer foothold by developing the skills, confidence, and connections they need to move forward in their careers. We anticipate a team composed of researchers and trainees at all career stages.

**Approach:** The composition of the team as regards career stage will be analyzed. Researchers will be asked to allocate a select amount of time over the duration of the grant to mentorship for more junior researchers/trainees, as applicable. The amount of time will be proportionate to the number of mentees who require mentorship and the number of mentors. Mentorship will be provided to all more junior team members. The nature of mentoring activities will be subject to the roles/fields of study of those involved. Senior researchers, and researchers in general, often have many demands on their time; therefore, analyzing the mentorship resources and needs in advance will allow us to allocate time appropriately, to set realistic minimums and encourage surpassing them.

**Measurability:** A set number of dedicated hours of mentorship will be outlined for each mentor/mentee pairing, based on the resources available and the duration of the proposed work. Mentor will be responsible for outlining mentorship activities and reporting them to the NPI.

**BACKGROUND, RATIONALE, AND PRESENT STATE OF KNOWLEDGE**

**High-level Background.** Sodium glucose co-transporter 2 (SGLT2) inhibitors and glucagon like peptide-1 (GLP1) analogues have revolutionized care and fundamentally changed the clinical approach to individualized pharmacotherapy for people living with type 2 diabetes mellitus (T2DM).28–32 Both classes of medications reduce a person’s risk of myocardial infarction, stroke, cardiovascular mortality, and all-cause mortality.28–30,32 With SGLT2 inhibitors, the number needed to treat (NNT) to prevent myocardial infarction, stroke, or death from cardiovascular causes is approximately 80 (over ~3 years).28–30 SGLT2 inhibitors also reduce a person’s risk of end-stage kidney disease (NNT 25, ~2 years) and the composite of heart failure or cardiovascular death (NNT 20, ~2 years).1–3 GLP1 analogues have comparable cardiovascular benefits (NNT 80, ~2 years), and a recent clinical trial and meta-analysis suggests they may also reduce a person’s risk of renal failure or heart failure.33,34

Guidelines now preferentially recommend SGLT2 inhibitors and GLP1 analogues as second-line agents for adults with T2DM who have established or increased risk of cardiovascular disease35,36; for adults with diabetes who have heart failure or chronic kidney disease, guidelines recommend SGLT2 inhibitors.35,36 Despite guidelines, however, the uptake of both classes of medications into clinical practice has been slow.37–40 Slow uptake is common with new medications for chronic diseases. In the case of SGLT2 inhibitors, this is exacerbated by an important, albeit rare, adverse side effect of the medication: risk of diabetic ketoacidosis (DKA) (number need to harm = 200, ~1-year).41–43 This potentially fatal outcome is known as SGLT2i-associated DKA, and it may be attributable to genetic factors.44

Owing to the risk of DKA, some hospitals in Ontario do not allow SGLT2 inhibitors to be used during a patient’s hospitalization; such policies are based on expert opinion that patients who are in hospital are at an increased baseline risk of DKA.43,45 However, the risk of SGLT2i-associated DKA among hospitalized patients has not been quantified or methodically studied, and such hospital policies may have unintended consequences. First, patients may miss out on receiving these potentially life-saving treatments. Second, patients may instead be started on medications that are inferior to SGLT2 inhibitors (e.g., sulfonylurea, insulin), and that carry their own risks (e.g., hypoglycemia, weight gain).46  Hospitalized patients are typically those at highest risk of cardiovascular events, and thus may have the most to gain from a medication that reduces those risks.

In the case of GLP1 analogues—these medications have rarely been used in hospitals in Ontario because they were only recently added to the Ontario drug formulary (in 2019) and were not on hospital formularies until 2020. Physicians are less familiar with GLP1 analogues, which may explain why they are rarely prescribed. Furthermore, because these medications were recently added to the formulary, studies assessing their safety and effectiveness in the inpatient setting are lacking.

**STATEMENT OF THE PROBLEM**

**[1] SGLT2 inhibitors and GLP1 analogues have the potential to be the most beneficial medications for adults with T2DM, but to date their uptake has been slow.** SGLT2 inhibitors and GLP1 analogues have impressive benefit profiles and are approved for adults with T2DM, which affects approximately 3 million Canadians.31 Multiple studies have demonstrated that the uptake of SGLT2 inhibitors and GLP1 analogues across North America has been slow (i.e., uptake of only 1.4% among those with T2DM and cardiovascular disease), and this is particularly true in the inpatient settings where these medications are rarely prescribed.37–40

**[2] Hospitalized patients are at highest risk of subsequent cardiovascular events.** Patients with diabetes are hospitalized more frequently than patients without diabetes, typically from diabetes-related complications (e.g., worsening glycemic control, heart failure, stroke, myocardial infarction).47,48 Studies have shown that patients with diabetes also experience unplanned readmissions to hospital due to hypoglycemia or hyperglycemia.49 Clinicians often must decide which diabetes medications to administer for diabetes management. If a newer medication is not considered, clinicians are forced to choose among medications such as insulin or sulfonylureas, which (i) do not improve cardiovascular events and (ii) commonly cause hypoglycemia and may lead to worse outcomes.

**[3]** **SGLT2i-associated DKA is rare, and the data supporting increased risk in hospitalized patients is based on weak evidence.** Our research team has published four observational studies, **all among outpatients**, that have consistently shown that the absolute risk of DKA with use of an SGLT2 inhibitor is approximately 0.5% within one year of starting the medication.37,42,43,50,51 In contrast, the evidence supporting an increased risk of SGLT2i-associated DKA among hospitalized patients is primarily based on case series data which, by definition, is at high risk of bias.

**[4] SGLT2i-associated DKA may be driven by genetic factors.** SGLT2i-associated DKA is rare, and most cases of this adverse event occur soon after initiating the medication.43 This, coupled with the findings of recent basic science studies,52–58 suggests that the risk might be related to genetic factors.

**[5] Slow uptake of these medications disproportionately affects vulnerable groups, exacerbating already-existing inequities.** T2DM disproportionately affects racial and ethnic minority groups, and among patients with T2DM, these groups have a higher burden of related complications, including cardiovascular disease and chronic kidney disease.8–12 Yet studies have shown that patients of non-white race are *less* likely to receive treatment with an SGLT2 inhibitor or GLP1 analogue, despite being among the populations who stand to benefit most.8,18,19 Inequities in the use of these medications have also been observed extend to older, more frail patients, as well as female sex.18,21,22

**KNOWLEDGE TO DATE, INCLUDING RATIONALE**

**Diabetes Mellitus.** In Ontario, 10% of the population has diabetes.14–17 Diabetes mellitus is the most common cause of end-stage renal disease, atraumatic amputation, and blindness in individuals between the age of 20 and 74.14,15,59 It is also a common cause of heart failure, coronary artery disease, and stroke.59,60 Approximately 75% of people with diabetes will die of cardiovascular disease, and T2DM reduces life expectancy by 10 years.60–62 63,64

**Overview of pharmacologic management for T2DM.** Metformin has been the recommended first-line treatment for patients with T2DM for the past 30 years.65–67 In the landmark UKPDS-34 trial, metformin reduced the risk of cardiovascular events; however, this has not been consistently observed in subsequent clinical trials.68–71 Two of the most-used second line agents were, and still are, sulfonylureas and DPP4 inhibitors; neither improve cardiovascular outcomes.28 Certain DPP4 inhibitors are associated with an increased risk of heart failure,72 and a recent meta-analysis demonstrated that 10% of patients started on a sulfonylurea experience hypoglycemia, in addition to the issue of weight gain.46 Fortunately, there are now newer classes of medications preferentially recommended by recent guidelines, such as SGLT2 inhibitors and GLP1 analogues, that have proven cardiovascular benefits, do not cause hypoglycemia, and do not cause weight gain.35,36

**An overview of the newer classes of diabetes medications.** Both SGLT2 inhibitors and GLP1 analogues have proven cardiovascular benefits and are now the preferred second-line agents for adults with T2DM at increased cardiovascular or renal risk.28,31,73,74 SGLT2 inhibitors inhibit the reabsorption of glucose at the proximal convoluted tubule leading to a modest reduction in hemoglobin A1C ~0.5%.75,76 They cause approximately 100g of glucose to be excreted into the urine each day,77 resulting in weight loss (~5 lbs), and reductions in both systolic blood pressure (~5 mmHg) and proteinuria. Large-scale, double-blind, randomized trials have also identified that the two most-prescribed SGLT2 inhibitors (empagliflozin and canagliflozin, both available in Ontario) reduce a person’s risk of myocardial infarction, stroke, cardiovascular mortality, and potentially all-cause mortality.28 Subsequent clinical trials identified that SGLT2 inhibitors also reduce a person’s risk of heart failure or renal failure (Table 1). Clinical trials published in the past 1-2 years have demonstrated that the heart failure and renal failure benefits extend to patients who do not have T2DM.1–5

GLP1 analogues slow gastric emptying, reduce glucagon secretion, and promote insulin secretion in a glucose-dependent manner.78 The two GLP1 analogues on the Ontario drug formulary are lixisenatide and semaglutide. Both are injectable medications, and semaglutide is the most used in Ontario because it is a once-weekly injection, as opposed to once daily (lixisenatide). GLP1 analogues reduce a person’s hemoglobin A1C by approximately 1%, and have additional benefits including weight loss (~8 lbs) and reductions in systolic blood pressure (~5 mmHg). Large-scale, double-blind, randomized trials have identified that both medications reduce a person’s risk of myocardial infarction, stroke, cardiovascular mortality, and potentially all-cause mortality.33,34 A recent meta-analysis of the cardiovascular outcome trials suggests there may be additional benefits of GLP1 analogues, including reductions in renal failure and heart failure.33,34 Some of the benefits of GLP1 analogues also extend to adults with increased body mass index who do not have diabetes.6,7 A final benefit shared by both SGLT2 inhibitors and GLP1 analogues are that they have been shown to improve the patient’s quality of life.79–81

Table 1. Summary of large randomized clinical trials for SGLT2i and GLP1a for adults with T2DM

|  |  |  |  |
| --- | --- | --- | --- |
|  | **CV events**30,82 | **Heart failure**82,83 | **Renal failure**30,82 |
| **Primary outcome** | Stroke, MI, CVD | Heart failure or CVD | Renal failure\* |
| SGLT2i arm | 10% | 3% | 1.5% |
| Placebo arm | 12% | 5% | 3% |
| Relative risk reduction | 10% [5%,15%] | 25% [18%,32%] | 38% [30%,44%] |
|  |  |  |  |
| GLP1a arm | 7% | NA | N/A |
| Placebo arm | 9% | N/A | N/A |
| Relative risk reduction | 14% [7%, 20%] | 11% [2%,18%]\*\* | 21% [13%,27%]\*\* |

Legend: SGLT2i = sodium glucose co-transporter 2 inhibitor; GLP1a = glucagon like peptide-1 analogue; MI = myocardial infarction; CVD = cardiovascular death; \*a composite of dialysis, transplantation, or a sustained estimated GFR of <15 ml per minute per 1.73 m2, a doubling of the serum creatinine level, or death from renal or cardiovascular causes. \*\*The heart failure and renal failure outcomes are based on a meta-analysis of the cardiovascular outcome trials.

**Use of SGLT2 inhibitors and GLP1 analogues in Canada.** In March 2022, our team published a study of nationwide SGLT2 inhibitor prescribing that showed the slow uptake to date.40 The slow uptake is unsurprising, and characteristic of most new medications used to treat chronic diseases.18,19,84–87 In the inpatient setting, the slow uptake of SGLT2 inhibitors into practice can likely be attributed to following: First, many hospitals in Canada implemented policies to restrict SGLT2 inhibitor prescribing in hospital. While these are slowly lifting—owing to the impressive benefits of SGLT2 inhibitors—there will likely be slow uptake at these hospitals because of a lack of familiarity with the medication class. Second, SGLT2 inhibitors have an important, albeit rare, associated risk of DKA, which can be potentially life-threatening.42,50,51 Finally, in the case of both SGLT2 inhibitors and GLP1 analogues, it is impossible for generalists to keep up with the latest guidelines for the myriad of conditions that affect their patients, and it is well-established that clinical practice guidelines alone are insufficient to change clinical practice.88 The existent disparities in the use of new diabetes medications and related equity concerns are discussed in our Statement on EDI and SGBA+.

**Common side-effects of SGLT2 inhibitors and GLP1 analogues.** The most common side-effects of SGLT2 inhibitors are light-headedness and genital yeast infection. The light-headedness is generally transient and resolves within days of starting the medication. Yeast infections of the genitalia affect 8% of women and 2% of men who receive an SGLT2 inhibitor. These infections are typically mild in nature and resolve with topical treatment. The most common side effects of GLP1 analogues are nausea and gastrointestinal upset. These can affect up to 30% of patients prescribed a GLP1 analogue, but typically improve over time. Neither SGLT2 inhibitors nor GLP1 analogues cause hypoglycemia.89

**Rare side-effects.** SGLT2 inhibitors are associated with an increased risk of DKA; this affects approximately 0.5% of patients within 1 year of starting the medication.37,42,43,50  There have been concerns that the SGLT2 inhibitor canagliflozin (but not other SGLT2 inhibitors) might be associated with an increased risk of amputation.90 A subsequent clinical trial91 and data from routine care, including two studies by our team, suggests against an increased risk of amputation.92,93 This is an area of active ongoing research, but is outside the purview of this submission.94 GLP1 analogues have a theoretical risk of thyroid cancer, and for that reason the medication is contraindicated for adults with a history of medullary thyroid cancer, familial thyroid cancer, and patients with multiple endocrine neoplasia 2 (MEN-2), and is cautioned for adults with a genetic predisposition to follicular or papillary thyroid cancer.95–97 Another potential rare risk is anaphylaxis, which to date has been observed in some observational studies.98,99

**SGLT2i-associated DKA.** After the approval of SGLT2 inhibitors, case reports of DKA began to emerge.39,45,100,101 DKA can be life-threatening and often requires admission to the intensive care unit.102 The reports of SGLT2i-associated DKA were surprising, because DKA typically affects patients with type 1 diabetes mellitus (T1DM) rather than T2DM, and because many of the cases were among patients with relatively normal glucose values (instances known as “euglycemic DKA”). Our team conducted multiple observational studies among outpatients that consistently identified an approximately two-fold higher relative risk of DKA when using an SGLT2 inhibitor compared to other classes of medications.37,42,43,50 Absolute risk of DKA was approximately 0.5% within 1 year of starting an SGLT2 inhibitor.37,42,43,50

**Risk of SGLT2i-associated DKA in hospital.** Our team’s meta-analysis confirmed that existing studies of SGLT2i-associated DKA were of outpatients in routine care or clinical trials.51 The inpatient data that do exist are a combination of case reports and case series primarily related to post-operative patients.103,104 **The largest available case series included 14 patients**.105 There are physiologic reasons why inpatients may be at high risk: for example, important triggers for DKA include myocardial infarction, severe dehydration, trauma, and recent surgery.102 Robust, methodological studies, like the work proposed herein, are needed to quantify this risk to hospitalized patients.

**The safety of starting an SGLT2 inhibitor in hospital.** There have been 3 recent clinical trials of SGLT2 inhibitor use in hospital.5,106,107 A recent meta-analysis confirmed that there are significant cardiovascular benefits when the medications are started in hospital, and that it is safe to do so: the analysis found, in patients with acute heart failure, the use of SGLT2 inhibitors either during their hospitalization or early after discharge resulted in 48% lower odds of rehospitalization for heart failure, without increased risk of acute kidney injury, hypotension, or hypoglycemia.108 These studies were under-powered to assess risk of SGLT2i-associated DKA, but the lack of a signal is reassuring.

**Identifying patients at highest risk of SGLT2i-associated DKA.** The available literature on the risk factors for SGLT2i-associated DKA, led primarily by our team, are summarized in Appendix A, Table 2. Using data from a US claims database (N=111,442), we implemented two supervised machine learning techniques to identify potential candidate predictors among 100 baseline variables.50 This work demonstrated that 80% of the included variables had little to no effect on a person’s risk of DKA (quantified using the relative importance value from gradient boosted tree model). A relatively small number of potential predictors had large relative importance values; these variables are summarized in the rightmost column of Appendix A, Table 2. Notably, an elevated A1C <10% and serum bicarbonate <18 mmol/L were strong risk factors. **In the inpatient setting, both tests can be readily ordered, which can help to mitigate risk of SGLT2i-associated DKA while patients are in hospital**.

**Pharmacologic management of T2DM in hospitalized patients.** In-hospital management of diabetes relies heavily on insulin use: Canadian national diabetes guidelines recommend use of insulin in critically ill patients, and continuation of home oral medications only in stable patients without contraindications.36 Our preliminary data from GEMINI identify that ~25% of patients receive a sulfonylurea in hospital, which is concerning given that sulfonylureas lack clinical benefits and have a propensity to cause hypoglycemia. Recent clinical trials of SGLT2 inhibitor use during hospitalization in patients with acute decompensated heart failure showed (i) reduced risk of rehospitalization for heart failure and (ii) improved patient-reported symptoms.5,106–108 For GLP1 analogues, a 2019 multicentre randomized trial examined the safety and effectiveness of the GLP1 analogue exenatide and found the medication (either alone or in combination with basal insulin) to be safe and effective for the management of hospitalized general medical patients with T2DM.109

**Barriers to starting a newer diabetes medication.** Two systematic reviews identified that common barriers to starting any new medication can be categorized as patient-level (e.g., cost, education, age), physician-level (e.g., familiarity with medications, risk tolerance), and organizational (e.g., access to medications).86,110 While systematic reviews on the barriers to prescribing newer diabetes medications are lacking, other studies have identified a lack of familiarity with these medications and concern about the risk of SGLT2i-associated DKA as barriers to prescribing.111–113 As discussed in our Statement on EDI and SGBA+, existing biases can also feature as barriers when it comes to prescribing newer diabetes medications.8,18–22

**Starting medications in the inpatient setting is an important opportunity.** Narrative reviews have identified that patients perceive medications initiated while in hospital as essential for their health.114 Studies show that starting new medications for chronic diseases in-hospital, including at the time of discharge, leads to improved medication adherence compared to deferring the decision to the outpatient setting.115–119 Other studies demonstrate that family physicians are more likely to continue medications started from a recent hospitalization, but are less likely to initiate a new prescription following a recent discharge from hospital.120,121A recent study from the US demonstrated that 72% of endocrinologists prescribed an SGLT2 inhibitor, compared to 23% internal medicine physicians and 21% of family medicine physicians.122–124 This aligns with qualitative research identifying that family physicians have a lack of familiarity with these medications, and prefer these medications are started by a specialist.125 Our preliminary data from GEMINI indicate that SGLT2 inhibitors and GLP1 analogues are rarely prescribed to inpatients—yet 40% of patients with diabetes in GEMINI had a history of cardiovascular disease, kidney disease, or heart failure, and thus are most likely to benefit from these classes of medications. Further, starting the medication in hospital means the patient can be closely monitored for side-effects and intolerance. Taken together, these points outline a need for research and knowledge translation focused on the inpatient setting.

**The potential importance of genetic variants to explain idiosyncratic adverse reactions: identifying patients at highest risk of DKA.** Idiosyncratic adverse reactions are rare, not dose-related, and often unpredictable.126 However, recent pharmacogenomic studies have identified that some of these seemingly idiosyncratic drug reactions can be explained by genetic factors.127–129 SGLT2i-associated DKA is not dose dependent, occurs soon after the medication has been started, and the exact mechanism for the adverse event remains unclear—for these reasons, genetic variants may be associated with this adverse outcome. Testing for genetic variants is feasible by way of low-cost genetic array technologies. Genetic variants have been shown to play an important role in modulating risk of rare adverse drug events in other clinical contexts, **as demonstrated by co-applicants Drs. Drögemöller and Wright** (e.g., genetic variants with large effect sizes for drug-induced liver injury and ototoxicity).127,128,130,131

**Pharmacogenomics overview.** Pharmacogenomics is the study of the interplay between the human genome and the science of pharmacology. A goal of pharmacogenomics is to identify if genetic variants can explain rare and seemingly idiosyncratic adverse drug reactions. Most often this is done using a genome wide association study (GWAS).132 This is the ideal approach when there is not one specific candidate genetic target. The human genome project identified that all individuals share the same 99.9% of genetic code, and that individual-level genetic diversity is explained by the remaining 0.1%. It is within this 0.1% that variants to individual genes can be found. These variants are referred to as single nucleotide variants, or more commonly, single polymorphisms (SNPs). GWAS analyzes each SNP and its association with a given outcome (e.g., an adverse drug reaction) to determine the level of statistical significance between each SNP and the outcome of interest. One clinical example of this approach was a study identifying whether genetic variants were associated with statin-induced myopathy (N = 85 cases and 90 controls).133 They identified a single SNP that was associated with 17-fold higher odds of statin-induced myopathy. It is rare in clinical epidemiology to find any patient-level characteristics with this strong an association with an adverse event, but it is possible to determine such strong associations with genomics. There are other similar examples whereby a single SNP was found to have a strong association for an adverse drug reaction (e.g., liver injury from flucloxacillin, cisplatin, and ototoxicity).134 As highlighted in a recent review article, the **sample size needed for GWAS for a rare adverse drug reaction is often less than 200 individuals**.134

**Why DKA might be related to genetic factors.** There are several potential genetic targets to consider. SGLT2 inhibitors can decrease urinary excretion of ketone bodies, which is mediated by sodium-coupled monocarboxylate transporter 1 (SLC5A8).53,135 An area of active research is understanding how expression of genetic variants responsible for SLC5A8 affect the handling of ketones in the kidney.52 Another potential genetic target is GLUT2.56,136 GLUT2 is a critical mediator of glucose entry into beta cells and affects the affinity for SGLT2 inhibitors. High affinity can affect glucose sensing and cause an absolute loss of beta cell insulin secretion.56 Other potential targets are genetic variants responsible for hepatic ketone metabolism, or genetic variants in the UGT1A9 and UGT2B4 enzymes which are known to breakdown SGLT2 inhibitors.54 There is also a possibility that the genetic variant might pertain to a subtype of diabetes, such as ketosis prone diabetes.137 Because there is no single potential variant to focus on, GWAS is an ideal approach.

**PROJECT DESIGN, METHODOLOGY, AND ANALYSIS**

Table 1. Methods Overview

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Objective 1** | **Objective 2** | **Objective 3** |
| **Data source** | GEMINI | GEMINI | GEMINI, ICES, Denmark |
| **Study population** | T2DM patients hospitalized 2015 – 2023 | T2DM patients hospitalized 2015 – 2023 | T2DM patients hospitalized 2015 – 2023 |
| **Exposure** | SGLT2i or GLP1 | SGLT2i | SGLT2i or GLP1 |
| **Comparator** | DPP4i or sulfonylurea | DPP4i or sulfonylurea | DPP4i or sulfonylurea |
| **Analytic approach** | Descriptive statistics and  logistic regression | Propensity score matching with Cox model | Propensity score matching with Cox model |
| **Study outcomes** | Predictors of SGLT2i or GLP1 utilization in hospital | Incident rate and incidence rate ratio for SGLT2i-associated DKA | Incident rate and incidence rate ratio for clinical outcomes |
| **Objective 4** | | | |
| **Data source** | Prospective case-control study; patient recruitment | **Analytic approach** | Saliva sample collection, processed through GWAS |
| **Study population** | T2DM patients on SGLT2i hospitalized with DKA (cases) and without DKA (controls) | **Study outcomes** | Genetic variants associated with SGLT2i-associated DKA |

Legend: GEMINI = General Medicine Inpatient Initiative; T2DM = type 2 diabetes mellitus; SGLT2i = sodium glucose co-transporter 2 inhibitor; GLP1 = glucagon like peptide-1 analogue; DPP4i= dipeptidyl peptidase 4 inhibitor; DKA = diabetic ketoacidosis; GWAS = genome-wide association study.

**GEMINI:** The General Medicine Inpatient Initiative (GEMINI) is Canada’s largest hospital data and analytics network. GEMINI provides granular clinical data with 98-100% accuracy across (i) detailed clinical patient data (e.g., demographics, diagnoses, vitals, bloodwork, medications, radiology); (ii) physician- (e.g., age, sex) and hospital-level data (e.g., patient volume); (iii) administrative inpatient data (e.g., care providers, cost, length-of-stay); and (iv) administrative data regarding **pre- and post-hospital care through linkage with ICES** (e.g., ambulatory visits, emergency department visits, readmission and mortality).138 GEMINI data are **updated quarterly**, enabling rapid research. At present, there are data from >1.8 million admissions across 31 hospitals, covering ~65% of all medical (e.g., general medicine, cardiology, etc.) and intensive care beds in Ontario. Each year GEMINI grows by approximately 400,000 admission and thus by 2023 will surpass ~2 million. GEMINI has built a cloud-based, innovative, high performance computing environment that allows virtual access through partnerships with the Vector Institute and HPC4Health, a Compute Canada-supported centre. **A linkage between GEMINI and ICES was completed in 2022. The linkage was via OHIP numbers, allowing us to link >98% of our population (as OHIP numbers are only missing in <2%).**

**ICES:** ICES includes longitudinal data for residents of Ontario. The data is primarily administrative data (e.g., diagnostic codes, procedural codes, demographics, vital status), but laboratory data from both inpatient and outpatient labs are now also available. Important limitations of ICES data include the lack of medication data for adults between the ages of 25 to 65, and the lack of granular inpatient data. However, because GEMINI focuses on inpatient data and includes inpatient medication data for all ages, the GEMINI-ICES linkage has created one of the most comprehensive health databases.

**Nationwide Danish Data Repository:** The nationwide database in Denmark is similar to ICES, and includes longitudinal data on nearly all Danish citizens.139–141The data is primarily administrative data (e.g., diagnostic codes, demographics, vital status) and laboratory data. Similar to ICES, it lacks granular inpatient data, but unlike ICES, it includes medication for all individuals regardless of age.

**A comparison of GEMINI, ICES, and the Nationwide Danish Data Repository** can be found below in Table 2.

Table 2. A comparison of GEMINI, ICES, and the Nationwide Danish Data Repository

|  |  |  |  |
| --- | --- | --- | --- |
|  | **GEMINI** | **ICES** | **Danish Database** |
| Population | Hospitalized patients in Ontario | Ontario residents | Danish residents |
| Sample size | ~1.8 million\* | 14 million | 6 million |
| Prescription data | All ages | Adults > 65 years | All ages |
| Inpatient labs | Yes | Yes | Yes |
| Outpatient labs | NA | Yes | Yes |
| ICD-10 codes | Yes | Yes | Yes |
| CCSR codes | Yes | Yes | Yes |

Legend: GEMINI = General Medicine Inpatient Initiative, ICD-10 = International Classification of Diseases, tenth revision. \*as of 2022; by 2023, it will surpass 2 million. CCSR = Clinical Classification Software Refined

**SEX- AND GENDER-BASED+ ANALYSIS**

Detailed discussion of our SGBA+ analysis plan can be found in our Statement on EDI and SGBA+. An overview of the SGBA+ analysis plan for objectives 1, 2, and 3 can also be found in Appendix A, Table 1.

**METHODS**

**Methods for Objective 1: Current** **SGLT2 inhibitor and GLP1 analogue use in hospital**

**Data source:** GEMINI database.

**Study population:** Patients over 18 years of age with T2DM who were hospitalized between 2015 and 2023 and received a sodium glucose co-transporter 2 (SGLT2) inhibitor or a glucagon like peptide-1 (GLP1) analogue during hospitalization.

**Definition of T2DM:** We will define T2DM using the clinical gold standard of hemoglobin A1C value ≥ 6.5%. For patients who do not have a hemoglobin A1C, we will use the International Classification of Diseases, tenth revision (ICD-10) code for T2DM. Doing so allowed us not to “miss” patients who have well-controlled diabetes (i.e., A1C less than 6.5%). We recently validated use of ICD-10 codes for adults with diabetes in GEMINI and have shown these codes have positive predictive value and negative predictive value exceeding 90%.142 If needed, we can leverage the Ontario Diabetes Database (through the GEMINI-ICES linkage) to further minimize misclassification: validation of the Ontario Diabetes Database against physician charts demonstrated sensitivity of 86% and specificity of 97%.143

**Data collection:** Within GEMINI, we will have access to patient- (described below) and physician-level characteristics (i.e., sex, years in practice, and sub-specialty training). The patient level variables will include demographics, proxies for socioeconomic status, frailty, comorbid conditions, and laboratory results; a complete list is provided in Appendix A, Table 3. Manual chart review will also be done to identify other variables not captured in GEMINI (e.g., body mass index, year of diabetes diagnosis) and to confirm the diagnosis of T2DM. The hospital-level variable will denote at which hospital the patient received care.

**Primary outcome:** Predictors of SGLT2 inhibitor and GLP1 analogue use in hospital.

**Analysis plan:** We will provide descriptive statistics to characterize patient- and physician-level variables associated with SGLT2 inhibitor and GLP1 analogue prescribing. Descriptive statistics stratified by both patient and physician sex will also be provided to identify sex-specific differences in prescribing. Stratified analyses will also be performed by other equity domains (i.e., frailty, age, socioeconomic status). A multivariable logistic regression model will be constructed that includes patient-, physician-, and hospital-level characteristics that relate to the odds of being prescribed a SGLT2 inhibitor; a similar model will be constructed for GLP1 analogues.138,144,145 A complete list of variables is provided in Appendix A, Table 3. Stratified analysis will be done to assess differences between hospital sites with and without a policy restricting SGLT2 inhibitor prescriptions to inpatients.

**Preliminary data:** Within GEMINI, data are available from 1.8 million hospitalizations. We have identified that approximately 540,000 hospitalizations were for adults with T2DM (median age 72 years, interquartile range 60 – 81); approximately 5% (~27,000) of these patients received an SGLT2 inhibitor during hospitalization and 1% (~5,400) received a GLP1 analogue. We have also calculated the number of patients with cardiovascular disease, heart failure, or renal failure who stood to benefit from an SGLT2 inhibitor or GLP1 analogue and did not receive one—we can now estimate that this represents ~25% of patients with T2DM in GEMINI.

**Limitations & mitigation strategies:** Because SGLT2 inhibitors and GLP1 analogues are expensive, an important predictor of their use will be whether a patient has a drug plan. GEMINI does not collect these data; however, for adults over 65 years of age in Ontario, medications are paid for by the government. Our preliminary data identify that the median age of adults with diabetes in GEMINI are 72 years, which mitigates this limitation.

**Methods for Objective 2: Risk of SGLT2i-associated DKA**

**Data source:** GEMINI database.

**Study population:** We will identify patients over 18 years of age with T2DM who were hospitalized between 2015 and 2023 and were prescribed an SGLT2 inhibitor during hospitalization. **Exclusion criteria:** Patients with type 1 diabetes mellitus (T1DM), patients on dialysis, and patients with diabetic ketoacidosis (DKA) on the first day of their hospitalization. Patients with T1DM will be excluded because SGLT2 inhibitors are not approved for this patient population; patients on dialysis will be excluded because SGLT2 inhibitors are contraindicated for them. We will exclude patients with DKA on the first day of their hospitalization as this indicates they were likely hospitalized because of DKA, rather than DKA being caused by SGLT2 inhibitor use in hospital.

**Outcome definition:** We will define DKA using the gold standard laboratory criteria of acidosis (pH <7.3 or anion gap >16, bicarbonate ≤18, presence of serum or urine ketones).146 This approach is superior to using ICD-10 codes because laboratory values establish the ground truth definition of DKA. **Primary outcome:** Inpatient DKA, defined using laboratory values. **Secondary outcomes**: Readmission for DKA within 180 days. Proportion of patients who had clear risk factors (as defined by our earlier paper50) for DKA prior to receiving an SGLT2 inhibitor (e.g., serum bicarbonate, hemoglobin A1C, recent DKA episode). As suggested in peer-review, we have also included a falsification endpoint of pneumonia defined using ICD-10 codes which have been previously validated within GEMINI (in-press).

**Analysis plan:** We will calculate the incidence rate of in-hospital DKA with SGLT2 inhibitor use and provide results stratified by patient sex. To provide relative risk estimate and absolute risk estimates, we will compare our results to the rate of DKA in patients who were prescribed another second-line medication that is known not to cause DKA, such as dipeptidyl peptidase 4 (DPP4) inhibitors or sulfonylureas. Propensity score (PS) matching using a 1:1 ratio and without replacement will be used to match patients, using a caliper width of equal to 0.2 of the standard deviation of the logit of the propensity score147 (see Appendix A, Tables 3 and 4 for list of variables to be included in the PS model).

**Preliminary data:** We have identified that 98% of patients with diabetes in GEMINI have T2DM rather than T1DM. We have identified approximately 27,000 patients received an SGLT2 inhibitor, ~135,000 received a sulfonylurea, and ~162,000 received a DPP4 inhibitor.

**Power calculation:** We used the formula by Rothman et al.148 to estimate the sample size required to rule out a modest increased risk (RR 1.50) of SGLT2i-associated DKA. Using an alpha of 1.96, power of 90%, and a conservative estimated baseline risk of DKA of 1% (owing to inpatients possibly being at higher risk than outpatients), our required sample size of patients receiving an SGLT2 inhibitor is 10,500.149 If the risk was closer to 0.5% we would require ~30,000 patients who received an SGLT2 inhibitor, which is achievable with data in 2023.

**Limitations & mitigation strategies:** One concern is the accuracy of using ICD-10 codes to rule out T1DM, as patients with T1DM are at the highest risk of DKA. Co-applicant Dr. Weisman has validated a method for the diagnosis of T1DM from administrative healthcare data in Ontario.150 Also, our preliminary data show that < 2% of patients within GEMINI have an ICD-10 code for T1DM; additionally, SGLT2 inhibitors are not approved for adults with T1DM. Thus, the number of patients in GEMINI will be low, and any misclassification to be minimal.

**Methods for Objective 3: Consequences of not receiving an SGLT2 inhibitor or GLP1 analogue**

**Data source:** We will utilize the GEMINI database with a linkage to ICES, and replicate our findings using the Nationwide Danish Data Repository (two cohorts).We will report results separately for each dataset and will not meta-analyze the results, given the differences in the age distributions between the two datasets. A comparison of GEMINI, ICES, and the Nationwide Danish Data Repository can be found above in Table 2.

**Study population:** We will use the TARGET Trial Framework.151 **Inclusion criteria:** Patients over 18 years of age with T2DM who were hospitalized between 2015 and 2023 and were newly prescribed either an SGLT2 inhibitor or a GLP1 analogue during their hospitalization in Ontario or Denmark. **Exclusion criteria:** Patients with T1DM, patients on dialysis, and patients with DKA on presentation to the hospital. **Comparator group:** patients who newly received another second-line medication (i.e., sulfonylurea, DPP4 inhibitor).

**Primary outcome:** We will assess the rate of a composite outcome including myocardial infarction, stroke, heart failure hospitalization, or renal failure over a 365-day follow up. **Secondary Outcomes:** We will evaluate the components of the composite. Myocardial infarction, stroke, and heart failure hospitalization will be defined using the validated ICD-10 codes, which have a PPV exceeding 90%.152–154 Renal failure, similar to the renal outcomes clinical trial, will be defined as new start dialysis or a doubling of the serum creatinine relative to the patient’s creatinine on hospital discharge.1,91 All of these outcomes are readily available in Ontario through the GEMINI-ICES linkage, and in the Danish dataset. **Secondary Outcomes (in-hospital outcomes):** In GEMINI, we will assess the rate of severe hypoglycemia (i.e., glucose <2.2 mmol/L) during the hospitalization (not performed in Denmark due to lack of glucose data). Because GLP1 analogues are associated with an increased risk of anaphylaxis, we will include this as a secondary outcome. Anaphylaxis will be defined using medication data: specifically, whether the patient received epinephrine at anaphylaxis dosing. We will also assess the rate at which SGLT2 inhibitors or GLP1 analogues are stopped in hospital after they are newly started; this will serve as a proxy that the medications were not tolerated. We will also compare the rate of re-admission with hypoglycemia during the subsequent 30 days after the patient’s initial discharge from hospital.

**Statistical Analysis plan:** We will perform 1:1 propensity score matching to adjust for baseline confounders (see Appendix A, Tables 3 and 4 for variables). Pair-wise comparisons will be made between SGLT2 inhibitors and another second-line diabetes medication (excluding GLP1 analogues) and between GLP1 analogues and another second-line diabetes medication (excluding SGLT2 inhibitors). The propensity score will be calculated for each of the pair-wise comparisons and within each dataset (i.e., Ontario and Denmark). Our approach of using a composite analysis aligns with the primary outcomes from the noted randomized trials. It also helps to reduce the risk of competing events, and the composite will be analyzed using a Cox Proportional hazards model.155,156 Schoenfeld residuals will be plotted to test the proportional hazards assumption. To assess any sex-specific differences, we will provide results stratified by sex. **Sensitivity analyses:** We will conduct a sensitivity analysis stratified by adults over age 65 years in Ontario because ICES lacks medication data for adults under 65 years. As suggested in peer-review, we have also included a falsification endpoint of pneumonia defined using ICD-10 codes previously validated within GEMINI (in-press).

**Preliminary data:** Using data from GEMINI, we have identified ~27,000 patients who received an SGLT2 inhibitor, ~5,400 who received a GLP1 analogue, ~135,000 who received a sulfonylurea, and ~162,000 who received a DPP4 inhibitor. Within the Danish repository we have identified ~45,000 patients who received an SGLT2 inhibitor and ~15,000 who received a GLP1 analogue. To identify how many of these patients started the medication in hospital requires funding for analyst support.

**Power calculation for SGLT2 inhibitors:** The available meta-analysis of clinical trials allowed us to calculate the expected rate of the **primary composite outcome** at 1-year, which is estimated to be 10% in the SGLT2 inhibitor arm and 14% in the placebo/comparator arm. Assuming these event rates, an alpha of 1.96, and 90% power, we will require a sample size of 1,200 patients who received an SGLT2 inhibitor.149 **Power calculation for GLP1 analogues:** The available meta-analysis of clinical trials allowed us to calculate the expected rate of the **primary composite outcome** at 1-year, which is estimated to be 10% in the GLP1 analogue arm and 12% in the placebo/comparator arm. Assuming these event rates, an alpha of 1.96, and 90% power, we will require a sample size of 4,800 patients who received a GLP1 analogue.149

**Potential limitations and mitigation strategies:** There are multiple approaches to account for competing risks. We anticipate completing sensitivity analyses such as the Fine-Gray approach and cause specific analyses. Without randomization, selection bias can always impact a study’s findings. We anticipate conducting additional secondary analyses to ensure are findings are robust, and calculating an E-value to quantify how unmeasured confounders might affect our results.157 For the small subset of patients within GEMINI under age 65 who have diabetes and are not part of the Ontario Drug Benefit program, there is a possibility that they would not have drug coverage for an SGLT2 inhibitor or GLP1 analogue, and therefore would not continue the mediation upon discharge. However, if that were the case, it is highly unlikely the patient would be started on one of these medications while in hospital, because doctors and pharmacists generally don’t prescribe medications for chronic diseases if the patient cannot access those medications on discharge. Additionally, our cohort from the Danish dataset will have associated medication information for adults of all ages, negating this limitation in that analysis.

**Methods for Objective 4: Identifying genetic variants associated with SGLT2i-associated DKA**

**Study setting:** We will conduct a prospective case-control study at hospitals in Canada and the US. Patients will be recruited from the general medical wards.

**Study Population:** We will include patients who are 18 years of age or older, with a diagnosis of T2DM, and who had received an SGLT2 inhibitor during the study period. We will exclude patients who are pregnant, have a diagnosis of T1DM, are unable to spit 10mL into a vial, or have a first degree relative who is already participating in the study.

**Case definition:** We will define cases as patients who were hospitalized with DKA at one of our study sites. The definition of DKA is based on other clinical trials evaluating DKA as a safety outcome and includes the following: serum bicarbonate ≤18 mmol/L, pH ≤7.30, and presence of ketones (blood or urine). SGLT2i-associated DKA will be defined as the combinationof DKA plus having received an SGLT2 inhibitor in the 7 days prior to presenting to the emergency department.

**Control definition:** We will define controls as patients who were hospitalized at one of our study sites and who did not have DKA at any point either during their current admission or within the past year.

**Data collection:** For cases, we will use the electronic medical record and patient interviews to collect data related to patient demographics (e.g., age, sex, weight, height, and self-reported race), comorbid conditions, medications, labs, current hospitalization, and DKA-related precipitating factors. Comorbid conditions include the date on which the patient was diagnosed with diabetes and the presence of conditions related to sequelae of diabetes (e.g., cardiovascular disease, renal failure), history of cancer, and known genetic disorders. Medication details will focus on diabetes medications, and more specifically on the patient’s SGLT2 inhibitor (e.g., adherence, SGLT2 inhibitor type). Potential precipitant factors for DKA include recent fasting, surgery, dietary changes, alcohol binge, or recent reduction in their insulin dose. For all patients (both cases and controls), we will collect the following laboratory data: hemoglobin A1C, glucose, pH, bicarbonate, anion gap, creatinine, ketones. For patients with multiple glucose, creatinine, or anion gap measurements, we will record the highest value. For patients with multiple pH or bicarbonate values, we will enter the lowest value. All controls, like the cases, will have had a diagnosis of T2DM. The controls will be further matched on sex and genetic ancestry; our data capture form for both cases and controls includes fields for the self-reporting of these data.

**Genetic sample collection:** The study will involve one visit to the participant at which point in time genetic samples will be collected using a DNA saliva collection kit (Oragene OG-600). For patients identified prospectively, the saliva sample collection will be performed while the patient is in hospital and then mailed to the lead site. For patients who were already discharged, the saliva kit will be mailed to them with instructions to complete their own saliva sampling and return the sample to the lead site.

**Genotyping:** After identifying and consenting patients and retrieving the saliva samples, we will send the samples for genome-wide genotyping (Illumina Global Screen Array -24). **All genomic analyses will be performed by Co-investigators Drs. Drögemöller and Wright, who are experts in pharmacogenomics.**

**Primary outcome:** Genetic variants associated with SGLT2i-associated DKA.

**Statistical power:** The use of **disease and** **drug-matched controls** has been shown to increase the power to identify genetic variants associated with adverse drug reactions that have prevalence rates of < 1%132; this approach has been successfully performed by our study team in past research.127,128 Co-investigators Drs. Drögemöller and Wright have conducted the power calculation: the total sample size needed to have power to detect genetic variants would be 50 patients with SGLT2i-associated DKA and matching controls. This sample size provides 85% power to find a significant association (P<5x10-8) of genetic variants (minor allele frequency ≥ 0.15; odds-ratio > 5) with SGLT2i-associated DKA (genpwr package used for power calculation).42,50,127,158 As shown by our study team’s prior work, rare adverse events require a much lower sample size than a study of common genetic variants.127,128

**Statistical analysis:** Following sample and variant quality control, additional variants will be imputed using the TOPMed panel using their Imputation Server. Genetic ancestry will be calculated using principal component analyses. GWAS will be performed with SAIGE, including genetic ancestry and the relevant clinical/demographic variables as covariates, to identify genetic variants associated with SGLT2i-associated DKA.

**Feasibility:** Our study has received REB approval at 10 sites as of December 2022 and is on track to expand approval to a total of 20 hospitals by the spring of 2023. We have partnered with The Centre for Applied Genomics (TCAG) lab in Toronto and have a contract in place for them to process all the samples for genomic testing. We have recruited 5 patients as of December 2022, which demonstrates our ability to recruit patients.

**Potential limitations and mitigation strategies:** The greatest challenge for any prospective study is patient recruitment, especially in the case of rare events or outcomes. As noted, we are on track to have 20 hospitals recruiting patients as of the spring of 2023. If each site enrolls 2-3 patients in the next year, then we will have completed recruitment of cases. In the event we are unable to meet our recruitment targets for controls, we have applied for access to the Canadian Longitudinal Study of Aging (CLSA) database; details on CLSA data below. PI Fralick is currently working with the CLSA data for another unrelated project and is thus now familiar with the dataset. Another limitation is that GWAS may not identify any genetic variants. If we do not find any variants that reach genome-wide significance (P < 5x10-8) in the GWAS analyses, we will apply gene-based testing, which will decrease the burden of multiple testing (P < 2x10-6) and increase our power to uncover novel associations. Further, if the GWAS analyses reveal that individual genetic variants only explain a small portion of the observed variability, we will investigate the utility of polygenic risk scores, which simultaneously take the effects of thousands of variants into account, to develop improved genomic predictors of SGLT2i-associated DKA. Co-investigators Drs. Drögemöller and Wright are well-positioned to conduct these analyses, as evidenced by their prior work.159

**CLSA data:** CLSA is composed of a national, stratified, random sample of over 50,000 Canadian women and men aged 45 to 85 years at the time of recruitment, selected randomly for inclusion. Within CLSA is a longitudinal cohort of 2,700 adults with T2DM, which includes data on clinical outcomes (e.g., diabetic ketoacidosis), genetic sequencing, and detailed socio-demographic characteristics (e.g., genetic ancestry) that will allow for matching to occur. For CLSA-sourced controls, we will define a control as a patient who was on an SGLT2 inhibitor for at least 1 year, because the majority of DKA events occur within 180 days of starting on an SGLT2 inhibitor. If the patient has continued the medication for 1 year, it is highly unlikely they experienced associated DKA; if they had, their medication would have been discontinued.

**KNOWLEDGE TRANSLATION**

**Stakeholder engagement:** Our study team includes both generalists and specialists, and we have engaged a patient partner with the support of the Diabetes Action Canada (DAC) Patient Engagement Goal Group. Our patient partner will be engaged in our project for the entirety of the study. Any infographics and public-facing videos or presentations will be presented to them for feedback and iterative improvement. We will meet with them once quarterly (or more as needed) to provide updates on the status of the project. DAC has agreed to disseminate our results to patients through its patient partner councils, its website, its Digital Health to Improve Diabetes Care program, and its extensive social network. We will also work with the Ontario General Medicine Quality Improvement Network, an Ontario Health program that promotes the use of GEMINI data across 30 hospitals to improve the quality of care (led by co-investigators Drs. Verma and Razak).

**Knowledge dissemination:**

**[1] Clinical Tool.** Our research team created and launched SGLT2Rx.com in 2022. The tool provides estimates for a patient’s risk of (i) cardiovascular outcomes, (ii) heart failure hospitalization, (iii) renal failure with the use of an SGLT2 inhibitor, in addition to details related to costs and side effects.28 The website also provides results for comparator classes of medications, including GLP1 analogues. The tool was constructed using the theoretical domains framework160 with input from patients, pharmacists, medical trainees, endocrinologists, nephrologists, and internists. The tool is intended for use by clinicians but also provides 1-page summaries in lay language that clinicians can print out for their patients. The tool does not collect or store any of the entered data, negating privacy concerns. The tool’s development was funded by a BioTalent grant. As the studies proposed herein are completed, we will be able to add new pages related to the inpatient risk of SGLT2i-associated DKA, as well as the long-term risks and benefits of starting on an SGLT2 inhibitor or GLP1 analogue in hospital.

**[2] Integration into EMR.** We have met with the informatics teams at Telus and Oscar EMR. Both have committed to incorporating our clinical tool into their electronic medical record systems. When the integration is complete, whenever a patient has diabetes in their record, the integrated version of our application will appear as an option in the toolbar, and any fields that can be populated by existing information in the record (e.g., age, recent bloodwork, etc.) will be pulled into the tool for ease-of-use.

**[3] Multimedia promotion via YouTube videos and podcasts.** We will create a series of 5-minutes videos that outline strategies for the safe prescribing and optimization of new diabetes medications (including SGLT2 inhibitors and GLP1 analogues), as well as cover topics related to understanding diabetes and the available medications. These videos will be self-produced, drawing on team members’ extensive content and clinical experience. Videos will be directed to healthcare providers and patients, freely accessible, and hosted online (e.g., YouTube). PI Fralick has created such videos before; these videos have focused on clinical epidemiology (e.g., propensity score methods, pharmacoepidemiology, machine learning) and have received over 85,000 views to date (6,000 per month). The findings from each objective will also be included in podcast episode for the *Rounds Table*. PI Fralick is the co-director of the *Rounds Table*, which averages 8,000 downloads per month, is listened to in 50 countries around the world, and has 500,000 downloads to date.

**[4] Additional approaches for knowledge dissemination**. **[4a]** **Website**: Our research team has a website where KT materials (e.g., infographics, links to SGLTRx.com and YouTube series) will be provided. **[4b]** **Targeted presentations:** for family physicians, diabetes nurse educators, and at Continuing Medical Education events. **[4c] Publication**: We plan to share our results through a pre-print server to allow it to be freely available and in a peer-reviewed journal.

**TIMELINES AND MILESTONES**

We anticipate a 3-year timeline:

Details of the timeline and associated milestones can be found in Appendix A, Table 5. Objective 1 to be completed by end of Year 1. Objective 2 to be completed by Year 1.5. Objective 3 to be completed by end of Year 3. Objective 4 will be pursued continually through all 3 years of the project, with anticipated completion by end of Year 3. Knowledge translations activities will span the duration of the project.

**STATEMENT OF COLLABORATION**

**Timeline

Description automatically generated**

Legend: KT = knowledge translation, GEMINI = General Medicine Inpatient Initiative, GWAS = genome-wide association study

**RESEARCH TEAM EXPERIENCE, EXPERTISE & TIME COMMITMENT**

**Overview:** Our team includes physicians who care for patients with diabetes in the outpatient setting (BP, AW, SS), and inpatient ward (MF, BP, AV, FR, SS). This includes physicians who work in underserviced areas of Northern Ontario (MF). Our team also has a rich background in epidemiology, statistics, machine learning, GWAS (AP), pharmacogenomics (GW, BD), and implementing research into clinical practice, including expertise in knowledge translation (BP, MM, AV, FR). Our team also includes graduate students (MC) and a patient partner (PL).

**Detailed:** **Dr. Mike** **Fralick** is study PI [8 hr/week]. He is General Internist and Clinician Scientist at Sinai Health, UHN, and the Sault Area Hospital. He is a site lead for GEMINI and has co-authored studies using data from ICES (N=7), GEMINI (N=7), and the Danish Database (N=3) with study team members. He is currently co-supervising two PhD student with co-investigator Dr. Biering-Sørensen**,** and has direct access to the Danish database as a result of the collaboration. Role: oversight of all aspects of proposed research. **Drs. Amol Verma & Fahad Razak** [2 hr/week] are co-creators of GEMINI, as well as Provincial Clinical Leads at Ontario Health (Quality). Role: knowledge translation expertise and expertise with the GEMINI data. **Dr. Laura Rosella** [2 hr/week] is site director for ICES UofT and Associate Professor in Epidemiology at the University of Toronto. Role: expertise in advanced epidemiologic methods including risk prediction; expertise and experience with ICES data. **Dr. Bruce Perkins** [2 hr/week] is Professor of Medicine, Clinician Scientist, Endocrinologist at Sinai, and is PI Fralick’s Faculty mentor. Role: supervision, content expertise, expertise in knowledge translation. **Dr. Muhammad Mamdani** [1 hr/week] is Professor of Medicine and VP of Data Science at Unity Health and mentor to PI Fralick. Role: content expertise in data science and advanced analytics. **Dr. Alanna Weisman** [1 hr/week] is Clinician Scientist and Endocrinologist at Sinai Health and UHN. Role: content expertise, expertise working with data at ICES. **Dr. Tor** **Biering-Sørensen** [2 hr/week] is Associate Professor and Epidemiologist at the University of Copenhagen. Role: expertise in the Danish Dataset. **Dr.** **Shohinee Sarma** [2hr/week] is an Endocrinologist and PhD student at UofT. Please note Dr. Sarma’s participation will be strictly in her role as Research Fellow, separate from her graduate studies. Role: content expertise and support for Objective 2. **Dr. Galen Wright** [1 hr/week] is Canada Research Chair in Neurogenomics and has expertise in the genomics of drug safety and effectiveness. Role: genomics analysis (with BD). **Dr. Britt Drögemöller** [1 hr/week] has extensive experience in pharmacogenomic analyses and has been recently awarded a Canada Research Chair in Pharmacogenomics and Precision Medicine. Role: genomic analysis (with GW). **Dr.** **Andrew** **Paterson** [1 hr/week] is Co-director of the Statistical Analysis Facility at The Centre for Applied Genomics at SickKids Hospital. His work identifies genetic variations focused on traits related to diabetes. Role: oversight of the genome-wide analysis studies conducted on the collected samples. **Paul Lea** is patient partner, living with type 2 diabetes. Role: advising on our knowledge translation activities, interpretation of study results from the lens of a patient, inclusion as a co-author on the manuscripts. For his activities to date, we have paid him for his time and we plan to continue to do so.

**PREVIOUS COLLABORATIONS BETWEEN TEAM MEMBERS:** Fralickis GEMINI site lead and has worked closely with Verma & Razak, who are co-creators of GEMINI. Fralick, Verma, and Razak are co-principal investigators on a Dalla Lana School of Public Health Interdisciplinary Data Science Seed Grant to develop a multicentre database of patients hospitalized with diabetes in Ontario across 30 hospitals called “GEMINI-DM,” a subset of GEMINI. The GEMINI-DM project also involves applicants Mamdani, Perkins, and Weisman as collaborators. Fralick, Verma, and Razak were also co-principal investigators for a COVID-19 trial assessing the effect of prone positioning for hospitalized patients (doi: 10.1136/bmj-2021-068585). To date, they have co-authored >10 publications together, including in *BMJ*; *Diabetes, Obesity and Metabolism*; *CMAJ*; and *Journal of Hospital Medicine*. Presently, they are collaborating on two grants looking at the effects of COVID-19 on hospital performance, and the effects of hospital capacity strain on quality of care. Rosella is also collaborating on these two grants and has co-authored on two of the 10 aforementioned publications.

Perkins is Faculty Mentor to Fralick. He has supervised and provided expertise on several of Fralick’s projects to date. Presently, Perkins is lead PI on a grant involving Fralick looking at developing an educational tool to mitigate DKA in patients with type 1 diabetes. Mamdani is also mentor to Fralick, having formally supervised his Research Fellowship in Applied Machine Learning at LKS-CHART (now DSAA). Fralick and Mamdani have worked together on several projects that utilize machine learning to improve clinical care. Fralick and Mamdani have co-authored >10 publications together.

Fralick, Wright, Drögemöller, and Paterson have collaborated on previous grant proposals regarding the work on genomic predictors of SGLT2i-associated DKA. Fralick and Sarma have collaborated on previous diabetes-related grant proposals. Fralick and Biering-Sørensen have collaborated internationally for the past several years and have co-authored 5 studies together. Weisman has collaborated with Fralick and other team members on previous diabetes-related grant applications. Lea joined Fralick’s research team as patient partner through Diabetes Action Canada in 2020 and has provided insight and feedback on the ongoing work, including the web application SGLT2Rx.com.

**Scheduled meetings:** For Objectives 1-3, we plan to have bi-weekly meetings with the relevant study team members. We will also have separate dedicated bi-weekly meetings for Objective 4, which includes the team members with expertise in genomics. Drs. Perkins and Mamdani have weekly meetings with PI Fralick in their roles as faculty mentors to him.

**REFERENCES**

1. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med*. 2019;381(21):1995-2008.

2. Packer M, Anker SD, Butler J, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *N Engl J Med*. Published online 2020:1-12.

3. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med*. 2020;383(15):1436-1446.

4. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. *N Engl J Med*. 2021;385(16):1451-1461.

5. Voors AA, Angermann CE, Teerlink JR, et al. The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial. *Nat Med*. Published online February 28, 2022. doi:10.1038/s41591-021-01659-1

6. Perez-Montes DE Oca A, Pellitero S, Puig-Domingo M. Obesity and GLP-1. *Minerva Endocrinol*. 2021;46(2):168-176.

7. Srivastava G, Kumar RB. Once-Weekly Semaglutide in Adults with Overweight or Obesity. *N Engl J Med*. 2021;385(1):e4.

8. Elhussein A, Anderson A, Bancks MP, et al. Racial/ethnic and socioeconomic disparities in the use of newer diabetes medications in the Look AHEAD study. *Lancet Reg Health Am*. 2022;6. doi:10.1016/j.lana.2021.100111

9. Nadruz W, Claggett B, Henglin M, et al. Widening Racial Differences in Risks for Coronary Heart Disease. *Circulation*. 2018;137(11):1195-1197.

10. Diabetes Canada Clinical Practice Guidelines Expert Committee, Crowshoe L, Dannenbaum D, et al. Type 2 Diabetes and Indigenous Peoples. *Can J Diabetes*. 2018;42 Suppl 1:S296-S306.

11. Golden SH, Brown A, Cauley JA, et al. Health disparities in endocrine disorders: biological, clinical, and nonclinical factors--an Endocrine Society scientific statement. *J Clin Endocrinol Metab*. 2012;97(9):E1579-639.

12. Peek ME, Cargill A, Huang ES. Diabetes health disparities: a systematic review of health care interventions. *Med Care Res Rev*. 2007;64(5 Suppl):101S-56S.

13. Dyck R, Osgood N, Lin TH, Gao A, Stang MR. Epidemiology of diabetes mellitus among First Nations and non-First Nations adults. *CMAJ*. 2010;182(3):249-256.

14. World Health Organization. *Global Report on Diabetes*.; 2016. http://www.who.int/about/licensing/copyright\_form/index.html

15. Sun H, Saeedi P, Karuranga S, et al. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res Clin Pract*. 2022;183:109119.

16. Ligthart S, van Herpt TTW, Leening MJG, et al. Lifetime risk of developing impaired glucose metabolism and eventual progression from prediabetes to type 2 diabetes: a prospective cohort study. *The Lancet Diabetes & Endocrinology*. 2016;4(1):44-51.

17. Kalyani RR, Golden SH, Cefalu WT. Diabetes and Aging: Unique Considerations and Goals of Care. *Diabetes Care*. 2017;40(4):440-443.

18. Eberly LA, Yang L, Eneanya ND, et al. Association of Race/Ethnicity, Gender, and Socioeconomic Status With Sodium-Glucose Cotransporter 2 Inhibitor Use Among Patients With Diabetes in the US. *JAMA Netw Open*. 2021;4(4):e216139.

19. Eberly LA, Yang L, Essien UR, et al. Racial, Ethnic, and Socioeconomic Inequities in Glucagon-Like Peptide-1 Receptor Agonist Use Among Patients With Diabetes in the US. *JAMA Health Forum*. 2021;2(12):e214182.

20. Ding D, Glied SA. *Disparities in the Use of New Diabetes Medications: Widening Treatment Inequality by Race and Insurance Coverage*. Commonwealth Fund; 2022. doi:10.26099/vabp-0g69

21. Campbell DB, Campbell DJT, Au F, et al. Patterns and Patients’ Characteristics Associated With Use of Sodium/Glucose Cotransporter 2 Inhibitors Among Adults With Type 2 Diabetes: A Population-based Cohort Study. *Can J Diabetes*. Published online August 9, 2022. doi:10.1016/j.jcjd.2022.08.002

22. Abdelhafiz AH, Pennells D, Sinclair AJ. A modern approach to glucose-lowering therapy in frail older people with type 2 diabetes mellitus. *Expert Rev Endocrinol Metab*. 2022;17(2):95-98.

23. Butt JH, Dewan P, Merkely B, et al. Efficacy and Safety of Dapagliflozin According to Frailty in Heart Failure With Reduced Ejection Fraction : A Post Hoc Analysis of the DAPA-HF Trial. *Ann Intern Med*. 2022;175(6):820-830.

24. Canadian Institute for Health Information. *Area-Level Equity Stratifiers Using PCCF and PCCF+Measuring Health Inequalities: A Toolkit*.; 2018. https://www.cihi.ca/sites/default/files/document/cphi-toolkit-area-level-measurement-pccf-2018-en-web.pdf

25. Postal Code Conversion Factor Plus (PCCF+). Statistics Canada. Accessed March 14, 2022. https://www150.statcan.gc.ca/n1/en/catalogue/82F0086X

26. Brown HK, Saha S, Chan TCY, et al. Outcomes in patients with and without disability admitted to hospital with COVID-19: a retrospective cohort study. *CMAJ*. 2022;194(4):E112-E121.

27. Canadian Association of University Teachers. *Underrepresented & Underpaid: Diversity & Equity Among Canada’s Post-Secondary Education Teachers (April 2018)*.; 2018. https://www.caut.ca/sites/default/files/caut\_equity\_report\_2018-04final.pdf

28. Fralick M, Colacci M, Odutayo A, Siemieniuk R, Glynn RJ. Lowering of hemoglobin A1C and risk of cardiovascular outcomes and all-cause mortality, a meta-regression analysis. *J Diabetes Complications*. 2020;34(11):107704-107704.

29. Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet*. 2019;393(10166):31-39.

30. McGuire DK, Shih WJ, Cosentino F, et al. Association of SGLT2 Inhibitors With Cardiovascular and Kidney Outcomes in Patients With Type 2 Diabetes. *JAMA Cardiology*. Published online October 2020. doi:10.1001/jamacardio.2020.4511

31. Clinical Practice Guidelines Committees. Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. *Canadian Journal of Diabetes*. 2018;42(Supplement 1):1-342.

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

33. Giugliano D, Scappaticcio L, Longo M, et al. GLP-1 receptor agonists and cardiorenal outcomes in type 2 diabetes: an updated meta-analysis of eight CVOTs. *Cardiovasc Diabetol*. 2021;20(1):189.

34. Gerstein HC, Sattar N, Rosenstock J, et al. Cardiovascular and Renal Outcomes with Efpeglenatide in Type 2 Diabetes. *N Engl J Med*. 2021;385(10):896-907.

35. American Diabetes Association Professional Practice Committee, Draznin B, Aroda VR, et al. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2022. *Diabetes Care*. 2022;45(Suppl 1):S125-S143.

36. Diabetes Canada Clinical Practice Guidelines Expert Committee, Lipscombe L, Butalia S, et al. Pharmacologic Glycemic Management of Type 2 Diabetes in Adults: 2020 Update. *Can J Diabetes*. 2020;44(7):575-591.

37. Fralick M, Colacci M, Thiruchelvam D, Gomes T, Redelmeier DA. Sodium-glucose co-transporter-2 inhibitors versus dipeptidyl peptidase-4 inhibitors and the risk of heart failure: A nationwide cohort study of older adults with diabetes mellitus. *Diabetes Obes Metab*. 2021;23(4):950-960.

38. McCoy RG, Van Houten HK, Deng Y, et al. Comparison of Diabetes Medications Used by Adults With Commercial Insurance vs Medicare Advantage, 2016 to 2019. *JAMA network open*. 2021;4(2):e2035792-e2035792.

39. Adkikari R, Blaha M. New insights into prescribing of SGLT2 inhibitors and GLP-1 receptor agonists by cardiologists in 2020: major barriers limiting role. *American College of Cardiology Website Jan*. Published online 2021.

40. Fralick M, Martins D, Tadrous M, Gomes T. Nationwide Trends in Dispensing of Sodium Glucose Cotransporter 2 Inhibitors. *Can J Hosp Pharm*. 2022;75(2):104-107.

41. Fralick M, MacFadden DR. A hypothesis for why sodium glucose co-transporter 2 inhibitors have been found to cause genital infection, but not urinary tract infection. *Diabetes Obes Metab*. Published online 2020. doi:10.1111/1744-1633.12020

42. Douros A, Lix LM, Fralick M, et al. Sodium-Glucose Cotransporter-2 Inhibitors and the Risk for Diabetic Ketoacidosis : A Multicenter Cohort Study. *Ann Intern Med*. 2020;173(6):417-425.

43. Fralick M, Schneeweiss S, Patorno E. Risk of Diabetic Ketoacidosis after Initiation of an SGLT2 Inhibitor. *N Engl J Med*. 2017;376(23):2300-2302.

44. Finucane FM. SGLT2 inhibitor-induced euglycaemic diabetic ketoacidosis may be due to abrupt, severe and transient impaired glucose sensing in susceptible individuals with a hitherto unrecognised beta cell SGLT variant. *Medical Hypotheses*. 2018;114:11-12. doi:10.1016/j.mehy.2018.02.025

45. Ogawa W, Sakaguchi K. Euglycemic diabetic ketoacidosis induced by SGLT2 inhibitors: Possible mechanism and contributing factors. *J Diabetes Investig*. 2016;7(2):135-138.

46. Schopman JE, Simon ACR, Hoefnagel SJM, Hoekstra JBL, Scholten RJP, Holleman F. The incidence of mild and severe hypoglycaemia in patients with type 2 diabetes mellitus treated with sulfonylureas: a systematic review and meta-analysis. *Diabetes/Metabolism Research and Reviews*. 2014;30(1):11-22. doi:10.1002/dmrr.2470

47. Aro S, Kangas T, Reunanen A, Salinto M, Koivisto V. Hospital Use Among Diabetic Patients and the General Population. *Diabetes Care*. 1994;17(11):1320-1329. doi:10.2337/diacare.17.11.1320

48. Choi J, Booth G, Jung HY, et al. Association of diabetes with frequency and cost of hospital admissions: a retrospective cohort study. *CMAJ open*. 2021;9(2):E406-E412.

49. McCoy RG, Lipska KJ, Herrin J, Jeffery MM, Krumholz HM, Shah ND. Hospital Readmissions among Commercially Insured and Medicare Advantage Beneficiaries with Diabetes and the Impact of Severe Hypoglycemic and Hyperglycemic Events. *Journal of General Internal Medicine*. 2017;32(10):1097-1105. doi:10.1007/s11606-017-4095-x

50. Fralick M, Redelmeier DA, Patorno E, et al. Identifying Risk Factors for Diabetic Ketoacidosis Associated with SGLT2 Inhibitors: a Nationwide Cohort Study in the USA. *J Gen Intern Med*. Published online 2021. doi:10.1007/s11606-020-06561-z

51. Colacci M, Fralick J, Odutayo A, Fralick M. SGLT2 inhibitors and the risk of diabetic ketoacidosis among adults with Type 2 Diabetes: A systematic review and meta-analysis. *medRxiv*. Published online 2021:2021.03.17.21253796-2021.03.17.21253796.

52. Heerspink HJL, Perkins BA, Fitchett DH, Husain M, Cherney DZI. Sodium Glucose Cotransporter 2 Inhibitors in the Treatment of Diabetes Mellitus: Cardiovascular and Kidney Effects, Potential Mechanisms, and Clinical Applications. *Circulation*. 2016;134(10):752-772.

53. Taylor SI, Blau JE, Rother KI. SGLT2 Inhibitors May Predispose to Ketoacidosis. *J Clin Endocrinol Metab*. 2015;100(8):2849-2852.

54. Francke S, Mamidi RNVS, Solanki B, et al. In vitro metabolism of canagliflozin in human liver, kidney, intestine microsomes, and recombinant uridine diphosphate glucuronosyltransferases (UGT) and the effect of genetic variability of UGT enzymes on the pharmacokinetics of canagliflozin in humans. *J Clin Pharmacol*. 2015;55(9):1061-1072.

55. Perry RJ, Rabin-Court A, Song JD, et al. Dehydration and insulinopenia are necessary and sufficient for euglycemic ketoacidosis in SGLT2 inhibitor-treated rats. *Nat Commun*. 2019;10(1):548.

56. Bonner C, Kerr-Conte J, Gmyr V, et al. Inhibition of the glucose transporter SGLT2 with dapagliflozin in pancreatic alpha cells triggers glucagon secretion. *Nat Med*. 2015;21(5):512-517.

57. Al Jobori H, Daniele G, Adams J, et al. Determinants of the increase in ketone concentration during SGLT2 inhibition in NGT, IFG and T2DM patients. *Diabetes Obes Metab*. 2017;19(6):809-813.

58. Okamoto A, Yokokawa H, Sanada H, Naito T. Changes in Levels of Biomarkers Associated with Adipocyte Function and Insulin and Glucagon Kinetics During Treatment with Dapagliflozin Among Obese Type 2 Diabetes Mellitus Patients. *Drugs R D*. 2016;16(3):255-261.

59. Huang ES, Laiteerapong N, Liu JY, John PM, Moffet HH, Karter AJ. Rates of Complications and Mortality in Older Patients With Diabetes Mellitus. *JAMA Intern Med*. 2014;174(2):251-251.

60. Franco OH, Steyerberg EW, Hu FB, Mackenbach J, Nusselder W. Associations of Diabetes Mellitus With Total Life Expectancy and Life Expectancy With and Without Cardiovascular Disease. *Arch Intern Med*. 2007;167(11):1145-1145.

61. Loukine L, Waters C, Choi BCK, Ellison J. Impact of diabetes mellitus on life expectancy and health-adjusted life expectancy in Canada. *Popul Health Metr*. 2012;10(1):7-7.

62. Leal J, Gray AM, Clarke PM. Development of life-expectancy tables for people with type 2 diabetes. *Eur Heart J*. 2009;30(7):834-839.

63. Zheng SL, Roddick AJ, Aghar-Jaffar R, et al. Association Between Use of Sodium-Glucose Cotransporter 2 Inhibitors, Glucagon-like Peptide 1 Agonists, and Dipeptidyl Peptidase 4 Inhibitors With All-Cause Mortality in Patients With Type 2 Diabetes. *JAMA*. 2018;319(15):1580-1580.

64. American Diabetes Association. Pharmacologic Approaches to Glycemic Treatment: *Standards of Medical Care in Diabetes—2018*. *Diabetes Care*. 2018;41:S73-S85.

65. Canadian Diabetes Association. Diabetes: Clinical Practice Guidelines. *Canadian Journal of Diabetes*. 2013;37:1-227.

66. Chamberlain JJ, Herman WH, Leal S, et al. Pharmacologic Therapy for Type 2 Diabetes: Synopsis of the 2017 American Diabetes Association Standards of Medical Care in Diabetes. *Ann Intern Med Annals.org*. 2017;1667326(10):572-578.

67. Inzucchi SE. Is it time to change the type 2 diabetes treatment paradigm? No! metformin should remain the foundation therapy for type 2 diabetes. *Diabetes Care*. 2017;40(8):1128-1132.

68. Maruthur NM, Tseng E, Hutfless S, et al. Diabetes medications as monotherapy or metformin-based combination therapy for type 2 diabetes: A systematic review and meta-analysis. *Ann Intern Med*. 2016;164(11):740-751.

69. Turner RC, Cull C a., Frighi V, Holman RR. Glycemic Control With Diet, Sulfonylurea, Metformin, or Insulin in Patients With Type 2 Diabetes Mellitus Progressive Requirement for Multiple Therapies (UKPDS 49). *JAMA*. 1999;281:2005-2012.

70. Griffin SJ, Leaver JK, Irving GJ. Impact of metformin on cardiovascular disease: a meta-analysis of randomised trials among people with type 2 diabetes. *Diabetologia*. 2017;60(9):1620-1629.

71. UK Prospective Diabetes Study. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998;352:854-865.

72. U.S. Food and Drug Administration (FDA). FDA Drug Safety Communication: FDA adds warnings about heart failure risk to labels of type 2 diabetes medicines containing saxagliptin and alogliptin. Published online 2018.

73. Association AD, American Diabetes Association. Standards of Medical Care in Diabetes—2022 Abridged for Primary Care Providers. *Clinical Diabetes*. 2022;40(1):10-38. doi:10.2337/cd22-as01

74. Cosentino F, Grant PJ, Aboyans V. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: The Task Force for diabetes, pre-diabetes …. *Eur Heart J*. Published online 2020. https://academic.oup.com/eurheartj/article-abstract/41/2/255/5556890

75. Hardman TC, Dubrey SW. Development and potential role of type-2 sodium-glucose transporter inhibitors for management of type 2 diabetes. *Diabetes Ther*. 2011;2(3):133-145.

76. Wu JHY, Foote C, Blomster J, et al. Effects of sodium-glucose cotransporter-2 inhibitors on cardiovascular events, death, and major safety outcomes in adults with type 2 diabetes: A systematic review and meta-analysis. *The Lancet Diabetes and Endocrinology*. 2016;4(5):411-419.

77. Food and Drug Administration. Canagliflozin drug label (2017). *Available online*. Published online 2017. Accessed March 10, 2022. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=204042

78. Goldenberg RM, Steen O. Semaglutide: Review and Place in Therapy for Adults With Type 2 Diabetes. *Can J Diabetes*. 2019;43(2):136-145.

79. Yang D, Zhang Y, Yan J, Liu M, An F. SGLT-2 inhibitors on prognosis and health-related quality of life in patients with heart failure and preserved ejection fraction: A systematic review and meta-analysis. *Front Cardiovasc Med*. 2022;9:942125.

80. Palmer SC, Tendal B, Mustafa RA, et al. Sodium-glucose cotransporter protein-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists for type 2 diabetes: systematic review and network meta-analysis of randomised controlled trials. *BMJ*. 2021;372:m4573.

81. Billings LK, Handelsman Y, Heile M, Schneider D, Wyne K. Health-Related Quality of Life Assessments with Once-Weekly Glucagon-Like Peptide-1 Receptor Agonists in Type 2 Diabetes Mellitus. *J Manag Care Spec Pharm*. 2018;24(9-a Suppl):S30-S41.

82. Sattar N, Lee MMY, Kristensen SL, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. *The Lancet Diabetes & Endocrinology*. Published online August 20, 2021:653-662.

83. Zannad F, Ferreira JP, Pocock SJ, et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. *Lancet*. 2020;396(10254):819-829.

84. Anderson TS, Lo-Ciganic WH, Gellad WF, et al. Patterns and predictors of physician adoption of new cardiovascular drugs. *Healthcare*. 2018;6(1):33-40. doi:10.1016/j.hjdsi.2017.09.004

85. Garjón FJ, Azparren A, Vergara I, Azaola B, Loayssa JR. Adoption of new drugs by physicians: a survival analysis. *BMC Health Services Research*. 2012;12(1). doi:10.1186/1472-6963-12-56

86. Lublóy Á. Factors affecting the uptake of new medicines: a systematic literature review. *BMC Health Services Research*. 2014;14(1). doi:10.1186/1472-6963-14-469

87. Steffensen FH. Diffusion of new drugs in Danish general practice. *Family Practice*. 1999;16(4):407-413. doi:10.1093/fampra/16.4.407

88. Grimshaw JM, Eccles MP, Lavis JN, Hill SJ, Squires JE. Knowledge translation of research findings. *Implementation Science*. 2012;7(1). doi:10.1186/1748-5908-7-50

89. Goncalves E, Bell DSH. Combination Treatment of SGLT2 Inhibitors and GLP-1 Receptor Agonists: Symbiotic Effects on Metabolism and Cardiorenal Risk. *Diabetes Ther*. 2018;9(3):919-926.

90. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med*. 2017;377(7):644-657.

91. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019;380(24):2295-2306.

92. Fralick M, Kim SC, Schneeweiss S, Everett BM, Glynn RJ, Patorno E. Risk of amputation with canagliflozin across categories of age and cardiovascular risk in three US nationwide databases: cohort study. *BMJ*. 2020;370. doi:10.1136/bmj.m2812

93. Yu OHY, Dell’Aniello S, Shah BR, et al. Sodium-Glucose Cotransporter 2 Inhibitors and the Risk of Below-Knee Amputation: A Multicenter Observational Study. *Diabetes Care*. 2020;43(10):2444-2452.

94. Ueda P, Svanström H, Melbye M, et al. Sodium glucose cotransporter 2 inhibitors and risk of serious adverse events: nationwide register based cohort study. *BMJ*. 2018;363. doi:10.1136/bmj.k4365

95. Kannan S, Nasr C. Should we be concerned about thyroid cancer in patients taking glucagon-like peptide 1 receptor agonists? *Cleve Clin J Med*. 2015;82(3):142-144.

96. Mali G, Ahuja V, Dubey K. Glucagon-like peptide-1 analogues and thyroid cancer: An analysis of cases reported in the European pharmacovigilance database. *J Clin Pharm Ther*. 2021;46(1):99-105.

97. Chiu WY, Shih SR, Tseng CH. A review on the association between glucagon-like peptide-1 receptor agonists and thyroid cancer. *Exp Diabetes Res*. 2012;2012:924168.

98. Pradhan R, Patorno E, Tesfaye H, et al. Glucagon-Like Peptide 1 Receptor Agonists and Risk of Anaphylactic Reaction Among Patients With Type 2 Diabetes: A Multisite Population-Based Cohort Study. *Am J Epidemiol*. 2022;191(8):1352-1367.

99. Quadri H, Ataallah B, Haggerty G. Anaphylactic Reaction to Dulaglutide: A Glucagon Like Peptide- 1 Receptor Agonist. *Journal of the Endocrine Society*. 2021;5(Suppl 1):A367.

100. Erondu N, Desai M, Ways K, Meininger G. Diabetic ketoacidosis and related events in the canaglif lozin type 2 diabetes clinical program. *Diabetes Care*. 2015;38(9):1680-1686.

101. Meyer EJ, Gabb G, Jesudason D. SGLT2 Inhibitor–Associated Euglycemic Diabetic Ketoacidosis: A South Australian Clinical Case Series and Australian Spontaneous Adverse Event Notifications. *Diabetes Care*. 2018;(August 2017):dc171721-dc171721.

102. Umpierrez G, Korytkowski M. Diabetic emergencies — ketoacidosis, hyperglycaemic hyperosmolar state and hypoglycaemia. *Nature Reviews Endocrinology*. 2016;12(4):222-232. doi:10.1038/nrendo.2016.15

103. Smith A, Holtrop J, Sadoun M. Post-Operative Euglycemic Diabetic Ketoacidosis in a Patient With SGLT-2 Inhibitor Use and Recent Sleeve Gastrectomy. *Cureus*. Published online 2021. doi:10.7759/cureus.14297

104. Wang R, Kave B, McIlroy E, Kyi M, Colman PG, Fourlanos S. Metabolic outcomes in patients with diabetes mellitus administered SGLT2 inhibitors immediately before emergency or elective surgery: single centre experience and recommendations. *British Journal of Anaesthesia*. 2021;127(1):e5-e7. doi:10.1016/j.bja.2021.03.023

105. Hamblin PS, Wong R, Ekinci EI, et al. SGLT2 Inhibitors Increase the Risk of Diabetic Ketoacidosis Developing in the Community and During Hospital Admission. *J Clin Endocrinol Metab*. 2019;104(8):3077-3087.

106. Bhatt DL, Szarek M, Gabriel Steg P, et al. Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure. *New England Journal of Medicine*. 2021;384(2):117-128. doi:10.1056/nejmoa2030183

107. Damman K, Beusekamp JC, Boorsma EM, et al. Randomized, double‐blind, placebo‐controlled, multicentre pilot study on the effects of empagliflozin on clinical outcomes in patients with acute decompensated heart failure (EMPA‐RESPONSE‐AHF). *European Journal of Heart Failure*. 2020;22(4):713-722. doi:10.1002/ejhf.1713

108. Salah HM, Al’Aref SJ, Khan MS, et al. Efficacy and safety of sodium-glucose cotransporter 2 inhibitors initiation in patients with acute heart failure, with and without type 2 diabetes: a systematic review and meta-analysis. *Cardiovasc Diabetol*. 2022;21(1):20-20.

109. Fayfman M, Galindo RJ, Rubin DJ, et al. A Randomized Controlled Trial on the Safety and Efficacy of Exenatide Therapy for the Inpatient Management of General Medicine and Surgery Patients With Type 2 Diabetes. *Diabetes Care*. 2019;42(3):450-456. doi:10.2337/dc18-1760

110. Medlinskiene K, Tomlinson J, Marques I, Richardson S, Stirling K, Petty D. Barriers and facilitators to the uptake of new medicines into clinical practice: a systematic review. *BMC Health Serv Res*. 2021;21(1):1198.

111. Ho CK, Turley A, Hammonds M. Evaluation of clinical practice regarding SGLT2 inhibitor use in patients with type 2 diabetes mellitus and established coronary artery disease in James Cook University Hospital. *Clin Med* . 2022;22(Suppl 4):88-89.

112. Singhal Preeti, Liu Grace, Miller Sophie, Latz Maria, Motiani Meghna, Van Herle Helga. Clinical Practice Patterns and Attitudes About Prescribing SGLT2 Inhibitors at a Single-Center Academic Safety-Net Hospital. *J Am Coll Cardiol*. 2021;77(18\_Supplement\_1):1543-1543.

113. Khunti K, Aroda VR, Bhatt DL, et al. Re-examining the widespread policy of stopping sodium-glucose cotransporter-2 inhibitors during acute illness: A perspective based on the updated evidence. *Diabetes Obes Metab*. 2022;24(11):2071-2080.

114. Fonarow GC. In-hospital initiation of statins: taking advantage of the “teachable moment.” *Cleve Clin J Med*. 2003;70(6):502, 504-506.

115. Atzema CL, Austin PC, Chong AS, Dorian P, Jackevicius CA. The Long-Term Use of Warfarin Among Atrial Fibrillation Patients Discharged From an Emergency Department With a Warfarin Prescription. *Ann Emerg Med*. 2015;66(4):347-354.e2.

116. Brown MT, Bussell JK. Medication adherence: WHO cares? *Mayo Clin Proc*. 2011;86(4):304-314.

117. Kristin Newby L, Kristinsson A, Bhapkar MV, et al. Early Statin Initiation and Outcomes in Patients With Acute Coronary Syndromes. *JAMA*. 2002;287(23):3087-3095.

118. Fonarow GC, Gawlinski A, Moughrabi S, Tillisch JH. Improved treatment of coronary heart disease by implementation of a Cardiac Hospitalization Atherosclerosis Management Program (CHAMP). *Am J Cardiol*. 2001;87(7):819-822.

119. Atzema CL, Jackevicius CA, Chong A, et al. Prescribing of oral anticoagulants in the emergency department and subsequent long-term use by older adults with atrial fibrillation. *CMAJ*. 2019;191(49):E1345-E1354.

120. Harder S, Thürmann P, Huber T, Rietbrock N. Prescription of drugs not listed in a clinic’s pharmacopoeia: supervision by clinical pharmacologists. *Eur J Clin Pharmacol*. 1991;40(6):561-564.

121. Grimmsmann T, Schwabe U, Himmel W. The influence of hospitalisation on drug prescription in primary care--a large-scale follow-up study. *Eur J Clin Pharmacol*. 2007;63(8):783-790.

122. Sangha V, Lipska K, Lin Z, et al. Patterns of Prescribing Sodium-Glucose Cotransporter-2 Inhibitors for Medicare Beneficiaries in the United States. *Circ Cardiovasc Qual Outcomes*. 2021;14(12):e008381.

123. Higson D, Turley A. 198 Primary care use of SGLT2 inhibitors in patients with type 2 diabetes mellitus and cardiovascular disease – are we missing a trick? *Heart*. 2021;107(Suppl 1):A153-A154.

124. Hinton W, Feher MD, Munro N, Joy M, de Lusignan S. Prescribing sodium-glucose co-transporter-2 inhibitors for type 2 diabetes in primary care: influence of renal function and heart failure diagnosis. *Cardiovasc Diabetol*. 2021;20(1):130.

125. Milder TY, Stocker SL, Baysari M, Day RO, Greenfield JR. Prescribing of SGLT2 inhibitors in primary care: A qualitative study of General Practitioners and Endocrinologists. *Diabetes Res Clin Pract*. 2021;180:109036.

126. Iasella CJ, Johnson HJ, Dunn MA. Adverse Drug Reactions: Type A (Intrinsic) or Type B (Idiosyncratic). *Clin Liver Dis*. 2017;21(1):73-87.

127. Drögemöller BI, Monzon JG, Bhavsar AP, et al. Association Between SLC16A5 Genetic Variation and Cisplatin-Induced Ototoxic Effects in Adult Patients With Testicular Cancer. *JAMA Oncol*. 2017;3(11):1558-1562.

128. Kowalec K, Wright GEB, Drögemöller BI, et al. Common variation near IRF6 is associated with IFN-β-induced liver injury in multiple sclerosis. *Nat Genet*. 2018;50(8):1081–1085.

129. Génin E, Schumacher M, Roujeau JC, et al. Genome-wide association study of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in Europe. *Orphanet J Rare Dis*. 2011;6:52.

130. Lin JJ, Loucks CM, Trueman JN, et al. Novel variant in glycophorin c gene protects against ribavirin-induced anemia during chronic hepatitis C treatment. *Biomed Pharmacother*. 2021;143:112195.

131. Tanoshima R, Khan A, Biala AK, et al. Analyses of Adverse Drug Reactions-Nationwide Active Surveillance Network: Canadian Pharmacogenomics Network for Drug Safety Database. *J Clin Pharmacol*. 2019;59(3):356-363.

132. Nelson MR, Bacanu SA, Mosteller M, et al. Genome-wide approaches to identify pharmacogenetic contributions to adverse drug reactions. *Pharmacogenomics J*. 2009;9(1):23-33.

133. SEARCH Collaborative Group, Link E, Parish S, et al. SLCO1B1 variants and statin-induced myopathy--a genomewide study. *N Engl J Med*. 2008;359(8):789-799.

134. Daly AK. Genome-wide association studies in pharmacogenomics. *Nat Rev Genet*. 2010;11(4):241-246.

135. Cohen JJ, Berglund F, Lotspeich WD. Renal tubular reabsorption of acetoacetate, inorganic sulfate and inorganic phosphate in the dog as affected by glucose and phlorizin. *Am J Physiol*. 1956;184(1):91-96.

136. Hodson DJ, Rorsman P. A Variation on the Theme: SGLT2 Inhibition and Glucagon Secretion in Human Islets. *Diabetes*. 2020;69(5):864-866.

137. Lebovitz HE, Banerji MA. Ketosis-Prone Diabetes (Flatbush Diabetes): an Emerging Worldwide Clinically Important Entity. *Curr Diab Rep*. 2018;18(11):120.

138. Verma AA, Pasricha SV, Jung HY, et al. Assessing the quality of clinical and administrative data extracted from hospitals: the General Medicine Inpatient Initiative (GEMINI) experience. *J Am Med Inform Assoc*. 2021;28(3):578-587.

139. Modin D, Claggett B, Jørgensen ME, et al. Flu Vaccine and Mortality in Hypertension: A Nationwide Cohort Study. *J Am Heart Assoc*. 2022;11(6):e021715.

140. Modin D, Claggett B, Sindet-Pedersen C, et al. Acute COVID-19 and the Incidence of Ischemic Stroke and Acute Myocardial Infarction. *Circulation*. 2020;142(21):2080-2082.

141. Modin D, Claggett B, Køber L, et al. Influenza vaccination is associated with reduced cardiovascular mortality in adults with diabetes: A nationwide cohort study. *Diabetes Care*. 2020;43(9):2226-2233.

142. Hodzic-Santor B Tamming D Fralick. Validation of the diagnostic accuracy levels of ICD-10 codes for diabetic ketoacidosis: A multicenter cross-sectional study. Published online 2022.

143. Hux JE, Booth GL, Slaughter PM, Laupacis A, editors., ed. Chapter 1: Acute Complications of Diabetes. In: *Diabetes in Ontario: An ICES Practice Atlas*. ; 2003.

144. Verma AA, Guo Y, Kwan JL, et al. Prevalence and Costs of Discharge Diagnoses in Inpatient General Internal Medicine: a Multi-center Cross-sectional Study. *Journal of General Internal Medicine*. 2018;33(11):1899-1904. doi:10.1007/s11606-018-4591-7

145. Verma AA, Guo Y, Kwan JL, et al. Patient characteristics, resource use and outcomes associated with general internal medicine hospital care: the General Medicine Inpatient Initiative (GEMINI) retrospective cohort study. *CMAJ Open*. 2017;5(4):E842-E849. doi:10.9778/cmajo.20170097

146. Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. *Diabetes Care*. 2009;32(7):1335-1343.

147. Austin PC. Optimal caliper widths for propensity‐score matching when estimating differences in means and differences in proportions in observational studies. *Pharmaceutical Statistics*. 2011;10(2):150-161. doi:10.1002/pst.433

148. Rothman KJ, Greenland S. Planning Study Size Based on Precision Rather Than Power. *Epidemiology*. 2018;29(5):599-603.

149. Rothman KJ, Boice JD. *Epidemiologic Analysis with a Programmable Calculator*. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health; 1979.

150. Weisman A, Tu K, Young J, et al. Validation of a type 1 diabetes algorithm using electronic medical records and administrative healthcare data to study the population incidence and prevalence of type 1 diabetes in Ontario, Canada. *BMJ Open Diabetes Res Care*. 2020;8(1):e001224.

151. Matthews AA, Danaei G, Islam N, Kurth T. Target trial emulation: applying principles of randomised trials to observational studies. *BMJ*. 2022;378. doi:10.1136/bmj-2022-071108

152. McCormick N, Lacaille D, Bhole V, Avina-Zubieta JA. Validity of myocardial infarction diagnoses in administrative databases: a systematic review. *PLoS One*. 2014;9(3):e92286.

153. McCormick N, Bhole V, Lacaille D, Avina-Zubieta JA. Validity of Diagnostic Codes for Acute Stroke in Administrative Databases: A Systematic Review. *PLoS One*. 2015;10(8):e0135834.

154. McCormick N, Lacaille D, Bhole V, Avina-Zubieta JA. Validity of heart failure diagnoses in administrative databases: a systematic review and meta-analysis. *PLoS One*. 2014;9(8):e104519.

155. Fralick M, Colacci M, Schneeweiss S, Huybrechts KF, Lin KJ, Gagne JJ. Effectiveness and Safety of Apixaban Compared With Rivaroxaban for Patients With Atrial Fibrillation in Routine Practice. *Annals of Internal Medicine*. 2020;172(7):463. doi:10.7326/m19-2522

156. Glynn RJ, Rosner B. Comparison of Risk Factors for the Competing Risks of Coronary Heart Disease, Stroke, and Venous Thromboembolism. *American Journal of Epidemiology*. 2005;162(10):975-982. doi:10.1093/aje/kwi309

157. VanderWeele TJ, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. *Ann Intern Med*. 2017;167(4):268-274.

158. Fralick M, Colacci M, Thiruchelvam D, Gomes T, Redelmeier DA. SGLT2 inhibitors versus DPP4 inhibitors and the risk of heart failure: A nationwide cohort study of older adults with diabetes mellitus. *Diabetes Obes Metab*. 2020;2(vember 2020). doi:10.1111/dom.14300

159. Johnson D, Wilke MAP, Lyle SM, et al. A systematic review and analysis of the use of polygenic scores in pharmacogenomics. *Clin Pharmacol Ther*. 2022;111(4):919-930.

160. Atkins L, Francis J, Islam R, et al. A guide to using the Theoretical Domains Framework of behaviour change to investigate implementation problems. *Implement Sci*. 2017;12(1):77.