THE INTEGRATION OF PATIENT PREFERENCES INTO QUANTITATIVE RISK-BENEFIT ASSESSMENT OF SODIUM GLUCOSE CO-TRANSPORTER-2 INHIBITORS FOR THE MANAGEMENT OF TYPE 2 DIABETES

by © Jennifer Donnan A Thesis submitted to the School of Graduate Studies in partial fulfillment of the requirements for the degree of

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Abstract

Background: The Sodium Glucose Co-Transporter-2 (SLGT2) Inhibitors are the newest class of antihyperglycemic medications available on the market. These agents have gained quick popularity due to demonstrated cardiovascular benefits among patients with pre-existing cardiovascular disease. While we have estimates for the probabilities of benefits and harms for SGLT2 inhibitors, the overall balance of risk and benefits that reflects the values of patients is unknown.

Objectives and Methods:

1. To conduct a systematic review and meta-analysis of the current state of knowledge surrounding post-market safety concerns of the SGLT2 inhibitors, including acute kidney injury (AKI), diabetic ketoacidosis (DKA), urinary tract infection (UTI), bone fracture and amputation, in patients with type 2 diabetes.
2. To estimate the strength of preferences, relative importance, and trade-offs that Canadians with type 2 diabetes make between characteristics of glucose-lowering medications using a discrete choice experiment (DCE).
3. To bring together Canadian patient preferences for attributes of diabetes therapies with probabilities of efficacy and safety retrieved from the literature, to compare the SGLT2 inhibitors and glucagon-like peptide-1 (GLP1) receptor agonists, using quantitative benefit-risk assessment (BRA) following the incremental net benefit (INB) framework.

Results: The analysis of the adverse outcomes of the SGLT2 inhibitors, suggested no significant increase in the risk of AKI, DKA, UTI (exception: high dose dapagliflozin) or bone fractures. Amputation was poorly reported, however CANVAS trials do show an increased risk. The DCE showed that all eight examined attributes for diabetes medications, including cost, risk of macrovascular and microvascular events, risk of minor side effects, severe hypoglycemia, serious long term consequences, and life expectancy were each shown to significantly influence choice. Life expectancy and cost were more important to patients. Finally, the BRA demonstrated that there was a minimal difference in INB between the SGLT2 inhibitors and the GLP1 receptor agonists, but favored the SGLT2 inhibitors (INB = 0.2) and results were consistent in sensitivity analysis.

Conclusion: This program of research used emerging methods, including a network meta-analysis, a DCE, and preference-weighted BRA to examine the balance between risks and benefits of the SGLT2 inhibitors and GLP1 agonists. These studies resulted in a final INB that favored SGLT2 inhibitors, though magnitude was small. More importantly, this research identifies several challenges and limitations, including gaps in methodological guidance that still exist to successfully integrate patient preferences into BRA.

Table of Contents

List of Figures

List of Tables

List of Abbreviations

aHR	Adjusted Hazard Ratio
AKI	Acute Kidney Injury
BRA	Benefit-Risk Assessment
CANVAS	Canagliflozin Cardiovascular Assessment Study
CI	Confidence Interval
DCE	Discrete Choice Experiment
DECLARE-TIMI	Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes
DKA	Diabetic Ketoacidosis
DPP-4	dipeptidyl peptidase-4 (DPP-4)
EMA	European Medicines Agency
EMPA-REG	Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes Trial
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration (United States)
GLP1	Glucagon Like Protein-1
HR	Hazard Ratio
IIA	Independence of Irrelevant Alternatives
IID	Independence of Identically Distributed
INB	Incremental Net Benefit

LEADER	Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome
MACE	Major Adverse Cardiovascular Events
MAR	Maximal Acceptable Risk
MCID	Minimal Clinically Important Difference
MeSH	Medical Subject Headings
MNL	Multinomial logit
MRS	Marginal Rate of Substitution
NMA	Network Meta-Analysis
NNT	Number Needed to Treat
NNH	Number Needed to Harm
OR	Odds Ratio
PhRMA	Pharmaceutical Research and Manufacturers of America
PICOS	Population, Intervention, Comparator, Outcome, Study Design
PROSPERO	International Prospective Register of Systematic Reviews
RCT	Randomized Controlled Trial
RR	Relative Risk
SGLT2	Sodium Glucose Co-Transporter 2
SUSTAIN-6	Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes
TZD	Thiazolidinediones

UTI	Urinary Tract Infection
WTP	Willingness to Pay

List of Appendices

1. Introduction and Overview

1.1 Type 2 Diabetes

Type 2 diabetes is a chronic disease that results from the body's inability use the insulin that it produces, or insulin resistance. Insulin is a hormone that is produced in response to glucose in the bloodstream and it regulates the amount glucose that remains in the blood by signaling to body cells to take in glucose to use as energy or store as fat. When cells are resistant to the actions of insulin, high levels of glucose remain in the blood and can lead to damage of the organs, nerves or blood vessels.[1]

The prevalence of type 2 diabetes in Canada, as of 2015, was about 3.4 million individuals or 9.3% of the population. However the prevalence is estimated to grow by 44% to 5 million Canadians or 12.1% of the population by the year 2025. These high rates of diabetes puts a tremendous strain on the health care system as this population experiences higher incidences of several co-morbidities including, but not limited to, cardiovascular disease, kidney disease, retinopathy, nerve damage, infections and amputations. Additionally, patient with diabetes typically experience a greater number of hospital stays and premature death.[2]

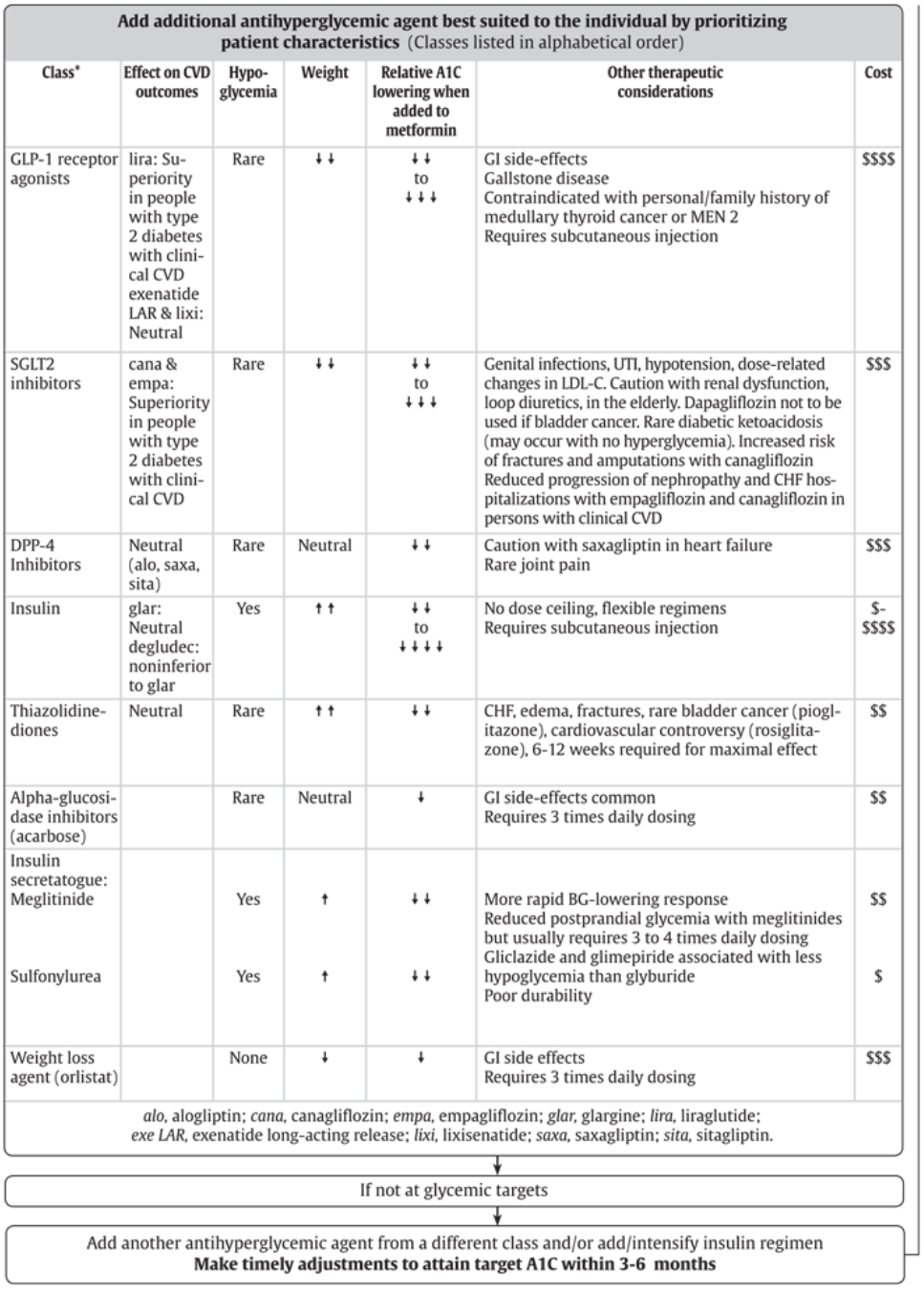
The increasing prevalence of type 2 diabetes is a result of a number of factors including the strong positive correlation with obesity and cardiovascular conditions like hypertension and hypercholesterolemia, all of which are related to poor diet and lifestyle choices. Other risk factors include: family history (first degree relative), history of

gestational diabetes or prediabetes, diagnosis of polycystic ovary syndrome, psychiatric conditions or obstructive sleep apnea, and a history of glucocorticoid mediation use.[3]

1.1.1 Management of Type 2 Diabetes

The management of type 2 diabetes has changes dramatically over the last century. Until the 1920s, when insulin was discovered, there was no known treatment for the condition. Insulin remained the only therapy until the 1950 when some oral antidiabetic agents were introduced to the Canadian market, first generation sulfonylureas like tolbutamide and biguanides like metformin. It was not until the 1980s when a few more products came to market making it easier to achieve blood glucose levels closer to the non-diabetic range.[4] Still despite several advancements, Canadian Clinical Practice Guidelines changed very little over the decades. Metformin has long been recommended as the first line therapy, and then a switch or add-on therapy was necessary and of the other available agents were considered acceptable alternatives. However, since 2016, we are seeing a shift in the recommendations for second line therapy as a result of tremendous advancements in therapy options.[5] Since 2008 three new classes of medications, the glucagon-like peptide-1 (GLP-1) Receptor Agonists, the dipeptidyl peptidase-4 (DPP-4) Inhibitors, and the sodium glucose co-transporter 2 (SGLT2) Inhibitors, which include 12 unique molecules, have become available. Figure 1-1 is a table of second line therapies and comes from the Diabetes Canada 2018 Clinical Practice Guidelines.

Figure 1-1 Diabetes Canada 2018 Clinical Practice Guidelines - Second-line Therapies



Add additional antihyperglycemic agent best suited to the individual by prioritizing patient characteristics (Classes listed in alphabetical order)

Class*	Effect on CVD outcomes	Hypo-glycemia	Weight	Relative A1C lowering when added to metformin	Other therapeutic considerations	Cost
GLP-1 receptor agonists	lira: Superiority in people with type 2 diabetes with clinical CVD exenatide LAR & lixi: Neutral	Rare	↓↓	↓↓ to ↓↓↓	GI side-effects Gallstone disease Contraindicated with personal/family history of medullary thyroid cancer or MEN 2 Requires subcutaneous injection	$$$$
SGLT2 inhibitors	cana & empa: Superiority in people with type 2 diabetes with clinical CVD	Rare	↓↓	↓↓ to ↓↓↓	Genital infections, UTI, hypotension, dose-related changes in LDL-C. Caution with renal dysfunction, loop diuretics, in the elderly. Dapagliflozin not to be used if bladder cancer. Rare diabetic ketoacidosis (may occur with no hyperglycemia). Increased risk of fractures and amputations with canagliflozin Reduced progression of nephropathy and CHF hospitalizations with empagliflozin and canagliflozin in persons with clinical CVD	$$$
DPP-4 Inhibitors	Neutral (alo, saxa, sita)	Rare	Neutral	↓↓	Caution with saxagliptin in heart failure Rare joint pain	$$$
Insulin	glar: Neutral degludec: noninferior to glar	Yes	↑↑	↓↓ to ↓↓↓↓	No dose ceiling, flexible regimens Requires subcutaneous injection	$-$$$$
Thiazolidinediones	Neutral	Rare	↑↑	↓↓	CHF, edema, fractures, rare bladder cancer (pioglitazone), cardiovascular controversy (rosiglitazone), 6-12 weeks required for maximal effect	$$
Alpha-glucosidase inhibitors (acarbose)		Rare	Neutral	↓	GI side-effects common Requires 3 times daily dosing	$$
Insulin secretatogue: Meglitinide		Yes	↑	↓↓	More rapid BG-lowering response Reduced postprandial glycemia with meglitinides but usually requires 3 to 4 times daily dosing	$$
Sulfonylurea		Yes	↑	↓↓	Gliclazide and glimepiride associated with less hypoglycemia than glyburide Poor durability	$
Weight loss agent (orlistat)		None	↓	↓	GI side effects Requires 3 times daily dosing	$$$

alo, alogliptin; *cana*, canagliflozin; *empa*, empagliflozin; *glar*, glargine; *lira*, liraglutide; *exe LAR*, exenatide long-acting release; *lixi*, lixisenatide; *saxa*, saxagliptin; *sita*, sitagliptin.

If not at glycemic targets

Add another antihyperglycemic agent from a different class and/or add/intensify insulin regimen
Make timely adjustments to attain target A1C within 3-6 months

* Listed by CV outcome data

Reprinted from Publication Canadian Journal of Diabetes, Vol 42 /Supplement 1, Diabetes Canada Clinical Practice Guidelines Expert Committee, Lipscombe L, Booth G, Butalia S, Dasgupta K, Eurich DT, et al., Pharmacologic Glycemic Management of Type 2 Diabetes in Adults. Can J Diabetes., Pages No. S93, Copyright (2018), with permission from Elsevier.

In 2007, during post-market surveillance, it was noted that commonly used antidiabetic agent, rosiglitazone, was associated with an increased risk of myocardial infarction and death.[6–8] This prompted a tightening in regulatory monitoring of diabetes agents, given the already high prevalence of cardiovascular co-morbidity in this population. As of 2008, the US FDA has required manufacturers demonstrate cardiovascular safety through randomized controlled trials prior to market approval for any new diabetes agents. Not only have the GLP-1 receptor agonists, the DPP-4 inhibitors, and the SGLT2 inhibitors all shown cardiovascular safety, but there are studies with the SGLT2 inhibitors and GLP-1 agonists that demonstrate cardiovascular benefit among individuals with existing cardiovascular disease.[9–13] These associated benefits have results in changes to the Canadian, [5] American[14] and European[15] Diabetes Guidelines which that now elevate certain SGLT2 inhibitors and GLP1 agonists to preferred second line status in individuals with existing cardiovascular disease.

1.1.1.1 Sodium Glucose Co-Transporter-2 Inhibitors

The SGLT2 inhibitors are the newest class of diabetes therapies to hit the Canadian market, with the approval of canagliflozin in 2014.[16] There are currently four SGLT2 inhibitors available in Canada including dapagliflozin, canagliflozin, empagliflozin and ertugliflozin, and a fifth agent, ipragliflozin that has been approved for use in Europe and Asia. The novel mechanism for this class of agents is that it causes glucose to leave the body through the urine. Typically, in a healthy individual no glucose is excreted through the urine

as it is reabsorbed from the glomerular filtrate by two SGLT proteins (SGLT1 and SGLT2), both of which act independently of insulin. The SGLT2 protein is responsible for the 90% of the reabsorption and this occurs at the first section of the proximal tubule, while only 10% is removed through the action of SGLT1 further down the tubule. For this reason, the drugs are designed to target the SGLT2 protein over SGLT1.[17]

In 2015, the first cardiovascular trial among the SGLT2 inhibitors was published. The Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG) trial, demonstrated a significant benefit in the empagliflozin group over placebo for the composite endpoint of death from cardiovascular causes, nonfatal myocardial infarction and nonfatal stroke (MACE) in individuals with preexisting cardiovascular disease.[9] These results were replicated in 2017 with the Canagliflozin Cardiovascular Assessment Study (CANVAS) showing a significant benefit with the SGLT2 inhibitor over placebo in the composite MACE outcome.[12] The Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes (DECLARE-TIMI) study published in 2019 did not show a reduction in MACE, however did show significant cardiovascular death and hospitalization for heart failure.[13] The SGLT2 inhibitors are the first class of agents to demonstrate cardiovascular benefit and as a result were promoted to the preferred second line agent among individuals who have existing cardiovascular comorbidities in the Diabetes Canada guidelines pharmacotherapy update in 2016.[18]

1.2 Systematic Reviews and Meta-Analyses

Systematic reviews and meta-analyses have become the gold standard approach to summarizing the totality of evidence on a particular topic in health care. A systematic review takes a structured approach to retrieve all the of available data on a topic and involves the following key steps:[19]

1. Defining the study question, including the population, intervention, comparator, outcome and study design (PICOS);
2. Establishing appropriate inclusion and exclusion criteria for the review;
3. Designing and executing a comprehensive search strategy;
4. Duplicate screening of search results using inclusion criteria;
5. Duplicate data abstraction of all the key data elements;
6. Critical appraisal of each of the included data sources; and
7. Summarizing the results.

The systematic approach allows for reproducibility of the findings and enables easy updates to the review. Perhaps the most critical step in this approach is the critical or quality appraisal. As summary of poorly conducted studies does not result in a high quality review. The critical appraisal allows for the contextualization of the findings according to the quality of available evidence and allows for discussion on potential source of bias.

1.2.1 Meta-Analyses

A meta-analysis can follow a systematic review when the identified studies from the systematic review are similar enough to be combined statistically. This approach was first described by Gene Glass in 1976,[20] however earlier examples of pooling data from multiple sources date back to early 1900's. This process first involves calculating summary statistics and measures of uncertainty from each of the included trials, then averaging the summary statistic, weighted by the inverse of the variance. Combining treatment effects from multiple studies improves reliability and statistical power.[19]

There is one key assumption that needs to be met to be able to conduct a meta-analysis, which is between study homogeneity. The included trials need to be similar enough to be pooled and interpreted together. That is, is the baseline population similar?; is the indication the same?; and, are the interventions and comparisons the same? This assumption can be assessed by comparing individual studies to answer these questions, and can also be tested statistically using the I-squared test. Typically, acceptable levels of heterogeneity are considered to be an I^2 value 50% or 50%. Levels greater than this, explanation and justification would need to be provided for pooling those trials.[19]

There are two basic models for analyzing the results of the meta-analysis depending on the degree of heterogeneity detected. Where little to no heterogeneity is detected, a fixed effect model can be used (equation 1). This model only accounts for within study variability in the error term, represented by σ_i^2. The second model is the random effects model, which takes into account both the within and between study heterogeneity,

represented by τ^2(equation 2). Using the random effects model will tend produce effect estimates with wider confidence intervals to account for this added variability.[19]

Fixed Effect Model: $Y_i = \Theta + e_i$ Where $e_i \sim N(\Theta, \sigma_i^2)$ (1)

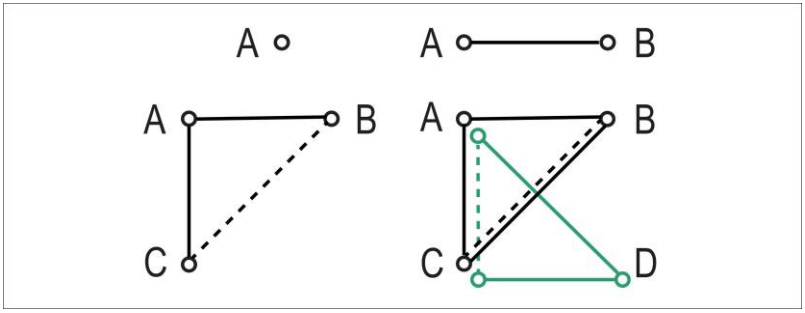
Random Effects Model: $Y_i = \Theta_i + e_i$ Where $e_i \sim N(\Theta, \sigma_i^2)$ and $\Theta_i \sim N(\Theta, \tau^2)$ (2)

1.2.2 Network Meta-Analyses

In the last decade, methods used for conducting meta-analyses have matured dramatically addressing many potential issues and barriers. One such advance has been the network meta-analysis (NMA), which was introduced by Salanti et al. in 2008.[21] This approach allows for the inclusion of indirect evidence alongside direct evidence. Figure 1-2 shows the relationships in meta and network meta-analyses. Each intervention can be represented as a node (e.g. A, B, etc.), and solid lines represent where two interventions have been compared in a head-to-head trial. In a pairwise meta-analysis there would be two or more studies that compare the same two interventions in similar populations (top right). One problem when examining new interventions is that they are often compared to placebo and not necessarily to the existing gold standard. Practically, we want to know which available interventions performs better, but this is challenging with little or very few direct comparisons. The NMA takes into account all the indirect evidence to overcome this barrier. That is, they can quantitatively make comparisons between two interventions via a third common comparator (e.g. placebo or other). In Figure 1-2 the dotted lines represent

the indirect comparisons that can be drawn from the available evidence. The diagram in the bottom right depicts an example where both direct and indirect evidence are pooled together to compare two alternatives.[22] It is not always the case that no direct evidence exists, but sometimes it is limited and direct evidence can be used to strengthen the existing direct evidence.

Figure 1-2. Pairwise versus network meta-analysis



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Network meta-analyses can be done using either a frequentist or Bayesian statistical approach, however the Bayesian method tends to be more commonly used due to its ability to integrate posterior distributions into the framework. When the Bayesian framework is used the results provide point estimates along with credible intervals, rather than confidence intervals used in frequentist approaches.

To be able to successfully conduct a NMA there are two assumptions that need to be considered in addition to the homogeneity assumption. The first is transitivity, which

concerns the validity of making indirect comparisons. This cannot be tested statistically, but rather individually examining the characteristics of each trial. The final assumption is consistency. This refers to the agreement/disagreement between the direct and indirect evidence of the same comparison where both direct and indirect evidence exists. This assumption can be tested statistically using one or more of the several proposed approaches, such as node-splitting, back calculation and global Q statistic.[23]

Despite being a major advance in meta-analysis methodologies, there are several drawbacks to using this approach. Probably the most important is the tendency to place too much trust on the results of network meta-analyses. Results can add context and strengthen the power in pairwise comparisons, and even draw comparisons where no direct evidence exists, however it must be understood that meeting the three assumptions successfully is challenging, and maybe even impossible. Pure indirect comparison estimate should be looked at as hypothesis generating only.[24]

1.3 Benefit-Risk Assessment

Benefit-Risk Assessment (BRA) is a process that is taken to evaluate if the intended benefits of a drug or medical device outweighs the potential harms. BRA's are often done at the time of regulatory approval as well as post market when new benefits and harms are identified in post market surveillance exercises. Though systematic reviews and meta-analyses are ideal starting points for identifying and quantifying benefits and harms, they are not tools that can address several important considerations when assessing the true

relevance of those benefits and risks. Aside from the risk of occurrence, other aspects to assess are the severity of the particular outcome, the expected time to onset, and the duration of the outcome.

Several regulatory agencies including the US Food and Drug Administration (FDA)[25] and the European Medicines Agency (EMA),[26] as well as the Pharmaceutical Research and Manufacturers of America (PhRMA)[27] have developed frameworks to encourage systematic approaches to BRA throughout the product lifecycle.[28] Taking a proactive approach to BRA increases the likelihood that drugs and devices that bare unacceptable risk are removed from the market in a timely fashion (e.g. rofecoxib,[29] troglitazone[30] and cisapride[31]), leading to better patient safety and improved health outcomes. The FDA's framework,[25] similar to the EMA framework, encourages a global assessment of the condition, possible therapies, the benefits and risks of those therapies and any uncertainties around the estimates for these factors. Then a value judgement or qualitative assessment is needed to bring that assessment together into a recommendation.

Typically, a complete structured BRA is only necessary when the decisions they are informing are complex. Where the evidence leads to obvious choices, this systematic process is not needed. Given the dramatic change in the landscape of available medications to treat type 2 diabetes, decisions regarding second-line therapies is complex with many benefits and risks that can play a role in decisions. Additionally, given that three new classes of medications have come to the market in the last decade alone, many of the newer products, despite early indications of unintended benefits, still have a great deal of

uncertainty around the true rates of benefits and risks. For this reason, formal BRA assessment is important.

1.3.1 Quantitative Approaches to Benefit-Risk Analysis

In addition to the frameworks outlined above, there are many measures that clinicians and researchers use to help quantify risks and benefits and the balance between the two. Figure 1-3 is a summary of the many proposed measures, from a review conducted by the ISPOR Risk-Benefit Working Group.[28] The *Unified Framework for Classification of Methods for Benefit-Risk Assessment,* proposed by Najafzadeh et al. (2015), further explores these measures categorizing them into three main sub-groups: 1) measures that are not weighted; 2) measures that are weighted by patient preferences, and 3) measures that are weighted with preferences of decision makers.[32] This framework also demonstrates that all of these metrics can be captured using a common formula (equation 3), and measure the incremental net benefit.

$$INB = \sum_{i=1}^{I} v_i T_i \Delta p_i - \mu \sum_{j=1}^{J} v_j T_j \Delta q_j \quad (3)$$

The INB quantifies the difference between the sum of the benefits from the sum of the harms between two interventions. In this equation the Δp_i represents the change in probability of beneficial outcome i, and Δq_j is the change in probability of a harmful outcome j, each weighted by the average time (T) that an individual is impacted by that

outcome and patient preference (*v*). The μ then represents the importance a decision maker places on harms over benefits. A μ=1 means importance is equal and a μ>1 indicates a higher importance on avoidance of harms. When mapping metrics like number needed to treat or number needed to harm (NNT/NNH), which are unweighted, the values for *v* and *T* would be set to equal one, and the INB would simply be a difference between the sum of the NNT and sum of the NNH.

Figure 1-3. Summary of Quantitative Measures of Benefit and Risk

Seq. No.	Title and quantitative approach	Parameters for assessment	Theoretical model and key features
1	Quantitative Framework for Risk and Benefit Assessment (QFRBA) [27,28,38–40,42–46]	Risk and benefit are defined and quantified separately; Risk focuses on adverse events or outcomes, defined as relative risk, attributable risk, population attributable risk. Benefit focuses on risk differences (i.e., relative risk reduction, absolute risk reduction).	Theoretically sound quantitative method; Probability driven assessment for risk of adverse events and benefits of improved outcomes; Relatively simple calculation; Often used for drug safety surveillance in industry and regulatory agencies.
2	Benefit-less-risk analysis (BLRA) [47,48]	Intensity scores are used to compare severity and frequency of adverse drug events (ADEs) and assigned for each patient. Data on observed benefit from the treatment are required. Proportionality constant determines how much penalty the ADEs offset benefit measure.	Simple empirical method with sound theoretical basis; Differences between treatments can be statistically analyzed (t-test or ANOVA); Requires subjective rankings of ADE intensity scores; Patient preferences are incorporated using a discounting process; Subjective ranking for ADEs and proportionality a potential threat to internal validity; Useful for comparing one drug treatment to a placebo or alternative treatment using clinical trial data.
3	Quality-adjusted Time Without Symptoms and Toxicity (Q-TWiST) [49–57]	Benefit measured as drug-attributed gain in quality-adjusted life-years (QALYs); Risk measured as drug-attributed loss of QALY Compare gain versus loss of QALY.	Statistical method can be conducted to compare alternative treatments; QALYs incorporate patients preference measurement changes over time; Validity of QALY measurements and differences between techniques are potential concerns; Widely used risk–benefit assessment technique in clinical oncology.
4	Number needed to treat (NNT) and number needed to harm (NNH) [27,28,58–60]	Benefit measure: number of persons treated (NNT) to avoid one person developing disease of interest (absolute risk reduction, Relative risk reduction); Risk measure: number of persons treated when one person experiences ADE (NNH); Ratio of NNT and NNH.	Well-defined quantitative framework; Simple calculation for RBA used for comparing treatment and control groups; Lack of strong statistical properties; Risk–benefit relation can be compared directly by NNT to NNH ratio; NNT should be lower than NNH for the drug to be valuable in term of risk benefit ratio; Widely used for RBA in different therapy areas; Difficult to incorporate more than one outcome (ADE or benefit reduction) simultaneously; Relative value of ADE versus benefit not considered.
5	Relative value adjusted number needed to treat (RV-NNT) [27,28]	Expands NNT to incorporate relative utility values (RV) based upon patient preferences; RV-NNH can be also be determined; Ratio of RV-NNT and RV-NNH.	Well-defined quantitative framework with relatively simple calculation; RV measures involve patient's preference for specific ADEs or avoidance of negative clinical outcomes; Similarly to NNT/NNH ratio, the RV-NNT must be higher than the RV-NNH for the drug to be valuable.
6	Minimum clinical efficacy (MCE) [27,28,61]	Benefit stated as efficacy difference between new treatment and conventional treatment or placebo; Harm stated as probability of AE (risk) in patients receiving new treatment vs. conventional treatment or placebo; Relative utility values may be considered.	Quantitative framework for integrating risk–benefit data into a single decision rule; New treatment is warranted over conventional treatment if efficacy exceeds probability of AE; More than one type of AEs can be considered; Lack of strong statistical properties; Does not incorporate uncertainty in the benefit or risk measurements; Applied primarily for cardiovascular treatments.
7	Incremental net health benefit (INHB) [17,62]	Risk measured as decrease in QALY; Benefit measured as improvement in QALY; INHB as relative gain or loss of QALYs due to treatment versus usual care or placebo.	Theoretically sound modeling method; Risk–benefit relation presented as an incremental difference; QALY data from clinical trials are required; Statistical variance in the estimates of both risks and benefits can be calculated; Potential application in clinical and regulatory decision-making.
8	Risk–benefit plane (RBP) and risk–benefit acceptability threshold (RBAT) [18,64]	Risk measured as relative probability of risk of AEs between treatment and control groups; Benefit measured as relative probability response between treatment and control groups; Visual application of risk–benefit comparisons.	Well-defined theoretical model; Two-dimensional plot with benefit measurement on x-axis, risk measurement on y-axis; An acceptable threshold of relative risk–benefit ratio can be plotted to visually compare with other treatments; Often used for explaining the phenomenon of drug safety surveillance.
9	Probabilistic simulation methods (PSM) and Monte Carlo simulation (MCS) [18,62–64]	Average difference in the probability of risk and benefit for the new therapy relative to conventional therapy; Incremental risk–benefit ratio (IRBR).	Framework applies incremental risk–benefit ratio; Joint density of benefit and risk scatter plot can be presented with a risk–benefit acceptability curve; Involves simulation modeling of uncertainty around the incremental risk–benefit differences; Statistical support incorporated using nonparametric bootstrap method and MCS.
10	Multicriteria decision analysis (MCDA) [45,46]	Benefit measured as clinically relevant end points from clinical trials; Risk measured as incidence of ADE, discontinuation rate, drug interactions, and other risk criteria; Decision tree model is developed to incorporate all key risks and benefits; Relative weights are of risks and benefits are assigned.	A decision tree describes clinical outcomes in a hierarchical manner; Decision-making tool incorporates evaluation of both drug's risks and benefits; Relative scores for alternative treatments can be calculated based on modeling; Data extraction from clinical trials are critical for internal validity; Missing data and uncertainty can be addressed. Implication for clinical and regulatory policy decision makings.
11	Risk–benefit Contour (RBC) [66]	Probability of potential benefit of treatment such as an increased survival rate; Probability of potential risk due to severe ADE or drug toxicity.	Graphical depiction of both benefit (x-axis) and risk (y-axis) measurements on a two-dimensional graph; Risk–benefit contours for comparative treatments are plotted as a set of nonlinear curves; For each individual patient, RBC scores can be identified with confidence intervals; Useful tool for clinical making decisions.
12	Stated preference method (SPM) or maximum acceptable risk (MAR) [67–77]	Relative utility values for therapeutic treatment alternatives; Vector of attribute levels for treatment options; Benefit–risk trade-off preferences estimated by probability of severe AEs versus benefit in terms of treatment success; Patient surveys required to provide data regarding value of benefit versus negative impact of risk.	SPM/MAR is based on hedonic-utility principles, and uses similar techniques to contingent valuation; Patient's preferences for benefit–risk trade-offs are incorporated.

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1.4 Patient Preferences in Risk-Benefit Analysis

One approach that is gaining popularity for capturing patient preferences in the BRA process, is choice modelling. This is a research area that focuses on modelling decision process and looking at the characteristics that influence those decisions. Choice modelling has long been used in the areas of marketing, economics and transportation as a method of measuring human decisions on activities and consumption. Effectively and accurately measuring human demand and needs and preferences for products and services allows for appropriately matching supply and setting market prices.[33] This approach has only more recently been used in health-care, as we aim to focus our delivery of healthcare in a more patient-centered manner.[34]

Choice modelling can either examine revealed preferences, which is to examine choices that individuals actually make in the real world (through sales data, administrative data, etc.), or stated preferences, which is to examine choice people make when presented with a hypothetical scenario. Both modelling approached provide insight in different settings.[35] Revealed preferences are important for examining existing choice alternatives, for example the choice between visiting a family physician or the emergency room for various issues. Stated preference, on the other hand, is valuable in assessing preferences

for choices that may not currently be available, or perhaps in decisions where individuals have not traditionally had much say (e.g. choice of drug therapy).

1.4.1 Discrete Choice Experiments

Discrete choice experiments (DCE) are one stated preference approach commonly used to quantitatively capture patient preferences for health care decisions.[34] It is grounded in multi-attribute utility theory which states that when people make choices between alternatives they take into consideration the qualities of those alternatives and then they make trade-offs on the performance of those qualities.

For example, if you making a choice between two pain relievers you may consider the effectiveness (likelihood of response), the time to effect, the risk of harm and the cost. Figure 1-4 is an example of a typical choice task that might be presented in a DCE. It give two alternatives and describes those alternatives based on the attributes considered important in making the choice. In this example, Alternative 1 performs better than Alternative 2 on likelihood of response and risk of stomach upset, however underperforms on time to effect and cost. Responders would make trade-offs, and select the one that best suits their needs. With repeated choice tasks, using new hypothetical alternatives described by the same attributes, it becomes possible to quantify the preference weights that respondents placed on each attribute, on average.

Figure 1-4. Sample Discrete Choice Experiment Choice Task

Scenario: It is 10 am and you have a busy work day ahead. Suddenly you have a really bad headache come on and you need to choose between two available therapies. Based on the qualities of the alternatives which therapy would you chose?

	Alternative A	Alternative B
Likelihood of response	90%	70%
Time to Effect	30 min	10 min
Cost	$10	$5
Risk of Stomach Upset	1%	10%
Choice	⌂	⌂

1.4.1.1 Design Considerations

There are several design elements to consider when building a survey to capture preference weights. The first step is to define the choice that you are attempting to measure and then selecting attributes and levels that are relevant to that choice. The attributes are the characteristics, like those described in the example above. Though there are potentially many attributes that could influence choice, especially in choices of drug therapy due to the many potential benefits and harms, you need to identify those that are most important in driving decisions. There are no gold standard approach to completing this step, but the most common approach is to review previously published studies, consult experts in their field and maybe conduct focus groups with the target population.[36]

The next decision is to determine if the alternatives will be labelled or not. In Figure 1-4, the choices are unlabeled and identified as “Alternative A” and “Alternative B”. Alternatively you could use a label which conveys some meaning beyond the order in which they are presented, for example “Old Drug” and “New Drug”. When labelled choice tasks

are used, you need to ensure all options are presented, while for unlabeled choice tasks, a subset can be used.[37]

Practically speaking, you need to ensure the survey does not over burden the respondents and that choices are easy to understand. This can be achieved by managing the number of attributes used and the number of choice tasks included, as well as keeping descriptions simple and even using pictures to support understanding of difficult concepts (e.g. risk). It is recommended to keep attributes to the minimum amount necessary, but not to exceed eight.[38] The more attributes that need to be considered, the more likely it is that responders will only look at their two or three most important and not even make trade-offs with the remainder.[39]

When it comes to experimental design a couple of things are taken into consideration. First is the design (a data matrix) which indicates which levels for each attribute will be presented in each choice task. A full factorial design is one in which all possible combination of attribute levels are presented in a survey. For a survey will six attributes, each with three levels, this would equate to 729 (3x3x3x3x3x3) choice tasks per survey participant. This is clearly not feasible and therefore attempts are made to design efficient surveys that only include a manageable number of choice tasks, or a fractional factorial design.[40] The design matrix is typically done with the assistance of a computer software program, with the intent of maximizing efficiency. This is achieved by ensuring all levels are presented the same number of times throughout the survey. The optimal design was historically thought to be an orthogonal design, which is where every pair of levels

occurs equally across all pairs of attributes. This view now as widely held anymore as it they are difficult to design and orthogonality is easily lost.[40] Orthogonality can be lost when attribute levels are not evenly spaced, when there is missing survey data, and when certain types of data coding are used. Instead we see an aim towards near-orthogonal designs (e.g. Bayesian efficient, D-efficient, S-efficient).[40]

The second design consideration is the number of choice tasks needed to be able to accurately estimate preference weights. This in part is determined by the design matrix discussed above, but is also a function of the utility function you are trying to estimate. Consider the list of attributes and levels presented in Table 1-1 that corresponds to the choice task in Figure 1-4.

Table 1-1. Sample of Discrete Choice Experiment Attribute and Levels

Attribute	Level
Likelihood of Response	90% of people will respond 80% of people will respond 70% of people will respond
Time to Effect	10 minutes 30 minutes 60 minutes
Cost	$1 per treatment $5 per treatment $10 per treatment
Risk of Stomach Upset	1% will experience 10% will experience 15% will experience

Each of the attributes are described using continuous variables and in a regression equation, the weight for each attribute could be captured in a single beta estimate per attribute, as in equation 4, where V_n = Utility; asc = alternative specific constant; β = coefficient; and X_n = attributes.

$$V_n = asc + (\beta_{resp} * X_{resp}) + (\beta_{time} * X_{time}) + (\beta_{cost} * X_{cost}) + (\beta_{stomach} * X_{stomach}) \quad (4)$$

Consider however, if we added the attribute "route of administration" with the levels "oral", "patch" and "injection". These are not continuous and therefore in the utility function you would need a beta estimate for each level.[40] To estimate the minimum number of choice tasks you need, you first need to know the number of parameters you need to estimate (beta estimates) and the number of alternatives you will include in each choice task (Equation 5). More practically speaking however, as a researcher you want to maximize the number of tasks without over-burdening the respondent.

Minimum number of choice tasks = (number of parameters) / (number of levels -1) (5)

Finally, before the survey is launched, assessments for data quality should be considered. DCE surveys can be challenging for respondents to grasp, especially if the attributes are complicated to understand (e.g. risk). Building in quality checks helps to mitigate poor quality data. One approach could be to include one or two dominant choice

tasks. These are choice tasks where there are no trade-offs to be made and the correct answer is obvious. One alternative would be better than the other on every attribute. When someone gets a dominant choice task wrong, it is a signal that they do not understand the survey or they are not reading and providing reflective responses.[41] Given that in a two alternative tasks there is a 50/50 chance that someone will select the correct answer by chance, it would be best to include two dominant choice tasks. Care needs to be made when using this approach to test data quality. The choice should be one that has a true dominant answer. Sometimes this is not feasible with some choices where people may legitimately have opposing preferences. Other way to assess data quality would be to set threshold for the time it would take to complete the survey to eliminate speeders, or to include one choice set twice to evaluate consistency (test-retest).[41]

1.4.1.2 Analysis

Several regression models can be used with DCE data. The very basic model being the multinomial logit (MNL) model. The MNL model has three key assumptions. The first is that the beta coefficients are fixed across respondents; the second is the *Independence of Irrelevant Alternatives* (IIA); and finally the *Independence of Identically Distributed* (IID) error components.[37] The IIA assumption is often referred to as the "red bus/blue bus problem" as this analogy provides a clear explanation of this restriction. If you consider a city with two modes of transportation, taking a red bus or walking, and 50% of people tend to select each option, therefore the odds of selecting either of these would be 1.0. If a third

option is add, a blue bus, then the IIA assumption implies the odds ratio would still be 1.0 between the red bus and walking (e.g. if 40% selected red bus, 40% selected walking and 20% selected the new blue bus, the odds ratio between the red bus and walking would still be 1.0 as an equal percent of people chose each option). The reality however is that most people who chose to walk, would still chose to walk even if a blue bus is added and the those who select the red bus would now split between the two buses (e.g. 25% red bus, 25% blue bus, and 50% walk). The IID assumption refers to the fact that any unobserved utility (error) is distributed independently and across alternatives and respondents. Despite these restricted limitations, the MNL model is quite widely used due to its ease in computation and interpretation.[42]

Other models include the nested logit, mixed logit and latent class models. The nested logit model, unlike the MNL, assumes that there is some correlation between a sub-set of alternatives in the model. For example there could be a relationship between the odds of selection of the blue bus or the red bus, as discussed previously. This means there is a partial relaxation of the IIA assumption. Mixed logit models allow for random parameters (accounts for preference heterogeneity) and variation in the variance condition associated with the random component (accounts for scale heterogeneity). Finally, latent class, allows for exploring heterogeneity through the estimation of coefficients for sub-classes of the population (e.g. males vs. female; those with cardiovascular disease vs. those without).[37]

1.5 Rationale and Objectives

There has been major shifts in the manner in which we approach second line therapy for type 2 diabetes, largely due to the demonstration of cardiovascular benefits in users of the SGLT2 inhibitors and the GLP1 receptor agonists with established cardiovascular disease.[10–13,43] These are the first classes of anti-hyperglycemic agents to demonstrate this benefit and have therefore been highlighted as preferred agents in patients with cardiovascular disease who have failed treatment with metformin in clinical practice guidelines.[5] As with all medications, the SGLT2 inhibitors and the GLP1 receptor agonists also come with risk of harms, some of which may still remain unmeasured given how little time either class has been available on the market.

It is unclear if either the SGLT2 inhibitors or the GLP1 receptor agonists performs better overall. To address this gap in our knowledge around these new classes of medications, we have conducted a series of studies to support a detailed comparison evaluating the balance of risks and benefits of these agents. The first two studies were focused on the unanticipated adverse effects of the SGLT2 inhibitors as identified by regulatory agencies. These were narrowly focused studies as there already existed an abundance of systematic reviews and meta-analyses on these agents, but one focused on these unanticipated outcomes was not available. The third study focused on gathering preference weights for attributes of diabetes medications, and the fourth study was a quantitative risk benefit assessment comparing SGLT2 inhibitors to GLP1 receptor agonists.

The specific objectives of this research were:

1. To conduct a systematic review and meta-analysis of the current state of knowledge surrounding key post-market safety concerns of the SGLT2 inhibitors compared to active and non-active comparators in patients with type 2 diabetes.
2. To conduct a systematic review and network meta-analysis of the dose-response relationship between SGLT2 inhibitors and UTI in individuals with type 2 diabetes compared to other diabetes therapies or placebo.
3. To estimate the strength of preferences, relative importance, and trade-offs that Canadians with type 2 diabetes make between characteristics of glucose-lowering medications.
4. To bring together Canadian patient preferences for attributes of diabetes therapies as well as probabilities of efficacy and safety retrieved from the literature quantitative benefit-risk assessment following the incremental net benefit framework.

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2. Co-Authorship Statement

Jennifer R. Donnan led each of the studies and was involved at every stage, including protocol development, search strategy design, screening, data extraction, quality appraisal, survey design, model building, analyses and manuscript preparation.

Eugene Chibrikov was involved in data cleaning and analysis support, manuscript revisions and final approval of the systematic review, meta-analysis, network meta-analysis and discrete choice experiment

Carlo A. Marra was involved in overall project conception, protocol development and manuscript revisions and final approval.

Kris Aubrey-Bassler was involved in overall project conception, protocol development and manuscript revisions and final approval.

Karissa Johnston was involved in overall project conception, protocol development and analysis support (discrete choice experiment), manuscript revisions and final approval.

Michelle Swab was involved in search strategy design, literature search, and manuscript revisions and final approval for the systematic review, meta-analysis and network meta-analysis.

Catherine Grandy was involved in screening, data extraction, quality appraisal and manuscript revisions and final approval for the systematic review, meta-analysis and network meta-analysis.

Jenna Hache was involved in screening, data extraction, quality appraisal and manuscript revisions and final approval for the systematic review, meta-analysis and network meta-analysis.

Daniel Curnew was involved in screening, data extraction, quality appraisal and manuscript revisions and final approval for the systematic review, meta-analysis and network meta-analysis.

Hai Nguyen was involved in interpretation of study results and final approval.

John-Michael Gamble supervised this research and was involved in overall project conception, protocol development, consensus on disagreements in data extraction, data analysis support, interpretation of results, manuscript revisions and final approval.

3. Comparative safety of the sodium glucose co-transporter 2 (SGLT2) inhibitors: A systematic review and meta-analysis[1]

3.1 Background

The sodium glucose co-transporter 2 (SGLT2) inhibitors are a novel drug class available for the management of type 2 diabetes. Clinical guidelines recommend the SGLT2 inhibitors as one of numerous potential pharmacologic approaches for second-line therapy following metformin failure or intolerance.[1,2] Some clinical guidelines recommend the SGLT2 inhibitor, empagliflozin, or the Glucagon-like peptide-1 (GLP1) receptor agonist, liraglutide, as preferred second-line therapies in patients with cardiovascular disease who have failed to achieve glycemic control while on monotherapy.[1] This paradigm shift in the management of type 2 diabetes is largely supported by evidence from recent landmark clinical trials.[3–5] In 2015 the EMPA-REG trial showed that the SGLT2 inhibitor, empagliflozin, significantly reduced the risk for composite endpoint of cardiovascular death, myocardial infarction, or stroke by 14% and all-cause mortality by 32%, in a population with existing cardiovascular disease after approximately 3 years of follow up.[5] The LEADER and SUSTAIN-6 trials have also demonstrated similar benefits with liraglutide and semaglutide.[3,4]

Considering the relative potential harms and benefits, clinicians and policy makers must continue to integrate new pharmacotherapeutic evidence to optimize health

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outcomes. Although the EMPA-REG trial showed that the SGLT2 inhibitor, empagliflozin, significantly reduces the risk of cardiovascular morbidity and mortality, regulatory agencies including the Food and Drug Administration (FDA), the European Medicines Agency (EMA) and Health Canada have issued safety warnings for several adverse events. These include acute kidney injury (AKI), diabetic ketoacidosis (DKA), urinary tract infections (UTI), bone fractures and lower limb amputations, based primarily on case report data.[6–14]

With respect to AKI, there is conflicting information coming forward from clinical trials and case reports. Despite early indication of a protective effect from SGLT2 inhibitors,[15] the FDA published in a safety communication in June 2016 that 101 cases of AKI were reported among users of canagliflozin and dapagliflozin.[10] To date, no meta-analysis of AKI has been published. In May 2015 the FDA published a safety update indicating an increased risk of UTI and DKA. Among patients taking SGLT2 inhibitors, they identified 19 cases of life-threatening infections that originated as a UTI, and 73 cases of DKA. However, to date clinical trial evidence does not support these potential risks. Four published meta-analyses of randomized control trials (RCT) and found no increased risk of UTIs, except within a sub-group of dapagliflozin,[15–18] and one study found an increased risk with empagliflozin 25mg users.[18] One meta-analysis on the risk of DKA currently exists, and shows no increased risk.[19] In January 2016, the FDA issued an expanded warning regarding a potential increased risk for fracture with canagliflozin.[12] Two published meta-analyses[20,21] of SGLT2 inhibitors did not find an increased risk, nor did a pooled analysis of eight canagliflozin trials.[22] Finally, in May 2017, the FDA supported earlier speculation of

increased risk of low limb amputation[9] with evidence gathered from re-analysis the CANVAS and CANVAS-R trials, demonstrating a two-fold increased risk.[23] No meta-analysis of RCTs currently exists with respect to amputation.

In light of recent guideline changes that promote earlier integration of the SGLT2 inhibitors into therapy, clinicians and policy makers need to continue examining the potential risks to their patients. Our objective is to address the current knowledge gap surrounding the post-market safety of the SGLT2 inhibitors compared to active and non-active comparators in patients with type 2 diabetes. We have conducted a systematic review and meta-analysis of RCTs to estimate the risk of AKI, DKA, UTI, bone fracture and lower limb amputation.

3.2 Methods and Analysis

3.2.1 Study Design

This study has been designed in accordance with the PRISMA statement on systematic reviews and meta-analysis (PRISMA Checklist in Section 1 of Appendix A).[24] This protocol has been registered (CRD42016038715) with PROSPERO (International Prospective Register of Systematic Reviews).[25,26]

3.2.2 Search Strategy

A comprehensive search strategy was developed with an experienced health science librarian. The search strategy for published studies was developed in the PubMed database,

and comprised of keywords and MEDLINE controlled vocabulary or Medical Subject Headings (MeSH). A methodological search filter was applied to identify RCTs[27] and the search was limited to English language publications. This search strategy served as a template for additional search strategies tailored to other databases, including the Cochrane Library, EMBASE and International Pharmaceutical Abstracts. In addition, the reference lists of topical review articles, editorials, and included studies were hand-searched to identify other potentially relevant studies. A list of search terms is provided in Section 2 of Appendix A.

The search for unpublished studies and materials included ProQuest Dissertations & Theses Global (ProQuest), and clinical trial registries (ClinicalTrials.gov). Inclusion of unpublished data from the FDA has been shown to substantially impact the effect estimates of meta-analyses of drug trials.[28]

3.2.3 Eligibility Criteria

We included RCTs with a study population consisting of patients 18 years of age and older with a diagnosis of type 2 diabetes. Studies were required to have a formal definition of type 2 diabetes based on established diagnostic criteria during the time of the study. No restriction was applied with respect to history of diabetes medication use. One of the RCT study groups was required to be one of the following SGLT2 inhibitors: canagliflozin, dapagliflozin, empagliflozin, ipragliflozin or any other investigational or approved SGLT2

inhibitor during study period. Eligible comparators included metformin, second-generation sulfonylureas (glyburide, gliclazide, glimepiride, glipizide –first generation sulfonylureas excluded as they are currently not used in clinical practice), basal insulins (NPH, lente, glargine, detemir, degludec), dipeptidyl peptidase-4 Inhibitors (DPP-4I) (alogliptin, linagliptin, saxagliptin, sitagliptin), GLP-1 agonists (dulaglutide, exenatide, liraglutide), thiazolidinediones (TZDs) (pioglitazone, rosiglitazone), alpha-glucosidase Inhibitors (acarbose) or placebo/no treatment. All premixed or acute care insulin protocols were excluded due to inconsistencies in dosing of the short-acting insulins. Any investigational agents other than SGLT-2 inhibitors were excluded.

The outcomes of this study include the serious safety events as highlighted through the federal regulatory drug safety communications.[6–14] These include: AKI, DKA, UTI, bone fractures, and lower limb amputations.

Studies were eligible regardless of duration of follow-up, or publication date; however, non-English citations were excluded. Language restriction does not appear to bias estimates of therapeutic interventions.[29,30]

3.2.4 Study Selection and Data Extraction

We used DistillerSR, a systematic review software,[31] for screening and data extraction. Studies went through a two-level screening process. First, titles and abstracts were reviewed using the inclusion and exclusion criteria. Any studies that meet those

criteria, or where a clear decision could not be made, moved to second level screening. At level two screening, full text articles were retrieved and the same criteria applied. Duplicate screening was carried out using the "liberal accelerated" method at both level one and level two, which was first applied by Khangura.[32] This method involves having a second reviewer only evaluate studies that were deemed not relevant by the lead reviewer. This reduces the overall number of papers that require duplicate screening without increasing the risk of having appropriate studies inadvertently excluded.

Information extracted included study characteristics (country, definitions of exposure(s) and controls), patient characteristics (sex, age, duration of diabetes) and outcome data (a complete list of extracted variables is available in Section 3 of Appendix A). Where the data conflicted between the published paper and other sources (e.g. ClinicalTrials.gov), the data from the published paper were used. Data were only supplemented from other sources when gaps in information existed. In cases where more than one publication reported data on the same study, preference was taken to studies that reported numbers of events (versus only relative risk or hazard ratio) and the most recent were used for data extraction. The exception to this rule was when there was a change to the intervention or comparator groups (e.g. drug, dose, etc.) for study extensions, then data from the original publication were used. Any disagreements were resolved through discussion and consensus. Where necessary, a third reviewer was consulted. All DistillerSR screening and extraction forms were created *a priori* and piloted using a small sample of eligible studies.

3.2.5 Risk of Bias Assessment

Each included study was critically appraised using the Cochrane Collaboration domain-based tool for assessing the risk of bias for RCTs.[33,34] This tool captures six main sources of bias, including: randomization sequence, allocation concealment, blinding of participant and researcher, blinded outcome assessment, incomplete outcome data and selective reporting. A seventh category captures any other potential sources of bias. Bias was assessed at the study level. Low risk of bias was defined as an assessment on the risk of bias tool that included no more than two categories with "unclear risk". Studies were defined as high risk if they had: three or more categories of "unclear risk"; one or more categories of "medium risk"; or one or more categories of "high risk". Publication bias was examined using funnel plots.

3.2.6 Data Synthesis

We conducted a series of pair-wise random effects meta-analyses to estimate the pooled treatment effect using relative risks, using the restricted maximum likelihood method.[35] The primary analysis was split into two comparisons, with the first between SGLT2 inhibitors and placebo, and the second SGLT2 inhibitors and any active comparator. Between-study variance was estimated using the restricted maximum likelihood method. If there were zero events reported, a default value of 0.5 was added to all groups within that study. Statistical heterogeneity was evaluated using the I^2 statistic, with significant heterogeneity defined as an $I2 > 50\%$.[36] To explore treatment effect heterogeneity, we conducted numerous subgroup analyses according to individual SGLT2 inhibitors, risk of

bias, and concurrent use of other diabetes medications. Concurrent/prior use was defined as any previous use of anti-diabetic agents that were used prior to enrollment or added as background therapy after enrollment. If patients could be therapy-naïve or have used other medications to meet enrollment criteria, then they were categorized as concurrent/prior use. Treatment-naïve was defined as patients that: have never had an anti-diabetic medication in the past, have not been on any other anti-diabetic medication in weeks leading up to enrolment, or, were able to go through a washout prior to enrolment. We also conduced sensitivity analyses to explore the impact of methodologic decisions within our analysis. First, we pooled studies that had at least one reported event. Second, we repeated our analyses using fixed-effects models. All analysis was conducted using R statistical software (version 3.4.1).

3.3 Results

3.3.1 Included Studies

A total of 2418 unique titles and abstracts were screened. Of these, 650 proceeded to full text screening. A total of 144 citations met our inclusion criteria, however 34 were excluded at the data extraction phase due to duplication of data, from the publication of extension studies or post-hoc analyses (Figure 3-1). A final total of 109 publications were included, representing 112 randomized populations.

Figure 3-1. Flow Diagram for Included Studies

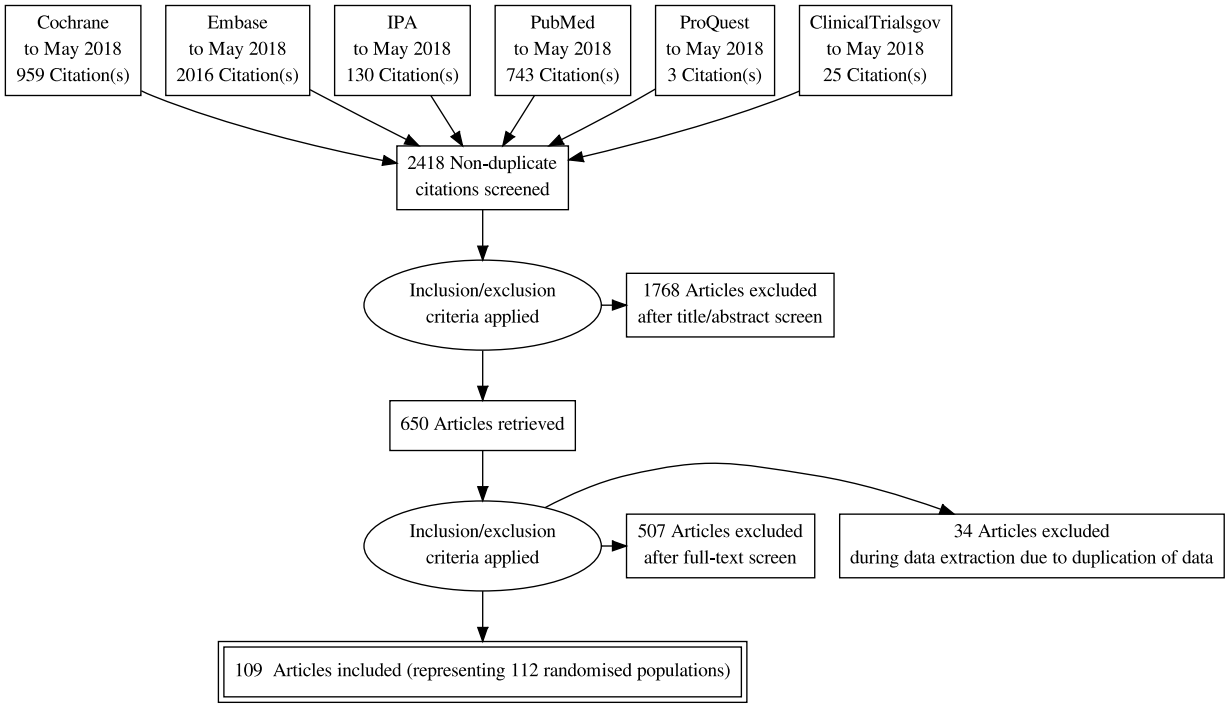


Table 3-1. Characteristics of Included Studies

NCT# Author and Year	Country	Study Duration (weeks)	Total Randomized	Background Therapies	Intervention(s)	Comparator(s)	Outcomes Reported
NCT01059825 Amin, 2015 [37]	International	12	328	Prior therapy stabilized to metformin	Ertugliflozin 1mg, 5 mg, 10mg , 25mg	Placebo, Sitagliptin 100mg	Urinary Tract Infection (UTI)
NCT01059825 Amin, 2015 [38]	International	4	194	Uncontrolled on 2 agents	Ertugliflozin 1mg, 5mg, 25mg	Placebo	UTI
NCT02157298 Araki, 2016 [39]	Japan	16	182	Prior insulin therapy DPP4 allowed	Dapagliflozin 5 mg	Placebo	UTI, Bone Fracture (BF)
NCT01368081 Araki, 2015 [40]	Japan	52	1160	Prior Sulfonylurea (SU)	Empagliflozin 10mg, 25mg	Metformin 500-2250mg/day	UTI, BF
NCT00528879 Bailey, 2013 [41]	International	102	546	Prior metformin	Dapagliflozin 2.5mg, 5mg, 10mg	Placebo	UTI, Acute Kidney Injury (AKI), BF
None Bailey, 2012 [42]	International	24	282	Treatment Naive	Dapagliflozin 1mg, 2.5mg, 5mg	Placebo	UTI, AKI, BF
NCT01164501 Barnett, 2014 [43]	International	52	741	Any prior therapies	Empagliflozin 10mg, 25mg	Placebo	UTI, DKA, BF
NCT01106651 Bode, 2015 [44]	International	104	716	Prior Naive mono or combo therapy	Canagliflozin 100mg, 300mg	Placebo	UTI, DKA, BF
NCT00855166 Bolinder, 2014 [45]	European	102	182	Prior metformin	Dapagliflozin 10mg	Placebo	UTI, BF
NCT01031680 Cefalu, 2015 [46]	International	52	922	Any prior therapies	Dapagliflozin 10mg	Placebo	UTI, AKI, BF
NCT01505426 Lu, 2016 [47]	Korea and Taiwan	24	171	Prior metformin	Ipragliflozin 50mg	Placebo	UTI, BF
NCT01422876 DeFronzo, 2015 [48]	International	52	686	Prior metformin	Empagliflozin 10mg, 25mg	Linagliptin 5mg	UTI

NCT00660907 Del Prato, 2015 [49]	International	208	816	Prior metformin	Dapagliflozin (mixed dose)	Glipizide (mixed doses)	UTI, BF
NCT00881530 Ferrannini, 2013 [50]	International	78	271	Treatment Naive	Empagliflozin 10mg, 25mg	Metformin 2000mg max	UTI, BF
NCT00881530 Ferrannini, 2013 [50]	International	78	388	Prior metformin	Empagliflozin 10mg, 25mg	Sitagliptin 100mg	UTI, BF
NCT00528372 Ferrannini, 2010 [51]	International	24	485	Treatment Naive	Dapagliflozin 2.5mg, 5mg, 10mg	Placebo	UTI
NCT01071850 Fonseca, 2013 [52]	India, Philippines, Columbia, Mexico, USA	12-	412	Treatment Naive	Ipragliflozin 12.5mg, 50mg, 150mg, 300mg	Placebo, Metormin 1500mg	UTI
NCT02229396 Frias, 2016 [53]	International	28	695	Prior metformin	Dapagliflozin 10mg	Exenatide 2mg	UTI, AKI, Diabetic Ketoacidosis (DKA)
NCT01719003 Hadjadj, 2016 [54]	International	24	1364	Treatment Naive	Empagliflozin 10mg, 25mg	Metformin 1000mg, 2000mg	UTI, DKA, BF
NCT01289990 Haering, 2015 [55]	International	76	666	Prior Metformin and SU	Empagliflozin 10mg, 25mg	Placebo	UTI
None Heise, 2013 [56]	Germany	4	78	Not described	Empagliflozin 10mg, 25mg, 100mg	Placebo	UTI
None Heise, 2013 [57]	Germany	9 days	48	Prior Naive mono or combo therapy	Empagliflozin 2.5mg, 10mg, 25mg, 100mg	Placebo	UTI
NCT00643851 Henry, 2012 [58]	International	24	603	Treatment Naive	Dapagliflozin 5mg	Placebo	UTI, BF
NCT00643851 Henry, 2012 [58]	International	24	603	Treatment Naive	Dapagliflozin 5mg	Metformin (mixed doses)	UTI, BF

NCT00859898 Henry, 2012 [58]	International	24	641	Treatment Naive	Dapagliflozin 10mg	Placebo	UTI, BF
NCT00859898 Henry, 2012 [58]	International	24	641	Treatment Naive	Dapagliflozin 10mg	Metformin (mixed doses)	UTI, BF
NCT00800176 Ikeda; 2015 [59]	International	12	398	Naive or metformin	Tofogliflozin 2.5mg, 5mg, 10mg, 20mg, 40mg	Placebo	UTI, DKA
NCT02220920 Inagaki, 2016 [60]	Japan	16	146	Prior insulin therapy	Canagliflozin 100mg	Placebo	UTI, DKA, BF
NCT01387737 Inagaki, 2015 [61]	Japan	52	1299	Any prior therapies washed-out	Canagliflozin 100mg, 200mg	No comparator	UTI, DKA, BF
NCT01022112 Inagaki, 2013 [62]	Japan	12	383	Any prior therapies washed-out	Canagliflozin 50mg, 100mg, 200mg, 300mg	Placebo	UTI, BF
NCT01413204 Inagaki, 2014 [63]	Japan	24	272	Any prior therapies washed-out	Canagliflozin 100mg, 200mg	Placebo	UTI, BF
NCT02175784 Ishihara, 2016 [64]	Japan	16	262	Prior insulin others allowed	Ipragliflozin 50mg	Placebo	UTI
NCT00984867 Jabbour, 2014 [65]	International	48	451	Prior DPP4 maybe metformin no others	Dapagliflozin 10mg	Placebo	UTI, BF
NCT01381900 Ji, 2015 [66]	International	18	678	Prior Metformin and maybe SU	Canagliflozin 100mg, 300mg	Placebo	UTI, BF
NCT01095653 Ji, 2014 [67]	Asia	24	393	Treatment Naive	Dapagliflozin 5mg, 10mg	Placebo	UTI, BF
NCT01023945 Kadokura, 2014 [68]	Japan	2	30	Treatment Naive or monotherapy	Ipragliflozin 50mg , 100mg	Placebo	UTI
NCT01193218 Kadowaki, 2015 [69]	Japan	52	547	Treatment Naive or monotherapy	Empagliflozin 10mg, 25mg	No comparator	UTI, BF

NCT00972244 Kaku, 2013 [70]	Japan	12	279	Treatment Naive or 1 or 2 agents at low dose	Dapagliflozin 1mg, 2.5mg, 5mg, 10mg	Placebo	UTI, BF
None Kaku, 2014 [71]	Japan	24	261	Treatment Naive or monotherapy	Dapagliflozin 5mg, 10mg	Placebo	UTI, BF
None Kaku, 2014 [72]	Japan	24	235	Treatment Naive or washout	Tofogliflozin 10mg, 20mg, 40mg	Placebo	UTI, BF
NCT01242215 Kashiwagi, 2015 [73]	Japan	52	245	Prior SU	Ipragliflozin 50mg	Placebo	UTI
NCT01057628 Kashiwagi, 2015 [74]	Japan	26	131	Treatment Naive or 1 or 2 agents at low dose	Ipragliflozin 50mg	Placebo	UTI
NCT00621868 Kashiwagi, 2014 [75]	Japan	12	361	Treatment Naive or washout	Ipragliflozin 12.5mg, 25mg, 50mg, 100mg	Placebo	UTI
NCT01316094 Kashiwagi,2015 [76]	Japan	52	165	Treatment Naive or 1 or 2 agents at low dose	Ipragliflozin 50mg	Placebo	UTI
NCT00663260 Kohan, 2014 [77]	International	104	252	Not described	Dapagliflozin 5mg, 10mg	Placebo	UTI, AKI, BF
NCT01210001 Kovacs, 2015 [78]	International	76	499	Prior pioglitazone and maybe metformin	Empagliflozin 10mg, 25mg	Placebo	UTI, BF
NCT00976495 Heerspink, 2013 [79]	International	12	75	Prior Metformin and maybe SU	Dapagliflozin 10mg	Placebo	UTI
NCT01106677 Lavalle-Gonzalez, 2013 [80]	International	52	1284	Prior Metformin and maybe SU but washed-out	Canagliflozin 100mg, 300mg	Sitagliptin 100mg	UTI, DKA, BF
NCT01042977 Leiter, 2014 [81]	International	52	964	Any prior therapies	Dapagliflozin 10mg	Placebo	UTI, AKI, BF
NCT00968812 Leiter, 2015 [82]	International	104	1450	Prior metformin	Canagliflozin 100mg, 300mg	Glimepiride 8mg	UTI, BF

NCT01422876 Lewin, 2015 [83]	International	52	677	Treatment Naive	Empagliflozin 10mg, 25mg	Linagliptin 5mg	UTI
NCT00263276 List, 2009 [84]	International	12	389	Treatment Naive	Dapagliflozin 2.5mg, 5mg, 10mg, 20mg, 50mg	Placebo, Metformin 1500mg max	UTI
NCT01646320 Mathieu, 2015 [85]	International	52	320	Prior metformin and DPP4	Dapagliflozin 10mg	Placebo	UTI, BF
NCT01392677 Matthaei, 2015 [86]	International	52	219	Prior Metformin and SU	Dapagliflozin 10mg	Placebo	UTI
None Mudaliar, 2014 [87]	International	12	44	Prior Metformin and maybe SU	Dapagliflozin 5mg	Placebo	UTI
NCT01947855 Nishimura, 2015 [88]	Japan	4	60	Treatment or monotherapy	Empagliflozin 10mg, 25mg	Placebo	UTI, DKA
NCT01340664 Qiu, 2014 [89]	International	18	279	Prior metformin	Canagliflozin 100mg, 300mg	Placebo	UTI
NCT01989754 Rodbard, 2016 [90]	International	26	218	Prior metformin and DPP4	Canagliflozin 300mg	Placebo	UTI, DKA, BF
NCT01289990 Roden, 2015 [91]	International	76	899	Treatment Naive	Empagliflozin 10mg, 25mg	Placebo, Sitagliptin 100mg	UTI, DKA
NCT00642278 Rosenstock, 2012 [92]	International	12	451	Prior metformin	Canagliflozin 50mg, 100mg, 200mg, 300mg, 600mg	Placebo, Sitagliptin 100mg	UTI
NCT01376557 Rosenstock, 2015[93]	United States	12	299	Prior metformin	Sotagliflozin 75 mg, 200mg, 400mg	placebo	UTI, BF
NCT01809327 Rosenstock, 2016 [94]	International	26	1186	Treatment Naive	Canagliflozin 100mg, 300mg	Metformin 500mg	UTI, DKA

NCT01606007 Rosenstock, 2015 [95]	International	24	534	Prior metformin	Dapagliflozin 10mg	Placebo	UTI, BF
NCT01306214 Rosenstock, 2014 [96]	International	52	563	Prior insulin therapy	Empagliflozin 10mg, 25mg	Placebo	UTI, DKA, BF
NCT01011868 Rosenstock, 2015 [97]	International	78	494	Prior insulin maybe metformin and SU	Empagliflozin 10mg, 25mg	Placebo	UTI, DKA
NCT00683878 Rosenstock, 2012 [98]	International	48	420	Treatment Naive or stabilized on pioglitazone	Dapagliflozin 5mg, 10mg	Placebo	UTI, BF
None Ross, 2015 [99]	International	16	983	Prior metformin	Empagliflozin 10mg, 25mg	Placebo	UTI
None Sasaki, 2015 [100]	Japan	7 days	40	Treatment Naive	Luseogliflozin 0.5mg, 1mg, 2.5mg, 5mg	Placebo	UTI
NCT01137812 Schernthaner, 2013 [101]	International	52	756	Prior Metformin and SU	Canagliflozin 300mg	Sitagliptin 100mg	UTI, BF
NCT01217892 Schumm-Draeger, 2014 [102]	International	16	400	Prior metformin	Dapagliflozin 5mg, 10mg, 20mg	Placebo	UTI, BF
None Seino, 2014 [103]	Japan	12	239	Treatment Naive	Luseogliflozin 0.5mg, 2.5mg, 5mg	Placebo	UTI
None Seino, 2014 [104]	Japan	12	282	Treatment Naive	Luseogliflozin 1mg, 2.5mg, 5mg, 10mg	Placebo	UTI, DKA
None Seino, 2014 [105]	Japan	24	158	Treatment Naive	Luseogliflozin 2.5mg	Placebo	UTI
NCT01081834 Stenlof, 2013 [106]	International	26	587	Treatment Naive or washout	Canagliflozin 100mg, 300mg	Placebo	UTI, BF
NCT00680745	International	48	597	Prior SU	Dapagliflozin	Placebo	UTI, BF

Strojek, 2014 [107]					2.5mg, 5mg, 10mg		
NCT00500331 Sykes, 2015 [108]	international	12	336	Treatment Naive	Remogliflozin 100mg, 200mg, 500mg, 1000mg, 2000mg	Placebo, Pioglitazone 30mg	UTI
NCT01370005 Tikkanen, 2015 [109]	International	12	825	Treatment Naive	Empagliflozin 10mg, 25mg	Placebo	UTI, DKA, BF
None Townsend, 2016 [110]	United States	6	171	Uncontrolled on 1-3 agents	Canagliflozin 100mg, 300mg	Placebo	UTI
None Wan Seman, 2016 [111]	Malaysia	12	110	Prior Metformin and SU	Dapagliflozin 10mg	Sulphonylureas (various agents)	UTI
NCT01137474 Weber, 2016 [112]	International	12	944	Any prior therapies	Dapagliflozin 10mg	Placebo	UTI, BF
NCT01195662 Weber, 2016 [113]	International	12	449	Any prior therapies	Dapagliflozin 10mg	Placebo	UTI, BF
NCT01106625 Wilding; 2013 [114]	International	52	469	Prior Metformin and SU	Canagliflozin 100mg, 300mg	Placebo	UTI, DKA, BF
NCT01117584 Wilding, 2013 [115]	International	12	343	Prior metformin	Ipragliflozin 12.5mg, 50mg, 150mg, 300mg	Placebo	UTI
NCT00357370 Wilding, 2009 [116]	International	12	71	Any prior therapies	Dapagliflozin 10mg, 20mg	Placebo	UTI
NCT00673231 Wilding, 2014 [117]	international	104	808	Prior insulin others allowed	Dapagliflozin 2.5mg, 5/10mg, 10mg	Placebo	UTI, BF
NCT01064414 Yale, 2014 [118]	International	52	269	Treatment Naive or 1 or 2	Canagliflozin 100mg, 300mg	Placebo	UTI, BF

NCT01316341 Zhao, 2015 [119]	China	9 days	24	Treatment Naive or 1 or 2	Empagliflozin 10mg, 25mg	Placebo	UTI
NCT01131676 Zinman, 2015 [5]	International	206	7028	Treatment Naive	Empagliflozin 10mg, 25mg	Placebo	UTI, AKI, DKA, BF
None Goto, 2012 [120]		24	168	Prior metformin	Ipragliflozin 50mg	Placebo	UTI
NCT02036515 Dagogo-Jack, 2017 [121]	International	26	463	Prior metformin and DPP4	Ertugliflozin 5mg, 15mg	Placebo	UTI, DKA, BF
NCT01734785 Maldonado-Lutomirsky, 2016 [122]	International	24	606	Prior metformin and DPP4	Empagliflozin 10mg, 25mg	Placebo	UTI, AKI, BF
NCT01289990 Merker, 2015 [123]	International	52	637	Prior metformin	Empagliflozin 10mg, 25mg	Placebo	UTI
NCT01032629 Neal, 2015 [124]	International	52	2074	Prior insulin therapy	Canagliflozin 100mg, 300mg	Placebo	UTI, BF
NCT01167881 Ridderstrale, 2014 [125]	International	104	1549	Prior metformin	Empagliflozin 25mg	Glimepiride 1-4mg	UTI, AKI, BF
NCT00495469 Sykes, 2015 [126]	UK	12	252	Treatment Naive	Remogliflozin 100mg, 250mg, 500mg, 1000mg	Placebo, Pioglitazone 30mg	UTI, BF
None Tanizawa, 2014 [127]	Japan	52	194	Treatment Naive	Tofogliflozin 20mg, 40mg	No comparator	UTI
None Tanizawa, 2014 [127]	Japan	52	602	Any prior therapies	Tofogliflozin 20mg, 40mg	No comparator	UTI
NCT01095666 Yang, 2014 [128]		24	444	Prior metformin	Dapagliflozin 5mg, 10mg	Placebo	UTI, BF

None Gupta, 2017 [129]		76	108	Treatment Naive	Empagliflozin 10mg, 25mg	Placebo, Sitagliptin 100mg	UTI
NCT02354235 Kadowaki, 2017 [130]	Japan	24	138	Prior Teneligliptin	Canagliflozin 100mg	Placebo	UTI, DKA, BF
NCT01734785 Softeland, 2017 [131]	International	24	333	Prior metformin	Empagliflozin 10mg, 25mg	Placebo	UTI, AKI, DKA, BF
NCT01958671 Terra, 2017 [132]	International	26	461	Treatment Naive	Ertugliflozin 5mg, 15mg	Placebo	UTI
NCT 01022112 Not Published[133]		12	383	Treatment Naive	Canagliflozin 50mg, 100mg, 200mg, 300mg	Placebo	BF
NCT02201004 Terauchi, 2017 [134]		16	211	Prior insulin therapy DPP4 allowed	Tofogliflozin 20mg, 40mg	Placebo	UTI
NCT01986855, Grunberger, 2018 [135]	International	52	468	Prior therapies (NOT metformin, pioglitazone)	Ertugliflozin 5mg, 15mg	Placebo	UTI, BF
NCT01999218, Hollander, 2018 [136]	International	52	1326	Prior metformin	Ertugliflozin 5mg, 15mg	Glimepiride	AKI, UTI, DKA, BF
Ito, 2017 [137]	Japan	24	66	Treatment Naive or prior therapy (NOT glitizone or insulin)	Ipragliflozin 50mg	Pioglitazone 15-30mg	UTI, DKA
NCT02099110, Pratley, 2018 [138]	International	52	1233	Prior metformin	Ertugliflozin 5mg, 15mg	Sitagliptin 100 mg	UTI, DKA, BF
NCT02033889, Rosenstock, 2018 [139]	International	26	621	Prior metformin	Ertugliflozin 5mg, 15mg	Placebo	UTI, DKA, F
Seino, 2018 [140]	Japan	16	233	Prior insulin	Luseogliflozin	Placebo	UTI

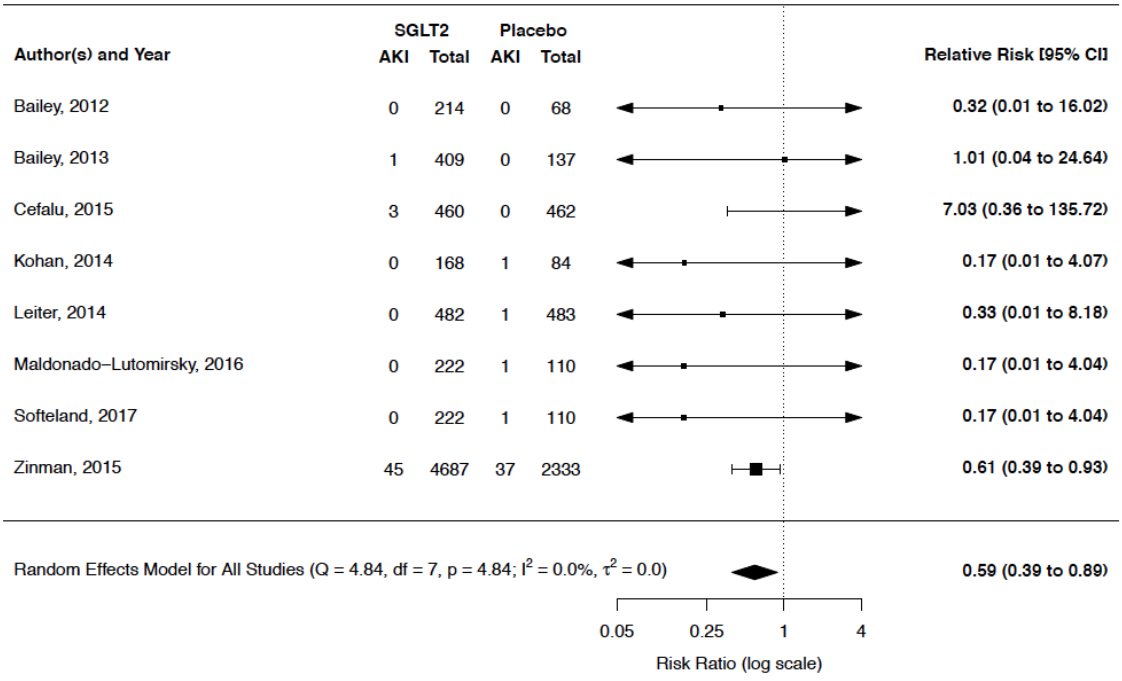
					2.5mg		
NCT02096705, Yang, 2017 [141]	Asia	24	272	Any prior antidiabetic	Dapagliflozin 10mg	Placebo	UTI, DKA
NCT02429258, Henry, 2018 [142]	Unclear	4	100	Background metformin	Dapagliflozin 10mg	Placebo	UTI
NCT01606007, Ekholm, 2017[143]	Unclear	24	534	Background metformin and saxagliptin	Dapagliflozin 10mg	Placebo	BF
Neal, 2017[23]	International	188	10,142	Any background therapy	Canagliflozin 100-300mg	Placebo	UTI, AKI, DKA, BF, Amputation (AMP)

3.3.2 Primary Analysis

Acute Kidney Injury

Acute kidney injury was reported in 11 RCTs (8 placebo comparison, and 3 active comparison trials): meta-analysis was only possible with placebo-controlled trials. Overall SGLT2 inhibitors were found to have a protective effect (RR 0.59; 95% CI 0.39-0.89, I^2 = 0.0%), however this is estimate is heavily weighted by one study using empagliflozin, the EMPA-REG trial (Figure 3-2).[5] Pooled estimate after removing the EMPA-REG trial was non-significant (RR 0.48; 95% CI 0.14-1.64; I^2 = 0.0%).

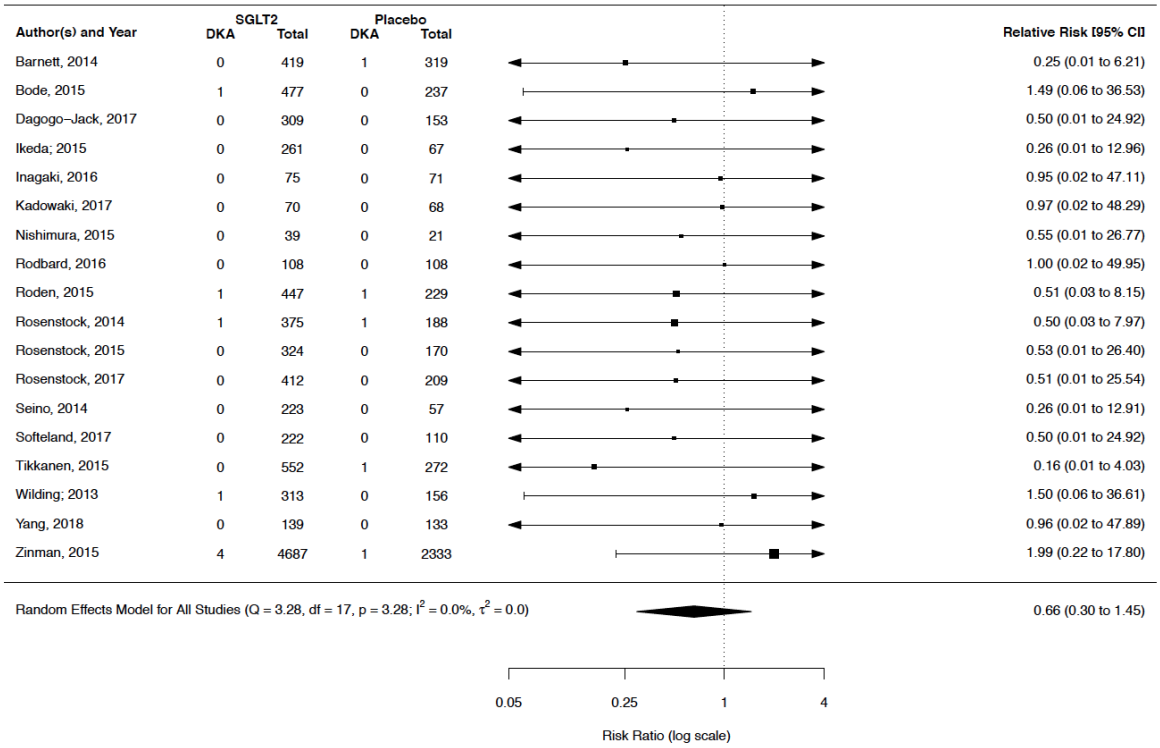
Figure 3-2. Risk of acute kidney injury with SGLT2 inhibitors compared to placebo



Diabetic Ketoacidosis

Diabetic ketoacidosis was reported in 26 RCTs (18 placebo comparisonc, 8 active comparisons, and 1 within class comparison trial). Neither placebo (RR 0.66; 95% CI 0.30-1.45, I^2 = 0.0%) (Figure 3-3) nor incretin (RR 0.43; 95% CI 0.069-2.75; I^2 = 0.0%; 3 Studies) (Forest plot, Section 4 of Appendix A) comparisons showed a significant difference in risk of DKA. Additional analysis using only placebo-controlled trials that had at least one event also yielded no significant difference (RR 0.73; 95% CI 0.25-2.16; I^2 = 0.0%; 7 studies) (Forest plot, Section 4 of Appendix A).

Figure 3-3. Risk of diabetic ketoacidosis from SGLT2 inhibitors compared to placebo



Urinary tract infections

Urinary tract infection was the most frequently reported outcome examined (110 of 112 studies reported). When compared to placebo, SGLT2 inhibitors as a class did not demonstrate a significant increased risk (RR 1.02; 95% CI 0.95-1.09), however subgroup analysis of the individual agents did show a significantly increased risk of UTIs in users of dapagliflozin (RR 1.21; 1.02-1.43), but not empagliflozin, canagliflozin, ipragliflozin or non-marketed SGLT2 inhibitors (grouped) (Figure 3-4). When compared to active treatments, SGLT2 inhibitors grouped together did not demonstrate an increased risk of UTIs over metformin, sulfonylureas, incretins or glitazones, though the confidence interval was very close to significant (RR 1.12; 95% CI 1.00-1.26) (Figure 3-5). When broken down by individual SGLT2 inhibitor, it was dapagliflozin that showed an increased risk of UTI over active comparators grouped together (RR 1.42; 95% CI 1.07-1.87) (Forest plot, Section 4 of Appendix A).

Figure 3-4. Risk of urinary tract infections with SGLT2 inhibitors compared to placebo

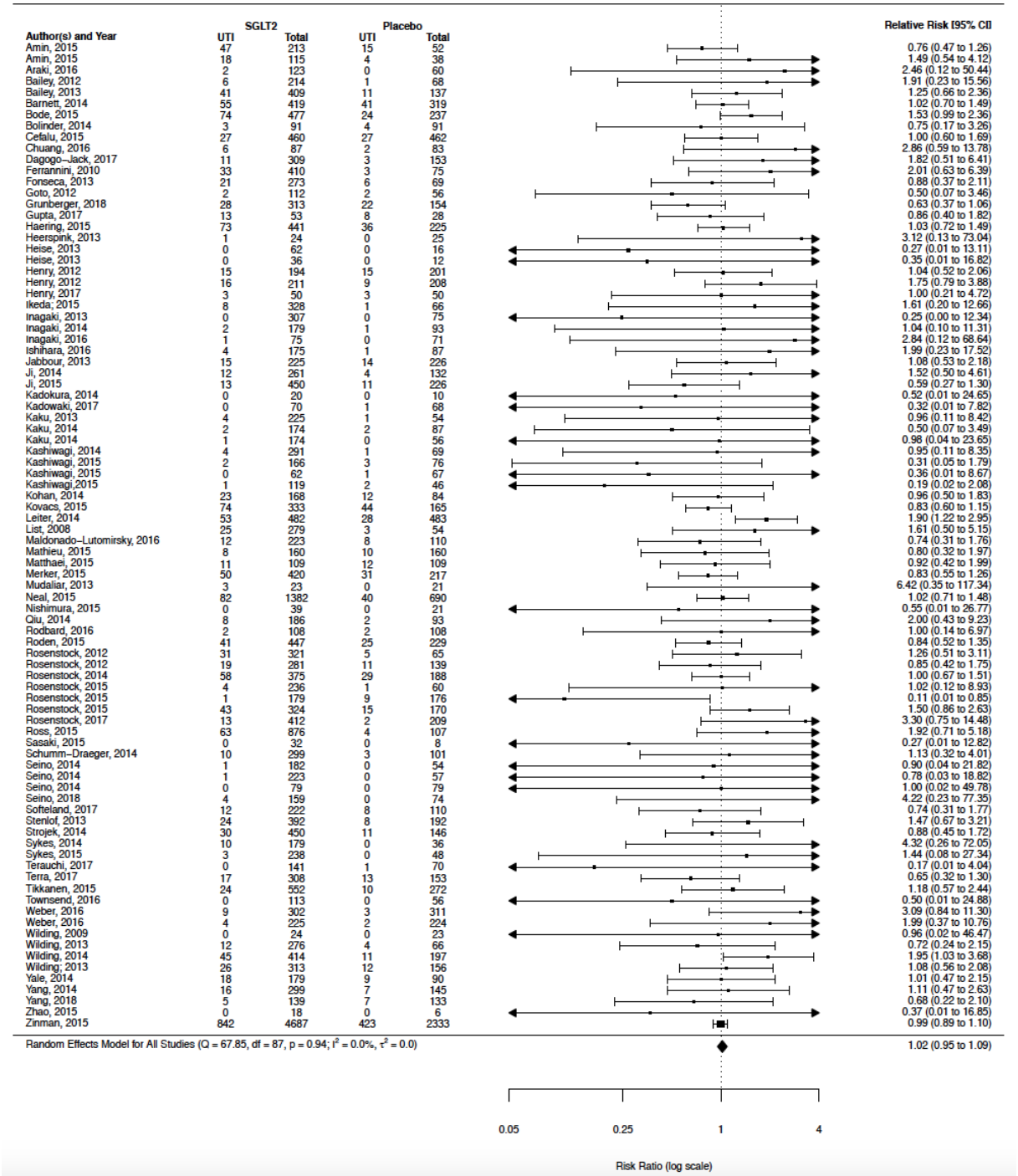
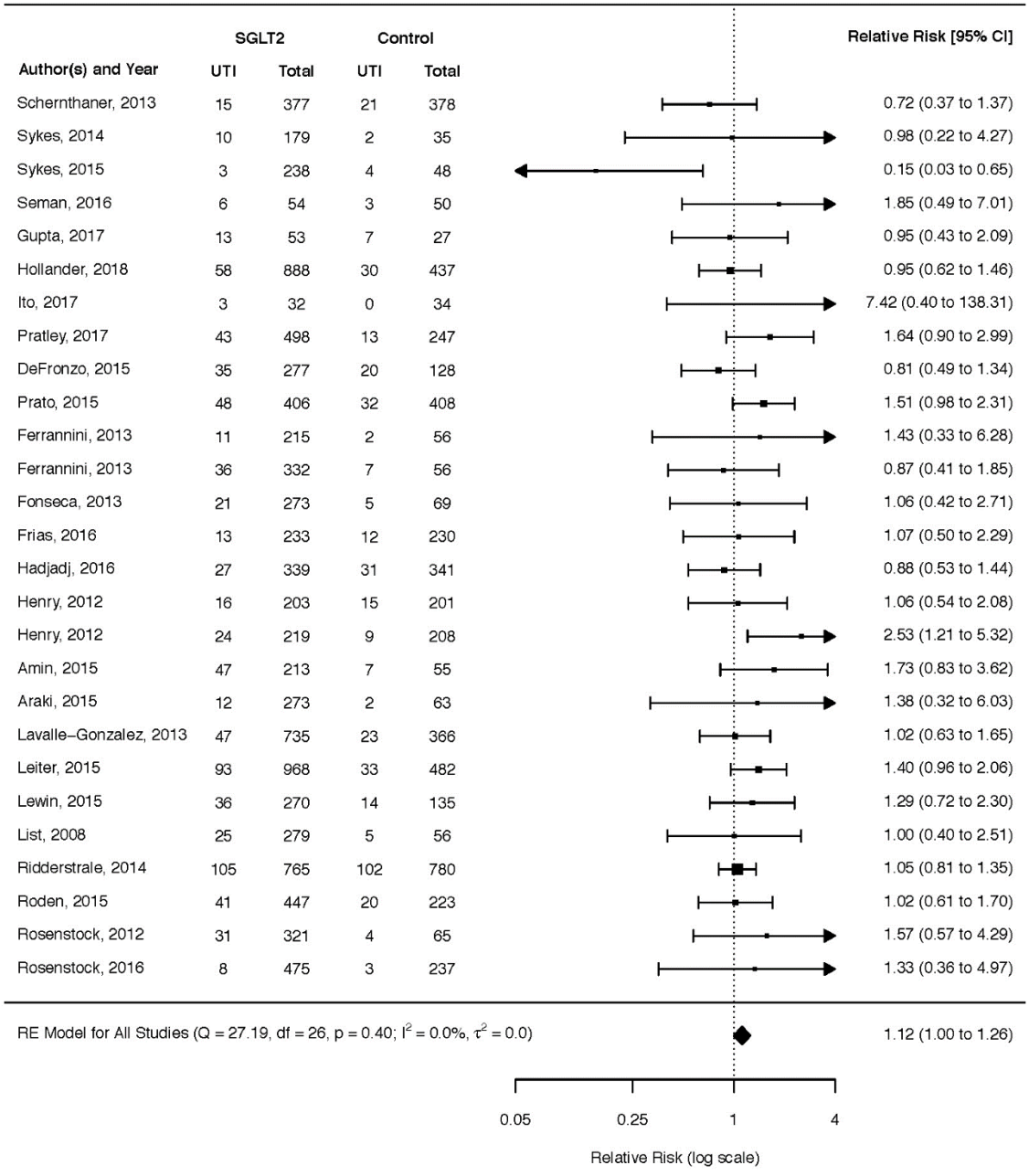


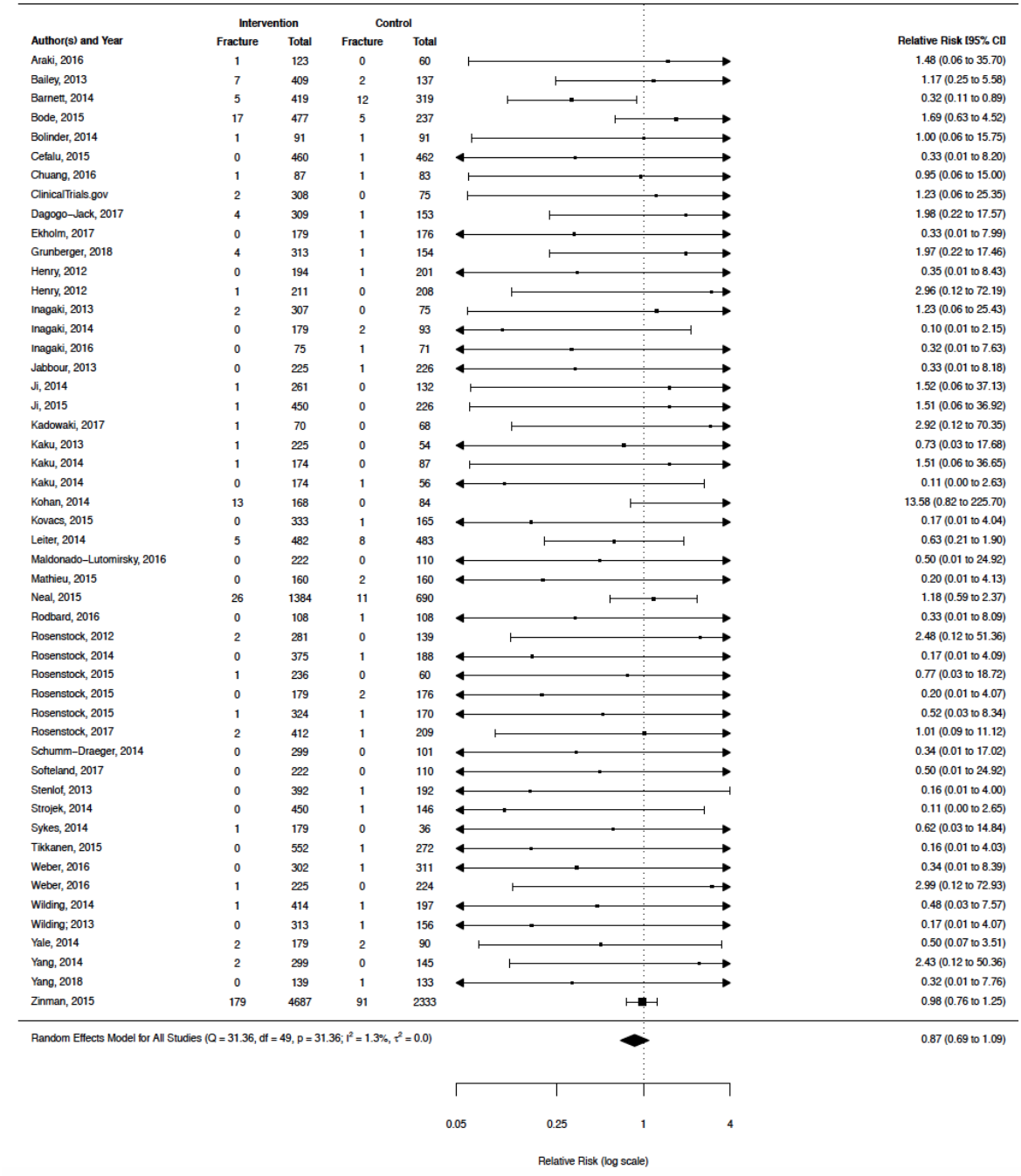
Figure 3-5. Risk of urinary tract infection with SGLT2 inhibitors compared to other active treatments



Bone Fracture

Bone fracture was reported in 63 RCTs (47 placebo comparisons, 14 active comparison, and 2 within class comparisons). SGLT2 inhibitors were not found to have an increased risk of fractures over placebo (RR 0.87; 95% CI 0.69-1.09) (Figure 3-6), metformin (RR 0.69; 95% CI 0.19-2.51; I^2 = 0.0%; 6 studies), sulfonylureas (RR 1.15; 95% CI 0.66-2.00; I^2 = 0.0%; 3 studies) or incretins (RR 1.38; 95% CI 0.31-6.17; I^2 = 0.0%; 3 studies). A sub-group analysis of canagliflozin compared to placebo alone, the agent identified by the FDA as having an increased risk, was also non-significant (RR 1.02; 95% CI 0.63-1.65; I^2 = 0.0%; 12 studies) (Additional forest plots, Section 4 of Appendix A).

Figure 3-6. Risk of fracture with SGLT2 inhibitors compared to placebo



Lower Limb Amputation

Data was identified on amputation for three studies[23,48,136]. One case of amputation was found in the clinicaltrials.gov data for trial number NCT01422876 in a user of empagliflozin 25mg, no cases were reported for other treatment groups. The second study reported data from the CANVAS program, showed a rate of amputation among users of canagliflozin (100-300 mg) was 6.3 per 1000 patient-years, compared to 3.4 per 1000 patient-years for placebo, this difference was statistically significant ($p<0.001$). Actual number of events were not reported. The third study reported one case in each of the treatment groups, ertugliflozin (1/888) and glimepiride (1/437).

3.3.2 Sub-group and Sensitivity Analyses

Several sub-group analyses were conducted to examine: the impact of prior and concurrent use of other anti-diabetic agents; the influence of risk of bias as per the quality appraisal; and the impact of the definition of UTI used as outlined in Table 3-2. Overall these additional analyses did not change the findings of the primary analysis. There was a decreased risk of AKI in the treatment-naïve group, and the low risk of bias group, but this was consistent with the main analysis and driven by the same one large study.[144] When the analyses were re-run using a fixed-effect models, the risk estimates remained the same or had slightly smaller confidence intervals. Forest plots for the fixed effects analysis are in Section 5 of Appendix A.

Table 3-2. Sub-group Analysis among Placebo Controlled Trials

Group	Relative Risk (95% CI, I^2)	# of Studies	Total # of outcomes/patients
Prior use of anti-diabetics			
AKI			
Prior/Concurrent Diabetes Therapy	0.51 (0.14-1.84; 0.72%)	6	90/10,651
Treatment Naïve	0.60 (0.39-0.92; 0.00%)	2	
DKA			
Prior/Concurrent Diabetes Therapy	0.65 (0.25-1.71; 0.00%)	14	13/14,353
Treatment Naïve	0.66 (0.16-2.71; 0.00%)	4	
UTI			
Prior/Concurrent Diabetes Therapy	1.04 (0.93-1.16; 8.22%)	64	3,405/39,331
Treatment Naïve	1.00 (0.91-1.10; 0.00%)	23	
Fracture			
Prior/Concurrent Diabetes Therapy	0.81 (0.57-1.14; 2.61%)	39	445/29,668
Treatment Naïve	0.79 (0.46-1.36; 6.30%)	11	
Risk of Bias			
AKI			
Low Risk of Bias	0.58 (0.38-0.89; 0.0%)	4	90/10,651
High Risk of Bias	0.71 (0.12-4.37; 25.5%)	4	
DKA			
Low Risk of Bias	0.85 (0.28-2.61; 0.0%)	10	13/14,353
High Risk of Bias	0.49 (0.003-71.59; 94.8%)	8	
UTI			
Low Risk of Bias	1.00 (0.92-1.08; 0.0%)	51	3,405/39,331
High Risk of Bias	1.05 (0.11-10.43; 99.7%)	37	
Fracture			
Low Risk of Bias	0.95 (0.76-1.18; 0.0%)	22	445/29,668
High Risk of Bias	0.58 (0.04-8.77; 97.0%)	27	
Definition of UTI			
UTI			
Predefined list of terms	0.99 (0.91-1.07; 0.0%)	19	3.405/39,331
Suggestive of UTI	1.13 (0.87-1.47; 0.0%)	11	
Positive culture	0.91 (0.51-1.62; 24.27%)	2	
As per investigator	0.82 (0.41-1.61; 0.0%)	2	
Not defined	1.08 (0.90-1.29; 15.47%)	54	

3.3.3 Risk of bias

Generally, studies were of good methodological quality, however numerous studies were deemed high risk of selective reporting after outcome data was retrieved from ClinicalTrials.gov that were not reported in the peer-reviewed publication (28%). Other potential sources of bias came from unclear reporting of methodological processes like

randomization sequence (32%) or blinded outcome assessment (17%), while most sources of bias came from lack of blinding of the researchers and participants (13%) and of the outcome assessors (9%). Risk of bias assessment for individual studies are available in Section 6 of the Appendix A. Funnel plots do not suggest of the presence of publication bias (see Section 7 of Appendix A).

3.4 Discussion

This study provides a comprehensive review of the RCT literature with respect to key safety outcomes identified through post-marketing surveillance systems and communicated to health professionals and the public by drug regulators. We pooled outcome data from over 100 RCTs (including unpublished data only available through ClinicalTrials.gov) to quantify the association between SGLT2 inhibitors and AKI, DKA, UTI, and bone fracture. We found that SGLT2 inhibitors as a class do not appear to increase the risk of DKA, UTI, and bone fracture, and may have a protective effect with respect to AKI, though this effect was heavily weighted by one large RCT. With respect to UTI, overall findings do not hold in subgroup analysis by individual drug, suggesting that increased risk of UTI is associated only with dapagliflozin.

Despite early indication of a protective effect from SGLT2 inhibitors on kidney function,[15] the FDA published in a safety communication in June 2016 that 101 cases of AKI were reported among users of canagliflozin and dapagliflozin.[10] SGLT2 inhibitors may provide a long-term protective effect on the kidneys via reduced trans-glomerular

pressure, similar to the effects of agents that target the renin–angiotensin–aldosterone (RAAS) axis.[145] Szalat et al. (2017) proposed three possible mechanisms that may explain the potential for an increased risk of AKI with SGLT2 inhibitors: 1) excessive diuresis leading to volume depletion, a particular concern for those who are hemodynamically unstable and volume-depleted; 2) a greater drop in trans-glomerular pressure due to the concomitant action of SGLT2 inhibition and RAAS blockade; and 3) renal medullary hypoxic injury, likely occurring in patients taking concomitant agents that impair medullary oxygenation (e.g. NSAIDS, radio-contract dyes).[145] Additional potential mechanisms of renal injury include an increase in the urinary uric acid level leading to both crystal dependent and crystal independent tubular injury, and activation of aldose reductase resulting in fructose generation ultimately leading to increased oxidative stress, uric acid, cytokine release and inflammation.[146] This systematic review highlights a lack of reporting of AKI with only 11 of 111 randomized comparisons having published data on this outcome. Though an overall protective effect was found, this finding was driven by one large RCT that compared empagliflozin to placebo. Evidence to support or refute the potential risk of AKI with use of canagliflozin or dapagliflozin was insufficient. Case reports filed with the FDA suggest that this adverse outcome frequently occurs early in therapy (within one month of initiation) and therefore this lack or reporting should not be due to the duration of clinical trials. Recent observational data also supports clinical trial data on AKI. Nadkarni et al. (2017) reported on the incidence of AKI among two cohorts comparing patients with type 2 diabetes using SGLT2 inhibitors to non-users.[147] After an average

follow-up time of 14 months, adjusted hazard ratios showed SGLT2 inhibitors to be protective in one cohort (aHR 0.4 [95% CI 0.2–0.7]; P= 0.004) and favoring SGLT2 inhibitors, though not statistically significant, in the second cohort (aHR 0.6 [95% CI 0.4–1.1]; P= 0.09). These findings were not driven by users of empagliflozin, rather 91.2% and 71.4% of SGLT2 inhibitor users in these cohorts were taking either canagliflozin or dapagliflozin respectively.

Reports of euglycemic DKA among patients with type 2 diabetes is concerning, as a diagnosis can easily be missed. Though rare, the SGLT2 inhibitors are thought to increase the risk by two potential mechanisms: 1) they increase urinary glucose excretion which leads to a reduction in insulin secretion and stimulates free fatty acid production which are later converted to ketone bodies; and 2) they stimulate glucagon secretion which may lead to an overproduction of ketone bodies.[148] An accurate assessment of the potential increased risk of DKA among users of SGLT2 inhibitors was difficult with the data reported within RCTs. Baseline incidence rates of DKA in patients with type 2 diabetes was found to be 1.34 per 1,000 person-years in a 20 year retrospective Danish cohort study, with declining incidence each year.[149] Therefore, most RCTs had insufficient sample size to detect any cases. Of the 16 RCTs that reported DKA, only 7 (representing 11,004 patients) had one or more cases. Our findings are consistent with published observational literature, which indicates no increased risk, however confidence intervals were wide. A case-control study using Truven MarketScan data (a large US claims database),[150] and a cross-sectional using the FDA Adverse Event Reporting System (FAERS) database[151] examining this issue have recently been published. Both studies used DPP-4 inhibitors as the active comparator

given they have no known risk for DKA and are used in a similar fashion as second line therapy in type 2 diabetes, and both showed significant increased risk with SGLT2 inhibiters (Case-Control: 7-fold increased risk among 140,352 patients; cross-sectional: HR 2.2; 95% CI 1.4-3.6, among 416,670). In contrast, the Danish cohort study did not find an increased risk of DKA in individuals taking SGLT2 inhibitors compared to other diabetes therapies (HR 1.6; 95% CI 0.6-3.5), although the upper bound of the 95% confidence interval does not rule out significant harm.[149] No meta-analyses assessing this outcome were found.

Given the mechanism of action of the SGLT2 inhibitors, which work by inhibiting glucose reabsorption in the kidney leading to increase glucose excretion in the urine, an increased risk of UTI is plausible. In May 2015 the FDA reported in a safety update that 19 cases of life-threatening kidney or blood infections that originated as a UTI had been identified in patients taking a SGLT2 inhibitor. However, a meta-analysis published in 2017, which is the largest to date, included 77 RCTs representing 50,820 patients and found no increased risk of UTIs in SGLT2 inhibitor users (RR 1.05; 95% CI 0.98-1.12).[17] The previous meta-analysis limited inclusion to studies of at least 24 weeks and having a full text publication. Our study findings are consistent and add to the literature via the inclusion of 35 more studies, resulting in a more precise effect estimate. Importantly, subgroup analysis of individual SGLT2 inhibitors suggest variation of UTI risk within class whereby dapagliflozin may increase UTI risk when compared to both placebo and active controls. A reasonable biologic mechanism for an increased risk of UTIs among dapagliflozin users is unclear, however some early pathophysiological studies suggest that the dose response relationship

with urinary glucose excretion seems to plateau at the beginning of the normal recommended doses for most SGLT2 inhibits[152–157], though continues through the normal dosing range for dapagliflozin[158].

In January 2016, the FDA issued an expanded warning regarding a potential increased risk for fracture with canagliflozin.[12] A disruption in calcium-phosphate homeostasis is one potentially contributing mechanism.[20] SGLT2 inhibitors increase serum phosphate levels via increased tubular reabsorption of phosphate. Increased phosphate levels then stimulate parathyroid hormone release which may enhance bone resorption leading to an increased fracture risk in patients using SGLT2 inhibitors.[159] In an RCT conducted by Bode et al. (2015), additional investigation into the change in bone mineral density in canagliflozin versus placebo users was conducted.[44] Their results showed a decreased placebo-corrected bone mineral density in the canagliflozin users at 2 years of 0.9-1.2% at the hip, 0.3-0.7% at the lumbar spine, 0.5% at the femoral neck, and 0.4% at the distal forearm. To date, two meta-analyses have been published examining the risk of fracture when comparing SGLT2 inhibitors to placebo.[20,21] Ruanpeng et al. (2017) included 20 RCTs, and Tang et al. (2016) included 38 RCTs. Neither meta-analysis in pooled or subgroup analysis of individual SGLT2 inhibitors demonstrated a significant increased risk of fracture. A pooled analysis of eight canagliflozin RCTs also found no increased risk.[22] The results of this current study support the existing literature, demonstrating risk neutrality, with the addition of new RCT literature (a total of 58 RCTs, 45 of which were placebo controlled).

To date research evidence on the risk of amputations among users of SGLT2 inhibitors is limited to results from the combined CANVAS and CANVAS-R trials. Only two other studies reported amputations, with one event per trial. Further data is needed to establish the true risk as well as to identify if this may be a class effect or agent specific.

3.4.1 Limitations

Although we conducted a comprehensive systematic review of RCTs of SGLT2 inhibitors, there are still limitations to be considered when interpreting our findings. First, our review focused on select adverse events and excluded any benefits. Though this narrows the focus and requires the consideration of additional literature to make clinical decisions on appropriate use of SGLT2 inhibitors, it also provides a succinct and in-depth assessment of the unexpected adverse effects that have been reported post-market. Secondly, several of the outcomes (e.g., AKI, DKA, limb amputations) we evaluated occur infrequently. This also resulted in these individual outcomes to be at a higher risk of selective reporting bias than the more common adverse effects. We did our best to account for this risk by supplementing unreported outcomes with data from clinicaltrials.gov, however it is possible the cases of these outcomes were not recorded or reported through either of these sources. Thirdly, certain outcomes may have been inadequately characterized within study reports. For example, while UTIs were commonly reported among RCTs included in this meta-analysis, data on complicated versus uncomplicated

infections were not. The FDA highlighted 19 cases of life-threatening infections stemming from UTIs. It is possible that SGLT2 inhibitors play a role in the progression of UTI to more complicated clinical outcomes. Fourth, the limited duration of included RCTs (36% of studies were less than 24 weeks and 63% less than one year) precludes the estimation of long-term effects of SGLT2 inhibitors. This may be important in case of declining bone integrity. Finally, it was difficult to accurately assess the methodological quality of the outcome assessment for the included studies given the fact we were examining secondary and rarely reported outcomes. It has been noted that traditional quality appraisal forms are not always well suited to systematic reviews of adverse events. This is due to the fact that sometimes data on adverse effects may be collected after allocation is known, or through self-assessment questionnaires.[160]

3.5 Conclusion

Despite the growing body of evidence on the new SGLT2 inhibitors, there remains minimal evidence demonstrating the comparative safety with respect to the more serious and unexpected outcomes. Current evidence from RCTs does not suggest an increased risk of harm with SGLT2 inhibitors, as a class, over placebo or active comparators with respect to the AKI, DKA, UTI or fracture. There appears to be treatment effect heterogeneity for the risk of UTI among specific SGLT2 inhibitors. Larger sample sizes and more long-term evidence is needed to refine our estimates of the risk of AKI, DKA, fracture and amputation among SGLT2 inhibitor users. In particular, the addition of observational studies to future

analyses would allow for larger samples and long term outcomes through the use of real world evidence.

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4. Dose Response of Sodium Glucose Co-Transporter-2 Inhibitors in Relation to Urinary Tract Infections: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials[2]

4.1 Background

The sodium glucose co-transporter-2 (SGLT2) inhibitors are a novel group of drugs for the treatment of type 2 diabetes mellitus. These products have several benefits including a moderate glycemic lowering effect, low risk of hypoglycemia, reductions in weight and blood pressure, and reduction in major adverse cardiovascular events.[1,2] The SGLT2 inhibitors are recommended as one of several options for second-line therapy, with empagliflozin and canagliflozin specifically recommended in clinical guidelines as the preferred second-line therapies for patients with pre-existing cardiovascular disease.[3] Their unique mechanism of action – inhibition of the reabsorption of glucose at the proximal renal tubule – results in increased urinary glucose excretion[4] and has led to speculation about an increased risk of urinary tract infections (UTIs).[5] According to a public safety advisory in the United States, there were 19 reported cases of life-threatening kidney or blood infections between March 2013 and October 2014 that originated as a UTI in individuals taking SGLT2 inhibitors.[6]

[2] A version of this manuscript has been published. Citation: Jennifer R Donnan, Catherine A Grandy, Eugene Chibrikov, Carlo Marra, Kris Aubrey-Bassler, Karissa Johnston, Michelle Swab, Jenna Hache, Daniel Curnew, Hai Nguyen, John-Michael Gamble. Dose Response of Sodium Glucose Co-Transporter-2 Inhibitors on Urinary Tract Infections: A Systematic Review and Network Meta-Analysis . CMAJ Open. 2018. vol. 6 no. 4. E594-E602. Reproduced with permission through the Creative Commons Licence.

Although product monographs for SGLT2 inhibitors identify an increased risk of UTI as a potential adverse effect, clinical trial evidence to date does not support this notion. Two published meta-analyses of randomized control trials (RCTs) found no increased risk of UTIs,[7,8] except within a sub-group of dapagliflozin users receiving a 10mg dose,[8] which indicated a potential dose-response relation. Such a dose-response relation is plausible given variation in the rate of urinary glucose excretion with individual agents (Table 4-1). Some of these agents have shown a clear dose-response relation, whereas others seem to reach a maximum for urinary glucose excretion with certain dosages. Moreover, prior meta-analyses were limited to studies with at least 24 weeks of follow-up. It is unlikely that development of a UTI would require months of treatment, and therefore data from short-term studies should also be considered. The specific question that we addressed in this systematic review and network meta-analysis was whether there is a dose-response relation between SGLT2 inhibitors and UTI in individuals with type 2 diabetes, relative to other diabetes therapies or placebo.

Table 4-1. Comparison of Urinary Glucose Excretion with SGLT2 Inhibitors

Drug	Reference	Mean 24 hour Urinary Glucose Excretion (UGE)	Dose Response
Empagliflozin	Zhao, 2015[9]	Day 1: 10mg (88g); 25 mg (83g) Day 9: 10mg (96g); 25 mg (83g)	No difference between 10 and 25 mg doses
	Kanada, 2013[10]	Day 1: 1mg(40g); 5mg (80g); 10mg (85g); 25mg (90g) Day 27: 1mg (41g); 5mg (77g); 10mg (81g); 25mg (93g) (Estimated from chart)	Dose response
	Scheen, 2014[11]	Day 1: 0.5mg (5g), 2.5mg (30g), 10mg (50g), 25mg (58g), 50mg (64g), 100mg (80g), 200mg (69g), 400 mg (90.8g), 800 mg (62g) (Estimated from chart)	Dose response up to about 100mg dose
	Product Monograph	10mg (64g); 25mg (78g)	Dose response
	Heise, 2013[12]	Day 1: 10mg (74 g); 25mg (90g); 100mg (81g)	Dose response up to 25mg dose
Dapagliflozin	Parkinson, 2016[13]	2.5mg (37.9 g), 5mg (45.2g), 10mg (86.4g)	Dose response
	Yang, 2014[14]	Day 10: 5mg (28g); 10 mg (41g)	Dose response
	Product Monograph	10mg: (~70 g); UGE approached a maximum at 20mg	Dose response to 20 mg dose
Canagliflozin	Iijima, 2015[15]	Ranged from 80g to 110g. Smallest at 25mg, no great difference at 100–400mg	Dose response to 100mg dose
	Devineni, 2015[16]	100–300mg: Ranged from 80–120g	Not clear
	Product Monograph	100-300mg: Ranged from 77-119g	Not clear
	Devineni, 2015[17]	50mg, 100mg, 300mg: increased in a dose-dependent manner	Dose response
Remogliflozin	Kapur, 2013[18]	20mg (67mmol), 50mg (97mmol), 150mg (168mmol), 500mg (223mmol), 1000mg (304mmol)	Dose response
	Dobbins, 2012[19]	200mg (509mmol); 1000mg (918mmol); 2000mg (574mmol)	Dose response to 1000mg
Ipragliflozin	Veltkamp, 2011[20]	A dose response is noted up to the 50/100mg dose. Actual change in UGE depended on study, 50g in one study and 80-90g in another.	Dose response to 50mg dose
	Kadokura, 2014[21]	50 mg (80.6g +/- 22.2g); 100mg (89.7 +/- 12.3g)	No difference between 50mg and 100 mg
Ertugliflozin	Amin, 2015[22]	1mg (46.33 g); 5mg (64.54g); 25mg (74.49g)	Dose response
Tofogliflozin	Ikeda, 2015[23]	2.5mg (217.9mmol), 5mg(272.3mmol), 10mg (346.2mmol), 20mg (396.0mmol), 40mg (402.9mmol)	Dose response
Sotogliflozin	Zambrowicz, 2015[24]	400mg (29.7)	Not clear
	Rosenstock, 2015[25]	75mg (~18g), 200mg (~66g), 400mg (55-60 g) (Estimated from chart)	Dose response to 200mg dose

4.2 Methods and Analysis

4.2.1 Study Design

This study was designed and reported in accordance with the PRISMA statement on systematic reviews and network meta-anlayses[26] (PRISMA Checklist Section on of Appendix B) and was registered with PROSPERO (www.crd.york.ac.uk/prospero/; no. CRD42016038715).[27]

4.2.2 Eligibility Criteria

For this review we sought to identify RCTs that compared an SGLT2 inhibitor with placebo, with no treatment, or with an active antidiabetic control. The SGLT2 inhibitor could be any one of the currently marketed or investigational agents, but excluded combined SGLT1/SGLT2 inhibitors. An active control could be any of the available oral antidiabetic agents with the exception of first generation sulphonylureas, because they are rarely used in practice. Patients had to be adults (≥ 18 yr) with type 2 diabetes. The studies had to report on the outcome of UTI, but were not limited by duration of follow-up, year of publication, or publication status. Inclusion was limited to studies published in English.

4.2.3 Search Strategy

A health science librarian (M.S.) conducted a comprehensive literature search. The search strategy was developed in the PubMed database (from inception to May 2018) and

was then translated for the Cochrane Library via Wiley (from inception to May 2018), Embase via Embase.com (from inception to May 2018) and International Pharmaceutical Abstracts databases via Ebsco (from inception to May 2018). Medical Subject Headings and keyword terms used to capture type 2 diabetes (e.g., "Diabetes Mellitus, Type 2"[Mesh] OR NIDDM[tw] OR t2dm[tw]) were combined with terms relating to SGLT2 inhibitors, including generic names, brand names, chemical names and compound codes as applicable. RCTs were identified with a methodological search filter.[28] The librarian also conducted multiple test searches to optimize the sensitivity and specificity of the search parameters. Reference lists of key articles were also screened (by J.R.D.). We identified unpublished (grey literature) RCT data by searching the *ProQuest Dissertations & Theses Global* and ClinicalTrials.gov databases. For the various search strategies, see Section 2 of Appendix B.

4.2.4 Study Selection and Data Extraction

DistillerSR software[29] was used to facilitate a 2-level screening process. First with titles and abstracts and then full text (performed by J.R.D., C.A.G., J.H., and D.C.). We used the “liberal accelerated” method of duplicate screening,[30] whereby a second reviewer screens only citations that have been rejected by the first reviewer.

For articles included in the review, one reviewer completed the data extraction, and another performed verification (performed by J.R.D., C.A.G. and J.H.) (for data extraction variables, see Section 3 of Appendix B). Where gaps existed, the extracted data were

supplemented with data from ClinicalTrials.gov. Where data from multiple sources conflicted, information from the published paper was used. Where multiple publications for the same study population existed (e.g., interim analyses or extension studies), the most recent publication was used. The exception to this rule was where the most recent publication involved a change in the drug dose, then the original publication was used.

4.2.5 Assessment of Risk of Bias

We used the Cochrane Collaboration domain-based risk assessment tool to identify sources of bias in each study.[31] This assessment was completed independently by one reviewer, with verification by a second reviewer (performed by J.R.D., C.A.G., J.H.). Each domain was identified as being "low", "high", or "unclear" risk of bias. In addition, the following rules were applied to assign an overall risk of bias: where all domains were considered to have low risk, the overall risk was low; where at least 1 domain was considered to have high risk, the overall risk was high; and where at least 1 domain was considered to have unclear risk (and no domain was considered to have high risk), the overall risk was considered to be unclear. We assessed publication bias using a funnel plot of placebo controlled trials.[31]

4.2.6 Data Synthesis

We conducted a Bayesian network meta-analysis of RCTs. The doses of SGLT2 inhibitors were categorized into 2 groups: “high dose” and “low dose”. These categories were defined on the basis of available marketed doses and urinary glucose excretion rates. Where 2 marketed doses were available for a given drug, the lower dose was categorized as “low” and the higher dose as “high”. All other studied doses to the extremes of the 2 marketed doses were categorized in the most proximal dose category. For example, a dose lower than the marketed dose would be considered “low dose”. Where 3 marketed doses were available, the middle dose was categorized with the group having the closest urinary glucose excretion rate. For experimental products, categories were defined by looking at the most commonly studied doses, and setting a threshold, as was done for the marketed products. We took this approach to avoid placing too much emphasis on ineffective or unsafe doses used in dose-finding studies (for threshold doses, see Section 4 of Appendix B).

We used a random-effects generalized linear model for binary data, with non-informative priors, to estimate the relative effects, credible intervals and rank probabilities of each of the comparators. We tested convergence of the Markov Chain Monte Carlo simulation (100,000 iterations) with the Gelman-Rubin diagnostic test and used the deviance information criterion to assess model fit. We examined rank probabilities by calculating the surface under the cumulative rank curve values. We tested heterogeneity

with the I^2 statistic for pairwise comparisons and assessed inconsistency by visually comparing the direct and indirect pooled estimates.

We conducted 3 sensitivity analyses. We altered the threshold between low and high doses to reflect uncertainty in the dose-response relation with urinary glucose excretion. We also restricted the analysis to studies of at least 24 weeks' duration. Finally, we restricted analysis to studies with a "low" overall risk of bias. All of the outcome data were analyzed using the gemtc package of R statistical software (version 3.4.1).

4.2.7 Ethics Approval

This study was a retrospective analysis of previously published data, and ethics approval was not required.

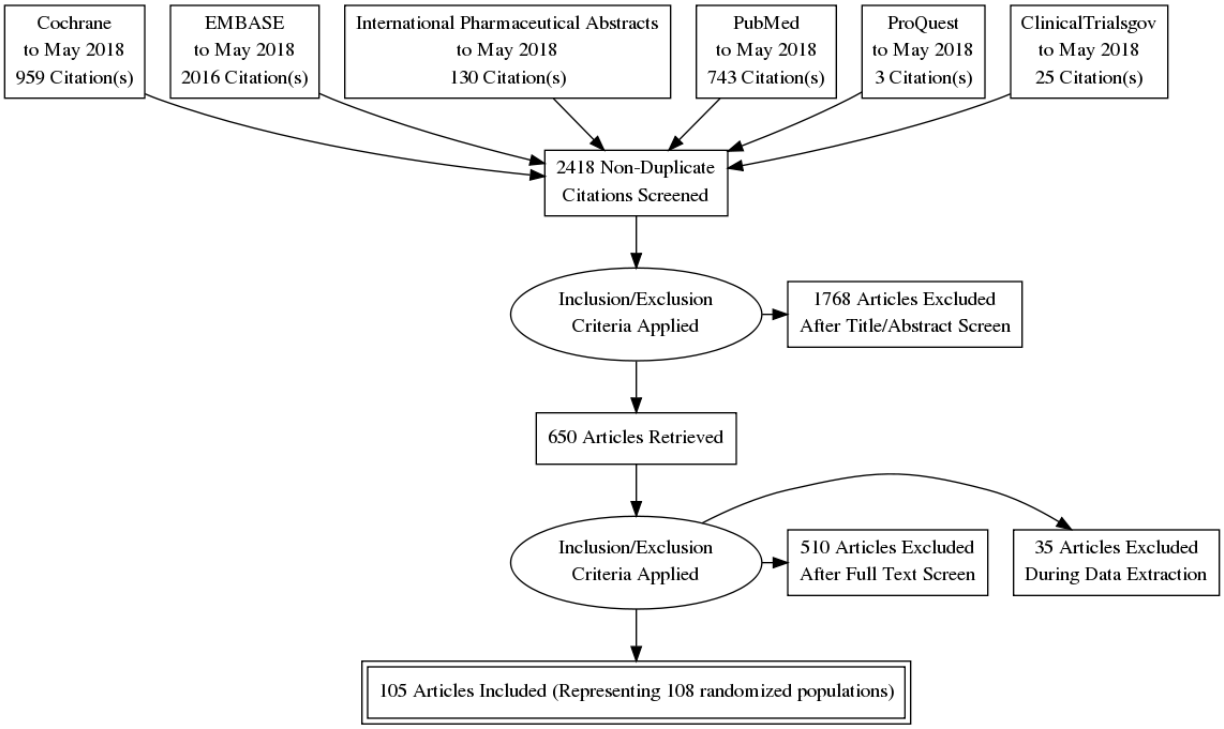
4.3 Results

4.3.1 Included Studies

In total, 2,418 titles and abstracts were screened, and 140 citations met our inclusion criteria. Of these, 35 were excluded because they represented duplicate data (extension studies, post-hoc analyses) or because mixed-doses or unstable doses were used. A final list of 105 publications were included (Figure 4-1), representing 108

randomized populations, 60,082 individuals, and 4,348 UTIs (Table 4-2). Three of the publications[34–36] reported on more than one randomized population.

Figure 4-1. Flow Diagram for Included Studies



Most studies examined either dapagliflozin (33 studies), empagliflozin (25 studies), canagliflozin (19 studies) or ipragliflozin (11 studies); 20 studies investigated 1 of 4 other agents (luseogliflozin, remogliflozin, tofogliflozin, and ertugliflozin). With respect to comparisons, 4 studies conducted only within class comparisons, 89 compared the study drug with placebo, 26 used an active comparator, and 9 included more than 1 unique comparator. Studies ranged from 1 to 208 weeks in duration.

Table 4-2. Characteristics of Included Studies

NCT# Author and Year	Country	Study Duration (weeks)	Total Randomized	Background Therapies	Intervention(s)	Comparator(s)
NCT01059825 Amin, 2015 [22]	International	12	328	Prior therapy stabilized to metformin	Ertugliflozin 1mg, 5 mg, 10mg , 25mg	Placebo, Sitagliptin 100mg
NCT01059825 Amin, 2015 [37]	International	4	194	Uncontrolled on 2 agents	Ertugliflozin 1mg, 5mg, 25mg	Placebo
NCT02157298 Araki, 2016 [38]	Japan	16	182	Prior insulin therapy DPP4 allowed	Dapagliflozin 5 mg	Placebo
NCT01368081 Araki, 2015 [39]	Japan	52	1160	Prior Sulfonylurea (SU)	Empagliflozin 10mg, 25mg	Metformin 500-2250mg/day
NCT00528879 Bailey, 2013 [40]	International	102	546	Prior metformin	Dapagliflozin 2.5mg, 5mg, 10mg	Placebo
None Bailey, 2012 [41]	International	24	282	Treatment Naive	Dapagliflozin 1mg, 2.5mg, 5mg	Placebo
NCT01164501 Barnett, 2014 [42]	International	52	741	Any prior therapies	Empagliflozin 10mg, 25mg	Placebo
NCT01106651 Bode, 2015 [43]	International	104	716	Prior naive mono or combo therapy	Canagliflozin 100mg, 300mg	Placebo
NCT00855166 Bolinder, 2014 [44]	European	102	182	Prior metformin	Dapagliflozin 10mg	Placebo
NCT01031680 Cefalu, 2015 [45]	International	52	922	Any prior therapies	Dapagliflozin 10mg	Placebo
NCT01505426 Lu, 2016 [46]	Korea and Taiwan	24	171	Prior metformin	Ipragliflozin 50mg	Placebo
NCT01422876 DeFronzo, 2015 [47]	International	52	686	Prior metformin	Empagliflozin 10mg, 25mg	Linagliptin 5mg
NCT00660907 Del Prato, 2015 [48]	International	208	816	Prior metformin	Dapagliflozin (mixed dose)	Glipizide (mixed doses)
NCT00881530 Ferrannini, 2013 [36]	International	78	271	Treatment naive	Empagliflozin 10mg, 25mg	Metformin 2000mg max
NCT00881530 Ferrannini, 2013 [36]	International	78	388	Prior metformin	Empagliflozin 10mg, 25mg	Sitagliptin 100mg
NCT00528372 Ferrannini, 2010 [49]	International	24	485	Treatment naive	Dapagliflozin 2.5mg, 5mg, 10mg	Placebo

NCT01071850 Fonseca, 2013 [50]	India, Philippines, Columbia, Mexico, USA	12	412	Treatment naive	Ipragliflozin 12.5mg, 50mg, 150mg, 300mg	Placebo, Metormin 1500mg
NCT02229396 Frias, 2016 [51]	International	28	695	Prior metformin	Dapagliflozin 10mg	Exenatide 2mg
NCT01719003 Hadjadj, 2016 [52]	International	24	1364	Treatment naive	Empagliflozin 10mg, 25mg	Metformin 1000mg, 2000mg
NCT01289990 Haering, 2015 [53]	International	76	666	Prior metformin and SU	Empagliflozin 10mg, 25mg	Placebo
None Heise, 2013 [12]	Germany	4	78	Not described	Empagliflozin 10mg, 25mg, 100mg	Placebo
None Heise, 2013 [54]	Germany	9 days	48	Prior naive mono or combo therapy	Empagliflozin 2.5mg, 10mg, 25mg, 100mg	Placebo
NCT00643851 Henry, 2012 [34]	International	24	603	Treatment naive	Dapagliflozin 5mg	Placebo
NCT00643851 Henry, 2012 [34]	International	24	603	Treatment naive	Dapagliflozin 5mg	Metformin (mixed doses)
NCT00859898 Henry, 2012 [34]	International	24	641	Treatment naive	Dapagliflozin 10mg	Placebo
NCT00859898 Henry, 2012 [34]	International	24	641	Treatment naive	Dapagliflozin 10mg	Metformin (mixed doses)
NCT00800176 Ikeda; 2015 [23]	International	12	398	Naive or metformin	Tofogliflozin 2.5mg, 5mg, 10mg, 20mg, 40mg	Placebo
NCT02220920 Inagaki, 2016 [55]	Japan	16	146	Prior insulin therapy	Canagliflozin 100mg	Placebo
NCT01387737 Inagaki, 2015 [56]	Japan	52	1299	Any prior therapies washed-out	Canagliflozin 100mg, 200mg	No comparator
NCT01022112 Inagaki, 2013 [57]	Japan	12	383	Any prior therapies washed-out	Canagliflozin 50mg, 100mg, 200mg, 300mg	Placebo
NCT01413204 Inagaki, 2014 [58]	Japan	24	272	Any prior therapies washed-out	Canagliflozin 100mg, 200mg	Placebo
NCT02175784 Ishihara, 2016 [59]	Japan	16	262	Prior insulin others allowed	Ipragliflozin 50mg	Placebo
NCT00984867 Jabbour, 2014 [60]	International	48	451	Prior DPP4 maybe metformin no others	Dapagliflozin 10mg	Placebo
NCT01381900 Ji, 2015 [61]	International	18	678	Prior metformin and maybe SU	Canagliflozin 100mg, 300mg	Placebo

NCT01095653 Ji, 2014 [62]	Asia	24	393	Treatment naive	Dapagliflozin 5mg, 10mg	Placebo
NCT01023945 Kadokura, 2014 [21]	Japan	2	30	Treatment naive or monotherapy	Ipragliflozin 50mg , 100mg	Placebo
NCT01193218 Kadowaki, 2015 [63]	Japan	52	547	Treatment naive or monotherapy	Empagliflozin 10mg, 25mg	No comparator
NCT00972244 Kaku, 2013 [1–3,3–10364]	Japan	12	279	Treatment naive or 1 or 2 agents at low dose	Dapagliflozin 1mg, 2.5mg, 5mg, 10mg	Placebo
None Kaku, 2014 [65]	Japan	24	261	Treatment naive or monotherapy	Dapagliflozin 5mg, 10mg	Placebo
None Kaku, 2014 [66]	Japan	24	235	Treatment naive or washout	Tofogliflozin 10mg, 20mg, 40mg	Placebo
NCT01242215 Kashiwagi, 2015 [67]	Japan	52	245	Prior SU	Ipragliflozin 50mg	Placebo
NCT01057628 Kashiwagi, 2015 [68]	Japan	26	131	Treatment naive or 1 or 2 agents at low dose	Ipragliflozin 50mg	Placebo
NCT00621868 Kashiwagi, 2014 [69]	Japan	12	361	Treatment naive or washout	Ipragliflozin 12.5mg, 25mg, 50mg, 100mg	Placebo
NCT01316094 Kashiwagi,2015 [70]	Japan	52	165	Treatment naive or 1 or 2 agents at low dose	Ipragliflozin 50mg	Placebo
NCT00663260 Kohan, 2014 [71]	International	104	252	Not described	Dapagliflozin 5mg, 10mg	Placebo
NCT01210001 Kovacs, 2015 [72]	International	76	499	Prior pioglitazone and maybe metformin	Empagliflozin 10mg, 25mg	Placebo
NCT00976495 Heerspink, 2013 [73]	International	12	75	Prior metformin and maybe SU	Dapagliflozin 10mg	Placebo
NCT01106677 Lavalle-Gonzalez, 2013 [74]	International	52	1284	Prior metformin and maybe SU but washed-out	Canagliflozin 100mg, 300mg	Sitagliptin 100mg
NCT01042977 Leiter, 2014 [75]	International	52	964	Any prior therapies	Dapagliflozin 10mg	Placebo
NCT00968812 Leiter, 2015 [76]	International	104	1450	Prior metformin	Canagliflozin 100mg, 300mg	Glimepiride 8mg
NCT01422876 Lewin, 2015 [77]	International	52	677	Treatment naive	Empagliflozin 10mg, 25mg	Linagliptin 5mg
NCT00263276 List, 2009 [78]	International	12	389	Treatment naive	Dapagliflozin	Placebo, Metformin 1500mg max

					2.5mg, 5mg, 10mg, 20mg, 50mg	
NCT01646320 Mathieu, 2015 [79]	International	52	320	Prior metformin and DPP4	Dapagliflozin 10mg	Placebo
NCT01392677 Matthaei, 2015 [80]	International	52	219	Prior metformin and SU	Dapagliflozin 10mg	Placebo
None Mudaliar, 2014 [81]	International	12	44	Prior metformin and maybe SU	Dapagliflozin 5mg	Placebo
NCT01947855 Nishimura, 2015 [82]	Japan	4	60	Treatment or monotherapy	Empagliflozin 10mg, 25mg	Placebo
NCT01340664 Qiu, 2014 [83]	International	18	279	Prior metformin	Canagliflozin 100mg, 300mg	Placebo
NCT01989754 Rodbard, 2016 [84]	International	26	218	Prior metformin and DPP4	Canagliflozin 300mg	Placebo
NCT01289990 Roden, 2015 [85]	International	76	899	Treatment naive	Empagliflozin 10mg, 25mg	Placebo, Sitagliptin 100mg
NCT00642278 Rosenstock, 2012 [86]	International	12	451	Prior metformin	Canagliflozin 50mg, 100mg, 200mg, 300mg, 600mg	Placebo, Sitagliptin 100mg
NCT01809327 Rosenstock, 2016 [87]	International	26	1186	Treatment naive	Canagliflozin 100mg, 300mg	Metformin 500mg
NCT01606007 Rosenstock, 2015 [88]	International	24	534	Prior metformin	Dapagliflozin 10mg	Placebo
NCT01306214 Rosenstock, 2014 [89]	International	52	563	Prior insulin therapy	Empagliflozin 10mg, 25mg	Placebo
NCT01011868 Rosenstock, 2015 [90]	International	78	494	Prior insulin maybe metformin and SU	Empagliflozin 10mg, 25mg	Placebo
NCT00683878 Rosenstock, 2012 [91]	International	48	420	Treatment naive or stabilized on pioglitazone	Dapagliflozin 5mg, 10mg	Placebo
None Ross, 2015 [92]	International	16	983	Prior metformin	Empagliflozin 10mg, 25mg	Placebo
None Sasaki, 2015 [93]	Japan	7 days	40	Treatment naive	Luseogliflozin 0.5mg, 1mg, 2.5mg, 5mg	Placebo
NCT01137812 Schernthaner, 2013 [94]	International	52	756	Prior metformin and SU	Canagliflozin 300mg	Sitagliptin 100mg
NCT01217892	International	16	400	Prior metformin	Dapagliflozin 5mg, 10mg, 20mg	Placebo

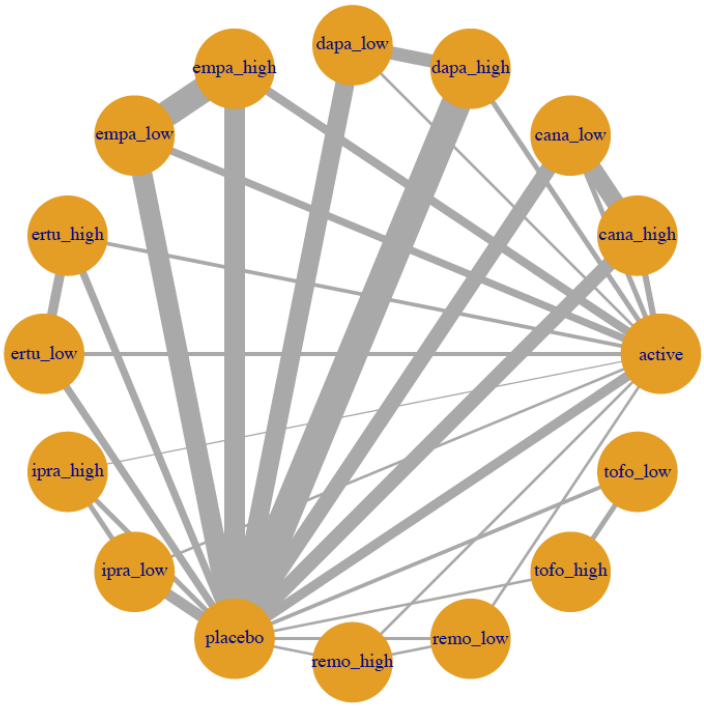
Schumm-Draeger, 2014 [95]						
None Seino, 2014 [96]	Japan	12	239	Treatment naive	Luseogliflozin 0.5mg, 2.5mg, 5mg	Placebo
None Seino, 2014 [97]	Japan	12	282	Treatment naive	Luseogliflozin 1mg, 2.5mg, 5mg, 10mg	Placebo
None Seino, 2014 [98]	Japan	24	158	Treatment naive	Luseogliflozin 2.5mg	Placebo
NCT01081834 Stenlof, 2013 [99]	International	26	587	Treatment naive or washout	Canagliflozin 100mg, 300mg	Placebo
NCT00680745 Strojek, 2014 [100]	International	48	597	Prior SU	Dapagliflozin 2.5mg, 5mg, 10mg	Placebo
NCT00500331 Sykes, 2015 [101]	International	12	336	Treatment naive	Remogliflozin 100mg, 200mg, 500mg, 1000mg, 2000mg	Placebo, Pioglitazone 30mg
NCT01370005 Tikkanen, 2015 [102]	International	12	825	Treatment naive	Empagliflozin 10mg, 25mg	Placebo
None Townsend, 2016 [103]	United States	6	171	Uncontrolled on 1-3 agents	Canagliflozin 100mg, 300mg	Placebo
None Wan Seman, 2016 [104]	Malaysia	12	110	Prior metformin and SU	Dapagliflozin 10mg	Sulphonylureas (various agents)
NCT01137474 Weber, 2016 [105]	International	12	944	Any prior therapies	Dapagliflozin 10mg	Placebo
NCT01195662 Weber, 2016 [106]	International	12	449	Any prior therapies	Dapagliflozin 10mg	Placebo
NCT01106625 Wilding; 2013 [107]	International	52	469	Prior metformin and SU	Canagliflozin 100mg, 300mg	Placebo
NCT01117584 Wilding, 2013 [108]	International	12	343	Prior metformin	Ipragliflozin 12.5mg, 50mg, 150mg, 300mg	Placebo
NCT00357370 Wilding, 2009 [109]	International	12	71	Any prior therapies	Dapagliflozin 10mg, 20mg	Placebo
NCT00673231 Wilding, 2014 [110]	international	104	808	Prior insulin others allowed	Dapagliflozin 2.5mg, 5/10mg, 10mg	Placebo
NCT01064414 Yale, 2014 [111]	International	52	269	Treatment naive or 1 or 2	Canagliflozin 100mg, 300mg	Placebo
NCT01316341 Zhao, 2015 [9]	China	9 days	24	Treatment naive or 1 or 2	Empagliflozin 10mg, 25mg	Placebo

NCT01131676 Zinman, 2015 [1]	International	206	7028	Treatment naive	Empagliflozin 10mg, 25mg	Placebo
None Goto, 2012 [112]	Not clear	24	168	Prior metformin	Ipragliflozin 50mg	Placebo
NCT02036515 Dagogo-Jack, 2017 [113]	International	26	463	Prior metformin and DPP4	Ertugliflozin 5mg, 15mg	Placebo
NCT01734785 Maldonado-Lutomirsky, 2016 [114]	International	24	606	Prior metformin and DPP4	Empagliflozin 10mg, 25mg	Placebo
NCT01289990 Merker, 2015 [115]	International	52	637	Prior metformin	Empagliflozin 10mg, 25mg	Placebo
NCT01032629 Neal, 2015 [116]	International	52	2074	Prior insulin therapy	Canagliflozin 100mg, 300mg	Placebo
NCT01167881 Ridderstrale, 2014 [117]	International	104	1549	Prior metformin	Empagliflozin 25mg	Glimepiride 1-4mg
NCT00495469 Sykes, 2015 [118]	UK	12	252	Treatment naive	Remogliflozin 100mg, 250mg, 500mg, 1000mg	Placebo, Pioglitazone 30mg
None Tanizawa, 2014 [35]	Japan	52	194	Treatment naive	Tofogliflozin 20mg, 40mg	No comparator
None Tanizawa, 2014 [35]	Japan	52	602	Any prior therapies	Tofogliflozin 20mg, 40mg	No comparator
NCT01095666 Yang, 2014 [14]	Not clear	24	444	Prior metformin	Dapagliflozin 5mg, 10mg	Placebo
None Gupta, 2017 [119]	Not clear	76	108	Treatment naive	Empagliflozin 10mg, 25mg	Placebo, Sitagliptin 100mg
NCT02354235 Kadowaki, 2017 [120]	Japan	24	138	Prior teneligliptin	Canagliflozin 100mg	Placebo
NCT01734785 Softeland, 2017 [121]	International	24	333	Prior metformin	Empagliflozin 10mg, 25mg	Placebo
NCT01958671 Terra, 2017 [122]	International	26	461	Treatment naive	Ertugliflozin 5mg, 15mg	Placebo
NCT02201004 Terauchi, 2017 [123]	Not clear	16	211	Prior insulin therapy DPP4 allowed	Tofogliflozin 20mg, 40mg	Placebo
NCT01986855,	International	52	468	Prior therapies (NOT metformin, pioglitazone)	Ertugliflozin 5mg, 15mg	Placebo

Grunberger, 2018 [124]						
NCT01999218, Hollander, 2018 [125]	International	52	1326	Prior metformin	Ertugliflozin 5mg, 15mg	Glimepiride
Ito, 2017 [126]	Japan	24	66	Treatment naive or prior therapy (NOT glitazone or insulin)	Ipragliflozin 50mg	Pioglitazone 15-30mg
NCT02099110, Pratley, 2018 [127]	International	52	1233	Prior metformin	Ertugliflozin 5mg, 15mg	Sitagliptin 100 mg
NCT02033889, Rosenstock, 2018 [128]	International	26	621	Prior metformin	Ertugliflozin 5mg, 15mg	Placebo
Seino, 2018 [129]	Japan	16	233	Prior insulin	Luseogliflozin 2.5mg	Placebo
NCT02096705, Yang, 2017 [130]	Asia	24	272	Any prior antidiabetic	Dapagliflozin 10mg	Placebo
NCT02429258, Henry, 2018 [131]	Not clear	4	100	Background metformin	Dapagliflozin 10mg	Placebo

We included all of the studies in the first run of the analysis. However, despite 200,000 iterations of the Markov Chain Monte Carlo simulation, assessment of the Gelman-Rubin statistic showed that many nodes did not approach convergence. There were also unexpected protective effects in comparisons that included luseogliflozin. On examination of study results, we found only 2 cases of UTI were reported across the 4 luseogliflozin studies, each of which was of short duration (7 days-24 weeks). After removal of these studies all nodes approached convergence. The deviance information criterion was also lower, indicating a better model fit. Figure 4-2 shows the network of available direct evidence without luseogliflozin.

Figure 4-2. Network Diagram



Most comparisons showed a non-significant difference in the risk of UTI (Table 4-3). Exceptions included comparisons of high dose dapagliflozin (≥10 mg) with placebo (odds ratio [OR] 1.30; 95% credible interval 1.09 – 1.57), with active comparators (OR 1.44; 95% credible interval 1.15 – 1.79), with empagliflozin at both high (OR 1.39; 95% credible interval 1.12 – 1.72) and low doses (OR 1.30; 95% credible interval 1.04 – 1.60) and with ertugliflozin at low doses (OR 1.43; 95% credible interval 1.01 – 2.01). Low-dose canagliflozin compared with active comparators also had significantly greater risk (OR 1.29; 95% credible interval 1.03 – 1.64). Examination of rank probabilities using surface under the cumulative rank curve values showed results that were consistent with the primary analysis. Specifically, high-dose dapagliflozin was the least favorable and high-dose remogliflozin and active comparators (grouped) were the most favorable with respect to risk of UTI (for the forest plot of placebo treatment comparisons and the list of surface under the cumulative rank curve values, see Section 5 of Appendix B)

Table 4-3. Risk of Urinary Tract Infections from SGLT2 Inhibitors: Odds Ratios and 95% Credible Intervals for Network Meta-Analysis Comparisons

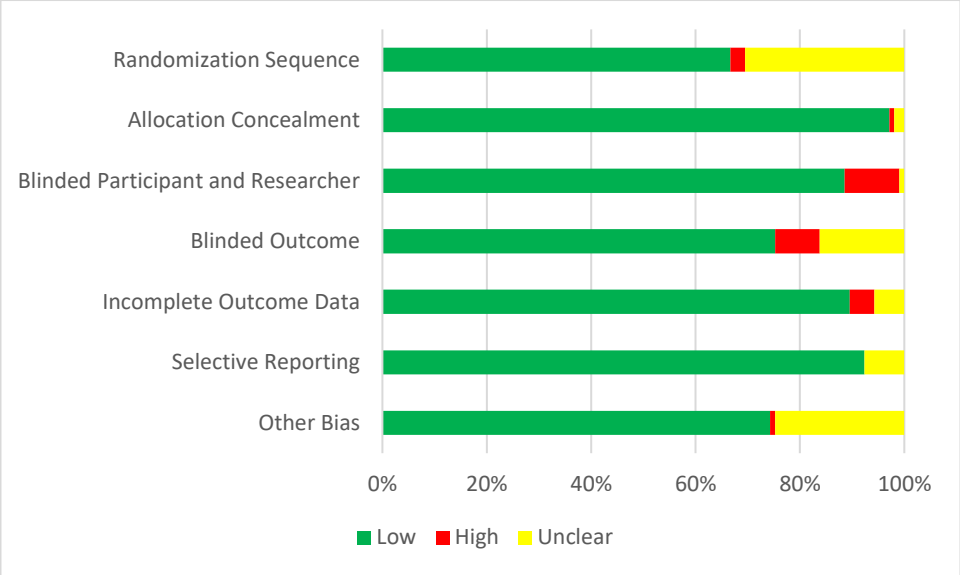
active	cana_high	cana_low	dapa_high	dapa_low	empa_high	empa_low	ertu_high	ertu_low	ipra_high	ipra_low	placebo	remo_high	remo_low	tofo_high	tofo_low
Active	1.184 (0.943, 1.484)	1.293 (1.027, 1.639)	1.438 (1.147, 1.789)	1.195 (0.915, 1.548)	1.03 (0.868, 1.235)	1.109 (0.923, 1.345)	1.202 (0.905, 1.609)	1.005 (0.746, 1.348)	1.106 (0.556, 2.214)	1.114 (0.626, 2.071)	1.101 (0.934, 1.314)	0.811 (0.255, 2.601)	1.11 (0.358, 3.619)	1.677 (0.26, 13.089)	1.618 (0.302, 10.502)
0.844 (0.674, 1.06)	cana_high	1.096 (0.9, 1.326)	1.214 (0.918, 1.56)	1.007 (0.738, 1.36)	0.874 (0.685, 1.103)	0.938 (0.733, 1.185)	1.012 (0.729, 1.448)	0.848 (0.598, 1.206)	0.929 (0.455, 1.946)	0.944 (0.52, 1.785)	0.929 (0.749, 1.146)	0.683 (0.21, 2.266)	0.931 (0.295, 3.062)	1.407 (0.215, 11.37)	1.359 (0.255, 9.426)
0.773 (0.61, 0.974)	0.913 (0.754, 1.112)	cana_low	1.113 (0.837, 1.447)	0.924 (0.678, 1.249)	0.798 (0.628, 1.009)	0.857 (0.672, 1.092)	0.923 (0.657, 1.317)	0.773 (0.54, 1.103)	0.856 (0.412, 1.792)	0.86 (0.471, 1.641)	0.852 (0.682, 1.06)	0.622 (0.194, 2.064)	0.849 (0.272, 2.831)	1.281 (0.202, 10.40)	1.238 (0.237, 8.496)
0.695 (0.559, 0.871)	0.824 (0.641, 1.089)	0.899 (0.691, 1.195)	dapa_high	0.833 (0.665, 1.052)	0.722 (0.581, 0.894)	0.772 (0.623, 0.962)	0.838 (0.6, 1.191)	0.701 (0.497, 0.992)	0.774 (0.377, 1.572)	0.776 (0.433, 1.445)	0.77 (0.638, 0.921)	0.564 (0.18, 1.856)	0.771 (0.252, 2.571)	1.165 (0.181, 9.716)	1.126 (0.21, 7.883)
0.837 (0.646, 1.093)	0.993 (0.735, 1.355)	1.083 (0.801, 1.475)	1.201 (0.95, 1.504)	dapa_low	0.864 (0.666, 1.132)	0.924 (0.715, 1.222)	1.006 (0.7, 1.47)	0.837 (0.586, 1.212)	0.932 (0.443, 1.941)	0.933 (0.502, 1.767)	0.921 (0.726, 1.167)	0.676 (0.208, 2.178)	0.919 (0.286, 3.116)	1.396 (0.217, 11.9)	1.344 (0.249, 10.04)
0.971 (0.81, 1.152)	1.145 (0.907, 1.459)	1.253 (0.991, 1.592)	1.386 (1.119, 1.721)	1.157 (0.884, 1.501)	empa_high	1.073 (0.946, 1.227)	1.158 (0.867, 1.588)	0.973 (0.711, 1.322)	1.07 (0.532, 2.168)	1.077 (0.606, 1.99)	1.063 (0.939, 1.222)	0.783 (0.246, 2.585)	1.072 (0.345, 3.534)	1.62 (0.257, 13.17)	1.559 (0.293, 10.59)
0.901 (0.743, 1.084)	1.066 (0.844, 1.365)	1.166 (0.916, 1.488)	1.295 (1.039, 1.605)	1.082 (0.818, 1.399)	0.932 (0.815, 1.057)	empa_low	1.08 (0.803, 1.477)	0.907 (0.659, 1.226)	0.993 (0.491, 2.038)	1.005 (0.567, 1.855)	0.994 (0.868, 1.13)	0.73 (0.23, 2.444)	0.997 (0.321, 3.302)	1.503 (0.239, 12.11)	1.454 (0.273, 9.827)
0.832 (0.621, 1.105)	0.988 (0.691, 1.372)	1.083 (0.759, 1.522)	1.194 (0.84, 1.667)	0.994 (0.68, 1.428)	0.864 (0.63, 1.153)	0.926 (0.677, 1.245)	ertu_high	0.834 (0.633, 1.106)	0.918 (0.443, 1.947)	0.933 (0.507, 1.825)	0.921 (0.679, 1.216)	0.67 (0.206, 2.282)	0.915 (0.286, 3.112)	1.405 (0.219, 11.11)	1.354 (0.242, 9.236)
0.995 (0.742, 1.34)	1.18 (0.83, 1.673)	1.293 (0.907, 1.852)	1.426 (1.008, 2.01)	1.195 (0.825, 1.705)	1.028 (0.756, 1.407)	1.102 (0.816, 1.519)	1.199 (0.904, 1.579)	ertu_low	1.117 (0.525, 2.293)	1.108 (0.607, 2.198)	1.098 (0.818, 1.466)	0.81 (0.247, 2.656)	1.09 (0.346, 3.652)	1.671 (0.262, 13.35)	1.603 (0.294, 11.40)
0.904 (0.452, 1.798)	1.076 (0.514, 2.199)	1.169 (0.558, 2.425)	1.293 (0.636, 2.654)	1.073 (0.515, 2.26)	0.935 (0.461, 1.881)	1.007 (0.491, 2.035)	1.09 (0.514, 2.256)	0.895 (0.436, 1.903)	ipra_high	1.006 (0.535, 1.921)	0.997 (0.498, 1.999)	0.719 (0.203, 3.128)	0.971 (0.267, 4.106)	1.561 (0.207, 12.19)	1.524 (0.228, 10.89)
0.898 (0.483, 1.598)	1.059 (0.56, 1.922)	1.162 (0.609, 2.121)	1.289 (0.692, 2.309)	1.072 (0.566, 1.991)	0.929 (0.502, 1.65)	0.995 (0.539, 1.763)	1.071 (0.548, 1.973)	0.902 (0.455, 1.647)	0.994 (0.521, 1.869)	ipra_low	0.987 (0.541, 1.746)	0.722 (0.208, 2.731)	0.98 (0.293, 3.733)	1.534 (0.22, 11.93)	1.476 (0.246, 9.623)
0.908 (0.761, 1.071)	1.077 (0.872, 1.336)	1.173 (0.944, 1.467)	1.299 (1.085, 1.567)	1.085 (0.857, 1.377)	0.94 (0.818, 1.065)	1.006 (0.885, 1.151)	1.086 (0.822, 1.473)	0.911 (0.682, 1.223)	1.003 (0.5, 2.007)	1.013 (0.573, 1.85)	placebo	0.734 (0.234, 2.418)	1.001 (0.325, 3.305)	1.512 (0.242, 12.13)	1.47 (0.278, 9.948)
1.233 (0.384, 3.927)	1.464 (0.441, 4.753)	1.607 (0.484, 5.144)	1.773 (0.539, 5.559)	1.479 (0.459, 4.802)	1.277 (0.387, 4.069)	1.37 (0.409, 4.343)	1.493 (0.438, 4.858)	1.235 (0.377, 4.044)	1.392 (0.32, 4.928)	1.385 (0.366, 4.799)	1.362 (0.414, 4.281)	remo_high	1.341 (0.438, 4.112)	2.079 (0.237, 22.26)	1.916 (0.256, 20.93)
0.901 (0.276, 2.791)	1.074 (0.327, 3.395)	1.178 (0.353, 3.68)	1.297 (0.389, 3.974)	1.088 (0.321, 3.495)	0.933 (0.283, 2.901)	1.003 (0.303, 3.12)	1.092 (0.321, 3.496)	0.917 (0.274, 2.892)	1.03 (0.244, 3.74)	1.021 (0.268, 3.411)	0.999 (0.303, 3.075)	0.746 (0.243, 2.283)	remo_low	1.502 (0.168, 16.43)	1.419 (0.189, 14.58)
0.596 (0.076, 3.852)	0.711 (0.088, 4.641)	0.78 (0.096, 4.947)	0.858 (0.103, 5.513)	0.716 (0.084, 4.618)	0.617 (0.076, 3.894)	0.665 (0.083, 4.18)	0.712 (0.09, 4.566)	0.598 (0.075, 3.815)	0.641 (0.082, 4.832)	0.652 (0.084, 4.538)	0.661 (0.082, 4.136)	0.481 (0.045, 4.213)	0.666 (0.061, 5.938)	tofo_high	0.976 (0.397, 2.371)
0.618 (0.095, 3.306)	0.736 (0.106, 3.926)	0.808 (0.118, 4.214)	0.888 (0.127, 4.755)	0.744 (0.1, 4.019)	0.641 (0.094, 3.412)	0.688 (0.102, 3.656)	0.739 (0.108, 4.136)	0.624 (0.088, 3.406)	0.656 (0.092, 4.39)	0.678 (0.104, 4.063)	0.68 (0.101, 3.591)	0.522 (0.048, 3.907)	0.705 (0.069, 5.288)	1.024 (0.422, 2.518)	tofo_low

Examination of the I^2 value for each of the comparisons showed homogeneity, with most values of I^2 at 0% (and all < 45%). When we back-calculated indirect risk estimates and compared them with direct evidence to assess for consistency, we found no major discrepancies between the estimates, which suggested that the consistency assumption was met (for the complete list of pairwise, indirect and pooled estimates, see Section 6 of Appendix B).

4.3.2 Risk of bias

Generally, the studies were of high methodologic quality. The overall quality assessment indicated that more than half of the studies (54 or 51%) were at low risk of bias. About one-third (31 or 30%) had unclear reporting of randomization sequence, and one-quarter (26 or 25%) had unclear or high risk of bias for blinded outcome assessment (Figure 4-3). No indication of publication bias was observed in the funnel plot (Section 7 of Appendix B).

Figure 4-3. Risk of Bias Assessment



4.3.3 Sensitivity Analysis

The results of the sensitivity analyses were consistent with those of the primary analysis. When the threshold between high and low doses was altered, high-dose dapagliflozin still showed an increased risk of UTI compared with placebo, active comparators and high-dose empagliflozin, but also showed an increased risk relative to low doses of ipragliflozin and ertugliflozin. The thresholds for dapagliflozin doses were not adjusted in this sensitivity analysis, because an alternate definition was not suitable. Ipragliflozin at low doses showed a significantly lower risk of UTI than high doses of canagliflozin, ertugliflozin, ipragliflozin, and dapagliflozin.

In the analysis of studies lasting 24 weeks or longer, fewer comparisons among experimental agents were possible. However, the findings were consistent with those of the primary analysis, whereby high-dose dapagliflozin had a high risk compared with placebo, active comparator and empagliflozin. Restriction of the analysis to studies with an overall low risk of bias (n=57) resulted in no significant differences among the drug regimens. In each of the sensitivity analyses, there were treatment arms with insufficient data to accurately estimate risk (for complete results of the sensitivity analyses, see Section 8 of Appendix B).

4.4 Discussion

The main findings of this study suggest no dose-response association between SGLT2 inhibitors and UTI risk; however, dapagliflozin (at doses ≥ 10 mg) appears to be an exception to this general finding. Specifically, high dose dapagliflozin compared with placebo, active comparators and empagliflozin was associated with a small increase in the risk of UTI.

Several other meta-analyses have reported on the association between SGLT2 inhibitors and UTIs[7,8,132–138] with inconsistent results, including increased risk with dapagliflozin[7,8,133], increased risk for SGLT2 inhibitors,[134,135] and no difference in risk.[136–138] However, given the continuing postmarketing surveillance of these new agents, new RCTs are being published rapidly, and these previous meta-analyses are quickly becoming outdated.[134,137] In addition, several studies have applied additional eligibility criteria, such

as including only marketed agents[133], placebo comparison trials[133] , or studies of a certain duration (e.g. > 24 wk).[7,8,133] The largest meta-analysis to date, which pooled results from 86 RCTs representing 50,880 patients, found no increased risk of UTIs (relative risk 1.03, 95% confidence interval 0.96 – 1.11).[138] Subgroup analysis by dose in this previous study also showed an increased risk only among users of dapagliflozin at a 10-mg dose.

A mechanism for the increased risk of UTI with dapagliflozin is not clear; however, there is variation in the pharmacokinetic and pharmacodynamic profiles of individual SGLT2 inhibitors. The SGLT2 inhibitors have shown a positive dose-effect relation with urinary glucose excretion, but this appears to have a ceiling effect with several agents. Maximum effects have been documented at about the starting doses for empagliflozin (10 mg)[9,12] and canagliflozin (100 mg)[15–17,139], but continued through the dosing range with dapagliflozin[13]. This may explain why the current study showed a dose-dependent relation for UTIs with dapagliflozin. It is unclear why an increased risk of UTI was observed with low-dose canagliflozin. Our sensitivity analysis showed a potential decreased risk of UTI among users of low-dose ipragliflozin (≤ 50mg) relative to those using high doses of canagliflozin, empagliflozin, ertugliflozin or ipragliflozin; high and low doses of dapagliflozin; or placebo. Pharmacodynamic evidence for ipragliflozin has been variable, with inconsistent estimates of the degree of urinary glucose excretion and the dose-response relation. However, there is also no indication that ipragliflozin is unique in any way that would support a physiological mechanism for the decreased risk of UTI. Further work is needed to examine this finding.

Our findings are consistent with previous findings supporting the lack of compelling data that would suggest a class effect in terms of UTI risk. Our study also extends the evidence by including additional studies, which has resulted in a more precise effect estimate. This study included as many studies as we could fine to investigate dose response encompassing both marketed and non-marketed agents, and active and inactive comparators in studies of any duration.

4.4.1 Limitations

This systematic review of the association between SGLT2 inhibitors and UTIs had some limitations. The outcome of UTI is very well reported, but we did not identify data on the progression of UTI to more serious infections. This gap in reporting makes it impossible to support or refute the concern that SGLT2 inhibitors may lead to serious infections. It is already known that, as a population, patients with diabetes have an increased risk of infections of all origins.[140] The 19 serious cases of UTI associated with SGLT2 inhibitors reported in the United States may be a result of increased vigilance for newly marketed drugs. The role of urinary glucose excretion in the pathogenesis of urinary tract infections is not well characterized. It has been postulated that increased urinary glucose excretion may not directly cause infections but rather may create a rich environment for bacterial growth and affect bacterial adherence to uroepithelial cells.[141–143] Because of the volume of studies included, it was not feasible to contact authors regarding these data. Other limitations included restriction to studies published in English, and verification of data

abstraction and bias assessment by a second reviewer, rather than independent duplication of abstraction and assessment. Finally, we found no study that compared 2 different SGLT2 inhibitors in a single trial; therefore the strength of evidence for comparisons between SGLT2 inhibitors is weak.

4.5 Conclusions

Current evidence does not support a dose-response risk profile for UTIs with SGLT2 inhibitors as a class. Although high doses of dapagliflozin (≥ 10 mg) did appear to be associated with increased risk, this risk was attenuated in an analysis restricted to RCTs at low risk of bias. Further studies are needed to quantify the association between SGLT2 inhibitors and more serious infections such as pyelonephritis.

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5. Capturing Patient Preferences towards Benefits and Risks of Second-line Diabetes Therapies: A Discrete Choice Experiment

5.1 Background

Guidelines recommend that metformin be initiated in all patients with type 2 diabetes without a contraindication. However, given the progressive nature of the disease, within three years of receiving monotherapy, 50% of patients are inadequately controlled and require add-on therapy.[1] In selecting a second-line agent, clinicians must make trade-offs between the potential benefits and harms in light of patient specific characteristics (e.g., level of hyperglycemia, comorbidities, cardiovascular risk, and preferences). More recent updates of the Canadian and American diabetes clinical practice guidelines[2,3] have also highlighted the importance of taking patient preferences into consideration. Individual patients may place different levels of importance on the various aspects of drug therapy. For instance, some may place an emphasis on the risk of weight gain, while others may place more of an emphasis on the risk of cardiovascular events. Given the choice, they would have to make trade-offs on the performance of various risks, benefits, and convenience factors. Clinicians may implicitly consider these trade-offs on behalf of their patients; however, they may not always be reflective of their patients' wishes.[4] It has been demonstrated in fact that preferences of clinicians and patients can differ substantially, whereby physicians underestimate the degree to which medication characteristics influenced their decisions.[5]

Consideration for patient preferences has become vitally important as it is recognized that the values of informed patients influence both treatment adherence and patient satisfaction.[6] As such, increasing attention has been placed on incorporating patient preferences into policy decisions, guideline development, and front-line patient care. Regulatory agencies including the European Medicines Agency[7] and the United States Food and Drug Administration[8] have recommended that preference data be included in regulatory approval applications. It is recognized that incorporating patient preferences helps to capture a perspective that cannot be gathered through clinical trial data.[9] Such preferences can be determined quantitatively through choice modelling techniques, such as discrete choice experiments (DCE).

A DCE is a survey method used get a quantitative estimate of the trade-offs individuals take into consideration when they make a decision. The approach has a long history in market research and transport economics, but has in the last couple of decades has been increasingly applied to health care decision analysis.[10] This survey method is built upon multi-attribute utility theory which refers to the idea that when people make choices between alternatives, they take into consideration the characteristics of those alternatives. They then make trade-offs based on these characteristics to settle on a final selection. For example, a drug may have the characteristics of efficacy, time to onset of effect, side effects, and cost. A DCE presents survey respondents with a series of choice tasks which outlines two or more alternatives with the attributes (characteristics) that are deemed to be important to consider to make a choice. Respondents are asked to choose their preferred

alternative by making trade-offs on the performance of the attributes. The descriptors used to describe performance (e.g. for an attribute "cost", the descriptor may be "$30", "$60" or "$90") are referred to as the *levels* and they come from a pre-specified list.

There have been several DCEs conducted in the diabetes population, however surveys have tended to focus on specific attributes such as adherence or weight gain, or have excluded insulin therapy.[11,1213] Importantly, Canadian patient preferences have not been elicited. The objective of this study was to measure the strength of preferences, relative importance, and trade-offs that patients with type 2 diabetes make between attributes of glucose-lowering medications.

5.2 Methods

5.2.1 Study Design

This DCE followed the general framework for good research practices as suggested by the International Society for Pharmacoeconomics and Outcomes Research.[14] The study was carried out in two phases. We first identified the attributes and levels of diabetes therapies that were shown to influence choice using qualitative methods. Second, we designed and implemented a survey that contained choice tasks to measure patients' preferences for the attributes of glucose-lowering therapies.

5.2.2 Identification of Attributes and Levels

A search of the medical literature was conducted using PubMed, to identify any choice modelling studies that had been previously published in the area of type 2 diabetes and more generally in medication therapy. This review helped to generate an initial list of attributes. To further refine the list of attributes and identify gaps, we supplemented our literature search with stakeholder (patients and clinicians) focus groups and interviews.

For the focus groups, individuals with type 2 diabetes were recruited through the family practice unit at Memorial University of Newfoundland using letters that were mailed by family physicians on behalf of the study team. Individuals were considered eligible if they were at least 18 years of age and had been diagnosed with type 2 diabetes by a health professional. They could have been at any stage of disease progression and did not have to be currently receiving medication therapy. Individuals also had to be able to communicate in English and must not have had any cognitive impairment that would prevent them from fully participating in a group discussion. Participants were offered a $10 gift card to a local grocery store as a thank-you for their time. Family physicians were also recruited through the family practice unit to participate in key informant interviews. Focus group participants answered a series of open-ended questions aimed at understanding the factors/attributes that they consider when starting a new diabetes medication. Once focus groups were complete, a preliminary list of attributes and levels was prepared and used as a starting point for discussion with clinicians participating in key informant interviews. Clinicians helped to refine the list and establish realistic and relevant levels for attributes. A formal

qualitative analysis of the focus groups and interviews was not conducted due to a low response rate of seven patients and three physicians. The information we heard was used to inform research team discussion and consensus on the attributes to be included. In general, patients were vague regarding their preferences and concerns when starting a new medication. They did not want other parts of their body impacted, but very rarely highlighted a specific concern. One issue they were passionate about was their preference against injectable therapy. They also were very confident in their physician's recommendations and trusted they were selecting the best therapy for them. As a result of these discussions, the study team decided to group attributes into reasonable categories (e.g. minor side effects) to enable a broader inclusion of potential risks and benefits of diabetes therapies. A final list of eight attributes, each containing three levels were identified as described above (Table 5-1).

Table 5-1. Attributes and Levels

Attribute	Description	Levels
Efficacy	Expected decrease in hemoglobin A1C (HbA1C)	0% reduction in HbA1C 1% reduction in HbA1C 2% reduction in HbA1C
Macrovascular events	Reduction in heart attack, stroke, or death from cardiovascular diseases	No reduction in risk 20% reduction in risk 40% reduction in risk
Microvascular events	Reduction in eye, kidney and nerve damage	No reduction in risk 20% reduction in risk 40% reduction in risk
Minor side effects	Risk of minor side effects (e.g. weight gain, stomach upset, skin rash, low energy)	0 out of 100 people 20 out of 100 people 40 out of 100 people
Severe hypoglycemia	Risk of severe hypoglycemic (low blood sugar) episodes over 10 years	0 out of 100 people 20 out of 100 people 40 out of 100 people
Serious side effects	Risk of a serious but rare side effect over a 10-year period	0 out of 100 people 2 out of 100 people 4 out of 100 people
Cost	Cost for one month supply	$30, $90, $150
Life Expectancy	Reduction in life expectancy	No change in life expectancy Increase in life expectancy by 1.5 years Increase in life expectancy by 3 years

5.2.3 Experimental Design

An unlabelled survey design was used,[15] meaning that alternatives were described as “Option A” and “Option B” without a descriptor that holds any meaning (e.g. new and old treatment) as we did not want participants to have any pre-conceived opinions about the alternatives. Two active alternatives were presented with each choice task, as well as an option to select neither.

A fractional factorial design was used with a total of 12 choice tasks generated by software package Sawtooth (Orem, UT; Version 9).[16] Two additional choice tasks made up of dominant questions were also included for quality assurance. In these dominant choice tasks, one of the alternatives was designed to be superior or equivalent to the other

alternative on all attributes. If participants choose the non-dominant alternative for either question, this indicates a lack of understanding of the survey question, and all choice data for that participant are eliminated from analyses. A total of 250 different survey designs were generated, making a balanced and D-efficient design. Efficiency aims to optimize the ability of the survey to characterize the widest range of choice sets, given that it is not feasible to include every possible combination of attributes and levels. Each attribute level appeared with the same frequency, however overlap was allowed, meaning that some choice tasks presented the same level for a given attribute. Efficiency was tested using simulated data.

At the beginning of the DCE portion of the survey, participants were asked to imagine that they were 55 years old and had diabetes that was not being well controlled with metformin (standard first line therapy), and required another medication. Then they were asked to choose one of the options in the choice task. When making their choice, participants had to make trade-offs between the descriptions. Choosing the neither option meant that they accepted natural progression of their disease without treatment (to view a sample choice task, refer Appendix C).

Additional questions including sociodemographic (e.g. age, sex, income, education), duration of diabetes, comorbidities, and current medication use were also collected. The survey tool was pilot tested among the study team as well as with a patient advisory council through the Newfoundland and Labrador Support for People and Patient-Oriented

Research and Trials (SUPPORT) group. Pilot respondents provided feedback on survey comprehension, technical ease and length. A sample of the final full survey is available in the supplementary appendix.

5.2.4 Study Sample and Elicitation Method

Participants were eligible to complete the survey if they were Canadian, 18 years of age or older, reported to have been diagnosed with type 2 diabetes by a health care professional and were able to complete a survey in the English language. Individuals were asked to participate regardless of their diabetes medication history. We recruited individuals to complete the survey through an online research company (*Research Now*) who used email solicitation of a sample of individuals with type 2 diabetes from across Canada. Screening questions on age and chronic health conditions were asked at the beginning of the survey to address eligibility criteria. To help ensure comprehension of the concepts explored in the survey, as well as the process for making choices, a 4-minute video was embedded in the survey to walk participants though the procedures and explain concepts that may not be easily understood (e.g., risk, percent and specific clinical outcomes). Participants could not proceed until the video concluded. Only data from respondents who completed the full survey were included. To maximize data quality, data from respondents who completed the survey in less than 7 minutes were excluded.

Traditionally, sample size estimation for DCEs have been done using one of several rules of thumb.[17–19] For example, one such rule of thumb is including a minimum of 10 observations for each independent variable.[20] For this study we wanted to estimate 15

parameters from the included attributes (one for cost, and 2 for each of the 7 other attributes) plus 3 stratification variables, for a total of 18 parameters and minimum sample of 180. Though other methods for estimating sample size for DCE in health care studies have been described,[21] they may overestimate required sample size when there are several parameters to estimate. Instead of limiting to the number estimated by the above rule of thumb, we chose to maximize sample size based on our available budget to ensure sufficient power and allow for more in-depth analysis. As such, our aim was to recruit 500 Canadians with type 2 diabetes.

5.2.5 Statistical analysis

Descriptive statistics were collected and qualitatively compared to national averages. Dominance of options, that is the consistent selection of either A or B within the choice tasks, was also examined. Preference weights for each of the attributes in the survey were quantified using generalized linear models whereby the beta-coefficients for each attribute represent the relative preference for that attribute, and the dependent variable is the stated preference for a hypothetical drug profile. Classic diagnostic assumption tests were used to examine linearity of the effect estimates for levels within each attribute. Marginal rate of substitution (MRS) was determined by taking the ratio of two coefficients. When cost is used in the MRS, it represents the willingness to pay (WTP) for the comparison attribute.

Each choice made within the DCE represents an observation in the dataset. The choice data was effects coded for all attributes, except cost which had continuous coding allowing for more interpretable WTP values. Though each attribute contained levels on a continuous scale, using the effects coding allowed for relaxation of the linearity assumption and to test for any non-linearity that exists within the preference weights.

All data were analysed using both Sawtooth (Lighthouse Studio) and R (version 3.4.1) statistical software packages (mlogit, mclogit). A counts analysis was conducted to assess the significance of each attribute on choice. Counts analysis examines the proportion of times a particular attribute level is chosen to the number of times it appears in the survey. We used a multinomial logit (MNL) model for the base analysis and then a mixed MNL to test the robustness of the analysis, to account for intra-respondent variation, and allow for the independence of irrelevant alternatives assumption (IIA) to be relaxed.[22] Interactions between attributes were assessed using a likelihood ratio test, where interactions with baseline characteristics (presence of cardiovascular disease, age (<65, >=65) and sex) were considered significant with a p-value<0.05. Exploratory post-hoc sub-group analyses were conducted to examine the impact of income, education and geographic location on overall findings.

5.2.6 Assessment of Validity and Reliability

We conducted several assessments to examine the validity and reliability of our findings using approaches outlined by Janssen et al. (2017).[23] Measurement validity was

assessed by comparing results with expectations for the weight and direction of estimates. Choice validity was assessed by looking for attribute dominance (always selecting a profile with a particular attribute level) through counts analyses, and task non-attendance (always selecting a profile in a certain position in the choice task). Finally, measurement reliability was assessed through the dominant choice task.

5.2.7 Ethical Considerations

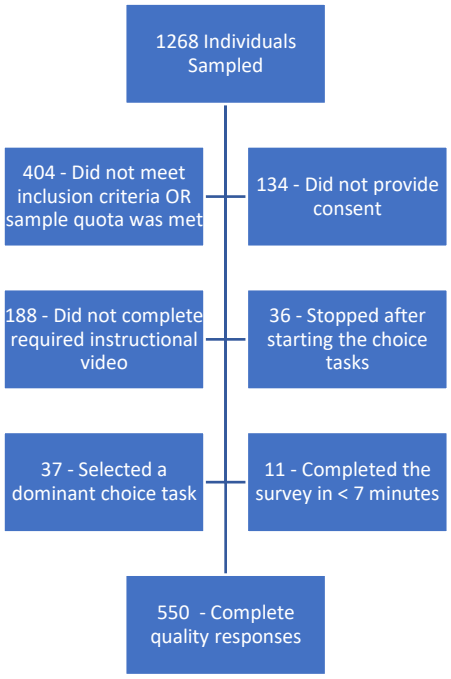
This study was carried out in accordance with the Tri-Council Policy Statement and approved by the Memorial University Research Ethics Board (#20171424).

5.3 Results

There were 1268 people sampled, and 550 respondents who completed the full survey. Of these, 37 were excluded due to choosing a non-dominant alternative among one of the dominant choice tasks (36[6.5%] chose one non-dominant and 1[0.2%] chose two non-dominant alternatives), and 11 (2.0%) were excluded due to completion in less than 7 minutes. Of the 502 included in the analysis, respondents took an average of 22.8 minutes (median = 14.0, interquartile range = 11.1 to 17.7 minutes) to answer the survey. None of the respondents exclusively selected option A, while 1(0.2%) exclusively selected option B, and 11(2.2%) exclusively chose to opt out, which reflected a preference for no therapy at all. Of the 718 individuals who did not complete the full survey, 404 were disqualified (due to not meeting the inclusion criteria or because sample quota was already met), 134 did not

provide consent, 188 did not complete the required informational video, and 36 quit while answering qualifying and choice task questions (Figure 5-1).

Figure 5-1. Flowchart of survey respondent recruitment



The average age of respondents was 59 years (SD=12), 59% were male, 55% had tried two or more oral medications, and 63% had diabetes for at least 6 years (Table 5-2). This is comparable to the Canadian population of individuals with Type 2 Diabetes, with slightly more males (56.3%, 2017).[24] However, our population tended to have a higher income and education levels, while we know that the prevalence of diabetes is higher among lower income individuals.[25]

Table 5-2. Respondent Characteristics

Characteristic	Number (%) N=502
Sex	
Female	208 (41.4%)
Male	294 (58.6%)
Marital Status	
Divorced / Separated	52 (10.4%)
Married / Common Law	347 (69.3%)
Single	88 (17.6%)
Widowed	14 (2.8%)
Employment Status	
Employed	212 (42.4%)
Retired	239 (47.8%)
Student	6 (1.2%)
Unemployed	43 (8.6%)
Level of Education	
Did not complete high school	19 (3.8%)
Graduated high school	69 (13.7%)
Some college/university	122 (24.3%)
Trade/technical/vocational training	68 (13.5%)
Bachelor's degree	122 (24.3%)
Graduate degree	62 (12.4%)
Professional degree	40 (8.0%)
Income	
Less than $25,000	55 (11.1%)
$25,000 to $49,999	105 (21.2%)
$50,000 to $74,999	122 (24.6%)
$75,000 to $99,999	90 (18.2%)
$100,000 or more	123 (24.8%)
Length of time with diabetes	
Less than a year	23 (4.6%)
1-2 years	45 (9.0%)
3-5 years	119 (23.8%)
6-10 years	117 (23.4%)
Greater than 10 years	196 (39.2%)
Number of different oral diabetes medications tried (present or past)	
None	34 (6.8%)
1 oral medication	184 (36.8%)
2 oral medications	149 (29.8%)
3 oral medications	77 (15.4%)
More than 3 oral medications	51 (10.2%)
I am not sure	5 (1.0%)
Use of injectable diabetes medications	
Yes	162 (32.4%)
No	338 (67.6%)
Cardiovascular Health Conditions	

No heart or stroke related conditions	174 (34.7%)
High blood pressure	269 (53.6%)
High cholesterol	246 (49.0%)
Other Health Conditions	
None	155 (30.9%)
Asthma or COPD	70 (13.9%)
Osteoarthritis	80 (15.9%)
Anxiety or depression	104 (20.7%)
Obesity	163 (32.5%)

All attributes were found to significantly influence choice with p-values all less than 0.01 for the within attribute chi-squared test, and followed the expected direction of preference (i.e. negative preference for worse outcomes or higher cost). Counts analysis showed that no particular attribute level dominated choice selection, with level selection ranging from 31.5% to 59.7%. Results of the mixed MNL model were used for interpretation of results, as these estimates take within respondent correlations into account (Table 5-3). Overall the mixed MNL model showed greater preferences weights for all attributes.

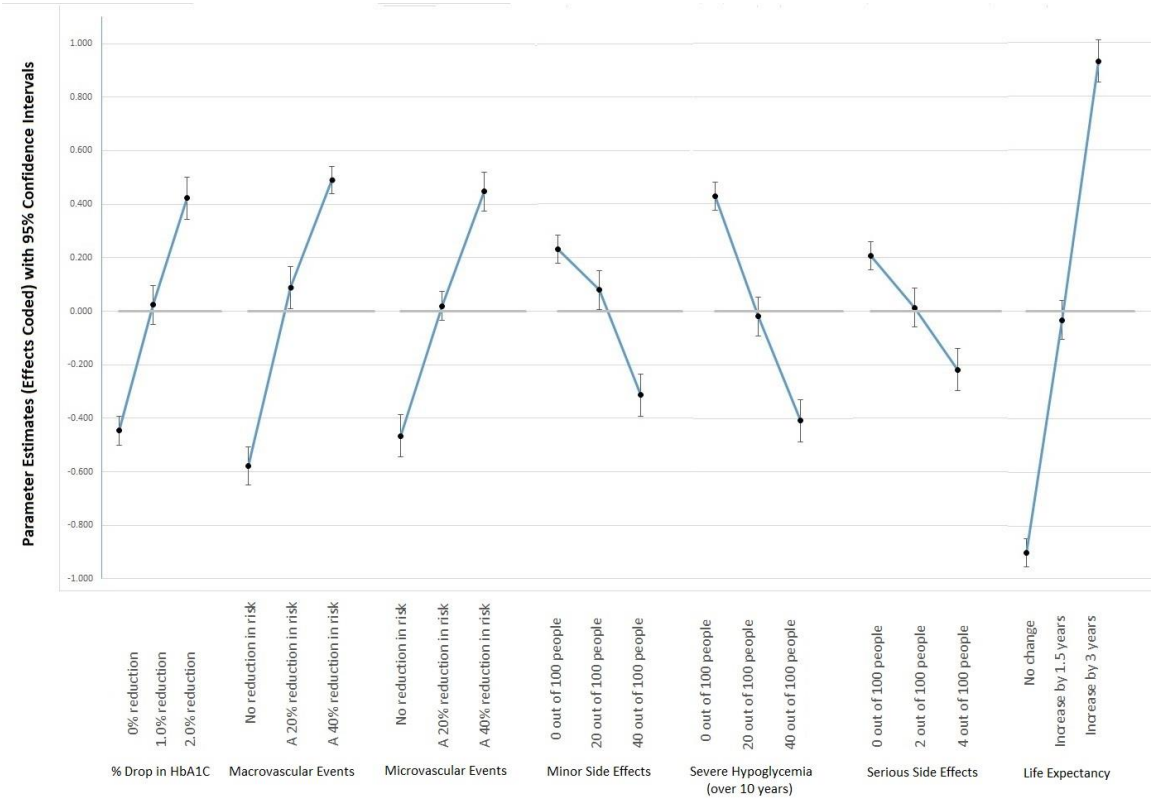
The effect estimates show that cost and life expectancy carried the most weight during decision making, with the greatest absolute value, while minor and serious side effects carried the least weight (Figure 5-2). Using the least desirable level for each attribute as the reference, odds ratios and marginal WTP were calculated. When all other attributes are held constant, the odds of an individual selecting the drug that increases life expectancy by 3 years is 6.2 times that of selecting a drug with no impact on life expectancy. The odds of selecting a drug with no chance of minor side effects is only 1.7 times that of selecting a drug with a 40% chance of a minor side effect (Table 5-3). All attributes meet the linearity assumption, showing a linear relationship between levels. On average, people were willing

to pay $134 per month for a medication that improved life expectancy by 3 years, compared to no change, but only $31 per month for a medication that would have no increased risk of serious side effects, instead of 4% risk of serious side effects (over 10 years).

Table 5-3. Weighted Estimates (Effect Coded) from Mixed Effects Models for Attributes of Diabetes Medications from the Discrete Choice Experiment

Attribute	Variable	Estimate	Std. Error	Lower CI	Upper CI	OR	WTP
Cost (per month)	Cost [per $CAD]	-0.818	0.045	-0.906	-0.731	NA	NA
% Drop in HbA1C	0% reduction	-0.446	0.028	-0.359	-0.251	Ref	Ref
	1.0% reduction	0.023	0.037	-0.050	0.096	1.6	$34.38
	2.0% reduction	0.422	0.040	0.344	0.500	2.4	$63.61
Macrovascular events	No reduction in risk	-0.579	0.028	-0.462	-0.347	Ref	Ref
	A 20% reduction in risk	0.088	0.037	0.016	0.159	1.9	$48.91
	A 40% reduction in risk	0.491	0.041	0.411	0.571	2.9	$78.48
Microvascular events	No reduction in risk	-0.467	0.026	-0.368	-0.266	Ref	Ref
	A 20% reduction in risk	0.019	0.037	-0.053	0.092	1.6	$35.66
	A 40% reduction in risk	0.447	0.040	0.369	0.526	2.5	$67.03
Minor side effects	0 out of 100 people	0.231	0.028	0.120	0.227	1.7	$39.72
	20 out of 100 people	0.080	0.037	0.007	0.153	1.5	$28.64
	40 out of 100 people	-0.311	0.038	-0.386	-0.235	Ref	Ref
Severe hypoglycemia (over 10 years)	0 out of 100 people	0.428	0.028	0.251	0.356	2.3	$61.33
	20 out of 100 people	-0.019	0.037	-0.092	0.053	1.5	$28.55
	40 out of 100 people	-0.409	0.041	-0.488	-0.329	Ref	Ref
Serious side effects (over 10 years)	0 out of 100 people	0.205	0.028	0.076	0.182	1.5	$31.10
	2 out of 100 people	0.013	0.037	-0.060	0.086	1.3	$17.00
	4 out of 100 people	-0.219	0.038	-0.293	-0.144	Ref	Ref
Life expectancy	No change	-0.897	0.029	-0.657	-0.544	Ref	Ref
	Increase by 1.5 years	-0.033	0.037	-0.104	0.039	2.4	$63.36
	Increase by 3 years	0.930	0.050	0.832	1.027	6.2	$133.95

Figure 5-2. Effect-coded estimates for attribute levels of diabetes therapies (n=502)



An examination of potential interactions between attributes using the likelihood ratio test showed that no combination of attribute levels resulted in a significant change in the main effects. Interactions between attributes and baseline characteristics using a CL model and likelihood ratio test were significant (p-value < 0.05 for all tests) between: 1) 40% reduction in macrovascular risk and the presence of existing cardiovascular disease, indicating those with cardiovascular disease placed a higher preference weight to this reduction; 2) cost and gender, indicating that females had a greater negative preference towards cost; and 3) life expectancy increased by 3 years and gender, indicating that males had a greater preference towards medications that increased life expectancy. Despite

significant interactions, the interpretation of the findings were not impacted, with odds ratios remaining consistent across models and therefore the most parsimonious model was selected.

Our respondent population was of a slightly higher income and education than the general population, and therefore a post-hoc sub-group analysis was done to examine the impact of these variables. This analysis demonstrated that while WTP was much higher for the higher income subgroup (e.g. $197 vs. $88 per month for a medication that improved life expectancy by three years) and high education subgroup (e.g. $194 vs. $102 per month for a medication that improved life expectancy by three years), overall ranking of attributes did not change substantially. The top two attributes of importance remained cost and life expectancy. However the for the lower income and lower education sub-groups "cost" ranked as the most important and for the higher income and higher education subgroups, "life expectancy" ranked most important. The least two important attributes also remained consistent. Rankings only changed where preference weights were already very close in the base case analysis.

A final subgroup analysis examined geographic variation across Canada. The sample was divided into Eastern (including Newfoundland and Labrador, Nova Scotia, New Brunswick and Prince Edward Island, n=65), Central (including Quebec and Ontario, n=232), and Western (including Manitoba, Saskatchewan, Alberta and British Columbia, n=169). Results demonstrated mostly consistent results across sub groups, with the exception of some preference weights for Eastern Canada (Table 5-4). Eastern Canadians showed a

higher WTP for efficacy, severe hypoglycemia, serious but rare side effects and life expectancy. This may be due to the small number of respondents in Eastern Canada or may be due to differences in preferences across attributes, further research is needed to understand if true differences exist.

Table 5-4. Sub-Group Analysis Examining Willingness to Pay by Geographic Region

Attribute	Variable	Eastern	Central	Western	Full
% Drop in HbA1C	0% reduction	Ref	Ref	Ref	Ref
	1.0% reduction	$68.19	$26.46	$33.73	$34.38
	2.0% reduction	$101.95	$59.24	$65.56	$63.61
Macrovascular events	No reduction in risk	Ref	Ref	Ref	Ref
	A 20% reduction in risk	$83.44	$49.68	$48.26	$48.91
	A 40% reduction in risk	$96.57	$90.48	$83.99	$78.48
Microvascular events	No reduction in risk	Ref	Ref	Ref	Ref
	A 20% reduction in risk	$38.51	$38.25	$39.06	$35.66
	A 40% reduction in risk	$78.58	$65.34	$73.80	$67.03
Minor side effects	0 out of 100 people	$40.95	$34.54	$55.45	$39.72
	20 out of 100 people	$18.99	$31.81	$26.41	$28.64
	40 out of 100 people	Ref	Ref	Ref	Ref
Severe hypoglycemia (over 10 years)	0 out of 100 people	$43.29	$29.11	$36.01	$31.37
	20 out of 100 people	$34.87	$26.18	$23.78	$28.55
	40 out of 100 people	Ref	Ref	Ref	Ref
Serious side effects (over 10 years)	0 out of 100 people	$58.17	$26.65	$34.02	$31.10
	2 out of 100 people	$40.80	$11.82	$15.61	$17.00
	4 out of 100 people	Ref	Ref	Ref	Ref
Life expectancy	No change	Ref	Ref	Ref	Ref
	Increase by 1.5 years	$54.67	$61.19	$62.54	$63.36
	Increase by 3 years	$155.45	$139.05	$121.12	$133.95

5.4. Discussion

There has been increasing interest into taking patient preferences into consideration for policy making, guideline development and patient-clinician interactions. Using choice modelling, we estimated relative preference weights for various attributes of diabetes therapies, and all eight attributes were shown to influence choice significantly. On average, patients weighted the potential for improved life expectancy and lower cost as more important than other risks and benefits measured, though improved cardiovascular outcomes, reduction in hemoglobin A1C and reduction in the risk of severe hypoglycemia also ranked as important.

Three prior studies have examined patient preferences for attributes of medications used in the management of type 2 diabetes using a DCE design.[11,14,26]. In the first, Hauber et al. surveyed patients in the United Kingdom and the United States. They found similar preferences between the two nations, and found that glucose control, risk of heart attack and potential for weight gain to be the biggest drivers of patient preferences. Mansfield et al. (2017) examined preferences from patients in both Spain and Germany, finding unique differences between populations. German respondents tended to most strongly oppose a higher risk of gastrointestinal symptoms, while Spanish respondents were most strongly opposed to the injectable route of administration. Finally, Janssen et al. (2018) examined a US population and found that patients tended to place the greatest weight on the duration of nausea each day and the choice between “pill” versus “pill with an injection”. It is difficult to draw direct comparisons between these previous studies and our current study as the

attributes selection and descriptions differed across studies. Previous studies tended to capture more specific attributes (e.g gastrointestinal symptoms, weight gain) and therefore were not able to measure patient preferences for some of the more serious outcomes like severe hypoglycemia, nephrotoxicity or retinopathy, or the very practical consideration of cost. Additionally, those studies that examined cardiovascular disease varied greatly, with one suggesting a cardiovascular harm[11] and the other a small cardiovascular benefit (5% reduction).[26] Though patients with diabetes inherently have an increased risk of cardiovascular events, the use of diabetes medications are generally not associated with an increased risk. Rather, newer medication classes have demonstrated significant reduction in the composite endpoint of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke (34% with empagliflozin in the EMPA-REG trial,[27] 13% with liraglutide in the LEADER trial,[28] and 26% with semaglutide in the SUSTAIN-6 trial[29]). Therefore, cardiovascular risk may play a bigger role in decision making for anti-diabetic medications than captured in previous studies. One additional important take away message from these previous studies is that preferences can vary between cultures and if patient preferences are to be considered in prescribing decisions, they need to be specific to the cultural context.

A limitation of these previous studies is the limited number of attributes captured. We chose to group attributes into relevant categories. This meant that we were able to capture a wide range of benefits and risks, without overburdening the survey respondents with too many attributes. Accurately modelling choices for medication selection is difficult

given the array of potential benefits and harms that could play a role in patient decisions. Pre-survey discussions with patients revealed that they were less concerned about specific side effects or benefits when they made their choices, but rather the impact on overall health. As a result of these discussions, we grouped outcomes into strategic categories (macrovascular, microvascular, minor side effects, and rare but severe side effects). While macrovascular events such as heart attack and stroke are often considered together in clinical trials and DCEs,[27–29] other outcomes are typically measured independently. With respect to patient preferences however, it is reasonable to think that patients would weight such groups similarly. Though outcomes are grouped together in this survey, when assessing the overall preference for one drug over another, the weights can be applied to unique outcomes (e.g. cancer and amputation) within a category, taking the specific probability of occurrence into account.

5.4.1 Limitations

We found it challenging to recruit and engage patients in the pre-survey stage of this study. Though we feel that we have captured the most important attributes in the survey based on patient and clinician input, a larger sample for our focus groups would have been beneficial. As with any DCE, we were faced with several limitations including ordering effect, hypothetical bias and framing effect which are inherent to these types of survey designs.[14] We did however use strategies to attempt to mitigate against each of these. Ordering effect, refers to the impact that the order of choice tasks has on choice outcomes.

The order of choice tasks were randomly varied across all versions to minimize the ordering effect. Hypothetical bias refers to the bias that is introduced due to the fact that participants are not making real choices, but rather putting themselves in hypothetical situations. While we only surveyed individuals with type 2 diabetes and presented them with realistic scenarios and realistic descriptors of the medications, not all individuals surveyed would have experienced each of the attributes presented. This could leave the potential for hypothetical bias. For example, not all patients would have experienced a severe hypoglycemic event and therefore may not be able to evaluate the relative weight of such an event compared to patients that have experienced a severe hypoglycemic event (or multiple events). Framing effect refers to the manner in which attributes or choices are described and the influence this has on choice. We attempted to minimize this by providing additional information and visual aid to improve respondents understanding of the attributes. For example, we included a mandatory 4-minute video before they completed choice tasks to ensure they have an understanding of the attributes and their impact on disease, however concepts of risk may still have been difficult for some respondents to fully understand. Finally, our sample was not fully representative of the general population with respect to income, education and language, a challenge that comes with using online survey companies. As such, these findings may not be fully generalizable to lower income segments of the population or those in predominantly French speaking parts of Canada. While we anticipate the rank order of attributes to remain fairly consistent, the preference weights may differ.

5.5 Conclusion

This study contributes to the growing literature base focused on quantitatively measuring patient preferences for various health care interventions. Using a DCE we found that all eight examined attributes for diabetes, including cost, risk of macrovascular and microvascular events, risk of minor side effects, severe hypoglycemia, serious long term consequences, and life expectancy were each shown to significantly influence choice. While cost and life expectancy carried the most weight, serious and minor side effects carried the least weight. These study findings can help guide and inform patient and clinician interactions regarding new therapy decisions.

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6. Incorporating Patient Preferences into a Quantitative Risk Benefit Analysis Comparing Sodium Glucose Co-Transporter-2 Inhibitors and Glucagon-Like Peptide-1 Receptor Agonists in Type 2 Diabetes.

6.1 Background

Type 2 diabetes affects approximately 8% of Canadian adults and substantially increases the risk of microvascular (e.g. retinopathy, neuropathy) and macrovascular (e.g. coronary heart disease, vascular disease) complications.[1,2] These complications lead to significant patient burden and contribute to management costs that are 1.5 to 2.5 times higher in people with diabetes compared to those without.[3,4] Metformin has been the long-standing first-line agent for the management of diabetes, with any other diabetes medication being considered acceptable second-line or add on options. However clinical practice guidelines are shifting due to the promising cardiovascular benefits seen in randomized controlled trials of the Sodium Glucose Co-Transporter-2 (SGLT2) inhibitors and the Glucagon-Like Peptide-1 (GLP1) receptor agonists in patients with pre-existing cardiovascular disease.[5–11] As a result are now the preferred second-line therapies for individuals with cardiovascular disease.[12,13]

Despite the cardiovascular benefits, these drugs also come with several potential harms. Drug regulators including the US Food and Drug Administration (FDA), Health Canada, and the European Medicines Agency have released advisories regarding several side effects identified in post market surveillance. For the SGLT2 inhibitors these include acute kidney injury (AKI)[14], diabetic ketoacidosis (DKA),[15] urinary tract infections (UTI),[16]

bone fractures[17] and lower limb amputations,[18,19] based primarily on case report data. For the GLP1 receptor agonists these include pancreatitis[20] and pre-cancerous findings in the pancreas.[21] As such, it is not clear if either the SGLT2 inhibitors or the GLP1 receptor agonists outperforms the other, and no head-to-head trials have been conducted. Risk benefit assessment (BRA) is one way to quantify differences in the benefit-risk balance of these agents. A BRA provides a summary measure of the trade-offs that exist between potential benefits and harms of medications. There are more than a dozen approaches to BRA found in the medical literature,[22] however most use unweighted metrics (e.g. number need to treat). This means that only probabilities of benefits and risks are considered and not the associated duration of, or preferences for, these outcomes. More modern methods for conducting BRA account for patient preferences or values and duration of impact.[23–26] Such preferences can be collected through conjoint analyses, such as discrete choice experiments (DCE). Though this is still an emerging approach, regulatory agencies including the European Medicines Agency (EMA)[27] and the Food and Drug Administration (FDA)[28] have recommended that preference data be included in regulatory approval applications.

Despite increased interest in measuring patient preferences for drug therapies, utilization of such data for conducting quantitative BRA in the type 2 diabetes population is lacking. In the context of the SGLT2 inhibitors and the GLP1 receptor agonists, this is especially interesting given the equal placement in clinical practice guidelines. This study will bring together Canadian patient preferences for attributes of diabetes therapies as well

as probabilities of efficacy and safety retrieved from the literature using the incremental net benefit (INB).

6.2 Methods

6.2.1 Study Design

We performed a quantitative benefit risk analysis that combined efficacy and safety probabilities with preference weights, captured as maximal acceptable risk (MAR), to measure the INB as described in the *Unified Framework for Benefit Risk Assessment*.[23] While other preference weight metrics can be used in the INB model, the MAR implicitly includes the duration of impact of the outcomes when preference weights are captured choice surveys. Quality adjusted life year (QALY) could also be used, but these utility weights are often gathered from multiple sources and not reflective of the trade-offs that patients make between alternatives.

The INB quantifies the difference between the sum of the benefits from the sum of the harms between two interventions, as shown in equation 1. In this equation the Δp_i represents the risk difference for a beneficial outcome i, and Δq_j is the risk difference for a harmful outcome j, each weighted by MAR. MAR represents the trade-offs people are willing to make between trade-offs. The μ variable then represents the importance a decision maker places on harms over benefits. A μ=1 means importance is equal and a μ>1 indicates a higher importance on avoidance of harms.

$$INB_{MAR} = \sum_{i=1}^{I} MAR_i \Delta p_i - \mu \sum_{j=1}^{J} MAR_j \Delta q_j \quad (1)$$

6.2.2 Population and Interventions

The population of interest includes adults, 18 years or older, living with type 2 diabetes and established cardiovascular disease. Interventions included the SGLT2 inhibitors as a class (empagliflozin, dapagliflozin, and canagliflozin) and the GLP1 receptor agonists as a class (semaglutide, liraglutide, lixisenatide, exenatide, and albiglutide).

6.2.3 Benefit and Harm Outcomes

To identify the outcomes important in the comparison of SGLT2 inhibitors to GLP1 receptor agonists, we conducted a literature review and consulted with clinicians. The focus was to address benefits and harms with demonstrated differences compared to placebo. A Value Tree is presented in Figure 6-1 and outlines all of the included outcomes. Beneficial outcomes included non-fatal myocardial infarction, non-fatal stroke, hospitalization for heart failure, a composite of microvascular outcomes (new or worsening nephropathy, or retinopathy), and all-cause mortality. These were considered benefits as SGLT2 inhibitors and GLP1 receptors have been shown to decrease the risk of occurrence. Though change in hemoglobin A1C values is typically used to measure efficacy of antihyperglycemic agents, it was not included in this BRA. As hemoglobin A1C is a surrogate marker for reduction in risk of micro and macrovascular disease complications, those harder endpoint were thought to be more appropriate. Likewise, a reduction in body weight has been demonstrated with both SGLT2 inhibitors and GLP1 agonists, however this is also a surrogate outcome for

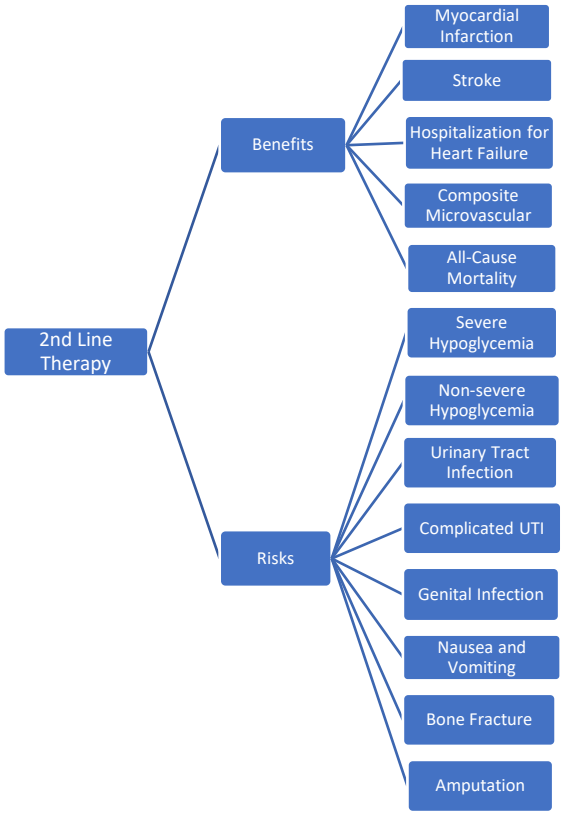
reduction of disease complications and measured on a continuous scale, and so was excluded from this analysis.

Harmful outcomes included non-severe and severe hypoglycemia, typical and complicated urinary tract infection, genital infection, nausea and vomiting, bone fracture and amputation. These outcomes have each been demonstrated or speculated to be elevated in one or both the SGLT2 inhibitors and GLP1 receptor agonists. Cancer, including but not limited to pancreatic cancer, was intended to be part of the model however this outcome was inconsistently captured. Additionally, the duration of follow-up within studies was also too short to capture true difference that may exist. Pancreatitis and diabetic ketoacidosis was also examined, and while speculated to be associated with GLP1 receptor agonists and SGLT2 inhibitors respectively, no meta-analyses have demonstrated this difference and therefore they were excluded from the model. To collect outcome probabilities we looked to the following sources in the following order: 1) network and pairwise meta-analyses; 2) randomized controlled trials; and 3) observational studies.

Network meta-analyses reported dichotomous outcomes in odds ratios and hazard ratios. Since the incidence of each of the outcomes was low (less than 10%), odds ratios and hazard ratios were considered equivalent estimates of risk.[29] Baseline rates for outcomes were estimated from the placebo arms of randomized controlled trials for SGLT2 inhibitors and GLP1 receptor agonists that examined populations with existing cardiovascular risk. Given some differences noted in baseline risk, two baseline probability rates were estimated, one for the SGLT2 inhibitors and one for the GLP1 receptor agonists, by using

median annual probability rates from respective groups of trials. The minimum and maximum probabilities were used as the range. Probability estimates for the SGLT2 inhibitors and GLP1 receptor agonists were estimated by multiplying the respective baseline probability rate by the corresponding risk estimate for each outcome.

Figure 6-1. Value Tree of Outcomes Captured in this Benefit Risk Assessment



6.2.3.1 Outcomes Preferences

The Maximal Acceptable Risk (MAR) was used as the preference weight, which were estimated from a previously conducted discrete choice experiment designed to inform the current BRA. The objective of the discrete choice experiment was to estimate the strength

of preferences and trade-offs that Canadian adults living with type 2 diabetes make between characteristics of glucose-lowering medications. To do this the survey was distributed across Canada through a survey company. Eligible and interested individuals completed 14 choice tasks where they were ask to select between two hypothetical diabetes medications. Drug were described with using eight attributes. We made the assumption that the preference weights for similar attributes would be close to the same. For example, we assumed that a cardiovascular event, whether it be a myocardial infarction or stroke, would carry a similar preference weight. The eight attributes included in the survey, along with associated descriptions, levels and resulting preference weights are provided in Table 6-1. Levels within the attributes behaved in a linear fashion and therefore for the purpose of this BRA, a single preference weight is used for each attribute.

Table 6-1. Attributes and Levels used in Discrete Choice Experiment to Solicit Preference Weights

Attribute	Description	Levels	Preference Weight (Standard Deviation)
Efficacy	Expected decrease in A1C	0% reduction in HbA1C 1% reduction in HbA1C 2% reduction in HbA1C	-0.525 (0.025)
Macrovascular events	Reduction in heart attack, stroke, or death from cardiovascular diseases	No reduction in risk 20% reduction in risk 40% reduction in risk	0.286 (0.024)
Microvascular events	Reduction in eye, kidney and nerve damage	No reduction in risk 20% reduction in risk 40% reduction in risk	0.373 (0.025)
Minor side effects	Probability of minor side effects (e.g. weight gain, stomach upset, skin rash, low energy)	0 out of 100 people 20 out of 100 people 40 out of 100 people	0.308 (0.024)
Severe hypoglycemia	Probability of severe hypoglycemic (low blood sugar) episodes over 10 years	0 out of 100 people 20 out of 100 people 40 out of 100 people	-0.193 (0.024)
Serious side effects	Probability of a serious but rare side effect over a 10-year period	0 out of 100 people 2 out of 100 people 4 out of 100 people	-0.296 (0.024)
Cost	Cost for one month supply	$30, $90, $150	-0.143 (0.024)
Life Expectancy	Change in life expectancy	No change in life expectancy Increase in life expectancy by 1.5 years Increase in life expectancy by 3 years	0.607 (0.026)

Table 6-2 presents the preference weights from the DCE that were assigned to each outcome along with estimated annual baseline probabilities and risk measures for both SGLT2 inhibitors and GLP1 receptor agonists.

Table 6-2. Preference Weights and Risk Estimates for SGLT2 Inhibitors and GLP1 Receptor Agonists used in the Incremental Net Benefit Model

	Discrete Choice Experiment Inputs		SGLT 2 Inhibitors			GLP1 Agonists		
	Preference Weight (std. error)	**Unit intervals from DCE**	**Annual Baseline Probability % (range)**[5–7,30]	**Risk Measure (95% CI)**	**Estimated Annual Probability % (95% CI)**	**Annual Baseline Probability % (range)**	**Risk Measure (95% CI)**	**Estimated Annual Probability % (95% CI)** [8–11,31]
Non-Fatal Stroke	0.373 (0.025)	20% reduction in risk	0.830 (0.6-1.3)	HR 0.98 (0.7-1.17)[32]	0.854	0.906 (0.6-1.3)	HR 0.86 (0.74-0.97) [32]	0.78
Non-Fatal Myocardial Infarction	0.373 (0.025)	20% reduction in risk	1.197 (1.0-3.9)	HR 0.86 (0.72-0.99) [32]	1.041	1.938 (1.0-3.9)	HR 0.93 (0.85-1.01) [32]	1.80
Hospitalization for Heart Failure	0.373 (0.025)	20% reduction in risk	0.946 (0.8-2.0)	HR 0.69 (0.61-0.79)[33]	0.719	1.478 (0.8-2.0)	HR 0.92 (0.82-1.03) [32]	1.36
Composite Microvascular Outcomes	0.308 (0.024)	20% reduction in risk	6.613 (2.3-6.6)	HR 0.62 (0.54-0.70) [6]	4.516	2.343 (2.3-6.6)	HR 0.84 (0.73-0.97)[10]	2.00
All-Cause Mortality	0.607 (0.026)	1.5 years of life gained	1.933 (1.6-3.5)	HR 0.77 (0.67-0.86) [32]	1.547	2.518 (1.6-3.5)	HR 0.88 (0.82-0.95) [32]	2.22
Severe Hypoglycemia	0.296 (0.024)	20% absolute risk	0.887 (0.2-1.5)	OR 0.82 (0.45-1.47)[34]	0.727	0.795 (0.2-1.5)	OR 0.71 (0.49 – 0.99) [34]	0.56
Non-Severe Hypoglycemia	0.193 (0.024)	20% absolute risk	8.987 (8.7-12.0)	OR 1.03 (0.96-1.09) [32]	8.987	10.107 (8.7-12.0)	OR 1.0 (0.96-1.04) [32]	7.58
Nausea and Vomiting	0.193 (0.024)	20% absolute risk	0.361 (0.0-0.7)	Prob = 118 events/2886 individuals over 5.7 years[30]	0.717	0.727 (0.0-0.7)	Prob = 517 events/4668 individuals over 3.8 years[10]	2.91
Urinary Tract Infection	0.193 (0.024)	20% absolute risk	3.699 (0.4-5.8)	OR 1.03 (0.95-1.11) [32]	3.81	0.349 (0.4-5.8)	OR 0.72 (0.53-0.99) [32]	0.25
Complicated UTI	0.143 (0.024)	2% absolute risk	0.567	Prob = 80 events/17,213 individuals over 0.75 years[35]	0.620	0.567*	Prob = 114 events/17,213 individuals over 0.75 years[35]	0.89
Genital Infection	0.193 (0.024)	20% absolute risk	0.396 (0.2-0.6)	RR 3.06 (2.73-4.43)[36]	1.212	0.396* (0.2-0.6)	Assumed equal to baseline risk	0.40
Bone Fracture	0.143 (0.024)	2% absolute risk	1.240 (0.2-1.3)	OR 1.16 (1.0-1.34) [32]	1.439	0.297 (0.2-1.3)	OR 1.320 (1.05-1.65) [32]	1.39
Amputation	0.143 (0.024)	2% absolute risk	0.362 (0.0-0.6)	OR 1.49 (1.17-1.90) [32]	0.539	0.268 (0.0-0.6)	OR 0.990 (0.78-1.26) [32]	0.27

6.2.4 Analysis

The MAR for each outcome was first calculated using equation (2), using life expectancy as the reference outcome. Patients would have inherently considered the

duration of impact for each of the attributes they considered in the discrete choice experiment and therefore the duration of impact is captured within the MAR value. The base case analysis also assumed that μ=1. The Δp_i and Δq_j in the MAR calculation (equation 2) refer to the difference between each level used to describe an attribute within the discrete choice experiment. For example, for macrovascular events the three levels used no reduction in risk, a 20% reduction in risk and a 40% reduction in risk. Therefore the Δp_i would be equal to 20%. The Δp_i and Δq_j then used within the INB calculation (equation 3) represent the actual difference in outcomes between the intervention and no intervention as identified in the literature.

$$MAR_{ij} = \frac{v_i/\Delta p_i}{v_j/\Delta q_j} \quad (2)$$

$$INB_{MAR} = \sum_{i=1}^{I} MAR_i \Delta p_i - \mu \sum_{j=1}^{J} MAR_j \Delta q_j \quad (3)$$

Several sensitivity analyses were conducted to test the robustness of the comparison. These included, where possible: 1) altering MAR between the lower and upper 95% confidence intervals; 2) altering baseline probabilities of outcomes within the 95% confidence intervals; and 3) altering intervention probabilities of outcomes between within the 95% confidence intervals. Each of these simulations, were conducted using Monte Carlo simulation with 10,000 iterations and a normal distribution was assumed. Further sensitivity tested: 1) various combinations of outcomes included in the mode (e.g. removing outcomes with data from observational studies, limiting to only cardiovascular outcomes, adding outcomes that were excluded from the base case due to statistically insignificant

differences (diabetic ketoacidosis); 2) excluding MAR; and 3) altered values of μ from 0.5 and 3, the value representing importance placed on harms over benefits.

6.3 Results

The primary analysis for the base case scenario favored the SGLT2 inhibitors by demonstrating an incremental net benefit over the GLP1 receptor agonists. The model showed that there was a 0.24% annual net probability of benefit over harm for the SGLT2 inhibitors compared to the GLP1 receptor agonists. This is to say, that if a cohort of 10,000 people were prescribed and SGLT2 inhibitor instead of a GLP1 receptor agonist, 24 additional people would experience a positive net benefit. This absolute difference is quite small and therefore it is not clear if this difference is of clinical importance. The greatest contributor to the difference in INB between drug classes was the impact of the composite in microvascular outcomes and nausea and vomiting.

Table 6-3. Calculation of Incremental Net Benefit for SGLT2 Inhibitors and GLP1 Receptor Agonists

			SGLT2 Inhibitors			GLP1 Agonists		
		MAR	**Change in % Probability over Baseline (Δp or Δq)**	$MAR_i\Delta p_i$	$MAR_j\Delta q_j$	**Change in % Probability over Baseline (Δp or Δq)**	$MAR_i\Delta p_i$	$MAR_j\Delta q_j$
Benefits	**Non-Fatal Stroke**	0.046	-0.025	0.001		0.13	0.006	
	Non-Fatal Myocardial Infarction	0.046	0.156	0.008		0.14	0.006	
	Hospitalization for Heart Failure	0.046	0.227	0.014		0.12	0.005	
	Composite Microvascular Outcome	0.038	2.097	0.096		0.34	0.014	
	All-Cause Mortality	1.000	0.387	0.445		0.30	0.302	
Harms	**Severe Hypoglycemia**	-0.028	-0.160		-0.006	0.23		-0.008
	Non-Severe Hypoglycemia	-0.017	0.000		0.006	2.53		0.000
	Nausea and Vomiting	-0.017	0.357		0.009	-2.19		0.052
	Urinary Tract Infection	-0.017	0.111		0.003	0.10		-0.002
	Complicated UTI	-0.109	0.053		0.009	-0.32		0.057
	Genital Infection	-0.017	0.816		0.019	0.00		0.000
	Bone Fracture	-0.109	0.198		0.035	-0.10		0.017
	Amputation	-0.109	0.177		0.031	0.00		0.000
	$INB_{MAR} = \sum_{i=1}^{I} MAR_i\Delta p_i - \mu \sum_{j=1}^{J} MAR_j\Delta q_j$			0.562	0.107		0.334	0.115
	Net Benefit		0.456			0.219		
	INB		**0.237**					

6.3.1 Sensitivity Analyses

The series of sensitivity analysis demonstrated that in almost all of model inputs leads to an INB that favors SGLT2 Inhibitors (Table 6-4). When estimates for baseline probability rates of outcomes were altered to reflect 95% confidence intervals, only 0.87% of iterations resulted in a negative INB, indicating a greater overall benefit for GLP1 agonists. When the intervention probability rates were altered to reflect 95% confidence intervals, results remained consistent with base case analysis with only 0.11% of iterations resulting in a favor for GLP1 receptor agonists. When the MAR was altered to reflect the

95% confidence interval, all iterations resulted in an INB favoring SGLT2 inhibitors (Table 6-4).

Table 6-4. Sensitivity Analyses for Monte Carlo Simulations

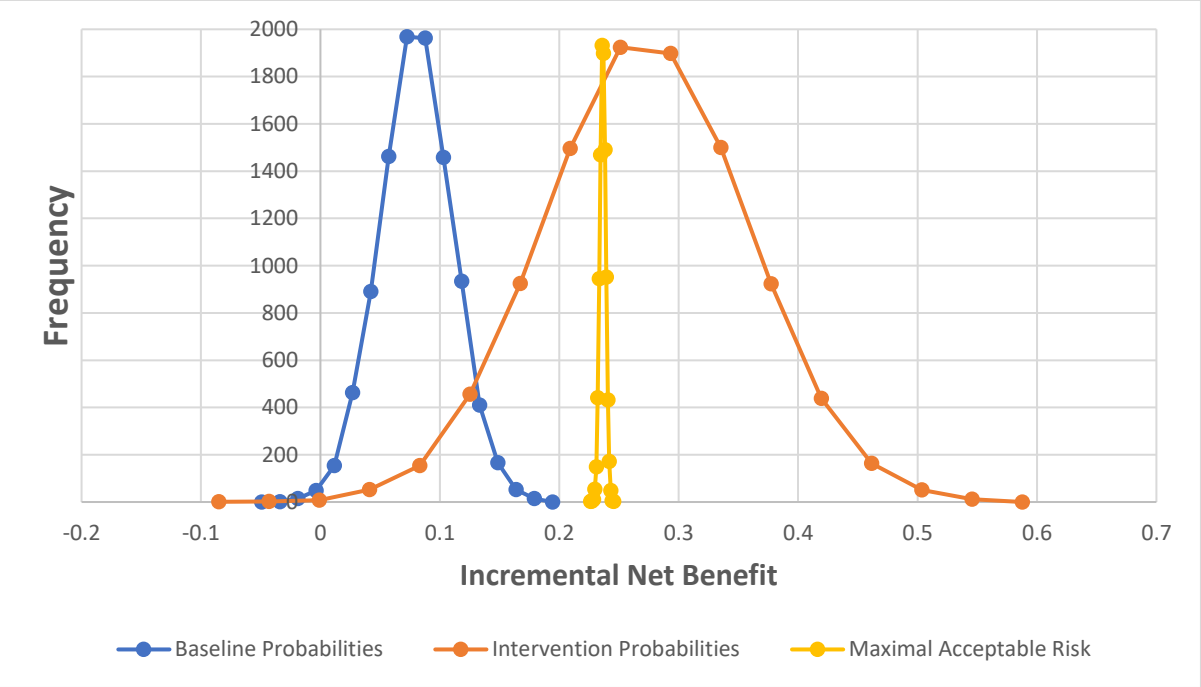
Sensitivity Analysis	Average INB	Standard Deviation	Minimum INB	Maximum INB	Probability of favoring GLP1 Agonist (%)
Baseline Outcome Probabilities	0.07	0.03	-0.05	0.37	0.87%
Intervention Outcome Probabilities	0.25	0.08	-0.12	0.54	0.11%
Maximal Acceptable Risk	0.24	0.00	0.23	0.24	0.0%

Further sensitivity analyses removed select outcomes from the model to assess impact. In the first analysis complicated UTI was removed as it was the only outcome gathered from observational studies, as well as gastrointestinal upset, as this outcome may have inconsistent reporting (INB = 0.145). The second analysis removed all outcomes, except for cardiovascular outcomes and all-cause mortality (INB = 0.147). A third analysis removed composite microvascular complications as this was the biggest contributor to INB, yet the baseline risks from RCTs varied dramatically (INB = 0.155). The final analysis added in ketoacidosis with estimates from an observational study[35] demonstrating an increased risk (INB = 0.229). Though some analyses narrowed the INB, all analyses favored the SGLT2 inhibitors.

When the MAR was excluded from the INB and only probabilities of outcomes were included, the INB equaled 2.8 in favor of SGLT2 inhibitors. The INB was heavily driven by microvascular benefit in the SGLT2 inhibitors and the high probability of nausea and vomiting in the GLP1 receptor agonists. In the final sensitivity analysis where μ was altered,

the INB did not change substantially. When μ=0.5 indicating a higher tolerance for harms, the INB=0.232; at μ=2, indicating a lower tolerance for harm, the INB=0.244; and when μ=3 INB=0.252.

Figure 6-2. Scatter Plots of Monte Carlo Sensitivity Analyses



6.4 Discussion

Based on the best available data on outcome probabilities for SGLT2 inhibitors and GLP1 receptor agonists, and preference weights from a Canadian DCE, SGLT2 inhibitors outperformed GLP1 receptor agonists with higher INB in diabetes patients with cardiovascular disease. Sensitivity analysis demonstrated that uncertainty within the parameters did not change the interpretation. Though results seemed to be fairly consistent

within sensitivity analyses, we must acknowledge that this model is very sensitive to some key inputs. Though clinical trial data demonstrated a microvascular benefit for the composite microvascular outcome for both SGLT2 inhibitors and GLP1 receptor agonists, it was the greatest contributor to difference in INB between classes. It must be noted that this outcome was not well reported among trials and therefore there is greater uncertainty. Composite microvascular, using the same definition, was only captured in one SGLT2 inhibitor trial and one GLP1 receptor agonist trial and therefore it is unknown if the effects seen can be generalized to the whole class. Also, it would be ideal to capture each microvascular outcome independently as it is unlikely that each system would respond to a drug in the same manner. However, definitions for outcomes differ dramatically across trials making this difficult to achieve. When looking to the literature on the impact of SGLT2 inhibitors and GLP1 receptor agonists on microvascular outcomes, it appears that both SGLT2 inhibitors and GLP1 receptor agonists have consistent renal benefits,[37] with much less data or certainty regarding neuropathy or retinopathy.

Generally, examples of quantitative BRA in the literature are limited and have typically limited model inputs to data from a single trial. While this greatly increases the internal validity, it is not practical for study questions like the one addressed in this paper for several reasons: 1) there may not be head-to-head trials comparing interventions of interest; 2) when available, data from meta-analyses of multiple well conducted trials is stronger than data from individual trials; and 3) outcomes of interest for a BRA may not all be reflected in a single trial.

Using data from multiple sources allowed us to capture the most recent and relevant estimates, however it also posed challenges with maintaining internal validity. Though most of our data came from placebo-controlled randomized controlled trials with very similar inclusion criteria of adults with type 2 diabetes and cardiovascular disease, rates of outcomes in the placebo arms differed across studies. This could be an indication of different baseline characteristics or differences in processes for capturing outcomes. For example, urinary tract infections were well documented in trials of SGLT2 inhibitors, but less commonly in GLP1 receptor agonists, perhaps due to no known increased risk for these agents. The GLP1 receptor agonists that did report on urinary tract infection tended to have lower rates, which may be a reflection on less diligent identification or different definitions used. Unfortunately, in many cases definitions for all secondary outcomes were not clearly presented. This difference in placebo group rates make it challenging to establish baseline rates for the BRA model. Another issue is that risk measures are not consistent across studies (e.g. odds ratio, hazard ratio, relative risk) and may not include number of events and population size, requiring some assumptions to be made. The INB model is also not able to accommodate outcomes that are captured on a continuous scale, like hemoglobin A1C or body weight. In this particular model we could justify the elimination of these outcomes, however other BRAs may provide an appropriate balance of risk and benefits with the exclusion of continuous outcomes.

There is also limited guidance and best practices for using preference weights derived from a DCE for BRA. While there is literature recommending best practices for DCE

survey style, generating efficient experimental designs, testing data quality and approaches to handling heterogeneity, there nothing recommending best practices for generating preference weights suitable for BRA.[38] For instance, guidance on: 1) ensuring risk is effectively communicated to participants; 2) the role of survey training materials (e.g. descriptions of attributes and levels); 3) whose preferences are most appropriate (e.g. patients, general public, clinicians); and 4) how to capture the necessary breadth of outcomes in a DCE. This last issue in particular is problematic for BRA of medications, as there are typically many benefits and harms that could be of interest and it is recommended that a DCE include no more than eight attributes to reduce responder burden. But it could be argued that even eight attributes is difficult to interpret when they are complex (e.g. measures of risk). In the DCE we conducted to support this BRA, it was decided to group like outcomes to be able to accommodate more of them. For instance, we presented cardiovascular outcomes together, assuming they would have similar preference weights. Given that this BRA demonstrated that it was the benefits (myocardial infarction, stroke, hospitalization for heart failure, composite microvascular outcome and all-cause mortality) that played the biggest role in INB, a DCE that examined these outcomes individually might give more insight into the preference-weighted differences in INB between SGLT2 inhibitors and GLP1 receptor agonists.

With respect to limitations specific to data used in this model, there were some outcomes that were only reported in a limited number of studies. Genital infections are a known risk for users of SGLT2 inhibitors due to its unique mechanism of action of increasing

urinary glucose excretion, however no evidence of risk among GLP1 receptor agonist users is known. Therefore we had to assume a risk equivalent to placebo arms for this outcome. Complicated urinary tract infections were also very poorly reported decreasing reliability of the estimates used. Though given the impact of complicated urinary tract infection on the overall model, more reliable estimates would likely not have changed interpretation. The best estimates for microvascular outcomes was a composite microvascular outcomes. This outcomes however encompassed renal deaths, meaning that renal deaths were captured in two outcomes used in our model (all-cause mortality and composite microvascular outcome). Given that the risk of all-cause mortality was similar between groups (Hazard Ratio=0.8 for SGLT2 inhibitors, and Hazard Ratio = 0.88 for GLP1 receptor agonists) this double counting should not have made an impact on the interpretation of the results.

Finally, while preference weights for the route of administration were not captured in the Canadian DCE, there is certainty evidence that patients place a higher preference on oral over injectable route when given the choice.[39–44] Had we been able to capture this in our model, it can be assumed that overall INB would be even greater for SGLT2 inhibitors.

6.5 Conclusions

While this BRA demonstrated a greater INB for the SGLT2 inhibitors over GLP1 receptor agonists, the actual benefit is quite small with 24 out of 10,000 treated experiencing a positive net benefit. Additionally, the challenges and limitations in using the INB model to capture the balance between preference-weighted benefits and risks in this

context are many. This study demonstrates the need for more guidance on conducting preference-weighted BRA for informing clinical decisions. Currently there is insufficient evidence to strongly recommend an SGLT2 inhibitor over a GLP1 receptor agonist.

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7. Discussion

7.1 General Discussion

This program of research set out to examine the balance between benefits and risks of the sodium-glucose co-transporter-2 (SGLT2) inhibitors. This was in response to recent changes to Canadian, American and European Clinical Practice Guidelines for type 2 diabetes which have indicated that agents in these classes should be the preferred second-line agents in patients with type 2 diabetes and cardiovascular disease. Aside from the glucose lowering and cardiovascular benefits, which have been the impetus for pushing SGLT2 inhibitors in this population, these agents have been associated with several other beneficial outcomes including weight loss (between 1.8 to 2.7 kg),[1] reduction of blood pressure (systolic: 3.4–5.4 mmHg and diastolic: 1.5–2.2 mmHg),[2–4] and renoprotection, including slower progression of kidney disease, and fewer clinically relevant renal events[5]. Chapters 2 and 3 of this thesis examined some of the unanticipated signals for adverse effects of the SGLT2 inhibitors, including acute kidney injury (AKI), diabetic ketoacidosis (DKA), urinary tract infections (UTI), bone fractures and amputations.[6] Other more well established side effects include genitourinary tract infections (Odds Ratio 5.06; 95% Confidence Interval 3.44, 7.45),[7] and volume depletion that could lead to postural dizziness, orthostatic hypotension or dehydration.[8] Knowledge of the estimated probabilities of each of these outcomes occurring can be found in the literature, however examination of the balance between risk and benefit while also accounting for the duration of impact or patient preferences for each of these outcomes has not been previously done.

To examine in balance of benefit and risks of the SGLT2 inhibitors we conducted four unique studies: 1) A systematic review and meta-analysis of the unanticipated adverse effects of the newest classes of antihyperglycemic agents, the SGLT2 inhibitors, captured in post-market surveillance; 2) A network meta-analysis of the dose response relationship with SGLT2 inhibitors and urinary tract infections (UTI); 3) A discrete choice experiment (DCE) to quantify patient preferences for attributes of diabetes therapies; and 4) a quantitative risk-benefit assessment using the INB model, as described in the "*Unified Framework for the Classification of Methods for Benefit-Risk Assessment*".[9]

The analysis of the unanticipated adverse outcomes of the SGLT2 inhibitors, as identified by regulatory agencies, suggested no significant increase in the risk of acute kidney injury (AKI), diabetic ketoacidosis (DKA), UTI, and bone fractures.[6] Amputation was poorly reported, however analysis of the CANVAS trials[10,11] does show an increased risk and warrants further review as new data are available. A sub-group analysis looking at risk of UTI, showed only dapagliflozin at doses 10mg or more were associated with an increased risk. Finding of the network meta-analysis of the dose response relationship of SGLT2 inhibitors and UTI were consistent with the previous meta-analysis showing dapagliflozin high dose to be the only category to be associated with an increased risk.[12]

The DCE estimated preferences weights that were consistent with what would be expected. All eight examined attributes for diabetes, including cost, risk of macrovascular and microvascular events, risk of minor side effects, severe hypoglycemia, serious long term consequences, and life expectancy were each shown to significantly influence choice. As

expected life expectancy and cost were more important in the decision making process. Minor and serious but rare side effects carried the least weight.

Finally, the BRA demonstrated that there was a minimal difference in INB between the SGLT2 inhibitors and the GLP1 receptor agonists. The SGLT2 inhibitors demonstrated a greater INB and these results were fairly consistent in sensitivity analysis. However given the overall benefit, a 0.2% probability of benefit for SGLT2 inhibitors over GLP1 receptor agonists, strong conclusions are not warranted. Additionally, some outcome probability estimates were not well reported, specifically consistent measures of microvascular outcomes, and changes in these estimates could lead to GLP1 agonists demonstrating greater benefit.

7.2 Patient Preferences and Benefit Risk assessment

The integration of patient preferences into BRA has been gaining much support over the last decade, both within the regulatory and clinical decision making contexts.[13–16] This is due in part to: 1) the development in evidence that the trade-offs that are made by patients differ from those made by clinicians and policy makers,[17] and 2) the move to include patients across the spectrum of health care research and development.

Research has shown that, when compared, the preferences for treatments differ between patients and clinicians. This has been demonstrated in various clinical areas, including obstetrics, cardiovascular disease, cancer gynecology and respiratory illness.[18–23] For example, one study showed that patients preferred a drug to exhibit a higher minimum

clinically important difference (MCID) compared to physicians when deciding to take an antihypertensive therapy.[18] This demonstrated that patients had a lower risk threshold compared to physicians in this clinical scenario. Interestingly, in another study, the opposite risk tolerance was shown for cancer therapy. While preferences differed in this scenario too, patients were far more likely to accept an intensive therapy with severe side effects and low chance of cure compared to physicians, nurses and even the general public.[19]

We are seeing patients actively engaged now throughout all areas of health research. From identifying research priorities to supporting study design, data collection and interpretation. In Canada, as of 2015, the Canadian Institutes for Health Research had committed $357 Million in funding to SPOR (Strategy for Patient Oriented Research) SUPPORT units across the country, with the expectation that that funding be matched one to one, translating into $700 Million from Canadian stakeholders.[24] The United States have seeing similar initiatives, with the Patient-Centered Outcomes Research Institute (PCORI) established to fund research that enables patients to be more engaged in their health care decisions.

7.2.1 Regulatory Context

In the regulatory arena, the European Medicines Agency (EMA), is currently re-evaluating the PrOACT-URL BRA Framework that they adopted in 2012, based on a more generic decision making framework[25] involving 12 steps (Figure 7-1). The PrOACT-URL Framework does not require a quantitative assessment to be carried out, though it does

recommend a quantitative approach when the decisions are complex and more ambiguous. In such cases the Multi-Criteria Decision Analysis (MCDA) was the preferred method.[26] MCDA fits within the PrOACT-URL Framework as many of the steps overlap. It involves group consensus among clinical experts and decision makers to define the problem, treatment options and criteria for assessing the treatment decision. Within MCDA these inputs are then used to generate a decision tree and quantify the different between treatment alternatives.[9] This process is valuable, as it incorporates the perspectives of clinicians and decision makers, it does not allow for the inclusion of patient preferences.[16] In the EMA's Roadmap to 2015, the need for a more systematic approach to integrate patient preferences into benefit-risk assessment are recommended, however official updates to the framework have not been completed.

Figure 7-1. European Medicines Agency 12-Step PrOACT-URL Framework

PROBLEM
1. Determine the nature of the problem and its context
2. Frame the problem

OBJECTIVES
3. Establish objectives that indicate the overall purposes to be achieved
4. Identify criteria for a) favorable effects; b) unfavorable effects

ALTERNATIVES
5. Identify the options to be evaluated against the criteria

CONSEQUENCES
6. Describe how the alternatives perform for each of the criteria

TRADE-OFFS
7. Assess the balance between the favorable and unfavorable effects

UNCERTAINITY
8. Report the uncertainty associated with the favorable and unfavorable effects
9. Consider how the balance between favorable and unfavorable effects is affected by uncertainty

RISK TOLERENCE
10. Judge the relative importance of the decision maker's risk attitude for this product
11. Report how this affected the balance reported in Step 9

LINKED DECISIONS
12. Consider the consistency of this decision with similar past decisions, and assess whether taking this decision could impact future decisions.

The United States Food and Drug Administration (FDA) updated their *Benefit-Risk Assessment in Drug Regulatory Decision Making* guidance document in 2018.[27] Within this framework there is an emphasis on being more patient-focused. In 2013, the FDA started to hold public meetings, webcasts and public dockets, to gather patient input on a variety of health conditions and treatments. Each meeting resulted in the preparation of a *Voice of the Patient* report which are then used to help to inform regulatory decisions. Additionally

the FDA released guidance on best practices for collecting and voluntary submitting patient preference data from industry.[28] This guidance document recommends that for straightforward decisions a qualitative assessment of patient preferences may suffice. These would include examples where there is a clear benefit for one product over another, or when there are few alternatives with very different risk benefit profiles. In more complex scenarios, like when there are many alternatives or cases with similar risk-benefit profiles, quantification of patient preferences with such approaches as stated preference surveys (e.g. discrete choice experiments) are warranted.[28] This document also provides guidance on best practices for: communication of risk; minimization of cognitive bias; ensuring logical soundness; relevance of choices to patients; data collection; analysis or data; and reporting standards.

In Canada, Australia and New Zealand, there are no formal guidelines or recommendations. Canada has initiated some pilot work to see how patient preferences, along with other stakeholder input, might be included in decision making. This work collected qualitative data only and had a limited scope of orphan drugs.[13] Canada is looking to other existing models, like those described above, and assessing suitability and feasibility within the Canadian context and build on lessons already learned.[29] In Australia the Therapeutics Goods Administration indicates that consideration for patient preferences is seen to be most relevant at the individual patient-clinician decision making stage.[30] There does not appear to be any active push towards capturing patient preferences at early stages of regulatory approval processes.

7.2.2 Clinical Context

Once drug products are approved for sale within a country, there is still much debate among clinicians, patients and patient advocates regarding the most appropriate place for that product in therapy. This is especially complex when there are already many products in a therapeutic area, as is the case with type 2 diabetes. As we have learned with the SGLT2 inhibitors and the GLP1 agonists, it is post market trials and surveillance where many of the most important safety concerns, and sometimes benefits, are identified. The need to update BRAs as new evidence is available is important for supporting regulatory and clinical decisions throughout the product's life cycle.

The guidance on the integration of patient preferences into BRA for informing clinical decisions is less well established. As described in the "*Unified Framework for the Classification of Methods for Benefit-Risk Assessment*"[9], there are several approaches to capture preference-weighted BRA measures, including but not limited to, relative value-adjusted, number needed to treat/harm, benefit-harm balance,[31] maximal acceptable risk (MAR), and incremental net benefit (INB) based on either relative value-adjusted life year (RVALY), quality adjusted life year (QALY) or MAR.[9] While each of these methods are promising, and have the added strength of capturing the benefit-risk balance through a more patient-centered approach, there are many challenges to implementation.

Very few published studies have attempted to quantify a preference-weighted BRA to compare available therapeutic alternatives for clinical decisions, and those that have also faced similar challenges.[32–34] In one recent example, Yebyo, et al. (2018) conducted a BRA

of statins for primary prevention of cardiovascular disease. They too were faced with many of the same challenges that we encountered. They based much of their outcome data on a network meta-analysis, but found that some outcomes were not well reported. When supplementing with data from large observational studies, due to a higher variance, data from these studies did not contribute much to the pooled benefit-risk balance estimate. They attempted to use population-based baseline estimates of risk, as they are thought to better reflect a real world population, however estimates were not available for all outcomes leading to data coming from multiple sources. Additionally, assumptions had to be made to extend the time horizon beyond the period studied in clinical trials used to estimate outcome probability.

7.2.3 Readiness for Using Discrete Choice Data to Support Benefit-Risk Assessment

The use of the stated preference method, discrete choice experiment (DCE), has probably become the most commonly used method for capturing patient preferences as it has gained considerable popularity across all areas of modelling health care decisions. As a method traditionally used in transport economics and marketing, publications providing best practices for use in health care are becoming more plentiful.[35–39] However publications providing guidance on some practical considerations for appropriately integrating preference weights into BRA are still lacking. Vass and Payne (2017) have highlighted some concerns with using DCEs to inform BRA, which are applicable in both the regulatory and clinical contexts.[40] These include:

1. **Communication of Risk:** It is well known that patients and general public have a difficult time interpreting information about risk, and the relative magnitude of risk.[41,42] This is true across various patient demographics and is amplified when investigators fail to effectively communicate such risks within the design of a DCE. A lack of understanding ultimately leads to compromised responses and subsequent analyses of results. While many researchers take the interpretation of risk into consideration in their design, there exists no gold standard for communicating risk which may result in inconsistent findings.
2. **Role of Training Materials:** The International Society of Pharmacoeconomics and Outcomes Research (ISPOR) has indicated in their best practice documents that every DCE should include an introduction explaining the role of the survey, descriptions of the attributes and levels used, and instructions on responding to questions.[37] It is recognized however, that this component of surveys is generally under-developed and these introductions are of mixed quality. With the use of online survey platforms, the use of interactive training materials is being introduced. It is speculated, but not proven, that interactive tools would increase engagement and therefore improve data quality.[43]
3. **Need to Take Account of Attitudes:** DCEs only account for preferences, but not attitudes. Attitudes represent a person's inherent feelings and thoughts, and may actually be a factor that influences choices. Some researchers advocate for a hybrid model that captures both attitudes and preferences.[44]

4. **Whose Risk Preferences:** There seems to be some consistency with the recommendation for the use of patient preferences to inform BRA, however this is different that the approach that has been used in health economic models, where it has been argued that the public's preferences are the most informative for policy makers. Therefore this shift from public to the patient perspective has led to some disagreement and inconsistency in the literature.[40]
5. **Analysis of Benefit-Risk Preference Data:** Results of DCE are often presented as average preferences as estimated from conditional logit models. It is likely however that not all patients would share the same preference distribution, and therefore mixed logit and latent class analysis may provide more insight into how segments of the population behave differently. There is however no guidance on how to use heterogenous DCE findings to inform regulatory decisions. Additionally, some other experts question whether the random utility framework (which a DCE is analysed under) is the most appropriate for BRA, and suggest perhaps a random regret minimization framework[45] would be a better fit. The random utility theory suggests that people attempt to maximize utility when they are choosing between alternatives, while the random regret minimization theory suggests that individuals aim to minimize the regret they experience when they forgo an option performs well. Random utility theory has been the mainstay of frameworks used in DCE anlaysis, regret minimization is a model that is still being explored.[46]

6. **Understanding the Generalizability of the Results:** The degree of uncertainty for preference weights is not consistently presented in published findings of DCEs. This is problematic for predicting generalizability. Just as in health economic model parameter reporting, best practices for reporting on DCE studies should also include a measure of uncertainty.

In addition to these concerns as already identified in the literature, our experiences in attempting to integrate patient preferences from a DCE into a quantitative BRA identified further unanswered questions and concerns. First, there is little consensus on the best approach to defining attributes and levels for DCE in healthcare. There is some push towards including a qualitative component to identify drivers of decisions, with some suggestions on specific techniques (e.g. nominal group technique),[47] however there is no official recommendations for best practices. When results of DCEs are meant to inform quantitative BRA, the guidance on the selection of the most appropriate outcomes (attributes) is non-existent. This is particularly important because medications have many potential side effects, and not all can be uniquely captured in a DCE. The selection and presentation of the most appropriate attributes is critical for survey integrity. In the DCE we conducted and described in Chapter 4, we decided, after consulting patients and clinicians and finally through team consensus, to group like outcomes together. This required the assumption that outcomes within the same group would be equally as desirable (or undesirable) to the respondent. For example, we grouped cardiovascular outcomes as a

single attribute, likewise minor but common side effects were grouped together. DCE methodology literature recommend limiting the number of attributes to six-eight for a single survey, however we were able to estimated preferences weights for more outcomes by grouping them into eight groups, rather than eight specific outcomes. While this approach holds promise, it is not clear if our assumptions hold true and thus requires further investigation.

Secondly, the DCE generates preference weights that cannot be compared to preference weights from other studies. This means that DCE have to be uniquely designed to meet the criteria for a specific BRA. It is unlikely that an existing DCE with the needed attributes and geographical perspective will already be available, leading to added resources and time to build the survey alongside a BRA. Finding ways to translate preference weights from DCE to more commonly used metrics, like QALY, would not only allow for comparison across studies but data from DCEs would be more generalizable and subsequently used more widely. Bansback et al (2012)[48] demonstrated how DCE could be used to estimate health state utility values, however more research needs to be done to see how preference weights from other DCEs could be anchored to health state utility values.

7.3 Implications for Clinical Practice

Globally we are seeing a push towards more patient-centered care. From including the patient voice in regulatory decisions, defining the health care research agenda, and

ensuring that patients are active participants in their own health care journey. Results from patient preference weighted BRA, like the one presented in this thesis, can be important for supporting shared decision making. While our DCE showed that life expectancy and cost were the most important drivers of decisions, when multiplied by the probability of specific outcomes, it was in fact the microvascular complications that were the greatest contributor to the difference in INB between SGLT2 inhibitors and GLP1 agonists. This knowledge can allow clinicians to tailor their patient interactions to focus on the key points for decision making.

Though not demonstrated in the present study, other types of analyses of discrete choice data would allow for capturing preferences of subgroups of the population. For example, it is also possible preferences could differ by gender or stage of disease and other patient characteristics. Knowledge of how patient preferences differ among various segments of the population could support the creation of sophisticated decision support tools. For example is it conceivable that electronic applications could be built to allow patients to provide data on key patient and preference characteristics, then the application could offer alternatives that best suit the individual and allow for a targeted physician interaction.

7.4 Areas for Future Research

As discussed, the integration of patient preferences into quantitative BRA is still an emerging field of research. Experts in the field continue to identify areas in need of more

research, clarification or guidance. My research program, as described in this dissertation, has further identified several questions. These are grouped according to the study in which they were identified, and broader questions are listed at the end.

7.4.1 Systematic Review and Meta-analyses of Safety Outcomes for SGLT2 Inhibitors

This meta-analysis of unanticipated safety outcomes, identified by regulatory agencies, did not support the notion of increased risk of urinary tract infections, diabetic ketoacidosis, acute kidney injury or bone fractures based on data from randomized controlled trials (RCT). However, data on acute kidney injury, diabetic ketoacidosis and complicated urinary tract infections was not well reported. There does seem to be an increase in the risk of amputation in users of canagliflozin, however this was demonstrated in only one set of studies (CANVAS and CANVAS-R)[49] and not reported in most other included trials. Generally, the lack of reporting for several of these outcomes highlights the need for: 1) better reporting in RCTs moving forward; and 2) greater attention placed on these outcomes in observational research.

7.4.2 Discrete Choice Experiment to Capture Patient Preferences Towards Characteristics of Diabetes Medications

As highlighted above, more research needs to be established to support the use of DCE data for BRA. This includes: 1) establishing best practices for communicating risk; 2) comparing training materials used to describe the considerations for DCE to respondents;

3) an exploration of statistical models, like latent class analysis, that allow for estimating preferences for various subgroups, and not limiting analysis to overall average preferences; 4) a study designed to determine the reliability of preference data when attributes are grouped (e.g. cardiovascular events); and methodological research to identify reliable methods to anchor DCE preference weights to more commonly used metrics like QALY.

7.4.3 Quantitative BRA Comparing SGLT2 Inhibitors and GLP1 Agonists

Many of the challenges and limitations identified within this BRA were resulting from questions and assumptions surrounding the inputs used in the model. With this in mind, the final results were not conclusive as the model was sensitive to potential changes in outcome estimates. One element that we were not able to capture in this BRA were things like progression of disease, time of onset, and frequency of outcomes. More sophisticated BRA models like discrete event simulation or Marcov modelling would allow these factors to be considered. While these models would be more reflective of the real world, it requires more inputs and therefore assumptions. Depending on the assumptions made, validity may be compromised.

7.4.4 General Areas for Future Research

Though not discussed in much detail within Chapter 4, we engaged patient who live with diabetes in focus groups to help identify important attributes of diabetes therapies for decision making. While patients were very keen to discuss their experiences with diabetes

and diabetes therapies, they did not have very specific comments about common outcomes of importance. When probed, their responses remained vague with comments like “I don’t want it to affect my other organs.” The only attribute that garnered any enthusiastic responses was regarding injection therapy. Patients were very opposed to injection therapy, however it is not clear if this was due to their understanding that injections (which to them was interpreted as insulin), meant that their disease was getting worse, or, if it was the route of administration itself causing opposition. It was also clear from discussions that patients placed a high degree of trust in their physicians, and did not tend to question their recommendations. These discussions with patients, and subsequently with colleagues, made me question if there are perhaps cultural differences within Canada with respect to patient readiness to engage in shared decision making, or, if perhaps this is a Canada wide phenomenon. We are constantly being encouraged to practice in a patient centered manner, and patient advocacy groups are certainly speaking up on behalf of patients, however there is no real evidence to show that the general patient population is prepared to take on this important role.

Finally, while I have discussed above how preference weighted BRA can support clinical practice and inform shared-decision making interactions, it is not clear what the most appropriate tools would be for doing this. More comparative effectiveness research on how benefit-risk data can be presented in decision support tools would bring some clarity to this issue. Important comparisons to consider would be: 1) physician support

versus patient support tools; 2) paper-based versus interactive electronic application; and 3) different approaches to presenting risk.

7.5 Conclusion

This program of research used emerging methods, including a network meta-analysis, a DCE, and preference-weighted BRA to examine the balance between risks and benefits of the SGLT2 inhibitors and GLP1 agonists. These studies resulted in a final INB that favored SGLT2 inhibitors, though as discussed, these findings were small in magnitude and may not be of clinical importance. More importantly, this research identifies several challenges and limitations, including gaps in methodological guidance that still exist to successfully integrate patient preferences into BRA. This is a developing field of research and a promising one for understanding how patient preferences influence benefit-risk balance and ultimately clinical decisions.

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Appendix A

Supporting documentation for the systematic review and meta-analysis of the risk of select safety outcomes with SGLT2 Inhibitors.

Section 1: PRISMA Checklist

(See Below)

Section/topic	#	Checklist item	Reported in Section
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	3.0
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	See publication Donnan (2019) BMJ Open
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3.1
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3.1
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3.2.1
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3.2.3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3.2.2
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3.2.4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	3.2.4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Appendix
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	3.2.5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	3.2.6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	3.2.6

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	3.2.5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	3.2.6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	3.3.1 figure 3-1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Appendix
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Appendix
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 3-1, Figure 3-2 – 3-6, Appendix
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figure 3-2 – 3-6
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Appendix
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Table 3-2
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	3.4
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	3.4.1
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	3.5
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	See Donnan (2019) BMJ Open

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Section 2: Search Strategies

Table A-1. Pubmed Search Strategy

		Search String	Results
1	Population	"Diabetes Mellitus, Type 2"[Mesh] OR NIDDM[tw] OR t2dm[tw] OR ((“type 2"[tw] OR "type ii"[tw] OR "adult onset"[tw] OR “mature onset”[tw] OR “late onset”[tw] OR “noninsulin-dependent”[tw] OR “non insulin dependent”[tw]) AND diabetes[tw])	167100
2	Intervention: SGLT2s	"Sodium-Glucose Transport Proteins/antagonists and inhibitors"[Mesh] OR "Sodium-Glucose Transporter 2"[Mesh] OR "sodium-glucose co-transporter 2"[tw] OR SGL2[tw] OR SGLT2[tw] OR gliflozin*[tw] OR "Canagliflozin"[Mesh] OR canagliflozin*[tw] OR invokana[tw] OR sulisent[tw] OR "TA 7284"[tw] OR TA7284[tw] OR "JNJ 28431754"[tw] OR JNJ28431754[tw] OR "2-(3-(4-ethoxybenzyl)-4-chlorophenyl)-6-hydroxymethyltetrahydro-2H-pyran-3,4,5-triol"[Supplementary Concept] OR dapagliflozin*[tw] OR farxiga[tw] OR forxiga[tw] OR “BMS 512148”[tw] OR BMS512148[tw] OR "empagliflozin"[Supplementary Concept] OR empagliflozin*[tw] OR jardiance[tw] OR "BI 10773"[tw] OR BI10773[tw] OR ipragliflozin[Supplementary Concept] OR ipragliflozin*[tw] OR suglat[tw] OR "ASP 1941"[tw] OR ASP1941[tw] OR "1,5-anhydro-1-(5-(4-ethoxybenzyl)-2-methoxy-4-methylphenyl)-1-thioglucitol"[Supplementary Concept] OR luseogliflozin*[tw] OR lusefi[tw] OR “TS 071”[tw] OR TS071[tw] OR "remogliflozin etabonate"[Supplementary Concept] OR remogliflozin*[tw] OR "KGT 1681"[tw] OR KGT1681[tw] OR "(2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(methylthio)tetrahydro-2H-pyran-3,4,5-triol" [Supplementary Concept] OR sotagliflozin*[tw] OR "LX 4221"[tw] OR LX4221[tw] OR "6-((4-ethylphenyl)methyl)-3',4',5',6'-tetrahydro-6'-(hydroxymethyl)spiro(isobenzofuran-1(3H),2'-(2H)pyran)-3',4',5'-triol" [Supplementary Concept] OR tofogliflozin*[tw] OR apleway[tw] OR deberza[tw] OR "CSG 452"[tw] OR CSG452[tw] OR "5-(4-chloro-3-(4-ethoxybenzyl)phenyl)-1-hydroxymethyl-6,8-dioxabicyclo(3.2.1)octane-2,3,4-triol" [Supplementary Concept] OR ertugliflozin*[tw] OR "PF 04971729"[tw] OR PF04971729[tw]	2936
3	#1 AND #2		2080
4	Study Type Filter: Cochrane Highly Sensitive Search Strategy for identifying randomized trials in	("randomized controlled trial"[pt] OR "controlled clinical trial"[pt] OR randomized[tiab] OR placebo[tiab] OR "clinical trials as topic"[Mesh:NoExp] OR randomly[tiab] OR trial[ti]) NOT (animals[mh] NOT humans[mh])	1065055

	MEDLINE: sensitivity- and precision-maximizing version (2008 revision). Available at http://handbook.cochrane.org/chapter_6/box_6_4_b_cochrane_hsss_2008_sensprec_pubmed.htm		
5	#3 AND #4		743

Table A-2: Cochrane Library Search Strategy

#1	([mh "Diabetes Mellitus, Type 2"] or NIDDM or t2dm or (("type 2" or "type ii" or "adult onset" or "mature onset" or "late onset" or "noninsulin-dependent" or "non insulin dependent") and (diabetes)))	25,454
#2	([mh "Sodium-Glucose Transport Proteins"/ai] or [mh "Sodium-Glucose Transporter 2"] or "sodium-glucose co-transporter 2" or SGL2 or SGLT2 or gliflozin* or [mh canigliflozin] or canagliflozin* or invokana or sulisent or "TA 7284" or TA7284 or "JNJ 28431754" or JNJ28431754 or dapagliflozin* or farxiga or forxiga or "BMS 512148" or BMS512148 or empagliflozin* or jardiance or "BI 10773" or BI10773 or ipragliflozin or suglat or "ASP 1941" or ASP1941 or luseogliflozin* or lusefi or "TS 071" or TS071 or remogliflozin* or "KGT 1681" or KGT1681 or sotagliflozin* or "LX 4221" or LX4221 or tofogliflozin* or apleway or deberza or "CSG 452" or CSG452 or ertugliflozin* or "PF 04971729" or PF04971729)	1,082
#3	#1 AND #2	959

Table A-3: Embase Search Strategy

No.	Query	Results
#5	#3 AND #4	2,016
#4 - EMBASE RCT filter from	random*:ab,ti OR placebo*:de,ab,ti OR (double NEXT/1 blind*):ab,ti	1,533,336

Wong 2006, best balance of sensitivity and specificity		
#3	#1 AND #2	4,869
#2	'sodium glucose cotransporter 2'/de OR 'sodium glucose cotransporter 2 inhibitor'/exp OR 'sodium-glucose co-transporter 2':ab,ti OR sgl2:ab,ti OR sglt2:ab,ti OR gliflozin*:ab,ti OR canagliflozin*:ab,ti OR invokana:ab,ti OR sulisent:ab,ti OR 'ta 7284':ab,ti OR ta7284:ab,ti OR 'jnj 28431754':ab,ti OR jnj28431754:ab,ti OR dapagliflozin*:ab,ti OR farxiga:ab,ti OR forxiga:ab,ti OR 'bms 512148':ab,ti OR bms512148:ab,ti OR empagliflozin*:ab,ti OR jardiance:ab,ti OR 'bi 10773':ab,ti OR bi10773:ab,ti OR ipragliflozin*:ab,ti OR suglat:ab,ti OR 'asp 1941':ab,ti OR asp1941:ab,ti OR luseogliflozin*:ab,ti OR lusefi:ab,ti OR 'ts 071':ab,ti OR ts071:ab,ti OR remogliflozin*:ab,ti OR 'kgt 1681':ab,ti OR kgt1681:ab,ti OR sotagliflozin*:ab,ti or 'LX 4221':ab,ti or LX4221:ab,ti or tofogliflozin*:ab,ti or apleway:ab,ti or deberza:ab,ti or 'CSG 452':ab,ti or CSG452:ab,ti or ertugliflozin*:ab,ti or 'PF 04971729':ab,ti or PF04971729:ab,ti	6,675
#1	'non insulin dependent diabetes mellitus'/de OR niddm:ab,ti OR t2dm:ab,ti OR ('type 2':ab,ti OR 'type ii':ab,ti OR 'adult onset':ab,ti OR 'mature onset':ab,ti OR 'late onset':ab,ti OR 'noninsulin dependent':ab,ti OR 'non insulin dependent':ab,ti AND diabetes:ab,ti)	258,521

Table A-4: IPA Search Strategy

#	Query	Limiters/ Expanders	Results
S1	TX NIDDM OR t2dm OR (("type 2" OR "type ii" OR "adult onset" OR "mature onset" OR "late onset" OR "noninsulin dependent" OR "non insulin dependent") AND (diabetes))	Search modes - Boolean/Phrase	6,110
S2	TX "sodium-glucose co-transporter 2" OR sgl2 OR sglt2 OR gliflozin OR canagliflozin OR invokana OR sulisent OR "ta 7284" OR ta7284 OR "jnj 28431754" OR jnj28431754 OR dapagliflozin* OR farxiga OR forxiga OR "bms 512148" OR bms512148 OR empagliflozin* OR jardiance OR "bi 10773" OR bi10773 OR ipragliflozin* OR suglat OR "asp 1941" OR asp1941 OR luseogliflozin* OR lusefi OR "ts 071" OR ts071 OR remogliflozin* OR "kgt 1681" OR kgt1681 OR sotagliflozin* OR "LX 4221" OR LX4221 OR tofogliflozin* OR apleway OR deberza OR "CSG452" OR CSG452 OR ertugliflozin* OR "PF 04971729" OR PF04971729	Search modes - Boolean/Phrase	337
S3	S1 AND S2	Search modes - Boolean/Phrase	267
S4	TI randomized OR AB randomized OR TI randomised OR AB randomised OR TI placebo OR AB placebo OR TI randomly OR AB randomly OR TI trial	Search modes - Boolean/Phrase	59,232
S5	S3 AND S4	Search modes - Boolean/Phrase	130

Table A-5: ProQuest Search Strategy

all(NIDDM OR t2dm OR (("type 2" OR "type ii" OR "adult onset" OR "mature onset" OR "late onset" OR "noninsulin-dependent" OR "non insulin dependent") AND (diabetes))) AND all("sodium-glucose co-transporter 2" OR SGL2 OR SGLT2 OR gliflozin* OR canagliflozin* OR invokana OR sulisent OR "TA 7284" OR TA7284 OR "JNJ 28431754" OR JNJ28431754 OR dapagliflozin* OR farxiga OR forxiga OR "BMS 512148" OR BMS512148 OR empagliflozin* OR jardiance OR "BI 10773" OR BI10773 OR ipragliflozin OR suglat OR "ASP 1941" OR ASP1941 OR luseogliflozin* OR lusefi OR "TS 071" OR TS071 OR remogliflozin* OR "KGT 1681" OR KGT1681 OR sotagliflozin* OR "LX 4221" OR LX4221 OR tofogliflozin* OR apleway OR deberza OR "CSG 452" OR CSG452 OR ertugliflozin* OR "PF 04971729" OR PF04971729)	**3**

Section 3: List of Extracted Variables

Table A-6. List of Extracted Variables

Variable Extraction	Notes
NCT Number, Author and Year	
Country in which the study was conducted	International if applicable
Start and End years	
Observation Period (# of weeks)	
Total number of participants randomized	
Number of Males	
Number of Females	
Background diabetes therapy	
Intervention 1: SGLT2 Agent	This was captured for as many interventions that were used.
Intervention 1: Dose	
Intervention 1: Number of Persons	
Intervention 1: Mean Age	
Intervention 1: Age SD	
Intervention 1: Mean baseline HbA1C	
Intervention 1: A1C SD	
Comparison 1: SGLT2 Agent	This was captured for as many comparison groups that were used.
Comparison 1: Dose	
Comparison 1: Number of Persons	
Comparison 1: Mean Age	
Comparison 1: Age SD	

Comparison 1: Mean baseline HbA1C	
Comparison 1: A1C SD	
Acute Kidney Injury Reported (yes/no)	
Urinary Tract Infection Reported (yes/no)	
Definition of UTI	
Ketoacidosis Reported (yes/no)	
Bone Fracture Reported (yes/no)	
Amputation Reported (yes/no)	
AKI: Outcomes in Intervention 1(n/N)	This was captured for each individual intervention and control group
AKI: Outcomes in Comparison 1 (n/N)	
UTI: Outcomes in Intervention 1(n/N)	
UTI: Outcomes in Comparison 1 (n/N)	
DKA: Outcomes in Intervention 1(n/N)	
DKA: Outcomes in Comparison 1 (n/N)	
BF: Outcomes in Intervention 1(n/N)	
BF: Outcomes in Comparison 1 (n/N)	
Amp: Outcomes in Intervention 1(n/N)	
Amp: Outcomes in Comparison 1 (n/N)	

Section 4: Additional Forest Plots

Figure A-1. Risk of Urinary Tract Infection with SGLT2 Inhibitors Compared to Placebo, break down by agent

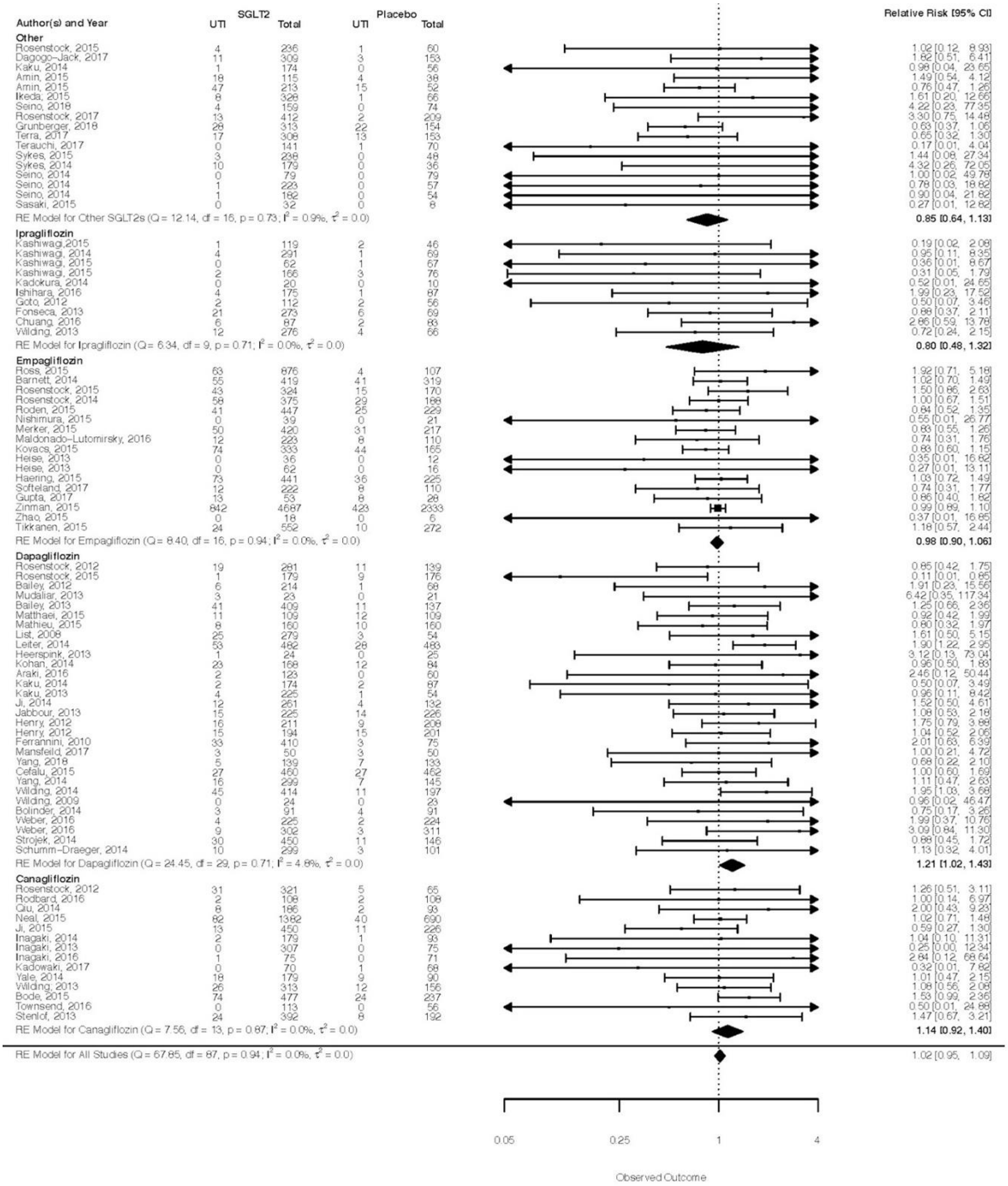


Figure A-2. Figure 1. Risk of Urinary Tract Infection with SGLT2 Inhibitors Compared to Active Comparators, Breakdown by Agent

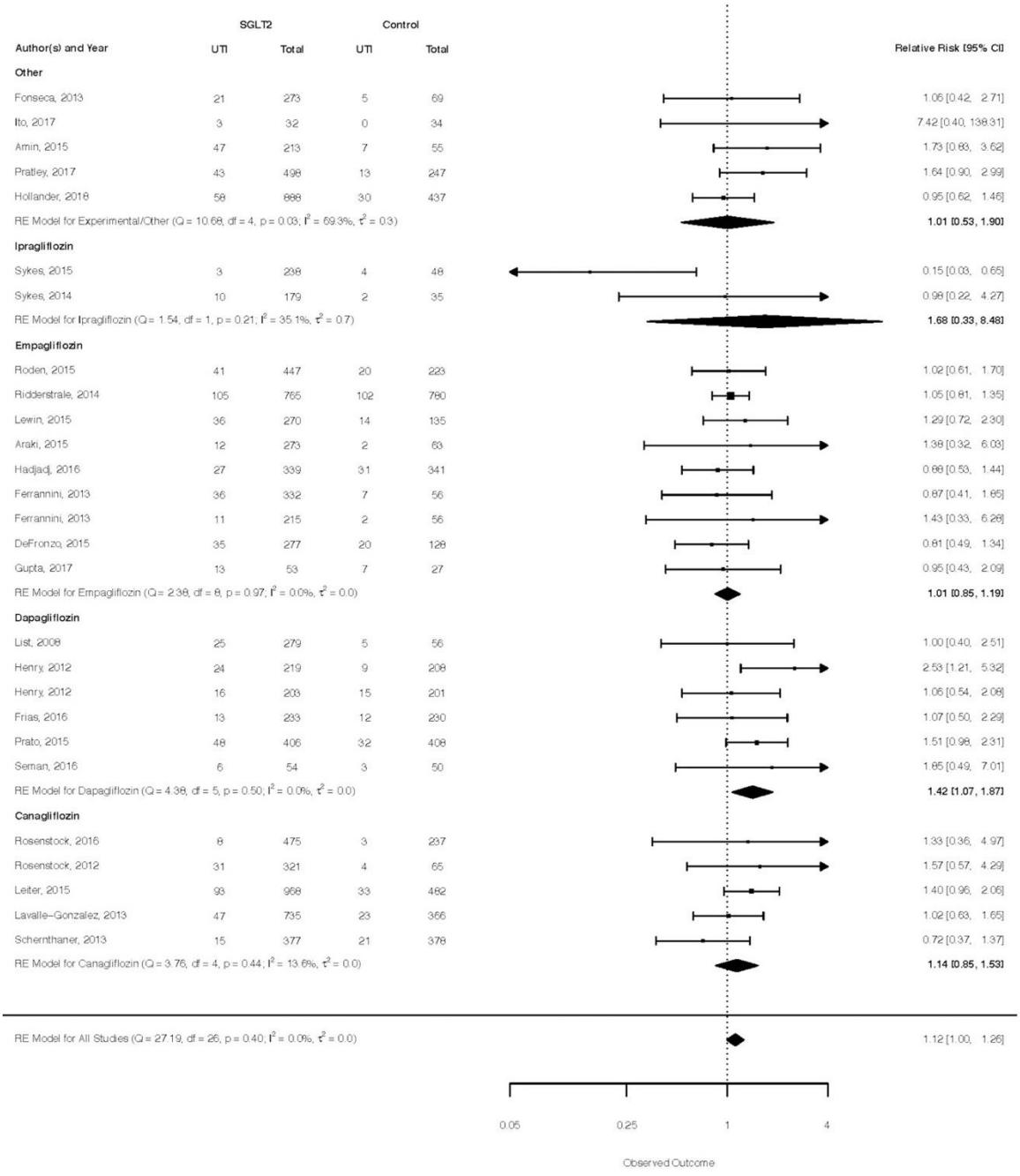


Figure A3: Risk of Acute Kidney Injury with SGLT2 Inhibitors compared to Active Comparators

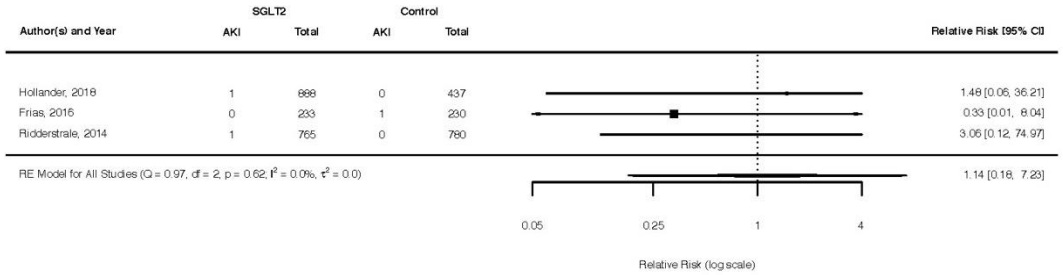


Figure A4: Risk of Acute Kidney Injury with SGLT2 Inhibitors Compared to Placebo; excluding EMPA-REG.

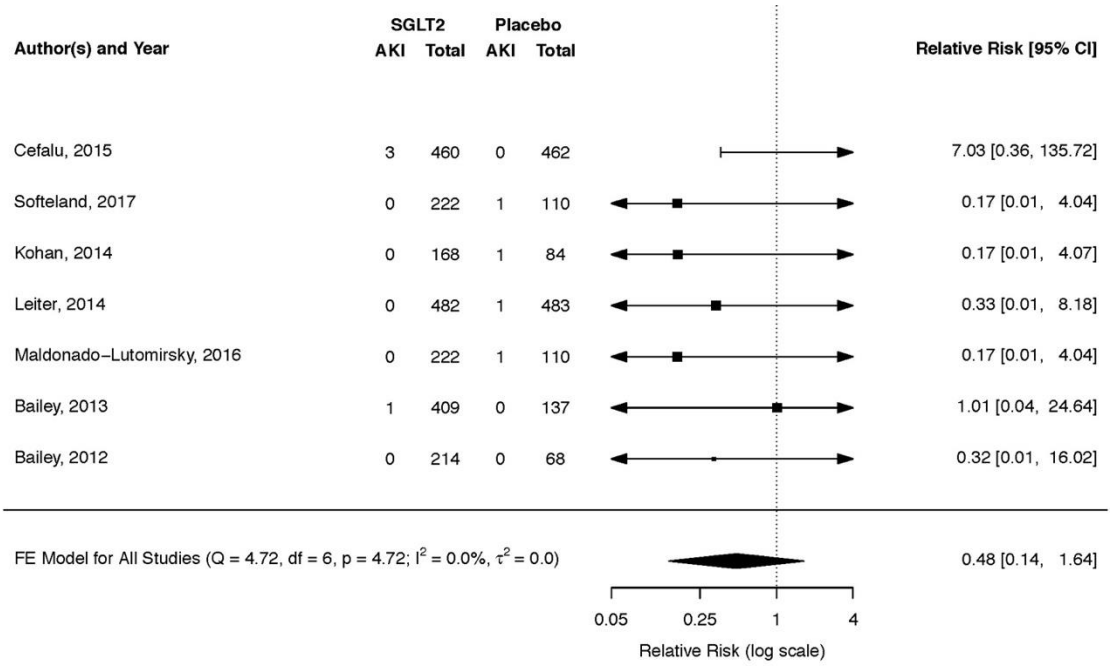


Figure A5. Risk of Ketoacidosis among users of an SGLT2 Inhibitor compared to an Incretin

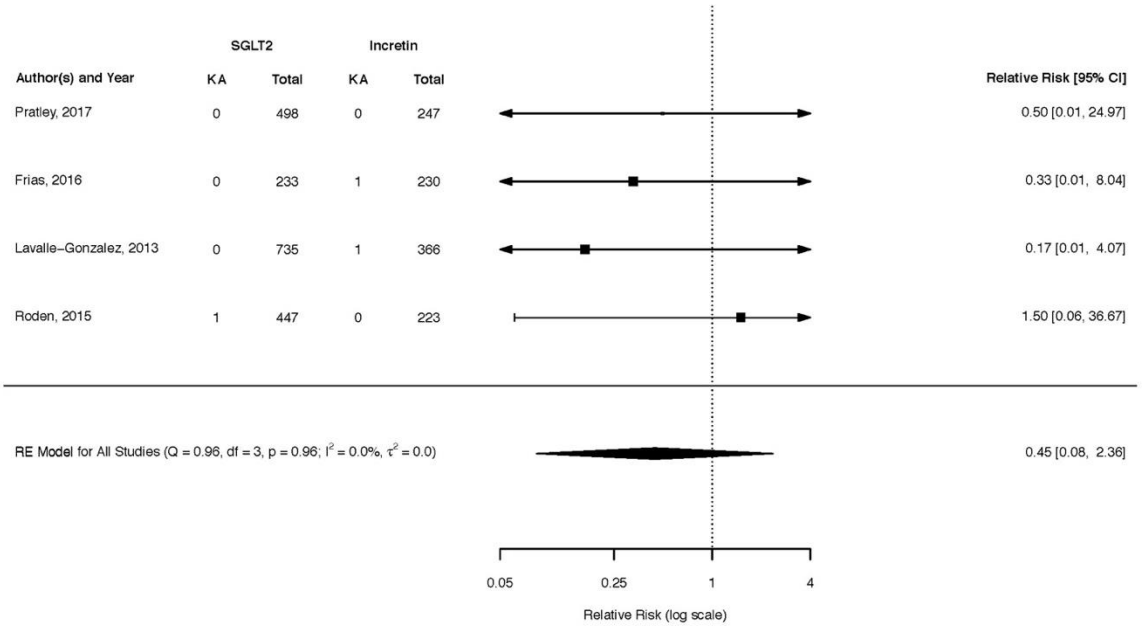


Figure A6. Risk of Ketoacidosis among users of an SGLT2 Inhibitor Compared to Placebo in Studies with at least one Outcome

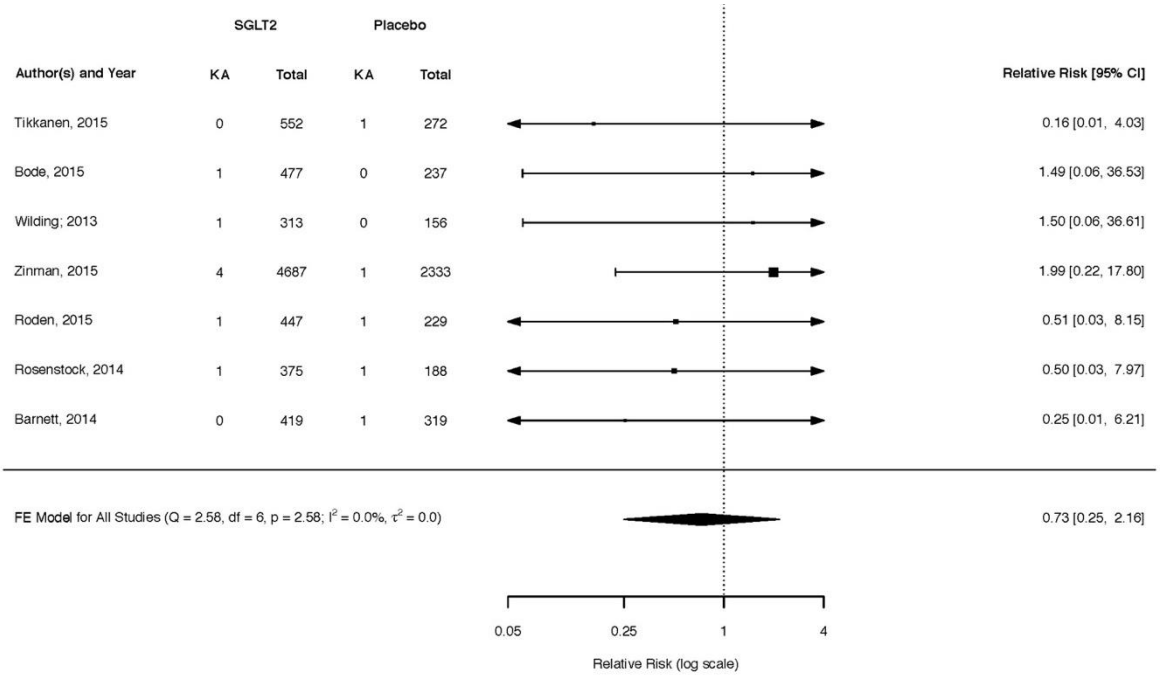


Figure A7. Risk of Urinary Tract Infections among users of SGLT2 Inhibitors Compared to Active Controls

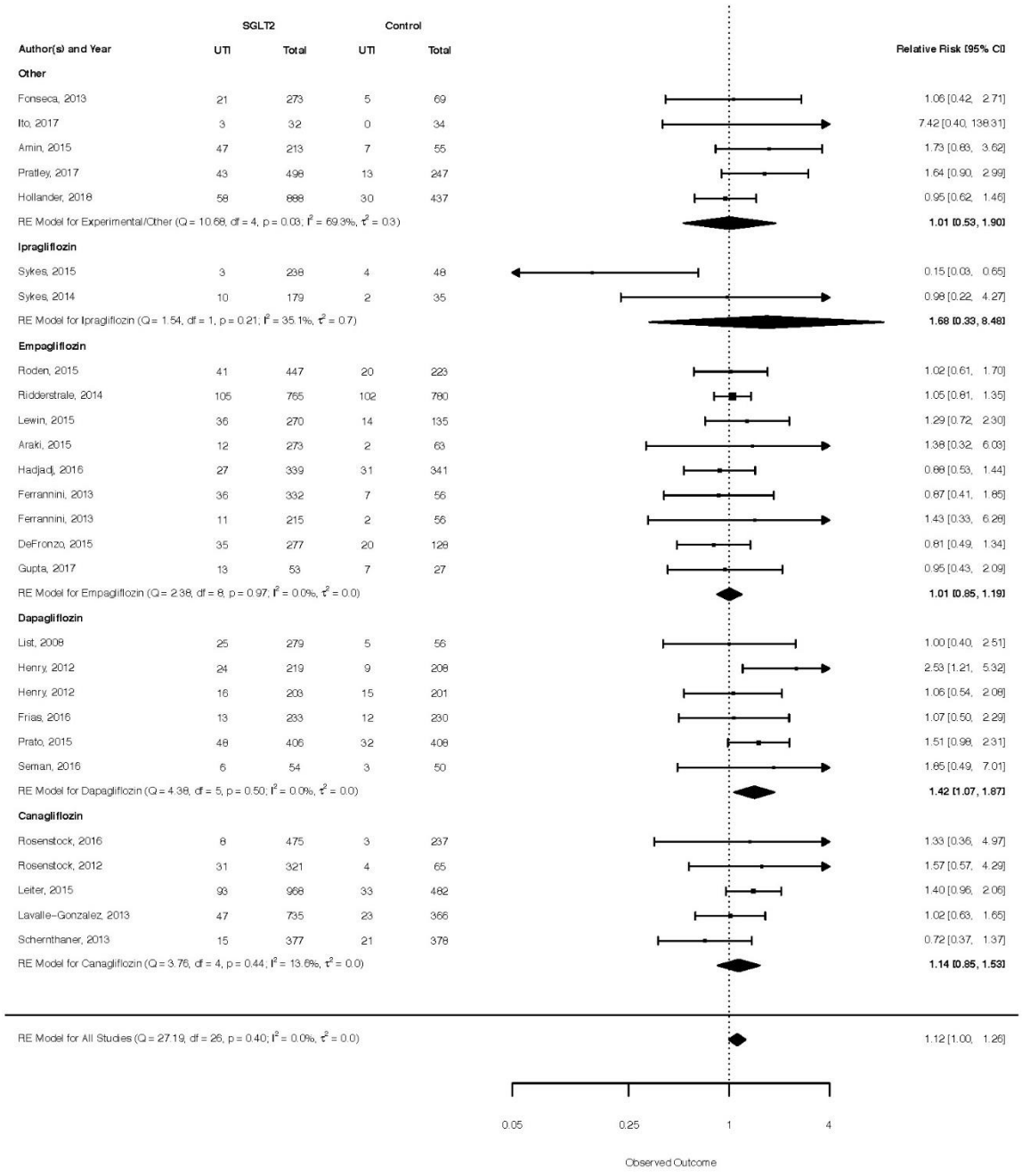


Figure A8: Risk of Fracture with SGLT2 Inhibitors compared to Metformin

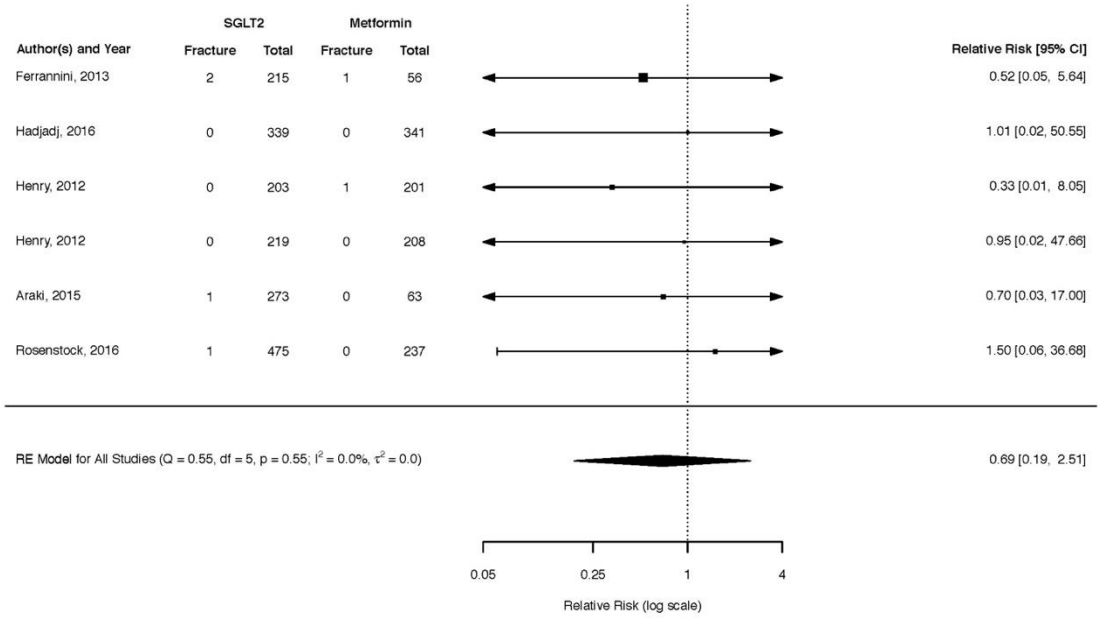


Figure A9: Risk of Fracture with SGLT2 Inhibitors compared to Sulfonylureas

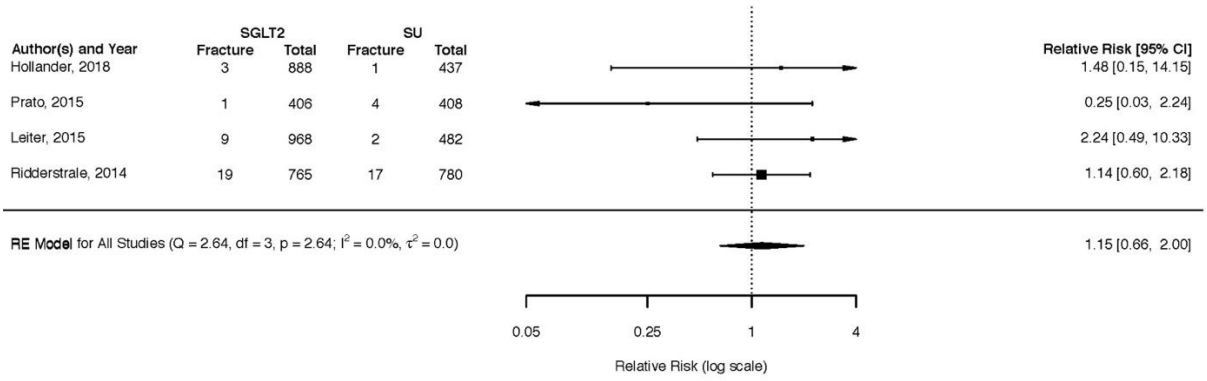


Figure A10: Risk of Fracture with SGLT2 Inhibitors compared to Incretins

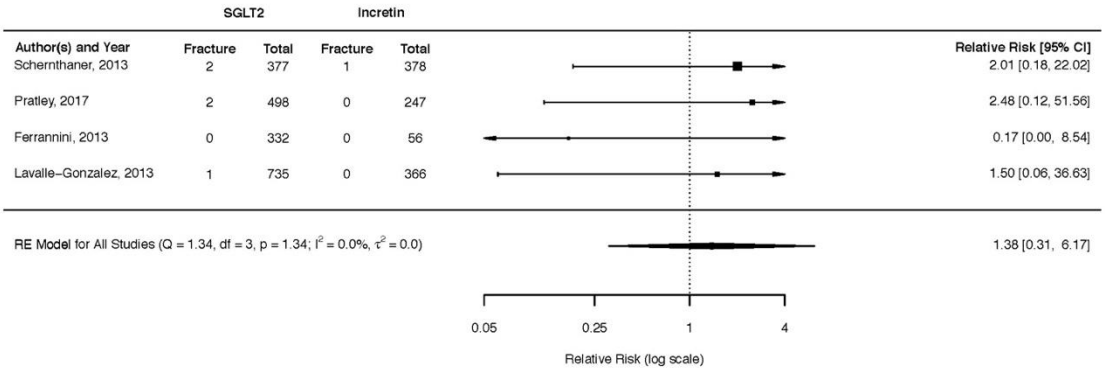
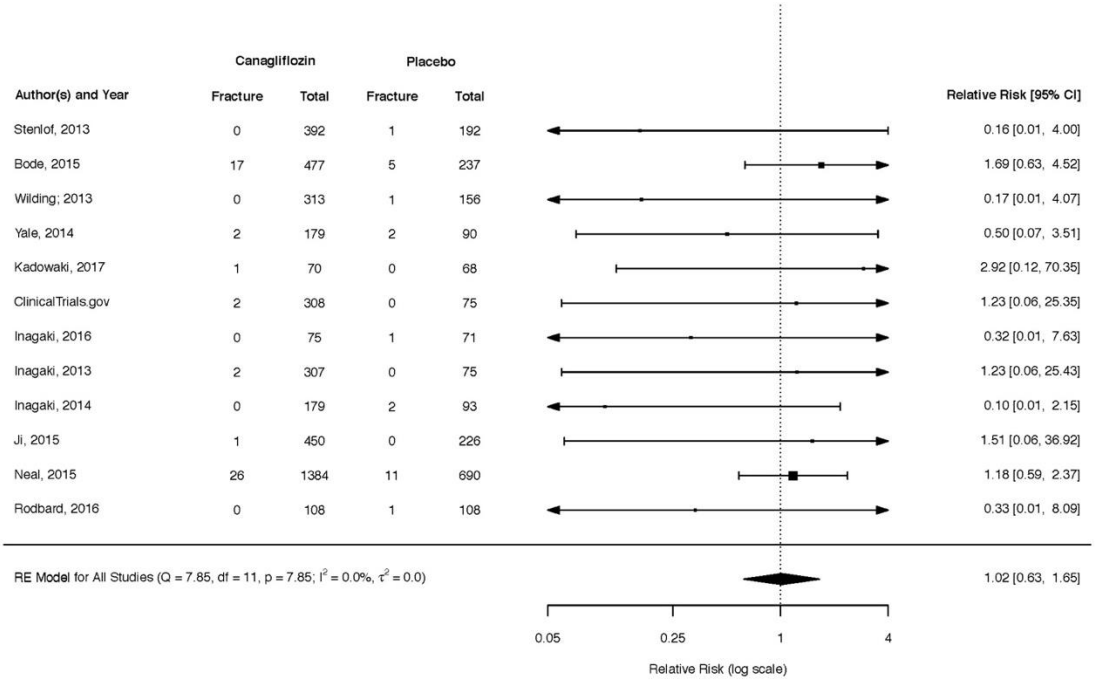


Figure A11: Risk of Fracture with Canagliflozin compared to Placebo



Section 5: Forest Plots for Fixed Effects Analysis

Figure A12. Risk of Acute Kidney Injury with SGLT2 Inhibitors compared to Placebo - Fixed Effect Model

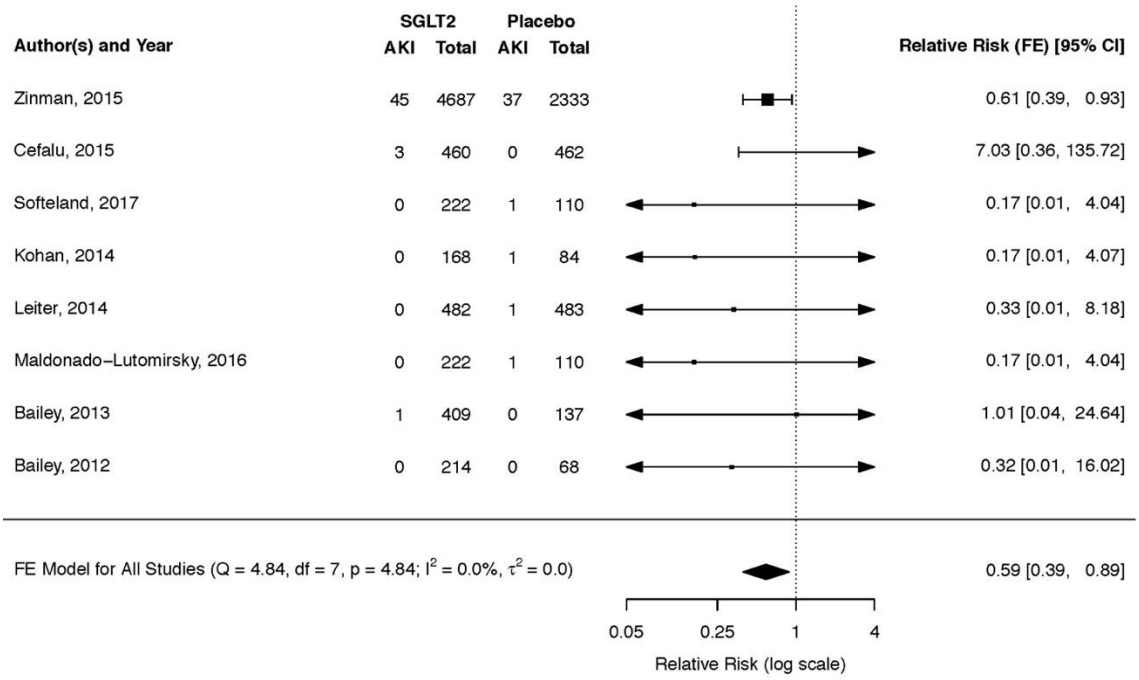


Figure A13. Risk of Diabetic Ketoacidosis with SGLT2 Inhibitors compared to Placebo - Fixed Effect Model

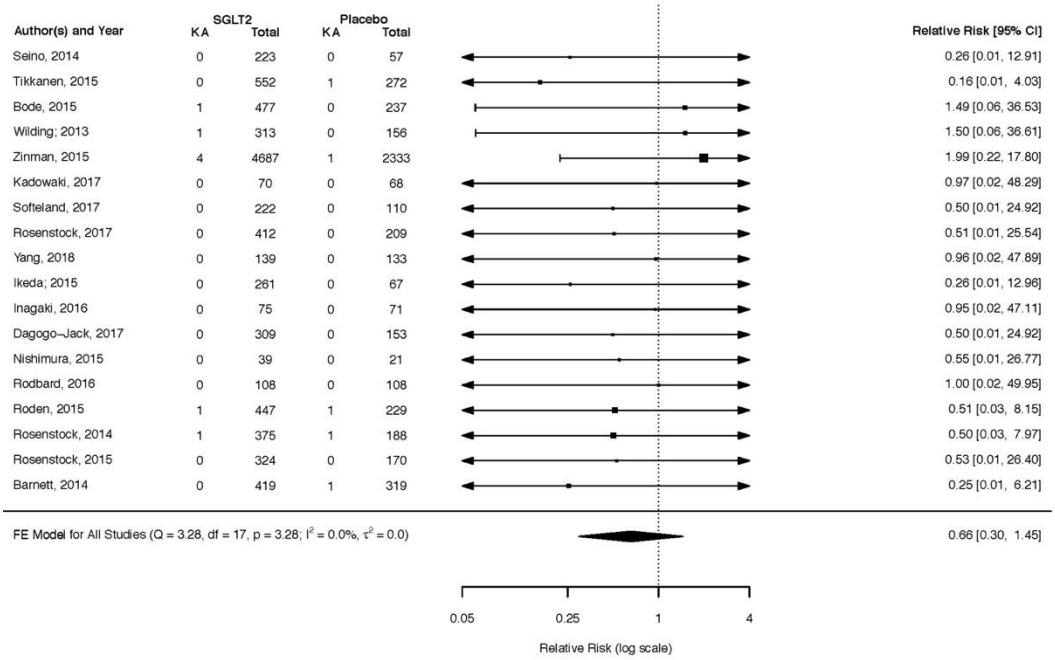


Figure A14.Risk of Urinary Tract Infection with SGLT2 Inhibitors compared to Placebo - Fixed Effect Model

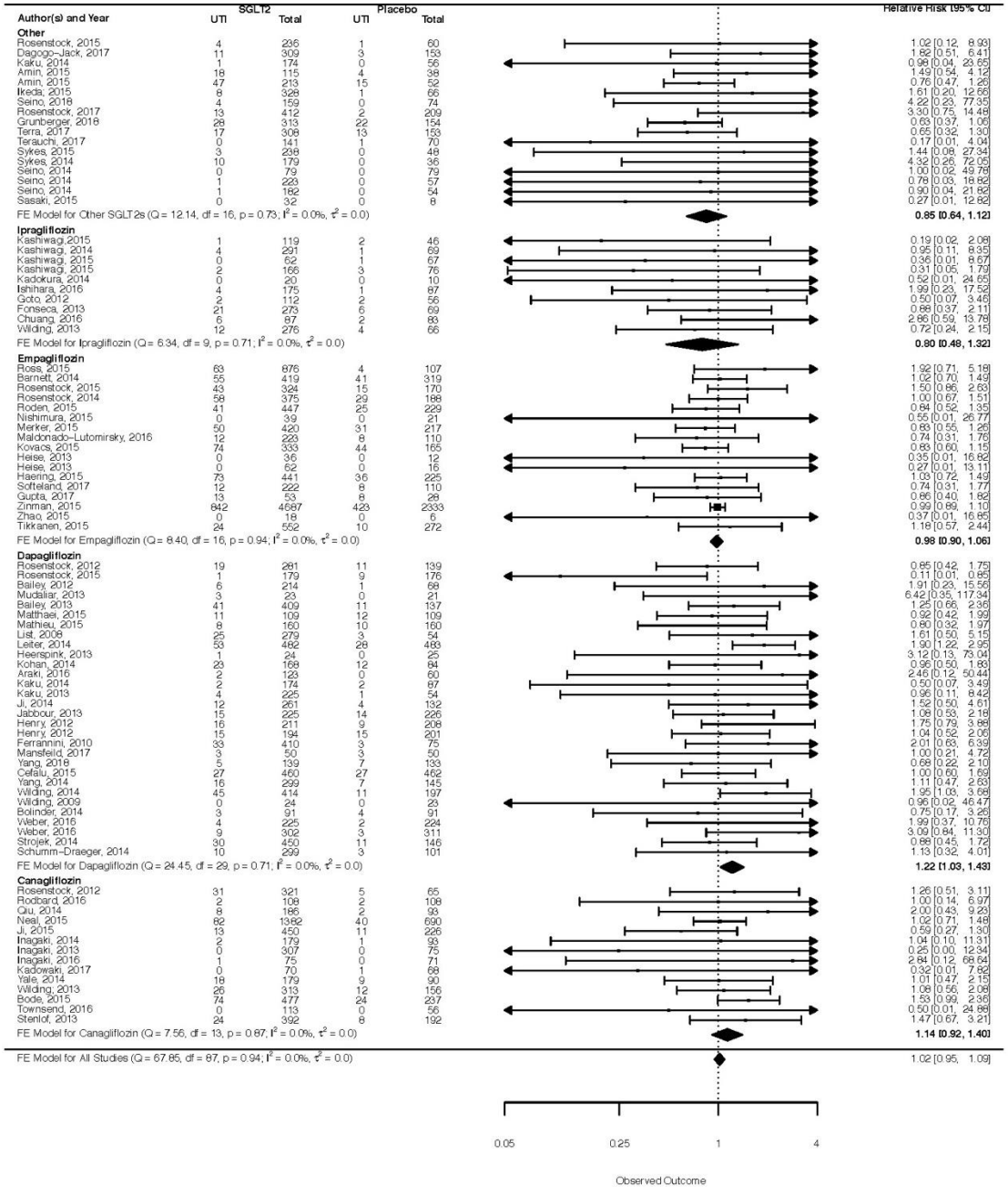
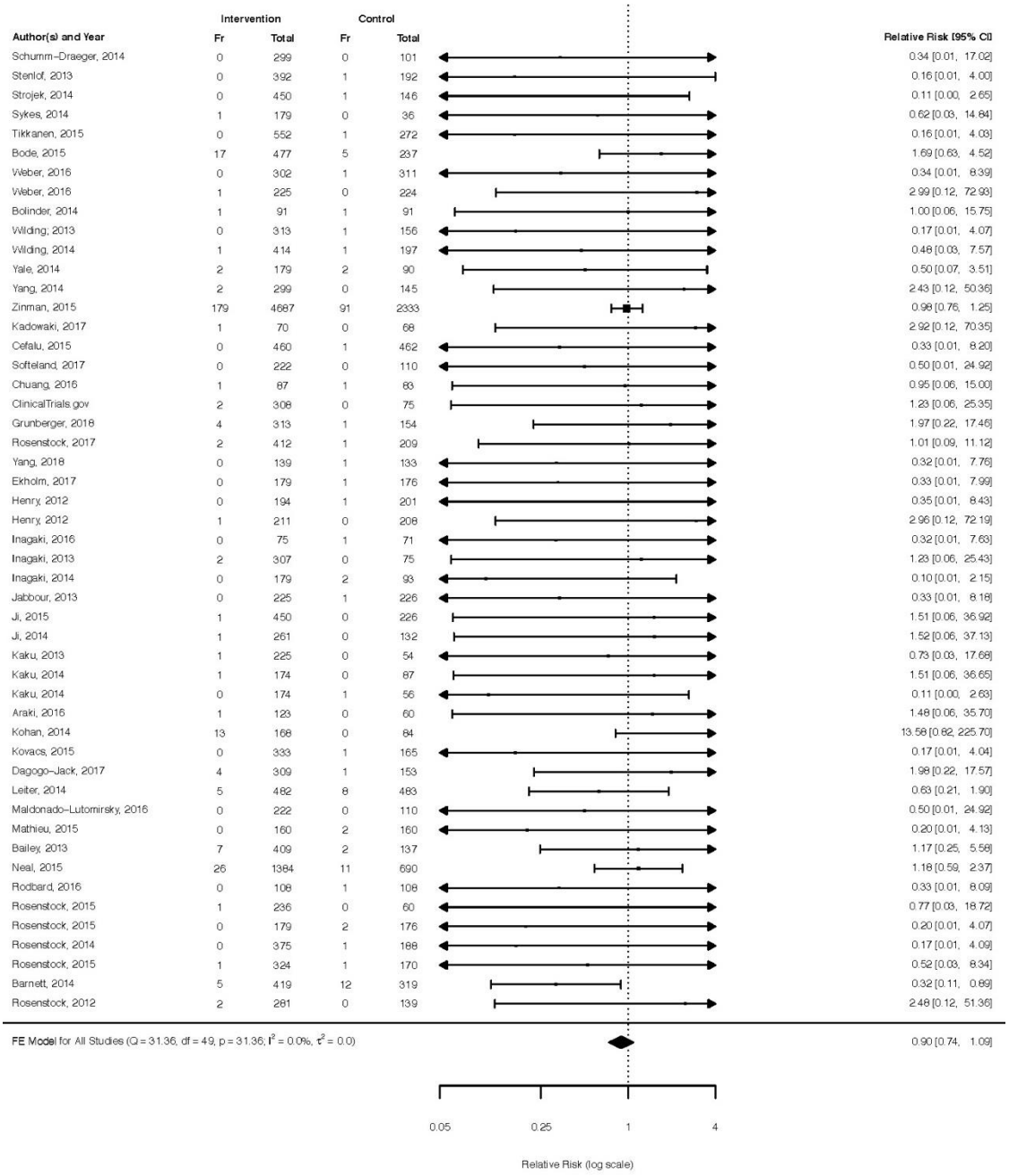


Figure A15. Risk of Fracture with SGLT2 Inhibitors compared to Placebo - Fixed Effect Model



Section 6: Risk of Bias Assessment

Table A7. Risk of Bias Assessment for Included Studies

Author and Year	NCT#	Randomization Sequence	Allocation concealment	Double Blinding	Blinded Outcome Assessment	Incomplete Outcome	Selective Reporting	Other	Overall Assessment
Amin, 2015	NCT01059825	Low	Low	Low	Low	Low	Low	Low	low
Amin, 2015	NCT01059825	Unclear	Unclear	Low	Unclear	Low	Unclear	Unclear	high
Araki, 2016	NCT02157298	Unclear	Low	Low	Low	Low	Low	Unclear	low
Araki	NCT01368081	Low	Low	Medium	Unclear	Low	High	Unclear	high
Bailey, 2013	NCT00528879	Low	Low	Low	Low	Medium	Unclear	Unclear	high
Bailey, 2012	None	Low	Low	Low	Low	Low	Low	Low	low
Barnett, 2014	NCT01164501	Low	Low	Low	Low	Low	High	Unclear	high
Bode, 2015	NCT01106651	Low	Low	Low	Low	Low	High	Unclear	high
Bolinder, 2014	NCT00855166	Low	Low	Low	Low	low	Low	Unclear	low
Cefalu, 2015	NCT01031680	Low	Low	Medium	Low	Low	High	Low	high
Chuang, 2016	NCT01505426	Low	Low	Low	Low	Low	Low	Unclear	low
DeFronzo, 2015	NCT01422876	Low	Low	Low	Unclear	Low	Low	Unclear	low
Prato, 2015	NCT00660907	Low	Low	Low	Low	Low	High	Unclear	high
Ferrannini, 2013	NCT00881530	High	High	High	High	Low	High	Unclear	high
Ferrannini, 2010	NCT00528372	Unclear	Unclear	Low	Unclear	Unclear	Unclear	Unclear	high
Fonseca, 2013	NCT01071850	Unclear	Low	Low	Low	Low	Low	Unclear	low
Frias, 2016	NCT02229396	Low	Low	Low	Low	Low	Low	Unclear	low
Hadjadj, 2016	NCT01719003	Low	Low	Low	Low	Low	High	Unclear	high
Haering, 2015	NCT01289990	Low	Low	Low	Unclear	Low	Low	Unclear	low
Heise, 2013	None	Low	Low	Unclear	Unclear	Low	Unclear	Unclear	high

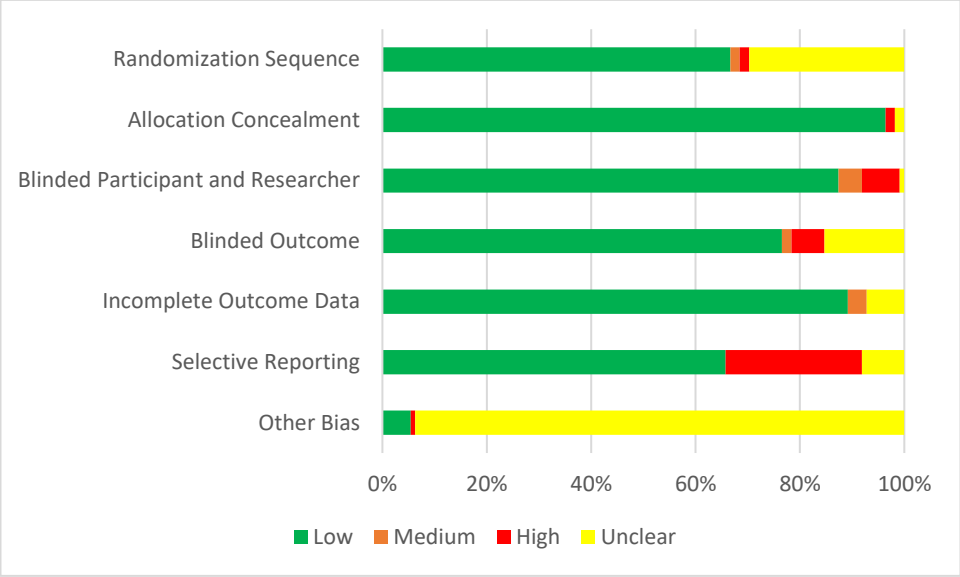
Heise, 2013	None	Unclear	Low	Low	Low	Low	Low	Unclear	low
Henry, 2012	NCT00643851	Low	Low	Low	Low	Low	High	Unclear	high
Henry, 2012	NCT00859898	Low	Low	Low	Low	Low	High	Unclear	high
Ikeda; 2015	NCT00800176	Unclear	Low	Low	Unclear	Low	Low	Unclear	high
Inagaki, 2016	NCT02220920	Low	Low	Low	low	Low	Low	Unclear	low
Inagaki, 2015	NCT01387737	Unclear	Low	High	High	Medium	Unclear	Unclear	high
Inagaki, 2013	NCT01022112	Low	Low	Low	Low	Low	High	Unclear	high
Inagaki, 2014	NCT01413204	Low	Low	Low	Low	Low	High	Unclear	high
Ishihara, 2016	NCT02175784	Unclear	Low	Medium	Low	Low	Low	Low	high
Jabbour, 2013	NCT00984867	Unclear	Low	Medium	Low	Low	High	Unclear	high
Ji, 2015	NCT01381900	Low	Low	Low	Low	Low	High	Unclear	high
Ji, 2014	NCT01095653	Low	Low	Low	Low	Low	High	Unclear	high
Kadokura, 2014	NCT01023945	Low	Low	Low	Low	Low	Low	Unclear	low
Kadowaki, 2015	NCT01193218	Low	Low	Low	Medium	Low	High	Unclear	high
Kaku, 2013	NCT00972244	Low	Low	Low	Unclear	Low	High	Unclear	high
Kaku, 2014	none	Unclear	low	Low	Unclear	Medium	Unclear	Unclear	high
Kaku, 2014	None	Low	Low	Low	Low	Low	Low	Unclear	low
Kashiwagi, 2015	NCT01242215	Low	Low	Low	Unclear	Low	Low	Unclear	low
Kashiwagi, 2015	NCT01057628.	Low	Low	Low	Low	Low	Low	Unclear	low
Kashiwagi, 2014	NCT00621868	Unclear	Low	Low	Low	Low	Low	Unclear	low
Kashiwagi,2015	NCT01316094	Unclear	Low	Low	Low	Low	Low	Unclear	low
Kohan, 2014	NCT00663260	Unclear	Low	Low	Unclear	Low	Low	Unclear	high
Kovacs, 2015	NCT01210001	Low	Low	Low	Medium	Low	High	Unclear	high
Heerspink, 2013	NCT00976495	Low	Low	Low	Low	Low	Low	Unclear	low

Lavalle-Gonzalez, 2013	NCT01106677	Low	Low	Low	Low	Low	High	Unclear	high
Leiter, 2014	NCT01042977	Low	Low	Low	Low	Unclear	Low	Unclear	low
Leiter, 2015	NCT00968812	Low	Low	Low	Low	Low	High	Unclear	high
Lewin, 2015	NCT01422876	Unclear	Low	Low	Low	Low	Low	Low	low
List, 2008	NCT00263276	Unclear	Low	Low	Low	Unclear	Low	Unclear	high
Mathieu, 2015	NCT01646320	Low	Low	Low	Low	Low	Low	Unclear	low
Matthaei, 2015	NCT01392677	Low	Low	Low	Low	Low	Low	Unclear	low
Mudaliar, 2013	None	Unclear	Low	Low	Low	Unclear	Low	Unclear	high
Nishimura, 2015	NCT01947855	Unclear	Low	Low	Low	Low	Low	Unclear	low
Qiu, 2014	NCT01340664	Low	Low	Low	Low	Low	Low	Unclear	low
Rodbard, 2016	NCT01989754	Low	Low	Low	Low	Low	Low	Unclear	low
Roden, 2015	NCT01289990	Low	Low	Low	Low	Low	High	Unclear	high
Rosenstock, 2012	NCT00642278	Unclear	Low	Low	Low	Low	Low	Unclear	low
Rosenstock, 2015	NCT01376557	Unclear	Low	Low	Low	Low	Low	Unclear	low
Rosenstock, 2016	NCT01809327	Low	Low	Low	Low	Low	High	Unclear	high
Rosenstock, 2015	NCT01606007	Low	Low	Low	Low	Low	Low	Unclear	low
Rosenstock, 2014	NCT01306214	Low	Low	Low	Low	Low	High	Unclear	high
Rosenstock, 2015	NCT01011868	Low	Low	Low	Low	Low	High	Unclear	high
Rosenstock, 2012	NCT00683878	Unclear	Low	Low	Low	Low	Low	Unclear	low
Ross, 2015	None	Unclear	Low	Low	Low	Low	Low	Unclear	low
Sasaki, 2015	None	Low	Low	Medium	High	Unclear	Unclear	High	high
Schernthaner, 2013	NCT01137812	Low	Low	Low	Low	Low	Low	Unclear	low
Schumm-Draeger, 2014	NCT01217892	Low	Low	Low	Low	Low	Low	Unclear	low

Seino, 2014	None	Low	Low	Low	Low	Low	Low	Unclear	low
Seino, 2014	None	Low	Low	Low	Low	Low	Low	Unclear	low
Seino, 2014	None	Low	Low	Low	Low	Low	Low	Unclear	low
Stenlof, 2013	NCT01081834	Unclear	Low	Low	Unclear	Low	Low	Unclear	high
Strojek, 2014	NCT00680745	Low	Low	Low	Low	Low	High	Unclear	high
Sykes, 2015	NCT00500331	Unclear	Low	Low	Low	Low	Low	Unclear	low
Tikkanen, 2015	NCT01370005	Medium	Low	Low	Low	Low	Low	Unclear	high
Townsend, 2016	None	Unclear	Low	Low	Low	Low	Low	Unclear	low
Seman, 2016	None	Unclear	Low	High	High	Unclear	Unclear	Unclear	high
Weber, 2016	NCT01137474	Low	Low	Low	Low	Medium	High	Unclear	high
Weber, 2016	NCT01195662	Low	Low	Low	Low	Low	High	Unclear	high
Wilding; 2013	NCT01106625	Low	Low	Low	Low	Low	High	Unclear	high
Wilding, 2013	NCT01117584	Unclear	Low	Low	Low	Low	Low	Unclear	low
Wilding, 2009	NCT00357370	Unclear	Low	Low	Low	Low	Low	Unclear	low
Wilding, 2014	NCT00673231	Low	Low	Low	Low	Low	High	Unclear	high
Yale, 2014	NCT01064414	Unclear	Low	Low	Low	Low	Low	Unclear	low
Zhao, 2015	NCT01316341	Medium	Low	Low	Low	Low	Low	Unclear	high
Zinman, 2015	NCT01131676	Low	Low	Low	Low	Low	Low	Low	low
Goto, 2012	None	Unclear	Low	Low	Unclear	Low	Low	Unclear	high
Dagogo-Jack, 2017	NCT02036515	Low	Low	Low	Unclear	Low	Low	Unclear	low
Maldonado-Lutomirsky, 2016	NCT01734785	Unclear	Low	Low	Unclear	Low	Low	Unclear	high
Merker, 2015	NCT01289990	Unclear	Low	Low	Low	Low	Low	Unclear	low
Neal, 2015	NCT01032629	Low	Low	Low	Low	Low	Low	Unclear	low
Ridderstrale, 2014	NCT01167881	Low	Low	Low	Low	Low	Low	Unclear	low
Sykes, 2014	NCT00495469	Low	Low	Low	Low	Low	Low	Unclear	low

Tanizawa, 2014	None	Low	Low	High	High	Low	Low	Unclear	high
Yang, 2014	NCT01095666	Unclear	Low	Low	Low	Low	Low	Unclear	low
Gupta, 2017	None	Low	Low	Low	Low	Low	Low	Unclear	low
Kadowaki, 2017	NCT02354235	Low	Low	Low	Low	Low	Low	Unclear	low
Softeland, 2017	NCT01734785	Low	Low	Low	Low	Low	Low	Unclear	low
Terra, 2017	NCT01958671	Low	Low	Low	Low	Low	Low	Unclear	low
ClinicalTrials.gov		Low	Low	Low	Low	Low	Low	Unclear	low
Terauchi, 2017	NCT02201004	Low	Low	Low	Low	Low	Low	Unclear	low
Grunberger, 2018	NCT01986855	Low	Low	High	High	High	Low	Unclear	high
Hollander, 2018	NCT01999218	Low	Low	Low	Low	Low	Low	Unclear	Low
Ito, 2017		Low	Low	High	High	Low	Low	Unclear	High
Pratley, 2017	NCT02099110	Low	Low	Low	Low	Low	Low	Unclear	Low
Rosenstock, 2017	NCT02033889	Low	Low	Low	Low	Low	Low	Unclear	Low
Seino, 2018		Low	Low	Low	Low	Low	Low	Unclear	Low
Yang, 2018	NCT02096705	Low	Low	Low	Low	Low	Low	Unclear	Low
Mansfeild, 2017	NCT02429258	Low	Low	Low	Low	Low	Low	Unclear	Low
Ekholm, 2017	NCT01606007	Unclear	Low	Low	Low	High	High	Unclear	High

Figure A16. Risk of Bias Assessment



Section 7: Assessment of Publication Bias

Figure A17. Funnel Plot for Placebo Controlled Trials: Acute Kidney Injury

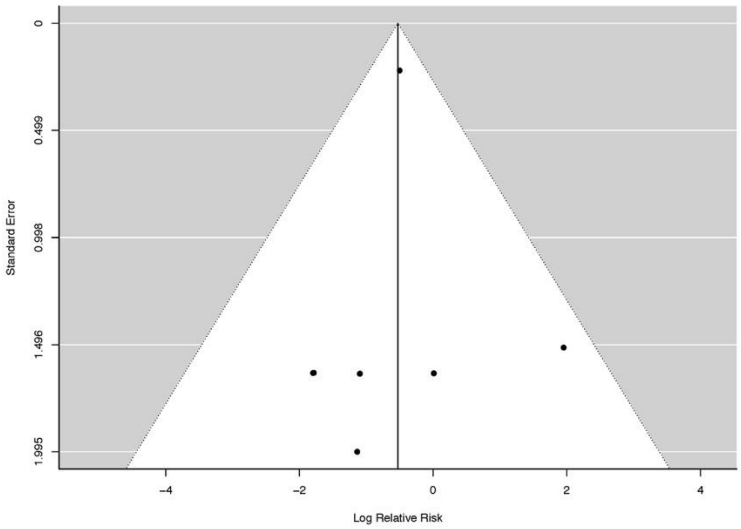


Figure A18. Funnel Plot for Placebo Controlled Trials: Urinary Tract Infection

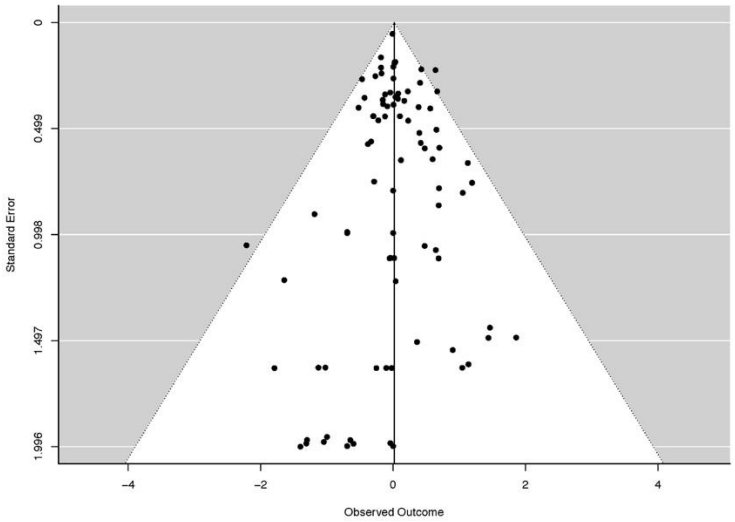


Figure A19. Funnel Plot for Metformin Controlled Trials: Urinary Tract Infection

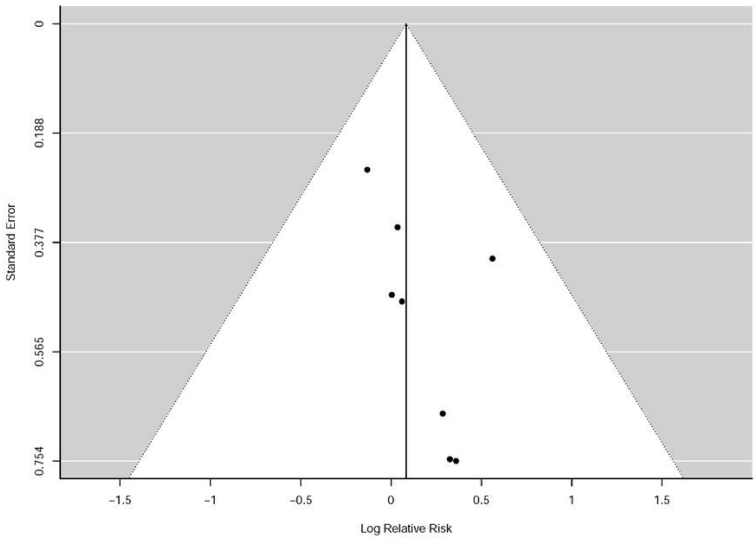


Figure A20. Funnel Plot for Sulfonylurea Controlled Trials: Urinary Tract Infection

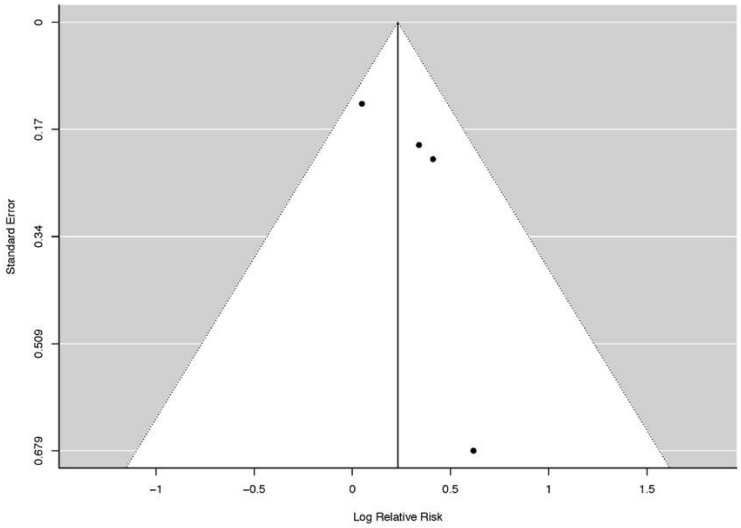


Figure A21. Funnel Plot for Incretin Controlled Trials: Urinary Tract Infection

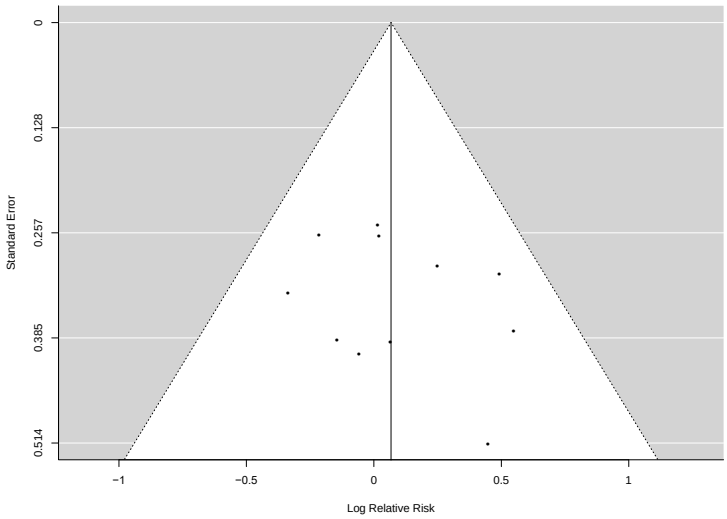
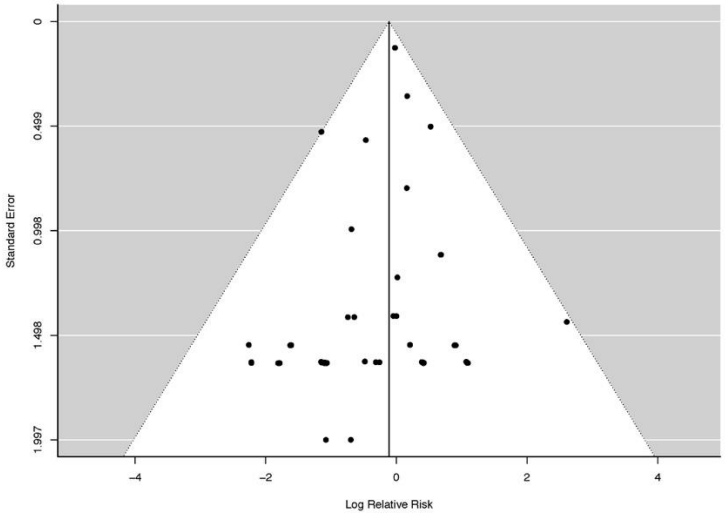


Figure A22. Funnel Plot for Placebo Controlled Trials: Fracture



Appendix B

Supporting documentation for the systematic review and network meta-analysis of the dose response relationship between SGLT2 inhibitors and urinary tract infections

Section 1: PRISMA Checklist

(See Below)

Section/topic	#	Checklist item	Reported in Section
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	4.0
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	See publication Donnan (2019) CMAJ Open
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4.1
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4.1
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4.2.1
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4.2.2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4.2.3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4.2.4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4.2.4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Appendix
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4.2.5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4.2.6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	4.2.6

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	4.2.5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	4.2.6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	4.3.1 figure 4-1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Appendix
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Appendix
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 4-2 – 4-3 Appendix
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Table 4-2 – 4-3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Figure 4-3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	4.3.3 Appendix
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	4.4
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	4.4.1
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	4.5
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	See Donnan (2019) CMAJ Open

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Section 2: Search Strategies

Table B1. Pubmed Search Strategy

		Search String	Results
1	**Population**	"Diabetes Mellitus, Type 2"[Mesh] OR NIDDM[tw] OR t2dm[tw] OR ((“type 2"[tw] OR "type ii"[tw] OR "adult onset"[tw] OR “mature onset”[tw] OR “late onset”[tw] OR “noninsulin-dependent”[tw] OR “non insulin dependent”[tw]) AND diabetes[tw])	167100
2	**Intervention: SGLT2s**	"Sodium-Glucose Transport Proteins/antagonists and inhibitors"[Mesh] OR "Sodium-Glucose Transporter 2"[Mesh] OR "sodium-glucose co-transporter 2"[tw] OR SGL2[tw] OR SGLT2[tw] OR gliflozin*[tw] OR "Canagliflozin"[Mesh] OR canagliflozin*[tw] OR invokana[tw] OR sulisent[tw] OR "TA 7284"[tw] OR TA7284[tw] OR "JNJ 28431754"[tw] OR JNJ28431754[tw] OR "2-(3-(4-ethoxybenzyl)-4-chlorophenyl)-6-hydroxymethyltetrahydro-2H-pyran-3,4,5-triol"[Supplementary Concept] OR dapagliflozin*[tw] OR farxiga[tw] OR forxiga[tw] OR “BMS 512148”[tw] OR BMS512148[tw] OR "empagliflozin"[Supplementary Concept] OR empagliflozin*[tw] OR jardiance[tw] OR "BI 10773"[tw] OR BI10773[tw] OR ipragliflozin[Supplementary Concept] OR ipragliflozin*[tw] OR suglat[tw] OR "ASP 1941"[tw] OR ASP1941[tw] OR "1,5-anhydro-1-(5-(4-ethoxybenzyl)-2-methoxy-4-methylphenyl)-1-thioglucitol"[Supplementary Concept] OR luseogliflozin*[tw] OR lusefi[tw] OR “TS 071”[tw] OR TS071[tw] OR "remogliflozin etabonate"[Supplementary Concept] OR remogliflozin*[tw] OR "KGT 1681"[tw] OR KGT1681[tw] OR "(2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(methylthio)tetrahydro-2H-pyran-3,4,5-triol" [Supplementary Concept] OR sotagliflozin*[tw] OR "LX 4221"[tw] OR LX4221[tw] OR "6-((4-ethylphenyl)methyl)-3',4',5',6'-tetrahydro-6'-(hydroxymethyl)spiro(isobenzofuran-1(3H),2'-(2H)pyran)-3',4',5'-triol" [Supplementary Concept] OR tofogliflozin*[tw] OR apleway[tw] OR deberza[tw] OR "CSG 452"[tw] OR CSG452[tw] OR "5-(4-chloro-3-(4-ethoxybenzyl)phenyl)-1-hydroxymethyl-6,8-dioxabicyclo(3.2.1)octane-2,3,4-triol" [Supplementary Concept] OR ertugliflozin*[tw] OR "PF 04971729"[tw] OR PF04971729[tw]	2936
3	**#1 AND #2**		2080
4	**Study Type Filter: Cochrane Highly Sensitive**	("randomized controlled trial"[pt] OR "controlled clinical trial"[pt] OR randomized[tiab] OR placebo[tiab] OR "clinical trials as topic"[Mesh:NoExp] OR randomly[tiab] OR trial[ti]) NOT (animals[mh] NOT humans[mh])	1065055

	Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision). Available at http://handbook.cochrane.org/chapter_6/box_6_4_b_cochrane_hsss_2008_sensprec_pubmed.htm		
5	**#3 AND #4**		743

Table B2: Cochrane Library Search Strategy

#1	([mh "Diabetes Mellitus, Type 2"] or NIDDM or t2dm or (("type 2" or "type ii" or "adult onset" or "mature onset" or "late onset" or "noninsulin-dependent" or "non insulin dependent") and (diabetes)))	25,454
#2	([mh "Sodium-Glucose Transport Proteins"/ai] or [mh "Sodium-Glucose Transporter 2"] or "sodium-glucose co-transporter 2" or SGL2 or SGLT2 or gliflozin* or [mh canigliflozin] or canagliflozin* or invokana or sulisent or "TA 7284" or TA7284 or "JNJ 28431754" or JNJ28431754 or dapagliflozin* or farxiga or forxiga or "BMS 512148" or BMS512148 or empagliflozin* or jardiance or "BI 10773" or BI10773 or ipragliflozin or suglat or "ASP 1941" or ASP1941 or luseogliflozin* or lusefi or "TS 071" or TS071 or remogliflozin* or "KGT 1681" or KGT1681 or sotagliflozin* or "LX 4221" or LX4221 or tofogliflozin* or apleway or deberza or "CSG 452" or CSG452 or ertugliflozin* or "PF 04971729" or PF04971729)	1,082
#3	#1 AND #2	959

Table B3: Embase Search Strategy

No.	Query	Results
#5	#3 AND #4	2,016
#4 - EMBASE RCT filter from Wong 2006, best balance of sensitivity and specificity	random*:ab,ti OR placebo*:de,ab,ti OR (double NEXT/1 blind*):ab,ti	1,533,336
#3	#1 AND #2	4,869
#2	'sodium glucose cotransporter 2'/de OR 'sodium glucose cotransporter 2 inhibitor'/exp OR 'sodium-glucose co-transporter 2':ab,ti OR sgl2:ab,ti OR sglt2:ab,ti OR gliflozin*:ab,ti OR canagliflozin*:ab,ti OR invokana:ab,ti OR sulisent:ab,ti OR 'ta 7284':ab,ti OR ta7284:ab,ti OR 'jnj 28431754':ab,ti OR jnj28431754:ab,ti OR dapagliflozin*:ab,ti OR farxiga:ab,ti OR forxiga:ab,ti OR 'bms 512148':ab,ti OR bms512148:ab,ti OR empagliflozin*:ab,ti OR jardiance:ab,ti OR 'bi 10773':ab,ti OR bi10773:ab,ti OR ipragliflozin*:ab,ti OR suglat:ab,ti OR 'asp 1941':ab,ti OR asp1941:ab,ti OR luseogliflozin*:ab,ti OR lusefi:ab,ti OR 'ts 071':ab,ti OR ts071:ab,ti OR remogliflozin*:ab,ti OR 'kgt 1681':ab,ti OR kgt1681:ab,ti OR sotagliflozin*:ab,ti or 'LX 4221':ab,ti or LX4221:ab,ti or tofogliflozin*:ab,ti or apleway:ab,ti or deberza:ab,ti or 'CSG 452':ab,ti or CSG452:ab,ti or ertugliflozin*:ab,ti or 'PF 04971729':ab,ti or PF04971729:ab,ti	6,675
#1	'non insulin dependent diabetes mellitus'/de OR niddm:ab,ti OR t2dm:ab,ti OR ('type 2':ab,ti OR 'type ii':ab,ti OR 'adult onset':ab,ti OR 'mature onset':ab,ti OR 'late onset':ab,ti OR 'noninsulin dependent':ab,ti OR 'non insulin dependent':ab,ti AND diabetes:ab,ti)	258,521

Table B4: IPA Search Strategy

#	Query	Limiters/ Expanders	Results
S1	TX NIDDM OR t2dm OR (("type 2" OR "type ii" OR "adult onset" OR "mature onset" OR "late onset" OR "noninsulin dependent" OR "non insulin dependent") AND (diabetes))	Search modes - Boolean/Phrase	6,110
S2	TX "sodium-glucose co-transporter 2" OR sgl2 OR sglt2 OR gliflozin OR canagliflozin OR invokana OR sulisent OR "ta 7284" OR ta7284 OR "jnj 28431754" OR jnj28431754 OR dapagliflozin* OR farxiga OR forxiga OR "bms 512148" OR bms512148 OR empagliflozin* OR jardiance OR "bi 10773" OR bi10773 OR ipragliflozin* OR suglat OR "asp 1941" OR asp1941 OR luseogliflozin* OR lusefi OR "ts 071" OR ts071 OR remogliflozin* OR "kgt 1681" OR kgt1681 OR sotagliflozin* OR "LX 4221" OR LX4221 OR tofogliflozin* OR apleway OR deberza OR "CSG452" OR CSG452 OR ertugliflozin* OR "PF 04971729" OR PF04971729	Search modes - Boolean/Phrase	337
S3	S1 AND S2	Search modes - Boolean/Phrase	267
S4	TI randomized OR AB randomized OR TI randomised OR AB randomised OR TI placebo OR AB placebo OR TI randomly OR AB randomly OR TI trial	Search modes - Boolean/Phrase	59,232
S5	S3 AND S4	Search modes - Boolean/Phrase	130

Table B5: ProQuest Search Strategy

all(NIDDM OR t2dm OR (("type 2" OR "type ii" OR "adult onset" OR "mature onset" OR "late onset" OR "noninsulin-dependent" OR "non insulin dependent") AND (diabetes))) AND all("sodium-glucose co-transporter 2" OR SGL2 OR SGLT2 OR gliflozin* OR canagliflozin* OR invokana OR sulisent OR "TA 7284" OR TA7284 OR "JNJ 28431754" OR JNJ28431754 OR dapagliflozin* OR farxiga OR forxiga OR "BMS 512148" OR BMS512148 OR empagliflozin* OR jardiance OR "BI 10773" OR BI10773 OR ipragliflozin OR suglat OR "ASP 1941" OR ASP1941 OR luseogliflozin* OR lusefi OR "TS 071" OR TS071 OR remogliflozin* OR "KGT 1681" OR KGT1681 OR sotagliflozin* OR "LX 4221" OR LX4221 OR tofogliflozin* OR apleway OR deberza OR "CSG 452" OR CSG452 OR ertugliflozin* OR "PF 04971729" OR PF04971729)	3

Section 3: List of Extracted Variables

Table B6. Variables extracted from included RCTs

Variable Extraction	Notes
NCT Number, Author and Year	
Country in which the study was conducted	International if applicable
Start and End years	
Observation Period (# of weeks)	
Total number of participants randomized	
Number of Males	
Number of Females	
Background diabetes therapy	
Intervention 1: SGLT2 Agent	This was captured for as many interventions that were used.
Intervention 1: Dose	
Intervention 1: Number of Persons	
Intervention 1: Mean Age	
Intervention 1: Age SD	
Intervention 1: Mean baseline HbA1C	
Intervention 1: A1C SD	
Comparison 1: SGLT2 Agent	This was captured for as many comparison groups that were used.
Comparison 1: Dose	
Comparison 1: Number of Persons	
Comparison 1: Mean Age	
Comparison 1: Age SD	
Comparison 1: Mean baseline HbA1C	
Comparison 1: A1C SD	
Acute Kidney Injury Reported (yes/no)	
Urinary Tract Infection Reported (yes/no)	
Definition of UTI	
Ketoacidosis Reported (yes/no)	
Bone Fracture Reported (yes/no)	
Amputation Reported (yes/no)	
AKI: Outcomes in Intervention 1(n/N)	This was captured for each individual intervention and control group
AKI: Outcomes in Comparison 1 (n/N)	
UTI: Outcomes in Intervention 1(n/N)	
UTI: Outcomes in Comparison 1 (n/N)	
DKA: Outcomes in Intervention 1(n/N)	

DKA: Outcomes in Comparison 1 (n/N)	
BF: Outcomes in Intervention 1(n/N)	
BF: Outcomes in Comparison 1 (n/N)	
Amp: Outcomes in Intervention 1(n/N)	
Amp: Outcomes in Comparison 1 (n/N)	

Section 4: Thresholds for high and low dose SGLT2 inhibitors

Table B7. Dose categories for primary analysis

Category	Definition
Canagliflozin high dose	200 mg or more
Canagliflozin low dose	100 mg or less
Dapagliflozin high dose	10 mg or more
Dapagliflozin low dose	5 mg or less
Empagliflozin high dose	25 mg or more
Empagliflozin low dose	10 mg or less
Iprgliflozin high dose	100 mg or more
Ipragliflozin low dose	50 mg or less
Ertugliflozin high dose	15 mg or more
Ertugliflozin low dose	10 mg or less
Remogliflozin high dose	500 mg or more
Remogliflozin low dose	250 mg or less
Tofogliflozin high dose	40 mg or more
Tofogliflozin low dose	20 mg or less

Table B8. Dose categories for sensitivity analysis

Category	Definition
Canagliflozin high dose	100 mg or more
Canagliflozin low dose	50 mg or less
Dapagliflozin high dose	10 mg or more
Dapagliflozin low dose	5 mg or less
Empagliflozin high dose	10 mg or more
Empagliflozin low dose	2.5 mg
Iprgliflozin high dose	50 mg or more
Ipragliflozin low dose	25 mg or less
Ertugliflozin high dose	10 mg or more
Ertugliflozin low dose	5 mg or less
Remogliflozin high dose	1000 mg or more
Remogliflozin low dose	500 mg or less
Tofogliflozin high dose	20 mg or more
Tofogliflozin low dose	5 mg

Section 5: Additional Materials for the Primary Analysis

Figure B0-1. Forest plot of results on the primary analysis with placebo as the control

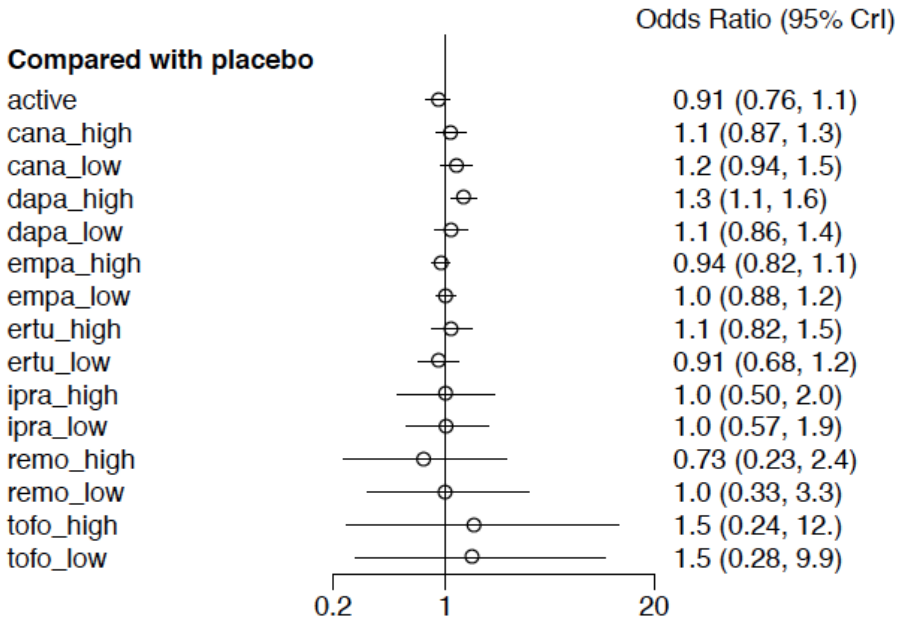


Table B9. Rank Probabilities according to the surface under the cumulative rank curve (SUCRA) values

Category	SUCRA
Active	**0.745**
Cana_high	**0.427**
Cana_low	**0.292**
Dapa_high	**0.173**
Dapa_low	**0.414**
Empa_high	**0.701**
Empa_low	**0.543**
Ertu_high	**0.393**
Ertu_low	**0.677**
Ipra_high	**0.537**
Ipra_low	**0.503**
Placebo	**0.562**
Remo_high	**0.694**
Remo_low	**0.518**
Tofo_high	**0.407**
Tofo_low	**0.415**

Section 6: Breakdown of pairwise, indirect and pooled estimates

Figure B0-2. Breakdown of pairwise, indirect, and pooled estimates

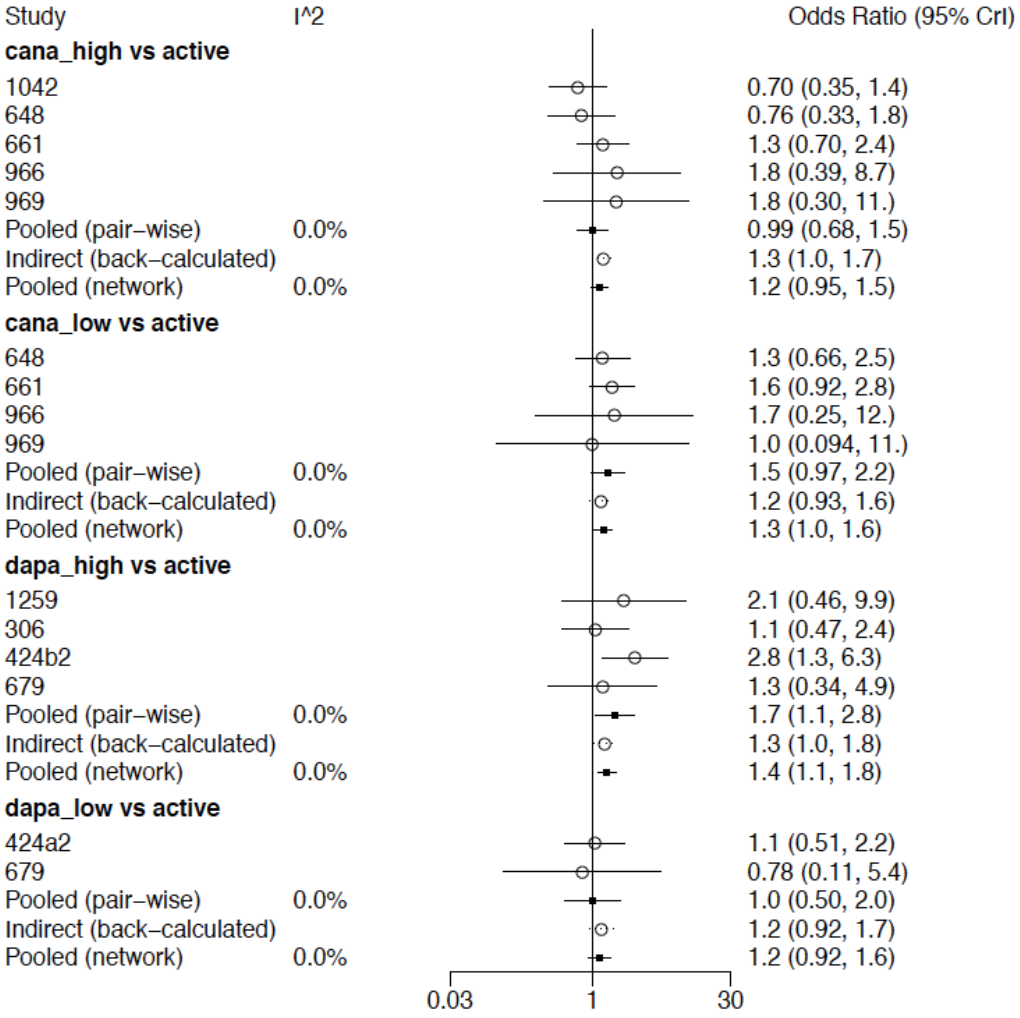


Figure B2 Continued. A. Breakdown of pairwise, indirect, and pooled estimates

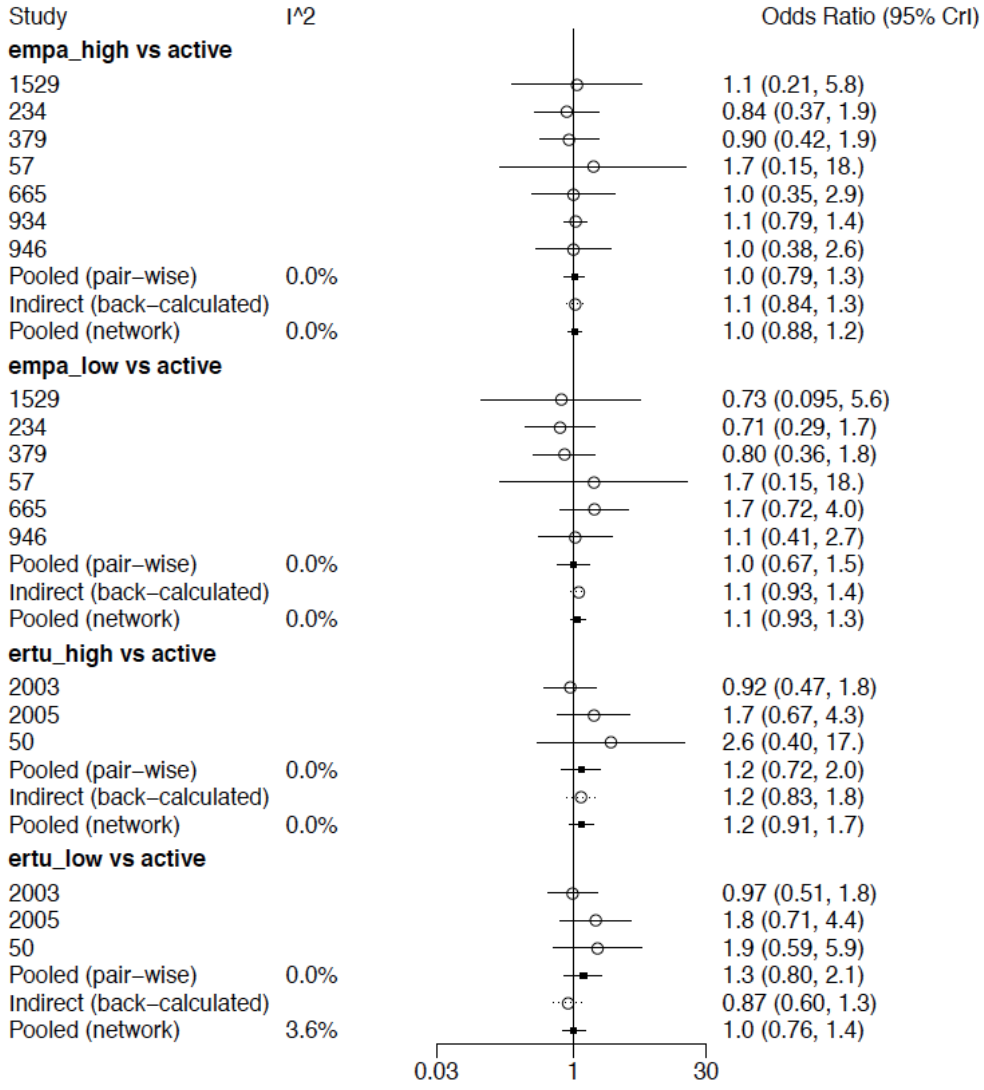


Figure B2 Continued. A. Breakdown of pairwise, indirect, and pooled estimates

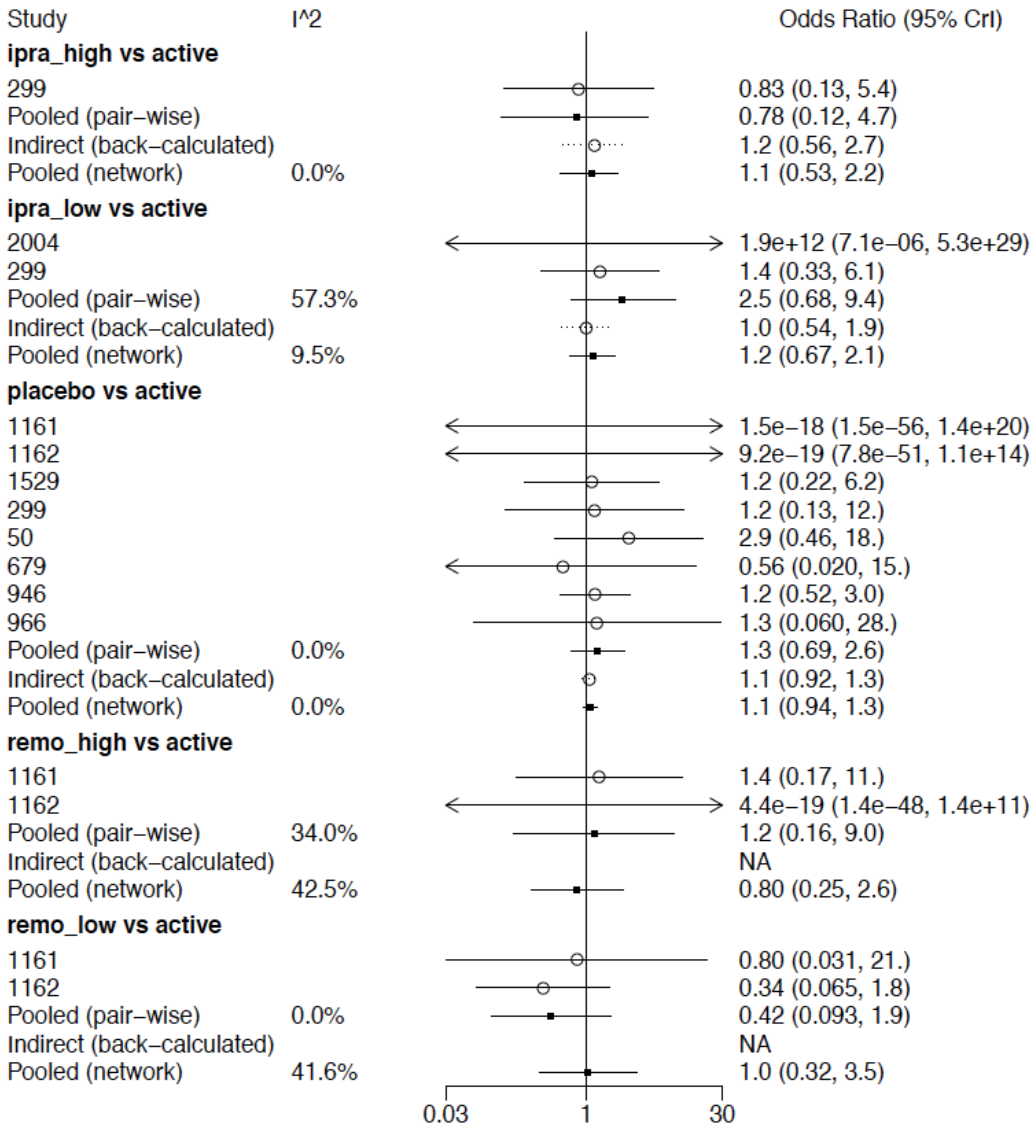


Figure B2 Continued. A. Breakdown of pairwise, indirect, and pooled estimates

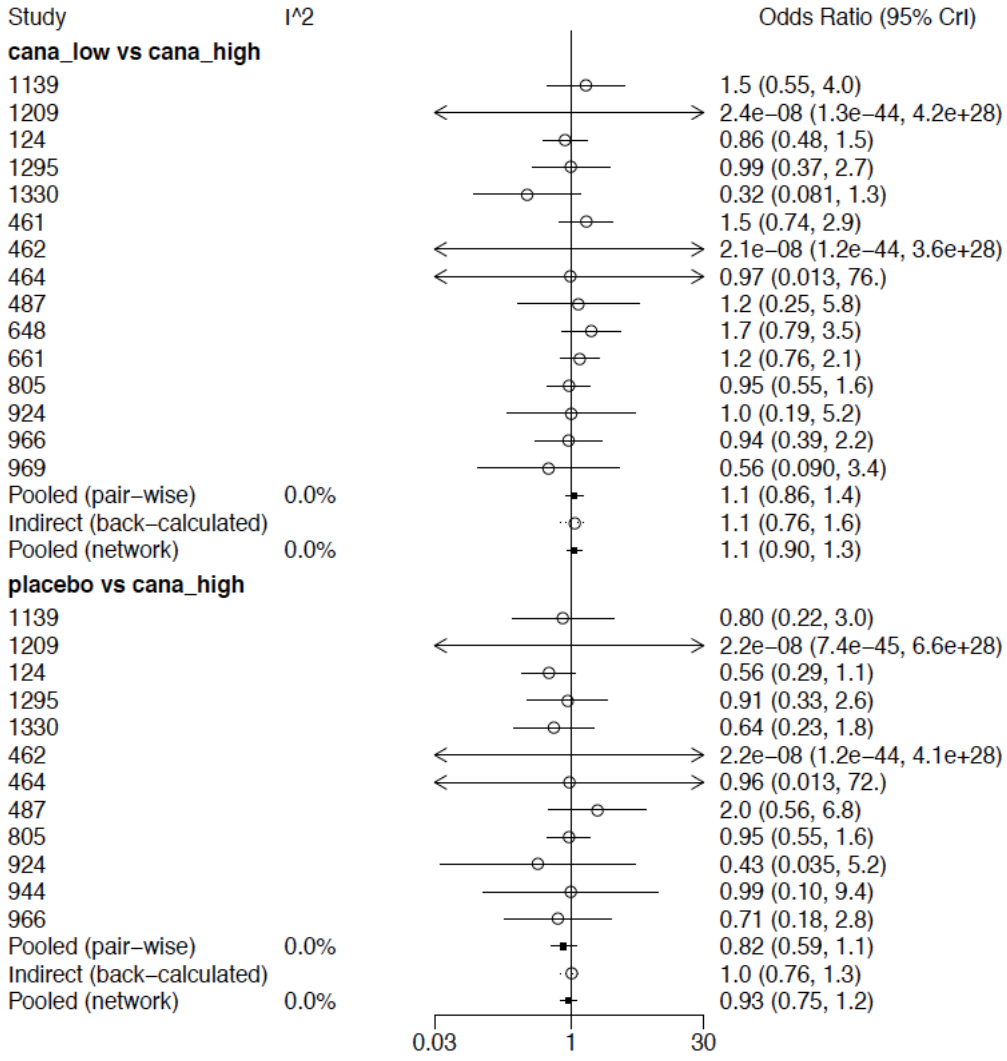


Figure B2 Continued. A. Breakdown of pairwise, indirect, and pooled estimates

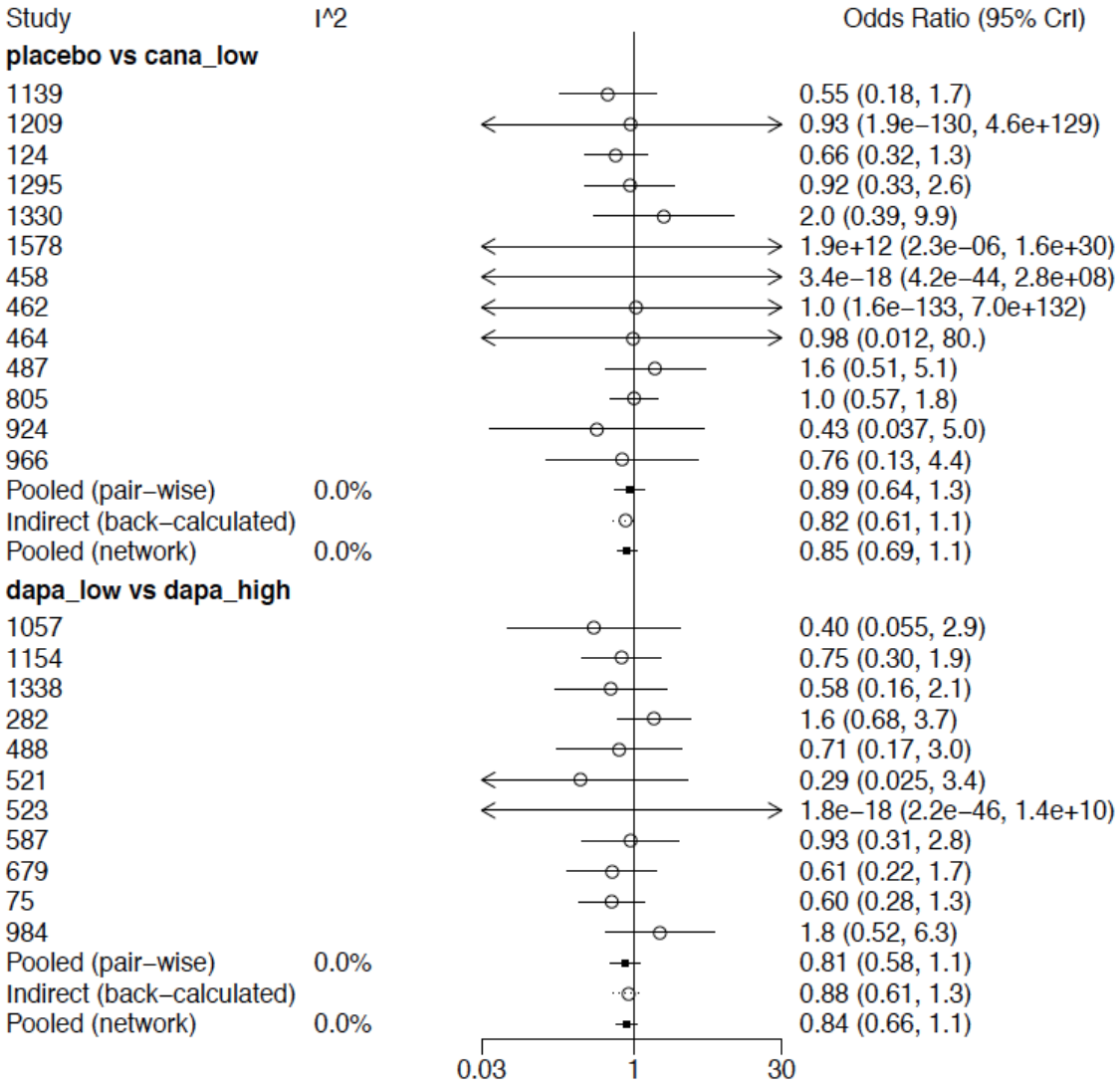


Figure B2 Continued. A. Breakdown of pairwise, indirect, and pooled estimates

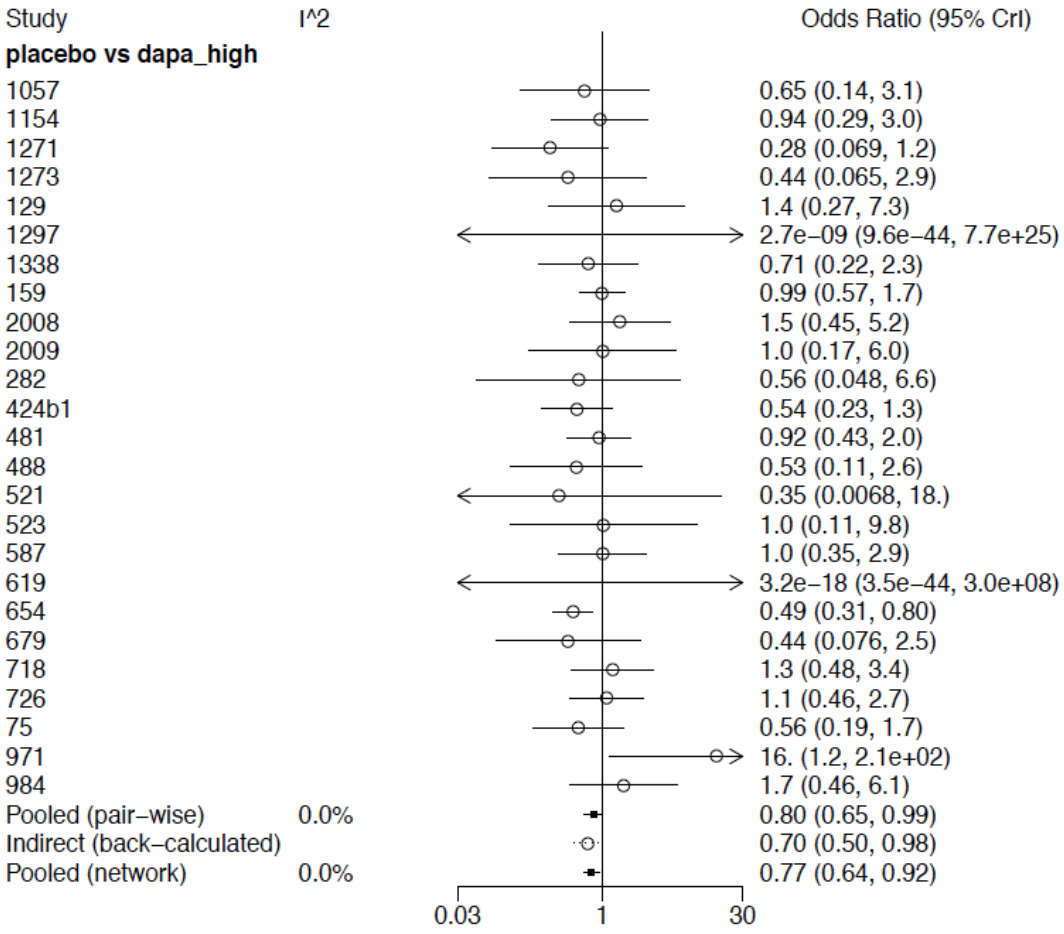


Figure B2 Continued. A. Breakdown of pairwise, indirect, and pooled estimates

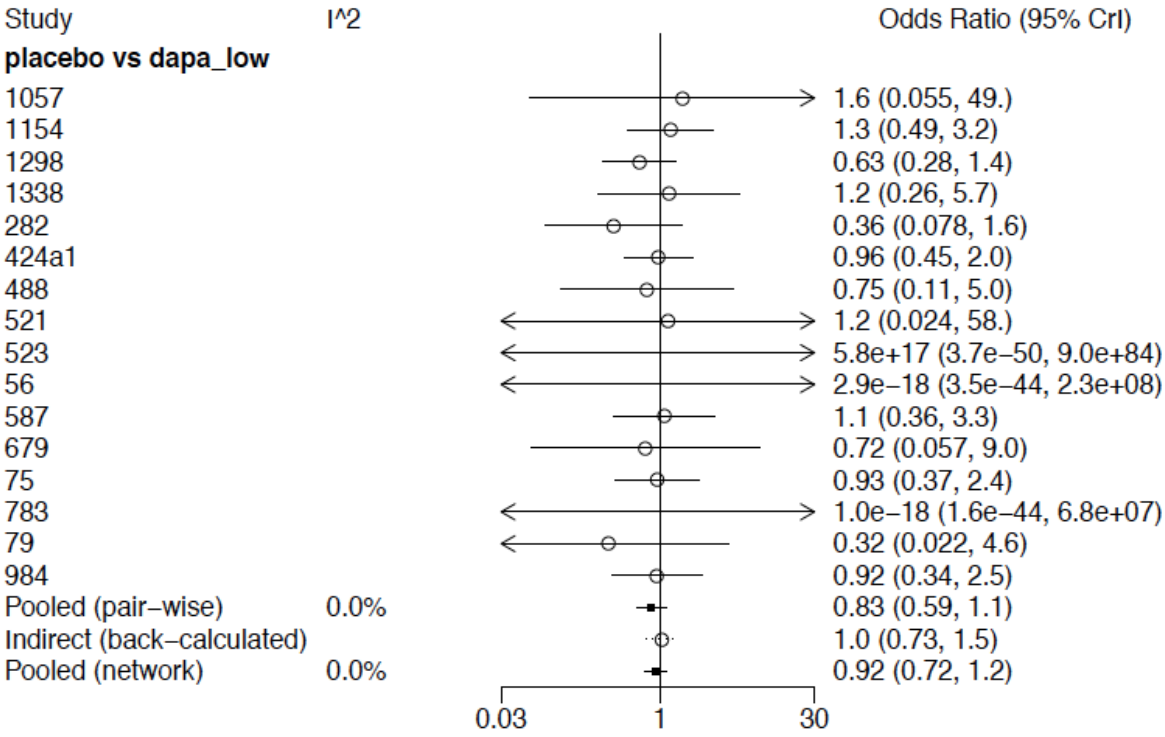


Figure B2 Continued. A. Breakdown of pairwise, indirect, and pooled estimates

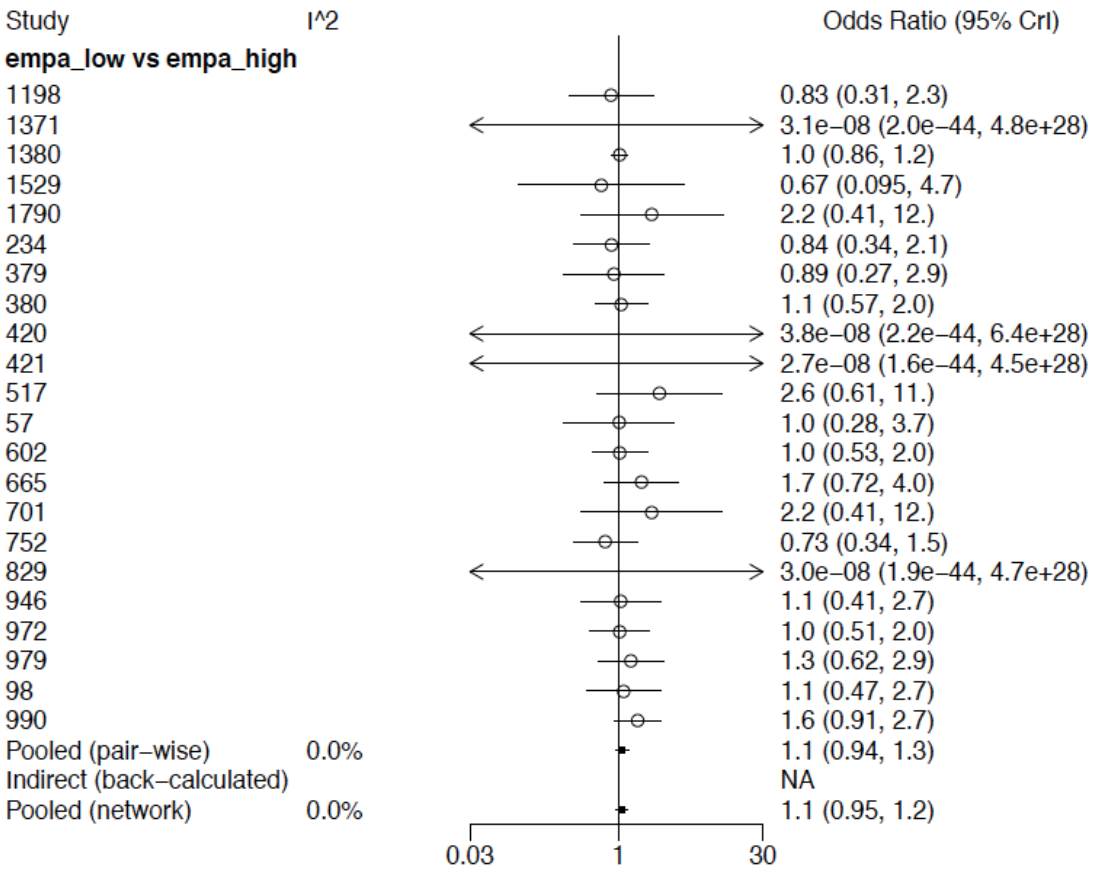


Figure B2 Continued. A. Breakdown of pairwise, indirect, and pooled estimates

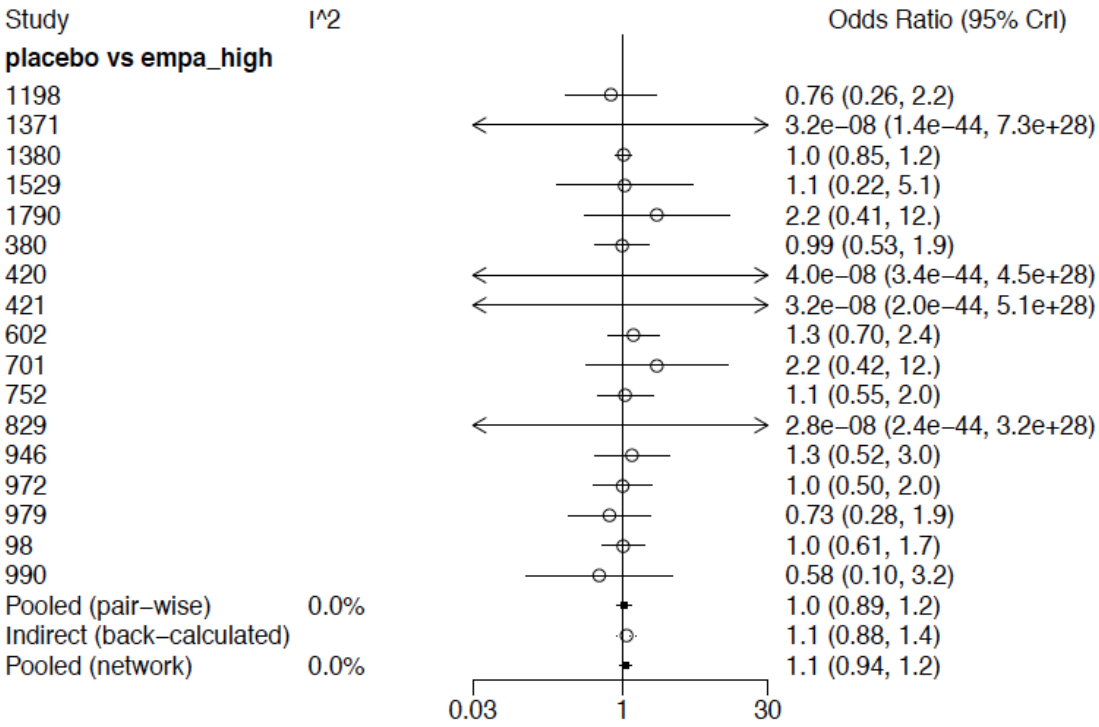


Figure B2 Continued. A. Breakdown of pairwise, indirect, and pooled estimates

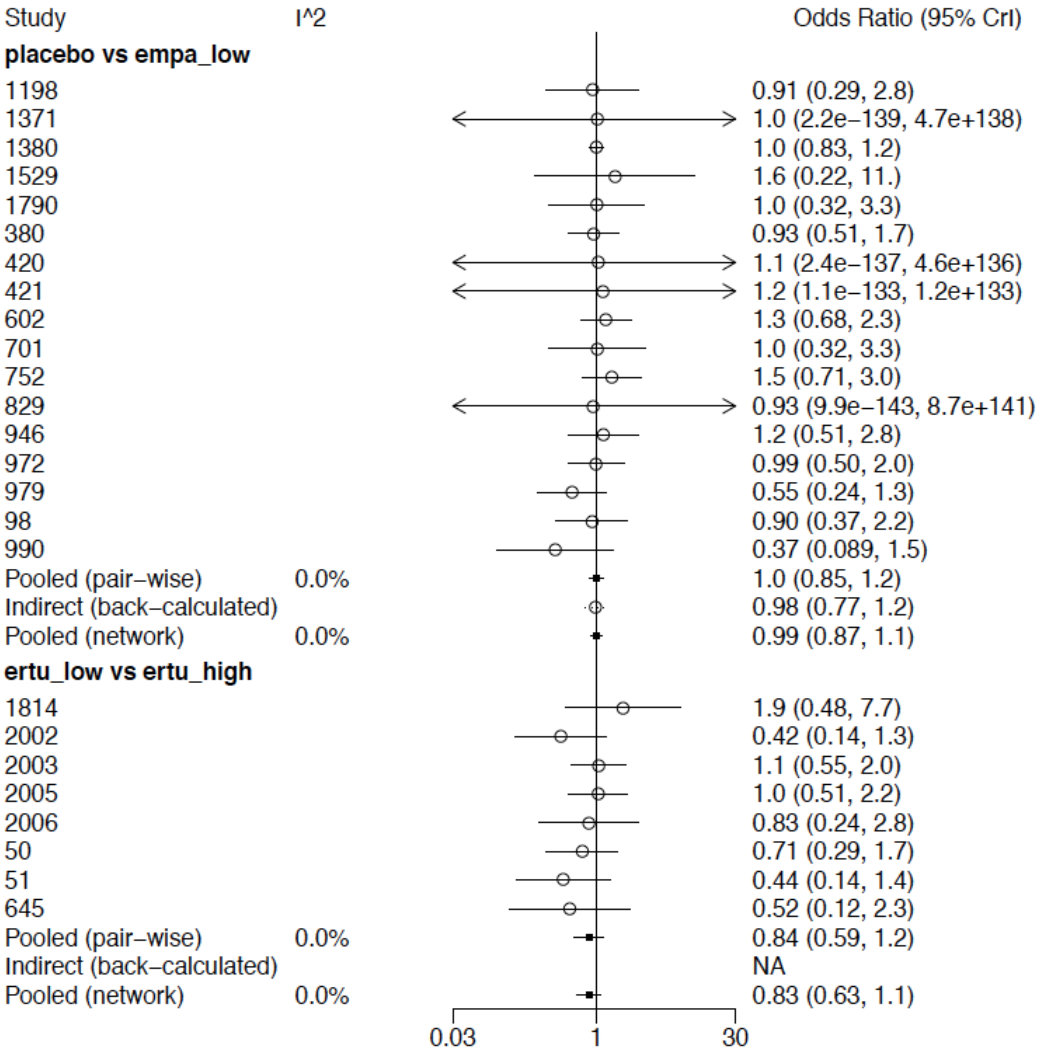


Figure B2 Continued. A. Breakdown of pairwise, indirect, and pooled estimates

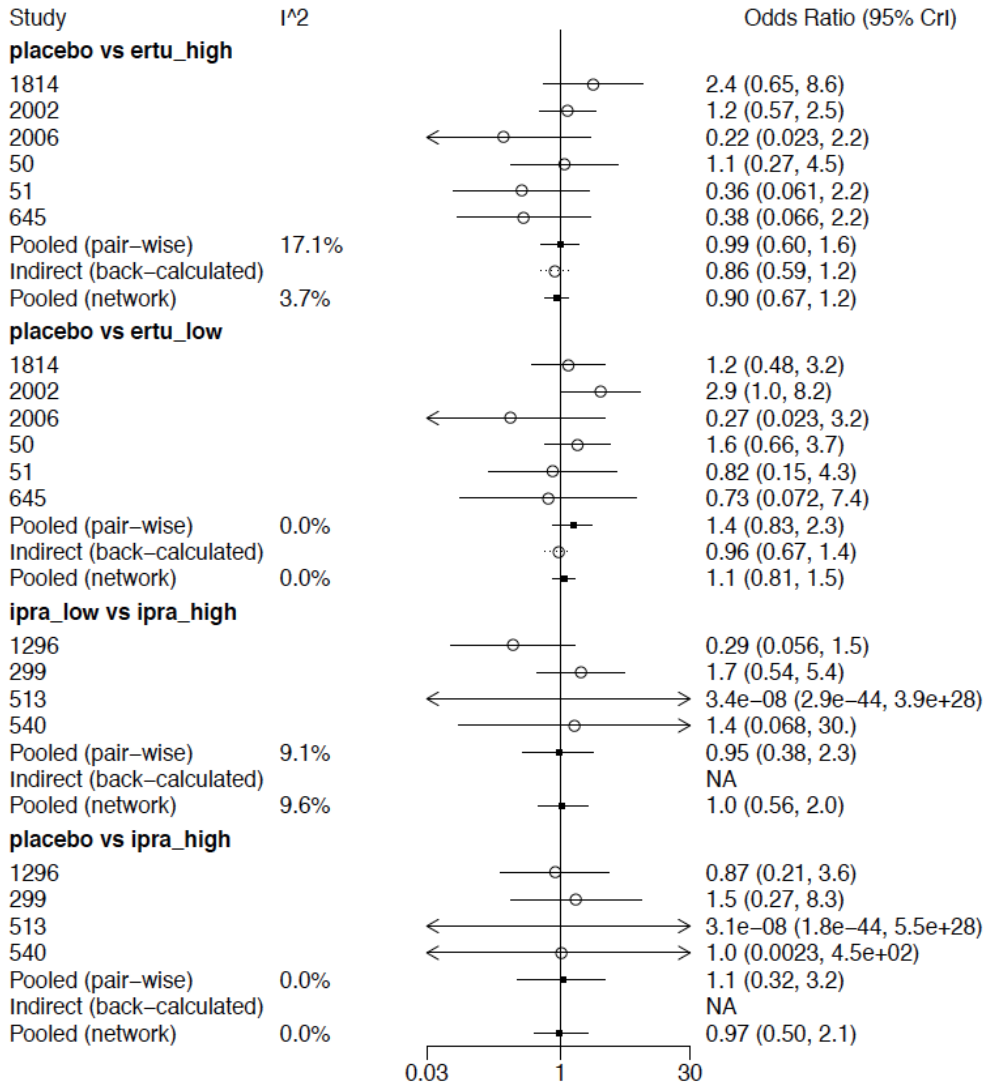


Figure B2 Continued. A. Breakdown of pairwise, indirect, and pooled estimates

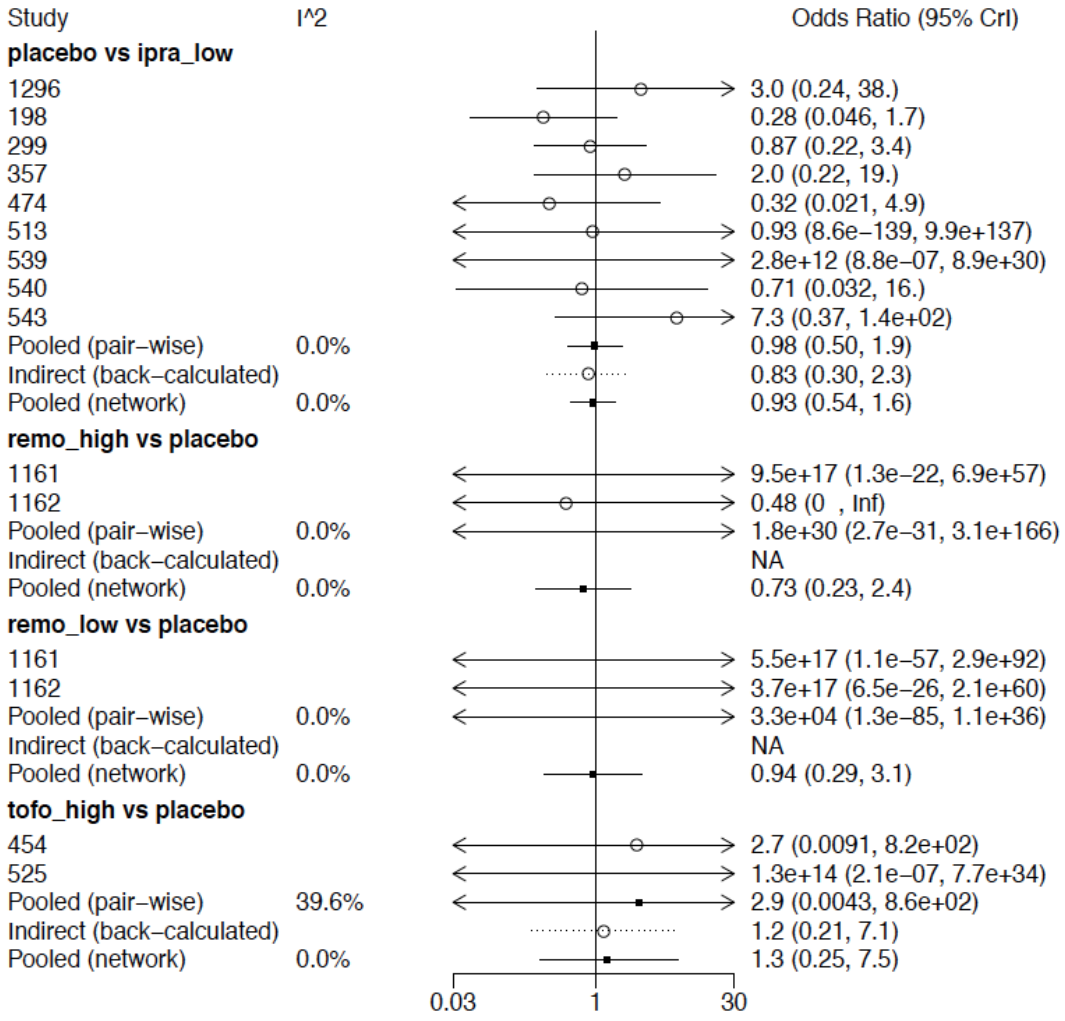
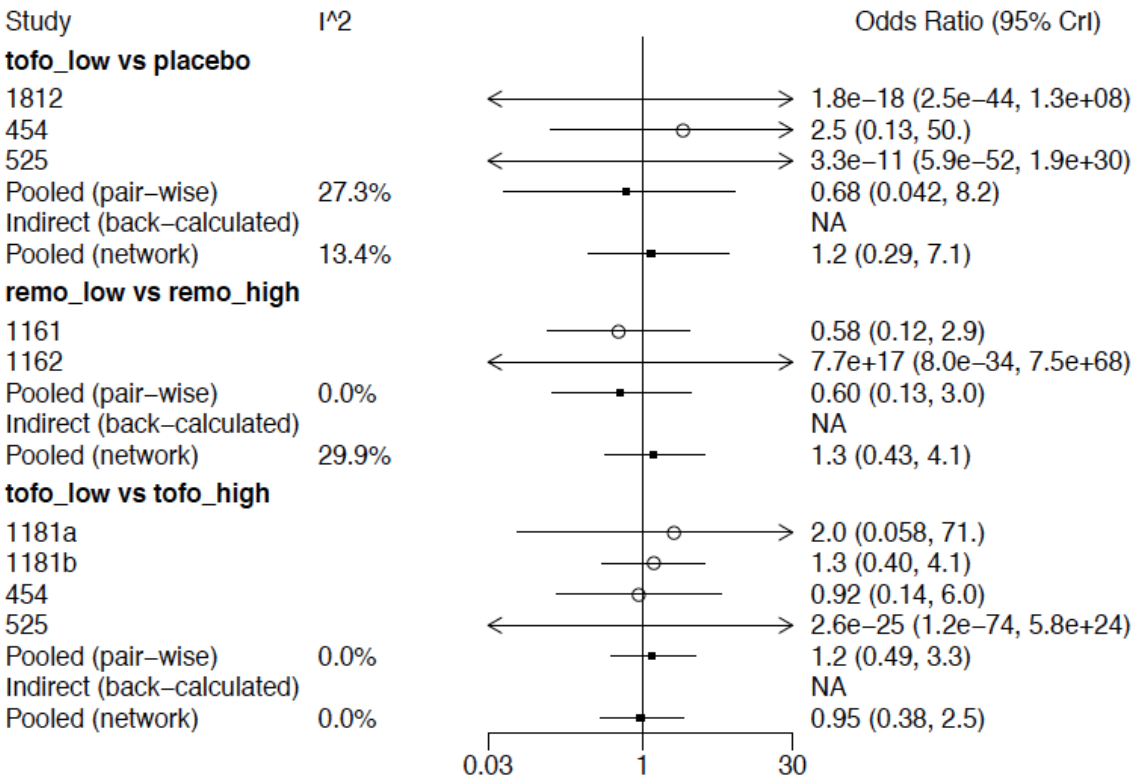


Figure B2 Continued. A. Breakdown of pairwise, indirect, and pooled estimates



Section 7: Risk of Bias Assessment

Table B10. Risk of Bias Assessment for Included Studies

NCT# Author and Year	Randomization Sequence	Allocation concealment	Double Blinding	Blinded Outcome Assessment	Incomplete Outcome	Selective Reporting	Other	Overall Assessment
NCT01059825 Amin, 2015 [77]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low
NCT01059825 Amin, 2015 [78]	Unclear Risk	Unclear Risk	Low Risk	Unclear Risk	Low Risk	Unclear Risk	Unclear risk	Unclear
NCT02157298 Araki, 2016 [79]	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	Unclear
NCT01368081 Araki, 2015 [80]	Low Risk	Low Risk	High Risk	Unclear Risk	Low Risk	High Risk	Unclear risk	High
NCT00528879 Bailey, 2013 [81]	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear Risk	Unclear risk	High
None Bailey, 2012 [82]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low
NCT01164501 Barnett, 2014 [83]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Low Risk	Low
NCT01106651 Bode, 2015 [84]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Low Risk	Low
NCT00855166 Bolinder, 2014 [85]	Low Risk	Low Risk	Low Risk	Low Risk	low Risk	Low Risk	Low Risk	Low
NCT01031680 Cefalu, 2015 [86]	Low Risk	Low Risk	High Risk	Low Risk	Low Risk	High Risk	Low Risk	High
NCT01505426 Lu, 2016 [87]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low
NCT01422876 DeFronzo, 2015 [88]	Low Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk	Low Risk	Unclear
NCT00660907	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Low Risk	Low

Del Prato, 2015 [89]								
NCT00881530 Ferrannini, 2013 [90]	High Risk	High Risk	High Risk	High Risk	Low Risk	High Risk	Unclear risk	High
NCT00528372 Ferrannini, 2010 [91]	Unclear Risk	Unclear Risk	Low Risk	Unclear Risk	Unclear Risk	Unclear Risk	Unclear risk	Unclear
NCT01071850 Fonseca, 2013 [92]	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear
NCT02229396 Frias, 2016 [93]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low
NCT01719003 Hadjadj, 2016 [94]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Low Risk	Low
NCT01289990 Haering, 2015 [95]	Low Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk	Low Risk	Unclear
None Heise, 2013 [96]	Low Risk	Low Risk	Unclear Risk	Unclear Risk	Low Risk	Unclear Risk	Unclear risk	Unclear
None Heise, 2013 [97]	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear
NCT00643851 Henry, 2012 [98]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Low Risk	Low
NCT00859898 Henry, 2012 [98]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Low Risk	Unclear
NCT00800176 Ikeda; 2015 [99]	Unclear Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk	Unclear risk	Low
NCT02220920 Inagaki, 2016 [100]	Low Risk	Low Risk	Low Risk	low Risk	Low Risk	Low Risk	Low Risk	High
NCT01387737 Inagaki, 2015 [101]	Unclear Risk	Low Risk	High Risk	High Risk	High Risk	Unclear Risk	Unclear risk	Low

NCT01022112 Inagaki, 2013 [102]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Low Risk	Low
NCT01413204 Inagaki, 2014 [103]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Low Risk	High
NCT02175784 Ishihara, 2016 [104]	Unclear Risk	Low Risk	High Risk	Low Risk	Low Risk	Low Risk	Low Risk	High
NCT00984867 Jabbour, 2014 [105]	Unclear Risk	Low Risk	High Risk	Low Risk	Low Risk	High Risk	Unclear risk	Low
NCT01381900 Ji, 2015 [106]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Low Risk	Low
NCT01095653 Ji, 2014 [107]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Low Risk	Low
NCT01023945 Kadokura, 2014 [108]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High
NCT01193218 Kadowaki, 2015 [109]	Low Risk	Low Risk	Low Risk	High Risk	Low Risk	High Risk	Unclear risk	Unclear
NCT00972244 Kaku, 2013 [110]	Low Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	High Risk	Low Risk	High
None Kaku, 2014 [111]	Unclear Risk	low Risk	Low Risk	Unclear Risk	High Risk	Unclear Risk	Unclear risk	Low
None Kaku, 2014 [112]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear
NCT01242215 Kashiwagi, 2015 [113]	Low Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk	Low Risk	Low
NCT01057628 Kashiwagi, 2015 [114]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear
NCT00621868	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear

Kashiwagi, 2014 [115]								
NCT01316094 Kashiwagi,2015 [116]	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear
NCT00663260 Kohan, 2014 [117]	Unclear Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk	Unclear risk	High
NCT01210001 Kovacs, 2015 [118]	Low Risk	Low Risk	Low Risk	High Risk	Low Risk	High Risk	Unclear risk	Low
NCT00976495 Heerspink, 2013 [119]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low
NCT01106677 Lavalle-Gonzalez, 2013 [120]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Low Risk	Unclear
NCT01042977 Leiter, 2014 [121]	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk	Low
NCT00968812 Leiter, 2015 [122]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Low Risk	Unclear
NCT01422876 Lewin, 2015 [123]	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear
NCT00263276 List, 2009 [124]	Unclear Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Unclear risk	Low
NCT01646320 Mathieu, 2015 [125]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low
NCT01392677 Matthaei, 2015 [126]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear
None Mudaliar, 2014 [127]	Unclear Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Unclear risk	Unclear
NCT01947855	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low

Nishimura, 2015 [128]								
NCT01340664 Qiu, 2014 [129]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low
NCT01989754 Rodbard, 2016 [130]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low
NCT01289990 Roden, 2015 [131]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Low Risk	Unclear
NCT00642278 Rosenstock, 2012 [132]	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low
NCT01809327 Rosenstock, 2016 [134]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Low Risk	Low
NCT01606007 Rosenstock, 2015 [135]	Low Risk	Low Risk	Low Risk	Low risk	Low Risk	Low Risk	Low Risk	Low
NCT01306214 Rosenstock, 2014 [136]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Low Risk	Low
NCT01011868 Rosenstock, 2015 [137]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Low Risk	Unclear
NCT00683878 Rosenstock, 2012 [138]	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear
None Ross, 2015 [139]	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High
None Sasaki, 2015 [140]	Low Risk	Low Risk	High Risk	High Risk	Unclear Risk	Unclear Risk	High Risk	Low
NCT01137812 Schernthaner, 2013 [141]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low

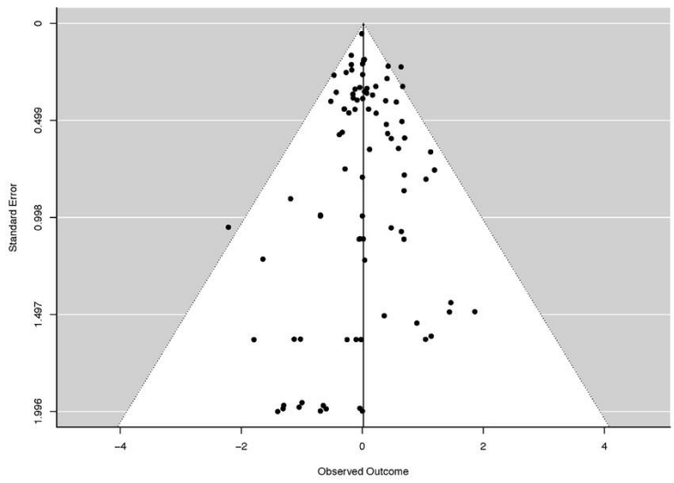
NCT01217892 Schumm-Draeger, 2014 [142]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low
None Seino, 2014 [143]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low
None Seino, 2014 [144]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low
None Seino, 2014 [145]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear
NCT01081834 Stenlof, 2013 [146]	Unclear Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk	Unclear Risk	Low
NCT00680745 Strojek, 2014 [147]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Low Risk	Unclear
NCT00500331 Sykes, 2015 [148]	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High
NCT01370005 Tikkanen, 2015 [149]	High Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	Unclear
None Townsend, 2016 [150]	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High
None Wan Seman, 2016 [151]	Unclear Risk	Low Risk	High Risk	High Risk	Unclear Risk	Unclear Risk	Unclear Risk	High
NCT01137474 Weber, 2016 [152]	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	High Risk	Unclear Risk	Low
NCT01195662 Weber, 2016 [153]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Low Risk	Low
NCT01106625	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Low Risk	Unclear

Wilding; 2013 [154]								
NCT01117584 Wilding, 2013 [155]	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear
NCT00357370 Wilding, 2009 [156]	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low
NCT00673231 Wilding, 2014 [157]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Low Risk	Unclear
NCT01064414 Yale, 2014 [158]	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High
NCT01316341 Zhao, 2015 [159]	High Risk	Low Risk	Low Risk	Low risk	Low Risk	Low Risk	Unclear Risk	Low
NCT01131676 Zinman, 2015 [9]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear
None Goto, 2012 [160]	Unclear Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk	Unclear risk	Unclear
NCT02036515 Dagogo-Jack, 2017 [161]	Low Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk	Low Risk	Unclear
NCT01734785 Maldonado-Lutomirsky, 2016 [162]	Unclear Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk	Unclear risk	Unclear
NCT01289990 Merker, 2015 [163]	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low
NCT01032629 Neal, 2015 [164]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low
NCT01167881 Ridderstrale, 2014 [165]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low
NCT00495469	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High

Sykes, 2015 [166]								
None Tanizawa, 2014 [167]	Low Risk	Low Risk	High Risk	High Risk	Low Risk	Low Risk	Unclear Risk	Unclear
NCT01095666 Yang, 2014 [168]	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low
None Gupta, 2017 [169]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low
NCT02354235 Kadowaki, 2017 [170]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low
NCT01734785 Softeland, 2017 [171]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low
NCT01958671 Terra, 2017 [172]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low
NCT02201004 Terauchi, 2017 [174]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High
NCT01986855, Grunberger, 2018 [175]	Low Risk	Low Risk	High Risk	High Risk	High Risk	Low Risk	Unclear Risk	Low
NCT01999218, Hollander, 2018 [176]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High
Ito, 2017 [177]	Low Risk	Low Risk	High Risk	High Risk	Low Risk	Low Risk	Unclear risk	Low
NCT02099110, Pratley, 2018 [178]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low
NCT02033889, Rosenstock, 2018 [179]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low
Seino, 2018 [180]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low
NCT02096705,	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low

Yang, 2017 [181]								
NCT02429258, Henry, 2018 [182]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low

Figure B3. Funnel Plot for Placebo Controlled Trials: Urinary Tract Infection



Section 8: Results of Sensitivity Analyses

Table B11. Risk of Urinary Tract Infection among users of SGLT2 Inhibitors: Threshold for high and low dose SGLT2 inhibitors changed in sensitivity analysis

	active	cana_high	cana_high	cana_low	dapa_high	dapa_low	empa_high	empa_low	ertu_high	ertu_low	ipra_high	ipra_low	placebo	remo_high	remo_low	tofo_high	tofo_low
active	active	1.294 (1.024, 1.63)	1.186 (0.941, 1.48)	1.185 (0.398, 2.959)	1.414 (1.136, 1.779)	1.192 (0.907, 1.559)	1.061 (0.897, 1.264)	0.22 (0, 3.0 x10^{19})	1.25 (0.93, 1.667)	0.966 (0.717, 1.3)	1.268 (0.776, 2.225)	0.442 (0.148, 1.189)	1.094 (0.929, 1.297)	0.782 (0.243, 2.401)	1.032 (0.326, 3.264)	1.199 (0.175, 13.05)	1.383 (0.251, 15.3)
cana_hig	0.773 (0.614, 0.977)	cana_hig	0.914 (0.749, 1.114)	0.912 (0.315, 2.292)	1.097 (0.831, 1.45)	0.92 (0.674, 1.264)	0.823 (0.638, 1.045)	0.168 (0, 2.4 x10^{18})	0.964 (0.68, 1.375)	0.747 (0.52, 1.071)	0.986 (0.585, 1.728)	0.342 (0.113, 0.934)	0.848 (0.668, 1.056)	0.605 (0.182, 1.872)	0.799 (0.249, 2.536)	0.937 (0.133, 10.45)	1.073 (0.195, 11.68)
cana_high	0.843 (0.676, 1.063)	1.094 (0.898, 1.336)	cana_high	1 (0.346, 2.459)	1.197 (0.913, 1.58)	1.006 (0.728, 1.384)	0.898 (0.706, 1.146)	0.189 (0, 2.5 x10^{18})	1.052 (0.75, 1.504)	0.815 (0.572, 1.162)	1.08 (0.635, 1.903)	0.374 (0.125, 1.023)	0.924 (0.744, 1.156)	0.667 (0.205, 2.041)	0.867 (0.269, 2.792)	1.025 (0.145, 11.34)	1.161 (0.211, 13.08)
cana_low	0.844 (0.338, 2.51)	1.096 (0.436, 3.173)	1 (0.407, 2.891)	cana_low	1.199 (0.472, 3.618)	1.005 (0.387, 3.052)	0.9 (0.355, 2.666)	0.216 (0, 2.7 x10^{18})	1.058 (0.399, 3.18)	0.815 (0.309, 2.511)	1.094 (0.39, 3.518)	0.375 (0.096, 1.486)	0.926 (0.365, 2.724)	0.672 (0.157, 3.082)	0.891 (0.207, 3.992)	1.06 (0.13, 13.675)	1.265 (0.167, 13.57)
dapa_high	0.707 (0.562, 0.88)	0.912 (0.69, 1.203)	0.835 (0.633, 1.096)	0.834 (0.276, 2.118)	dapa_high	0.84 (0.659, 1.068)	0.75 (0.604, 0.928)	0.155 (0, 2.1 x10^{18})	0.881 (0.635, 1.23)	0.682 (0.485, 0.954)	0.893 (0.542, 1.599)	0.311 (0.104, 0.857)	0.772 (0.64, 0.923)	0.555 (0.176, 1.689)	0.724 (0.231, 2.327)	0.849 (0.123, 9.234)	0.972 (0.176, 11.13)
dapa_low	0.839 (0.642, 1.10)	1.086 (0.791, 1.483)	0.994 (0.723, 1.374)	0.995 (0.328, 2.583)	1.19 (0.936, 1.518)	dapa_low	0.89 (0.689, 1.17)	0.178 (0, 2.9 x10^{8})	1.046 (0.73, 1.521)	0.808 (0.563, 1.182)	1.066 (0.626, 1.907)	0.371 (0.122, 1.009)	0.917 (0.73, 1.176)	0.655 (0.2, 2.019)	0.872 (0.273, 2.828)	1.018 (0.147, 11.39)	1.174 (0.212, 13.36)
empa_high	0.942 (0.791, 1.11)	1.215 (0.957, 1.568)	1.113 (0.872, 1.417)	1.111 (0.375, 2.814)	1.333 (1.077, 1.655)	1.124 (0.855, 1.451)	empa_high	0.202 (0, 2.8 x10^{18})	1.176 (0.865, 1.587)	0.909 (0.666, 1.244)	1.189 (0.737, 2.083)	0.417 (0.14, 1.115)	1.03 (0.911, 1.167)	0.731 (0.239, 2.278)	0.977 (0.306, 3.07)	1.13 (0.168, 11.95)	1.307 (0.237, 14.02)
empa_low	4.546 (0, 2.5X10^{9})	5.94 (0, 3.4x10^{8})	5.29 (0, 3.1 x10^{8})	4.64 (0, 2.6 x10^{8})	6.449 (0, 3.6 x10^{8})	5.609 (0, 9.9 x10^{8})	4.961 (0, 2.7 x10^{8})	empa_low	6.02 (0, 3.2 x10^{8})	4.714 (0, 2.4 x10^{9})	6.074 (0, 3.3 x10^{8})	1.957 (0, 9.4 x10^{7})	5.217 (0, 2.8 x10^{8})	3.984 (0, 1.8 x10^{8})	5.452 (0, 2.6 x10^{8})	6.419 (0, 3.2 x10^{8})	7.858 (0, 3.5 x10^{8})
ertu_high	0.8 (0.6, 1.075)	1.038 (0.727, 1.47)	0.95 (0.665, 1.333)	0.945 (0.314, 2.506)	1.134 (0.813, 1.575)	0.956 (0.657, 1.371)	0.85 (0.63, 1.157)	0.166 (0, 2.4 x10^{18})	ertu_high	0.774 (0.587, 1.02)	1.009 (0.583, 1.866)	0.351 (0.118, 0.986)	0.876 (0.657, 1.17)	0.625 (0.197, 1.982)	0.822 (0.254, 2.726)	0.962 (0.138, 10.75)	1.104 (0.198, 12.62)
ertu_low	1.035 (0.769, 1.395)	1.339 (0.934, 1.925)	1.227 (0.86, 1.749)	1.228 (0.398, 3.24)	1.465 (1.048, 2.06)	1.237 (0.846, 1.775)	1.1 (0.804, 1.501)	0.212 (0, 3.0 x10^{18})	1.292 (0.98, 1.705)	ertu_low	1.311 (0.761, 2.417)	0.453 (0.149, 1.297)	1.133 (0.838, 1.527)	0.808 (0.258, 2.527)	1.064 (0.328, 3.538)	1.239 (0.18, 13.915)	1.44 (0.257, 15.93)
ipra_high	0.789 (0.449, 1.289)	1.014 (0.579, 1.71)	0.926 (0.526, 1.574)	0.914 (0.284, 2.565)	1.12 (0.625, 1.844)	0.938 (0.524, 1.596)	0.841 (0.48, 1.358)	0.165 (0, 2.9 x10^{18})	0.991 (0.536, 1.716)	0.763 (0.414, 1.314)	ipra_high	0.348 (0.117, 0.85)	0.864 (0.501, 1.384)	0.605 (0.179, 2.029)	0.811 (0.236, 2.794)	0.949 (0.128, 11.96)	1.078 (0.179, 12.82)
ipra_low	2.264 (0.841, 6.745)	2.923 (1.07, 8.832)	2.677 (0.978, 7.997)	2.665 (0.673, 10.46)	3.215 (1.167, 9.639)	2.697 (0.991, 8.193)	2.397 (0.896, 7.165)	0.511 (0, 7.7 x10^{18})	2.845 (1.014, 8.507)	2.206 (0.771, 6.7)	2.877 (1.177, 8.556)	ipra_low	2.482 (0.926, 7.36)	1.786 (0.411, 8.238)	2.374 (0.508, 11.44)	2.874 (0.293, 39.54)	3.247 (0.451, 41.11)
placebo	0.914 (0.771, 1.076)	1.179 (0.947, 1.498)	1.082 (0.865, 1.343)	1.079 (0.367, 2.736)	1.295 (1.083, 1.562)	1.09 (0.85, 1.369)	0.971 (0.857, 1.098)	0.192 (0, 2.7 x10^{18})	1.141 (0.854, 1.522)	0.882 (0.655, 1.194)	1.157 (0.722, 1.997)	0.403 (0.136, 1.08)	placebo	0.712 (0.232, 2.188)	0.947 (0.298, 2.962)	1.098 (0.162, 11.85)	1.275 (0.231, 13.64)

remo_high	1.279 (0.417, 4.12)	1.654 (0.534, 5.485)	1.5 (0.49, 4.881)	1.488 (0.324, 6.381)	1.801 (0.592, 5.676)	1.526 (0.495, 5.006)	1.368 (0.439, 4.191)	0.251 (0, 8.0 $x10^{18}$)	1.599 (0.504, 5.074)	1.238 (0.396, 3.879)	1.652 (0.493, 5.591)	0.56 (0.121, 2.433)	1.405 (0.457, 4.316)	remo_high	1.317 (0.415, 4.621)	1.583 (0.189, 18.29)	1.799 (0.246, 19.48)
remo_low	0.969 (0.306, 3.064)	1.252 (0.394, 4.016)	1.154 (0.358, 3.711)	1.122 (0.25, 4.827)	1.381 (0.43, 4.337)	1.147 (0.354, 3.665)	1.024 (0.326, 3.272)	0.183 (0, 4.2 $x10^{18}$)	1.217 (0.367, 3.93)	0.939 (0.283, 3.046)	1.233 (0.358, 4.233)	0.421 (0.087, 1.969)	1.056 (0.338, 3.358)	0.759 (0.216, 2.408)	remo_low	1.217 (0.135, 13.84)	1.381 (0.183, 15.98)
tofo_high	0.834 (0.077, 5.704)	1.067 (0.096, 7.519)	0.976 (0.088, 6.893)	0.943 (0.073, 7.675)	1.178 (0.108, 8.13)	0.982 (0.088, 6.784)	0.885 (0.084, 5.969)	0.156 (0, 1.4 $x10^{18}$)	1.04 (0.093, 7.259)	0.807 (0.072, 5.543)	1.053 (0.084, 7.787)	0.348 (0.025, 3.409)	0.91 (0.084, 6.158)	0.632 (0.055, 5.301)	0.822 (0.072, 7.415)	tofo_high	1.155 (0.275, 5.903)
tofo_low	0.723 (0.065, 3.99)	0.932 (0.086, 5.13)	0.861 (0.076, 4.74)	0.79 (0.074, 5.98)	1.029 (0.09, 5.67)	0.852 (0.075, 4.723)	0.765 (0.071, 4.225)	0.127 (0, 1.6 $x10^{18}$)	0.906 (0.079, 5.059)	0.694 (0.063, 3.887)	0.927 (0.078, 5.589)	0.308 (0.024, 2.217)	0.785 (0.073, 4.33)	0.556 (0.051, 4.071)	0.724 (0.063, 5.452)	0.866 (0.169, 3.643)	tofo_low

Table B12. Risk of Urinary Tract Infection among users of SGLT2 Inhibitors: RCTs of 24 weeks or longer

	active	cana_high	cana_low	dapa_high	dapa_low	empa_high	empa_low	ertu_high	ertu_low	ipra_low	placebo	tofo_high	tofo_low
active	active	1.202 (0.946, 1.531)	1.322 (1.029, 1.691)	1.37 (1.07, 1.755)	1.218 (0.902, 1.613)	1.037 (0.869, 1.24)	1.091 (0.889, 1.325)	1.106 (0.798, 1.539)	1.008 (0.719, 1.414)	1.548 (0.59, 4.329)	1.116 (0.932, 1.331)	14.47 (0.1, 1.9x10^9)	16.727 (0.1, 2.3 x10^9)
cana_high	0.832 (0.653, 1.057)	cana_high	1.101 (0.89, 1.357)	1.137 (0.843, 1.531)	1.011 (0.718, 1.405)	0.866 (0.668, 1.117)	0.91 (0.698, 1.178)	0.928 (0.612, 1.361)	0.84 (0.555, 1.25)	1.286 (0.488, 3.625)	0.927 (0.74, 1.165)	11.993 (0.1, 1.5 x10^9)	14.054 (0.1, 1.8 x10^9)
cana_low	0.757 (0.591, 0.971)	0.909 (0.737, 1.124)	cana_low	1.032 (0.765, 1.415)	0.919 (0.653, 1.287)	0.785 (0.604, 1.016)	0.828 (0.633, 1.079)	0.842 (0.559, 1.245)	0.763 (0.502, 1.149)	1.165 (0.439, 3.356)	0.844 (0.664, 1.069)	10.977 (0.1, 1.4 x10^9)	12.783 (0.1, 1.8 x10^9)
dapa_high	0.73 (0.57, 0.935)	0.88 (0.653, 1.187)	0.969 (0.707, 1.307)	dapa_high	0.89 (0.683, 1.152)	0.758 (0.605, 0.954)	0.797 (0.636, 1.015)	0.814 (0.549, 1.202)	0.737 (0.498, 1.087)	1.129 (0.443, 3.179)	0.814 (0.668, 0.994)	10.75 (0.1, 1.4 x10^9)	12.473 (0.1, 1.6 x10^9)
dapa_low	0.821 (0.62, 1.108)	0.99 (0.712, 1.393)	1.089 (0.777, 1.53)	1.124 (0.868, 1.463)	dapa_low	0.857 (0.648, 1.13)	0.9 (0.678, 1.193)	0.914 (0.601, 1.376)	0.831 (0.544, 1.285)	1.262 (0.485, 3.676)	0.919 (0.714, 1.18)	12.222 (0.1, 1.6 x10^9)	14.197 (0.1, 1.8 x10^9)
empa_high	0.964 (0.807, 1.151)	1.155 (0.895, 1.496)	1.274 (0.985, 1.655)	1.319 (1.048, 1.654)	1.167 (0.885, 1.543)	empa_high	1.05 (0.92, 1.211)	1.07 (0.75, 1.522)	0.972 (0.679, 1.385)	1.482 (0.581, 4.128)	1.072 (0.945, 1.237)	14.201 (0.1, 1.9 x10^9)	16.247 (0.1, 2.1 x10^9)
empa_low	0.917 (0.755, 1.125)	1.099 (0.849, 1.433)	1.208 (0.927, 1.581)	1.255 (0.986, 1.572)	1.112 (0.838, 1.474)	0.952 (0.826, 1.087)	empa_low	1.017 (0.713, 1.445)	0.926 (0.639, 1.325)	1.409 (0.542, 3.953)	1.021 (0.89, 1.172)	13.247 (0.1, 1.8 x10^9)	15.387 (0.1, 2.1 x10^9)
ertu_high	0.904 (0.65, 1.253)	1.078 (0.735, 1.634)	1.187 (0.803, 1.79)	1.228 (0.832, 1.821)	1.094 (0.727, 1.663)	0.935 (0.657, 1.333)	0.983 (0.692, 1.403)	ertu_high	0.911 (0.661, 1.256)	1.384 (0.518, 4.021)	1.004 (0.715, 1.413)	13.219 (0.1, 1.6 x10^9)	14.935 (0.1, 2.1 x10^9)
ertu_low	0.992 (0.707, 1.39)	1.191 (0.8, 1.802)	1.311 (0.87, 1.992)	1.356 (0.92, 2.009)	1.204 (0.778, 1.838)	1.028 (0.722, 1.474)	1.08 (0.755, 1.566)	1.098 (0.796, 1.513)	ertu_low	1.536 (0.565, 4.478)	1.104 (0.783, 1.556)	14.816 (0.1, 1.9 x10^9)	16.606 (0.1, 2.3 x10^9)
ipra_low	0.646 (0.231, 1.694)	0.778 (0.276, 2.047)	0.858 (0.298, 2.28)	0.886 (0.315, 2.255)	0.792 (0.272, 2.063)	0.675 (0.242, 1.721)	0.71 (0.253, 1.845)	0.723 (0.249, 1.93)	0.651 (0.223, 1.771)	ipra_low	0.729 (0.261, 1.849)	10.286 (0.1, 1.1 x10^9)	11.41 (0.1, 1.2 x10^9)
placebo	0.896 (0.752, 1.074)	1.079 (0.858, 1.352)	1.185 (0.936, 1.507)	1.228 (1.006, 1.496)	1.089 (0.847, 1.4)	0.933 (0.809, 1.059)	0.98 (0.853, 1.124)	0.996 (0.708, 1.399)	0.906 (0.642, 1.277)	1.372 (0.541, 3.832)	placebo	13.258 (0.1, 1.7 x10^9)	15.2 (0.1, 2.0 x10^9)
tofo_high	0.069 (0, 9.546)	0.083 (0, 11.945)	0.091 (0, 12.634)	0.093 (0, 12.868)	0.082 (0, 11.81)	0.07 (0, 9.905)	0.075 (0, 10.572)	0.076 (0, 10.575)	0.067 (0, 9.748)	0.097 (0, 16.374)	0.075 (0, 10.856)	tofo_high	1.151 (0.407, 3.225)
tofo_low	0.06 (0, 8.58)	0.071 (0, 10.561)	0.078 (0, 11.351)	0.08 (0, 12.017)	0.07 (0, 10.478)	0.062 (0, 8.894)	0.065 (0, 9.453)	0.067 (0, 10.11)	0.06 (0, 9.167)	0.088 (0, 16.223)	0.066 (0, 9.669)	0.869 (0.31, 2.455)	tofo_low

Table B13. Risk of Urinary Tract Infection among users of SGLT2 Inhibitors: RCTs with low overall risk of bias

	active	cana_high	cana_low	dapa_high	dapa_low	empa_high	empa_low	ertu_high	ertu_low	ipra_high	ipra_low	placebo	remo_high	remo_low	tofo_high	tofo_low
active	active	1.153 (0.9, 1.486)	1.273 (0.991, 1.659)	1.311 (0.948, 1.801)	1.142 (0.792, 1.624)	1.07 (0.867, 1.318)	1.126 (0.898, 1.408)	1.155 (0.82, 1.672)	1.17 (0.852, 1.625)	5.041 (0, 4.4 x10^6)	2.031 (0.507, 9.76)	1.118 (0.916, 1.373)	3.093 (0.594, 34.203)	1.827 (0.284, 22.183)	19924.691 (0.5, 1.1 x10^{12})	0 (0, 1.709)
cana_high	0.868 (0.673, 1.112)	cana_high	1.107 (0.881, 1.395)	1.137 (0.779, 1.647)	0.985 (0.667, 1.473)	0.928 (0.704, 1.217)	0.975 (0.732, 1.293)	1.004 (0.665, 1.539)	1.017 (0.682, 1.498)	4.367 (0, 3.9 x10^6)	1.773 (0.435, 8.468)	0.969 (0.756, 1.24)	2.685 (0.509, 29.242)	1.595 (0.242, 19.306)	17229.745 (0.4, 10x10^{12})	0 (0, 1.506)
cana_low	0.785 (0.603, 1.009)	0.903 (0.717, 1.135)	cana_low	1.028 (0.711, 1.461)	0.893 (0.596, 1.335)	0.839 (0.636, 1.105)	0.881 (0.663, 1.173)	0.906 (0.593, 1.388)	0.918 (0.619, 1.36)	3.926 (0, 3.6 x10^6)	1.595 (0.399, 7.542)	0.875 (0.684, 1.128)	2.415 (0.464, 27.213)	1.431 (0.22, 17.649)	15496.325 (0.4, 8.9 x10^{11})	0 (0, 1.255)
dapa_high	0.763 (0.555, 1.055)	0.88 (0.607, 1.284)	0.973 (0.685, 1.406)	dapa_high	0.872 (0.582, 1.317)	0.817 (0.593, 1.136)	0.861 (0.622, 1.196)	0.888 (0.55, 1.396)	0.895 (0.576, 1.389)	3.861 (0, 3.3 x10^6)	1.552 (0.372, 7.725)	0.857 (0.634, 1.154)	2.377 (0.448, 25.75)	1.41 (0.217, 16.993)	14823.795 (0.4, 8.8 x10^{11})	0 (0, 1.179)
dapa_low	0.876 (0.616, 1.262)	1.015 (0.679, 1.498)	1.12 (0.749, 1.678)	1.147 (0.759, 1.718)	dapa_low	0.939 (0.653, 1.352)	0.986 (0.686, 1.43)	1.014 (0.628, 1.65)	1.031 (0.644, 1.65)	4.492 (0, 4.0 x10^6)	1.771 (0.437, 8.911)	0.981 (0.702, 1.382)	2.727 (0.511, 29.589)	1.62 (0.245, 19.813)	17579.479 (0.4, 9.9 x10^{11})	0 (0, 1.542)
empa_high	0.935 (0.759, 1.154)	1.078 (0.822, 1.421)	1.192 (0.905, 1.573)	1.224 (0.881, 1.687)	1.065 (0.74, 1.532)	empa_high	1.051 (0.895, 1.248)	1.085 (0.74, 1.608)	1.094 (0.769, 1.575)	4.81 (0, 4.2 x10^6)	1.907 (0.476, 9.191)	1.044 (0.897, 1.231)	2.906 (0.557, 32.137)	1.719 (0.265, 21.302)	18330.414 (0.4, 1.0 x10^{12})	0 (0, 1.654)
empa_low	0.888 (0.71, 1.113)	1.025 (0.773, 1.366)	1.135 (0.852, 1.508)	1.162 (0.836, 1.609)	1.014 (0.699, 1.457)	0.952 (0.802, 1.117)	empa_low	1.03 (0.698, 1.542)	1.039 (0.726, 1.513)	4.566 (0, 3994267.3)	1.804 (0.452, 8.739)	0.994 (0.842, 1.181)	2.755 (0.531, 30.227)	1.633 (0.251, 19.929)	17526.623 (0.4, 1.0 x10^{12})	0 (0, 1.552)
ertu_high	0.866 (0.598, 1.22)	0.996 (0.65, 1.503)	1.103 (0.72, 1.687)	1.126 (0.716, 1.818)	0.986 (0.606, 1.591)	0.922 (0.622, 1.351)	0.971 (0.649, 1.433)	ertu_high	1.012 (0.729, 1.413)	4.514 (0, 3933190.85)	1.749 (0.431, 8.833)	0.964 (0.659, 1.401)	2.696 (0.498, 31.016)	1.583 (0.227, 19.639)	17390.842 (0.4, 1.1 x10^{12})	0 (0, 1.276)
ertu_low	0.855 (0.615, 1.174)	0.983 (0.668, 1.466)	1.089 (0.735, 1.615)	1.118 (0.72, 1.736)	0.97 (0.606, 1.553)	0.914 (0.635, 1.3)	0.962 (0.661, 1.378)	0.989 (0.708, 1.371)	ertu_low	4.457 (0, 3.8 x10^6)	1.715 (0.424, 8.574)	0.956 (0.674, 1.342)	2.643 (0.496, 29.13)	1.559 (0.234, 19.233)	16619.44 (0.4, 1.1 x10^{12})	0 (0, 1.335)
ipra_high	0.198 (0, 251425.252)	0.229 (0, 289292.489)	0.255 (0, 310942.969)	0.259 (0, 336532.192)	0.223 (0, 311090.452)	0.208 (0, 273398.179)	0.219 (0, 285191.094)	0.222 (0, 311563.626)	0.224 (0, 318376.048)	ipra_high	0.344 (0, 450071.979)	0.221 (0, 287548.879)	0.611 (0, 1.6 x10^6)	0.356 (0, 647848.163)	17757.948 (0, 1.0 x10^{16})	0 (0, 2.217)
ipra_low	0.492 (0.102, 1.971)	0.564 (0.118, 2.3)	0.627 (0.133, 2.504)	0.644 (0.129, 2.689)	0.565 (0.112, 2.289)	0.524 (0.109, 2.103)	0.554 (0.114, 2.21)	0.572 (0.113, 2.321)	0.583 (0.117, 2.36)	2.904 (0, 2.3 x10^6)	ipra_low	0.548 (0.116, 2.206)	1.533 (0.154, 21.193)	0.919 (0.079, 14.436)	9696.45 (0.2, 6.1 x10^{11})	0 (0, 0.918)
placebo	0.894	1.032	1.143	1.166	1.02	0.958	1.006	1.037	1.046	4.525	1.825	placebo	2.777	1.64	17400.128	0 (0, 1.586)

	(0.728, 1.092)	(0.807, 1.323)	(0.886, 1.461)	(0.866, 1.578)	(0.724, 1.424)	(0.813, 1.114)	(0.846, 1.188)	(0.714, 1.517)	(0.745, 1.483)	(0, 4.0 x10^{6})	(0.453, 8.655)		(0.534, 30.531)	(0.251, 19.914)	(0.4, 1.0 x10^{12})	
remo_high	0.323 (0.029, 1.684)	0.372 (0.034, 1.964)	0.414 (0.037, 2.156)	0.421 (0.039, 2.234)	0.367 (0.034, 1.956)	0.344 (0.031, 1.795)	0.363 (0.033, 1.885)	0.371 (0.032, 2.009)	0.378 (0.034, 2.015)	1.638 (0, 1814979.6)	0.652 (0.047, 6.481)	0.36 (0.033, 1.874)	remo_high	0.615 (0.123, 2.338)	6127.102 (0.1, 3.4 x10^{11})	0 (0, 0.646)
remo_low	0.547 (0.045, 3.52)	0.627 (0.052, 4.136)	0.699 (0.057, 4.541)	0.709 (0.059, 4.605)	0.617 (0.05, 4.079)	0.582 (0.047, 3.767)	0.612 (0.05, 3.984)	0.632 (0.051, 4.396)	0.642 (0.052, 4.278)	2.811 (0, 3.3 x10^{6})	1.089 (0.069, 12.661)	0.61 (0.05, 3.979)	1.626 (0.428, 8.149)	remo_low	9987.045 (0.2, 5.2 x10^{11})	0 (0, 1.324)
tofo_high	0 (0, 2.169)	0 (0, 2.565)	0 (0, 2.799)	0 (0, 2.838)	0 (0, 2.55)	0 (0, 2.318)	0 (0, 2.397)	0 (0, 2.458)	0 (0, 2.512)	0 (0, 2126164.491)	0 (0, 5.825)	0 (0, 2.405)	0 (0, 9.519)	0 (0, 4.518)	tofo_high	0 (0, 0.108)
tofo_low	88284.856 (0.6, 4.3x10^{10})	103442.313 (0.7, 5.1x10^{10})	112427.601 (0.8, 5.5 x10^{10})	115684.01 (0.8, 5.3X10^{10})	99715.501 (0.6, 4.3 x10^{10})	94261.008 (0.6, 4.3 x10^{10})	97057.308 (0.6, 4.4 x10^{10})	97662.444 (0.8, 5.0 x10^{10})	104667.932 (0.7, 4.6 x10^{10})	697961.179 (0.5, 3.1 x10^{11})	136121.482 (1.1, 7.4 x10^{10})	98100.585 (0.63, 4. x10^{10})	303620.293 (1.5, 3.6 x10^{11})	207019.82 (0.8, 2.2 x10^{11})	269994045.652 (9.3, 1.6 x10^{20})	tofo_low

Capturing Adult Patient Preferences towards Benefits and Risks of Second-line Therapies in Type 2 Diabetes: A Discrete Choice Experiment

Running Head: Patient Preferences towards Diabetes Medications: A Discrete Choice Experiment

Jennifer R. Donnan[a], Karissa Johnston[a], Eugene Chibrikov[a], Carlo A. Marra[a,b], Kris Aubrey-Bassler[c], Mehdi Najafzadeh[d], Hai Nguyen[a], John-Michael Gamble[a,e]

Supplementary Appendix

Complete Survey

Start

Survey on Diabetes Medication Preferences

Quota

[QUOTA: Quota]

Note:

This page only contains quota information and only appears in preview mode.

0% 100%

Consent

Survey on Diabetes Medication Preferences

Dear Participant,

My name is Jennifer Donnan and I am a PhD candidate at Memorial University's School of Pharmacy. As part of my research I am interested in finding out about the factors that influence patient's decisions when they start new diabetes drugs. This information will be used in further research that will attempt to measure patient preferences and discern how we can better use these preferences to make drug therapy decisions.

This survey should take between 20 and 30 minutes and will consist of:

1. Some background questions;

2. A short video that will help you to answer the questions that follow; and

3. A series of 16 questions where you will be asked to compare 2 hypothetical drugs, and choose which you would prefer.

It is entirely up to you to decide whether or not to take part in this research. You are free to not answer any question to which you are not comfortable responding, and you can choose to stop the survey at any time. Your confidentiality is important to us. Research Now will not release your identity to the research team, only the responses to this survey.

Should you have any further questions about this study, or if you wish to receive information on the results of this study, you can contact Jennifer Donnan at the contact information provided below. If you wish to speak with someone who is not involved in the study but can advise you on your rights as a participant in this study, you can contact the Ethics office at the contact information listed below.

Researcher:

Mrs. Jennifer Donnan, BSc.Pharm, MSc, MBA Phone: 709-739-8798 or by email at Jennifer.donnan@mun.ca

Ethics Office:

Health Research Ethics Authority Phone: 709-777-6974 or by email at info@hrea.ca

If you indicate your consent below, you do not give up your legal rights and do not release the researchers from their professional responsibilities.

Before you begin please note:

- You may encounter difficulties if you attempt to complete this survey using a mobile device; and
- You will not be able to navigate back once you leave each page.

Please indicate if you consent to participate in this survey.

Consent=1 ○ **I consent to participate**

Consent=2 ○ **I do not consent to participate**

0% 100%

QualifyingQuestions

Survey on Diabetes Medication Preferences

Screening Questions

Which of the following ailments do you suffer from?

QualifyingQuestions_1 ☐ Osteoporosis

QualifyingQuestions_2 ☐ High Cholesterol

QualifyingQuestions_3 ☐ Type 1 Diabetes

QualifyingQuestions_4 ☐ Type 2 Diabetes

QualifyingQuestions_5 ☐ COPD

QualifyingQuestions_6 ☐ Asthma

QualifyingQuestions_7 ☐ Chrohn's Disease

QualifyingQuestions_8 ☐ None of the above

QualifyingQuestion2

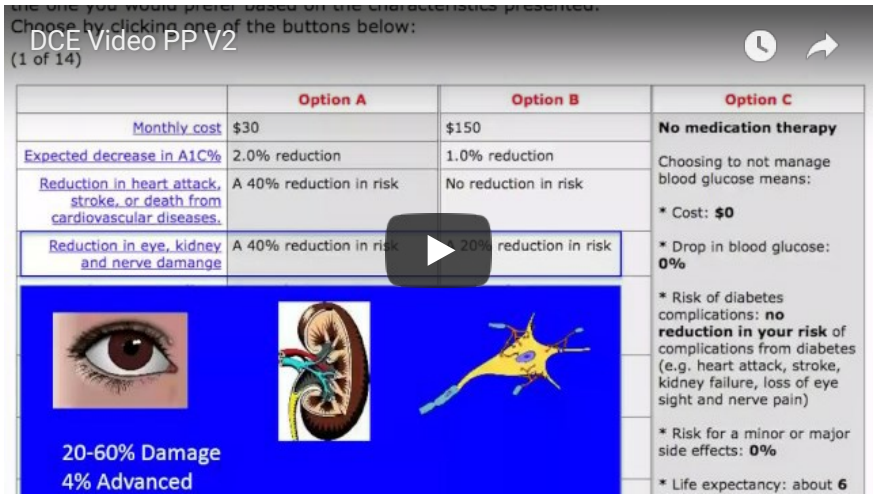
Please provide your age in the space provided. ____

0% 100%

DCEBackground1

Survey Part 2: Introduction

The main part of this survey will consist of 16 choice tasks like the one you will be introduced to in the video below. Please take 4 minutes to watch this video, as it will provide important tips on how to complete the choice tasks.



Q7_Random1

Imagine you are a 55 year old individual with type 2 diabetes. You have tried metformin (an oral diabetes medication) but you have not been able to get your blood sugar levels under control. You need to add an additional diabetes therapy. Consider the options below and select the one you would prefer based on the characteristics presented.
Choose by clicking one of the buttons below:

(1 of 14)

	Option A	Option B
Monthly cost	$30	$90
Expected decrease in A1C%	0% reduction	2.0% reduction
Reduction in heart attack, stroke, or death from cardiovascular diseases.	No reduction in risk	A 20% reduction in risk
Reduction in eye, kidney and nerve damage	A 40% reduction in risk	No reduction in risk
Risk of minor side effects (e.g. weight gain, stomach upset, skin rash, low energy)	0 out of 100 people	40 out of 100 people
Number of severe hypoglycemic (low blood sugar) episodes over 10 years	40 out of 100 people	20 out of 100 people
Risk of serious but rare side effects over a 10 year period	0 out of 100 people	2 out of 100 people
Reduction in life expectancy	No change in life expectancy	Increase in life expectancy by 1.5 years
	Q7_Random1 Select	Q7_Random1 Select

Option C

No medication therapy

Choosing to not manage blood glucose means:

* Cost: **$0**

* Drop in blood glucose: **0%**

* Risk of diabetes complications: **no reduction in your risk** of complications from diabetes (e.g. heart attack, stroke, kidney failure, loss of eye sight and nerve pain)

* Risk for a minor or major side effects: **0%**

* Life expectancy: about **6 years less** than the general population.

Q7_Random1

Select

0% 100%

Q7_Random2

Imagine you are a 55 year old individual with type 2 diabetes. You have tried metformin (an oral diabetes medication) but you have not been able to get your blood sugar levels under control. You need to add an additional diabetes therapy. Consider the options below and select the one you would prefer based on the characteristics presented.
Choose by clicking one of the buttons below:

(2 of 14)

	Option A	Option B
Monthly cost	$150	$30
Expected decrease in A1C%	2.0% reduction	1.0% reduction
Reduction in heart attack, stroke, or death from cardiovascular diseases.	A 40% reduction in risk	No reduction in risk
Reduction in eye, kidney and nerve damage	A 20% reduction in risk	No reduction in risk
Risk of minor side effects (e.g. weight gain, stomach upset, skin rash, low energy)	20 out of 100 people	20 out of 100 people
Number of severe hypoglycemic (low blood sugar) episodes over 10 years	0 out of 100 people	20 out of 100 people
Risk of serious but rare side effects over a 10 year period	0 out of 100 people	4 out of 100 people
Reduction in life expectancy	Increase in life expectancy by 3 years	Increase in life expectancy by 1.5 years
	Q7_Random2 Select	Q7_Random2 Select

Option C

No medication therapy

Choosing to not manage blood glucose means:

* Cost: **$0**

* Drop in blood glucose: **0%**

* Risk of diabetes complications: **no reduction in your risk** of complications from diabetes (e.g. heart attack, stroke, kidney failure, loss of eye sight and nerve pain)

* Risk for a minor or major side effects: **0%**

* Life expectancy: about **6 years less** than the general population.

Q7_Random2

Select

0% 100%

Q7_Random3

Imagine you are a 55 year old individual with type 2 diabetes. You have tried metformin (an oral diabetes medication) but you have not been able to get your blood sugar levels under control. You need to add an additional diabetes therapy. Consider the options below and select the one you would prefer based on the characteristics presented.
Choose by clicking one of the buttons below:

(3 of 14)

	Option A	Option B
Monthly cost	$150	$90
Expected decrease in A1C%	1.0% reduction	0% reduction
Reduction in heart attack, stroke, or death from cardiovascular diseases.	A 20% reduction in risk	A 40% reduction in risk
Reduction in eye, kidney and nerve damage	A 20% reduction in risk	A 20% reduction in risk
Risk of minor side effects (e.g. weight gain, stomach upset, skin rash, low energy)	0 out of 100 people	40 out of 100 people
Number of severe hypoglycemic (low blood sugar) episodes over 10 years	40 out of 100 people	0 out of 100 people
Risk of serious but rare side effects over a 10 year period	4 out of 100 people	2 out of 100 people
Reduction in life expectancy	No change in life expectancy	Increase in life expectancy by 1.5 years
	Q7_Random3 Select	Q7_Random3 Select

Option C

No medication therapy

Choosing to not manage blood glucose means:

* Cost: **$0**

* Drop in blood glucose: **0%**

* Risk of diabetes complications: **no reduction in your risk** of complications from diabetes (e.g. heart attack, stroke, kidney failure, loss of eye sight and nerve pain)

* Risk for a minor or major side effects: **0%**

* Life expectancy: about **6 years less** than the general population.

Q7_Random3

Select

0% 100%

Q7_Random4

Imagine you are a 55 year old individual with type 2 diabetes. You have tried metformin (an oral diabetes medication) but you have not been able to get your blood sugar levels under control. You need to add an additional diabetes therapy. Consider the options below and select the one you would prefer based on the characteristics presented.
Choose by clicking one of the buttons below:

(4 of 14)

	Option A	Option B
Monthly cost	$30	$150
Expected decrease in A1C%	0% reduction	1.0% reduction
Reduction in heart attack, stroke, or death from cardiovascular diseases.	A 20% reduction in risk	No reduction in risk
Reduction in eye, kidney and nerve damage	A 40% reduction in risk	No reduction in risk
Risk of minor side effects (e.g. weight gain, stomach upset, skin rash, low energy)	20 out of 100 people	40 out of 100 people
Number of severe hypoglycemic (low blood sugar) episodes over 10 years	40 out of 100 people	20 out of 100 people
Risk of serious but rare side effects over a 10 year period	2 out of 100 people	0 out of 100 people
Reduction in life expectancy	Increase in life expectancy by 3 years	No change in life expectancy
	Q7_Random4 Select	Q7_Random4 Select

Option C

No medication therapy

Choosing to not manage blood glucose means:

* Cost: **$0**

* Drop in blood glucose: **0%**

* Risk of diabetes complications: **no reduction in your risk** of complications from diabetes (e.g. heart attack, stroke, kidney failure, loss of eye sight and nerve pain)

* Risk for a minor or major side effects: **0%**

* Life expectancy: about **6 years less** than the general population.

Q7_Random4

Select

0% 100%

Q7_Fixed1

Imagine you are a 55 year old individual with type 2 diabetes. You have tried metformin (an oral diabetes medication) but you have not been able to get your blood sugar levels under control. You need to add an additional diabetes therapy. Consider the options below and select the one you would prefer based on the characteristics presented.
Choose by clicking one of the buttons below:

(5 of 14)

	Option A	Option B
Monthly cost	$150	$90
Expected decrease in A1C%	0% reduction	1.0% reduction
Reduction in heart attack, stroke, or death from cardiovascular diseases.	No reduction in risk	A 40% reduction in risk
Reduction in eye, kidney and nerve damage	A 20% reduction in risk	A 20% reduction in risk
Risk of minor side effects (e.g. weight gain, stomach upset, skin rash, low energy)	20 out of 100 people	0 out of 100 people
Number of severe hypoglycemic (low blood sugar) episodes over 10 years	40 out of 100 people	20 out of 100 people
Risk of serious but rare side effects over a 10 year period	2 out of 100 people	0 out of 100 people
Reduction in life expectancy	Increase in life expectancy by 1.5 years	Increase in life expectancy by 3 years
	Q7_Fixed1 Select	Q7_Fixed1 Select

Option C

No medication therapy

Choosing to not manage blood glucose means:

* Cost: **$0**

* Drop in blood glucose: **0%**

* Risk of diabetes complications: **no reduction in your risk** of complications from diabetes (e.g. heart attack, stroke, kidney failure, loss of eye sight and nerve pain)

* Risk for a minor or major side effects: **0%**

* Life expectancy: about **6 years less** than the general population.

Q7_Fixed1

Select

0% 100%

Q7_Random5

Imagine you are a 55 year old individual with type 2 diabetes. You have tried metformin (an oral diabetes medication) but you have not been able to get your blood sugar levels under control. You need to add an additional diabetes therapy. Consider the options below and select the one you would prefer based on the characteristics presented.
Choose by clicking one of the buttons below:

(6 of 14)

	Option A	Option B
Monthly cost	$90	$90
Expected decrease in A1C%	2.0% reduction	0% reduction
Reduction in heart attack, stroke, or death from cardiovascular diseases.	No reduction in risk	A 40% reduction in risk
Reduction in eye, kidney and nerve damage	A 20% reduction in risk	A 40% reduction in risk
Risk of minor side effects (e.g. weight gain, stomach upset, skin rash, low energy)	20 out of 100 people	0 out of 100 people
Number of severe hypoglycemic (low blood sugar) episodes over 10 years	20 out of 100 people	0 out of 100 people
Risk of serious but rare side effects over a 10 year period	4 out of 100 people	4 out of 100 people
Reduction in life expectancy	No change in life expectancy	Increase in life expectancy by 3 years
	Q7_Random5 Select	Q7_Random5 Select

Option C

No medication therapy

Choosing to not manage blood glucose means:

* Cost: **$0**

* Drop in blood glucose: **0%**

* Risk of diabetes complications: **no reduction in your risk** of complications from diabetes (e.g. heart attack, stroke, kidney failure, loss of eye sight and nerve pain)

* Risk for a minor or major side effects: **0%**

* Life expectancy: about **6 years less** than the general population.

Q7_Random5

Select

0% 100%

Q7_Random6

Imagine you are a 55 year old individual with type 2 diabetes. You have tried metformin (an oral diabetes medication) but you have not been able to get your blood sugar levels under control. You need to add an additional diabetes therapy. Consider the options below and select the one you would prefer based on the characteristics presented.
Choose by clicking one of the buttons below:

(7 of 14)

	Option A	Option B
Monthly cost	$30	$150
Expected decrease in A1C%	2.0% reduction	1.0% reduction
Reduction in heart attack, stroke, or death from cardiovascular diseases.	A 20% reduction in risk	A 40% reduction in risk
Reduction in eye, kidney and nerve damage	No reduction in risk	A 40% reduction in risk
Risk of minor side effects (e.g. weight gain, stomach upset, skin rash, low energy)	0 out of 100 people	40 out of 100 people
Number of severe hypoglycemic (low blood sugar) episodes over 10 years	0 out of 100 people	40 out of 100 people
Risk of serious but rare side effects over a 10 year period	0 out of 100 people	2 out of 100 people
Reduction in life expectancy	Increase in life expectancy by 3 years	Increase in life expectancy by 1.5 years
	Q7_Random6 Select	Q7_Random6 Select

Option C

No medication therapy

Choosing to not manage blood glucose means:

* Cost: **$0**

* Drop in blood glucose: **0%**

* Risk of diabetes complications: **no reduction in your risk** of complications from diabetes (e.g. heart attack, stroke, kidney failure, loss of eye sight and nerve pain)

* Risk for a minor or major side effects: **0%**

* Life expectancy: about **6 years less** than the general population.

Q7_Random6

Select

0% 100%

Q7_Random7

Imagine you are a 55 year old individual with type 2 diabetes. You have tried metformin (an oral diabetes medication) but you have not been able to get your blood sugar levels under control. You need to add an additional diabetes therapy. Consider the options below and select the one you would prefer based on the characteristics presented.
Choose by clicking one of the buttons below:

(8 of 14)

	Option A	Option B
Monthly cost	$30	$150
Expected decrease in A1C%	2.0% reduction	0% reduction
Reduction in heart attack, stroke, or death from cardiovascular diseases.	No reduction in risk	A 20% reduction in risk
Reduction in eye, kidney and nerve damage	A 40% reduction in risk	A 20% reduction in risk
Risk of minor side effects (e.g. weight gain, stomach upset, skin rash, low energy)	40 out of 100 people	20 out of 100 people
Number of severe hypoglycemic (low blood sugar) episodes over 10 years	0 out of 100 people	20 out of 100 people
Risk of serious but rare side effects over a 10 year period	2 out of 100 people	0 out of 100 people
Reduction in life expectancy	No change in life expectancy	Increase in life expectancy by 1.5 years
	Q7_Random7 Select	Q7_Random7 Select

Option C

No medication therapy

Choosing to not manage blood glucose means:

* Cost: **$0**

* Drop in blood glucose: **0%**

* Risk of diabetes complications: **no reduction in your risk** of complications from diabetes (e.g. heart attack, stroke, kidney failure, loss of eye sight and nerve pain)

* Risk for a minor or major side effects: **0%**

* Life expectancy: about **6 years less** than the general population.

Q7_Random7

Select

0% 100%

Q7_Random8

Imagine you are a 55 year old individual with type 2 diabetes. You have tried metformin (an oral diabetes medication) but you have not been able to get your blood sugar levels under control. You need to add an additional diabetes therapy. Consider the options below and select the one you would prefer based on the characteristics presented.
Choose by clicking one of the buttons below:

(9 of 14)

	Option A	Option B
Monthly cost	$90	$150
Expected decrease in A1C%	0% reduction	1.0% reduction
Reduction in heart attack, stroke, or death from cardiovascular diseases.	A 40% reduction in risk	A 20% reduction in risk
Reduction in eye, kidney and nerve damage	No reduction in risk	No reduction in risk
Risk of minor side effects (e.g. weight gain, stomach upset, skin rash, low energy)	0 out of 100 people	20 out of 100 people
Number of severe hypoglycemic (low blood sugar) episodes over 10 years	40 out of 100 people	0 out of 100 people
Risk of serious but rare side effects over a 10 year period	0 out of 100 people	4 out of 100 people
Reduction in life expectancy	No change in life expectancy	Increase in life expectancy by 3 years
	Q7_Random8 Select	Q7_Random8 Select

Option C

No medication therapy

Choosing to not manage blood glucose means:

* Cost: **$0**

* Drop in blood glucose: **0%**

* Risk of diabetes complications: **no reduction in your risk** of complications from diabetes (e.g. heart attack, stroke, kidney failure, loss of eye sight and nerve pain)

* Risk for a minor or major side effects: **0%**

* Life expectancy: about **6 years less** than the general population.

Q7_Random8

Select

0% 100%

Q7_Fixed2

Imagine you are a 55 year old individual with type 2 diabetes. You have tried metformin (an oral diabetes medication) but you have not been able to get your blood sugar levels under control. You need to add an additional diabetes therapy. Consider the options below and select the one you would prefer based on the characteristics presented.
Choose by clicking one of the buttons below:

(10 of 14)

	Option A	Option B
Monthly cost	$30	$90
Expected decrease in A1C%	2.0% reduction	0% reduction
Reduction in heart attack, stroke, or death from cardiovascular diseases.	A 20% reduction in risk	No reduction in risk
Reduction in eye, kidney and nerve damage	A 20% reduction in risk	A 20% reduction in risk
Risk of minor side effects (e.g. weight gain, stomach upset, skin rash, low energy)	20 out of 100 people	40 out of 100 people
Number of severe hypoglycemic (low blood sugar) episodes over 10 years	20 out of 100 people	40 out of 100 people
Risk of serious but rare side effects over a 10 year period	2 out of 100 people	4 out of 100 people
Reduction in life expectancy	Increase in life expectancy by 1.5 years	No change in life expectancy
	Q7_Fixed2 Select	Q7_Fixed2 Select

Option C

No medication therapy

Choosing to not manage blood glucose means:

* Cost: **$0**

* Drop in blood glucose: **0%**

* Risk of diabetes complications: **no reduction in your risk** of complications from diabetes (e.g. heart attack, stroke, kidney failure, loss of eye sight and nerve pain)

* Risk for a minor or major side effects: **0%**

* Life expectancy: about **6 years less** than the general population.

Q7_Fixed2

Select

0% 100%

Q7_Random9

Imagine you are a 55 year old individual with type 2 diabetes. You have tried metformin (an oral diabetes medication) but you have not been able to get your blood sugar levels under control. You need to add an additional diabetes therapy. Consider the options below and select the one you would prefer based on the characteristics presented.
Choose by clicking one of the buttons below:

(11 of 14)

	Option A	Option B
Monthly cost	$30	$90
Expected decrease in A1C%	2.0% reduction	2.0% reduction
Reduction in heart attack, stroke, or death from cardiovascular diseases.	No reduction in risk	A 40% reduction in risk
Reduction in eye, kidney and nerve damage	A 20% reduction in risk	A 40% reduction in risk
Risk of minor side effects (e.g. weight gain, stomach upset, skin rash, low energy)	0 out of 100 people	40 out of 100 people
Number of severe hypoglycemic (low blood sugar) episodes over 10 years	40 out of 100 people	20 out of 100 people
Risk of serious but rare side effects over a 10 year period	0 out of 100 people	4 out of 100 people
Reduction in life expectancy	Increase in life expectancy by 1.5 years	Increase in life expectancy by 3 years
	Q7_Random9 Select	Q7_Random9 Select

Option C

No medication therapy

Choosing to not manage blood glucose means:

* Cost: **$0**

* Drop in blood glucose: **0%**

* Risk of diabetes complications: **no reduction in your risk** of complications from diabetes (e.g. heart attack, stroke, kidney failure, loss of eye sight and nerve pain)

* Risk for a minor or major side effects: **0%**

* Life expectancy: about **6 years less** than the general population.

Q7_Random9

Select

0% 100%

Q7_Random10

Imagine you are a 55 year old individual with type 2 diabetes. You have tried metformin (an oral diabetes medication) but you have not been able to get your blood sugar levels under control. You need to add an additional diabetes therapy. Consider the options below and select the one you would prefer based on the characteristics presented.
Choose by clicking one of the buttons below:

(12 of 14)

	Option A	Option B
Monthly cost	$90	$150
Expected decrease in A1C%	1.0% reduction	0% reduction
Reduction in heart attack, stroke, or death from cardiovascular diseases.	No reduction in risk	A 40% reduction in risk
Reduction in eye, kidney and nerve damage	A 20% reduction in risk	No reduction in risk
Risk of minor side effects (e.g. weight gain, stomach upset, skin rash, low energy)	40 out of 100 people	20 out of 100 people
Number of severe hypoglycemic (low blood sugar) episodes over 10 years	0 out of 100 people	20 out of 100 people
Risk of serious but rare side effects over a 10 year period	2 out of 100 people	2 out of 100 people
Reduction in life expectancy	Increase in life expectancy by 3 years	No change in life expectancy
	Q7_Random10 Select	Q7_Random10 Select

Option C

No medication therapy

Choosing to not manage blood glucose means:

* Cost: **$0**

* Drop in blood glucose: **0%**

* Risk of diabetes complications: **no reduction in your risk** of complications from diabetes (e.g. heart attack, stroke, kidney failure, loss of eye sight and nerve pain)

* Risk for a minor or major side effects: **0%**

* Life expectancy: about **6 years less** than the general population.

Q7_Random10

Select

0% 100%

Q7_Random11

Imagine you are a 55 year old individual with type 2 diabetes. You have tried metformin (an oral diabetes medication) but you have not been able to get your blood sugar levels under control. You need to add an additional diabetes therapy. Consider the options below and select the one you would prefer based on the characteristics presented.
Choose by clicking one of the buttons below:

(13 of 14)

	Option A	Option B
Monthly cost	$30	$90
Expected decrease in A1C%	0% reduction	1.0% reduction
Reduction in heart attack, stroke, or death from cardiovascular diseases.	A 40% reduction in risk	A 20% reduction in risk
Reduction in eye, kidney and nerve damage	A 20% reduction in risk	A 40% reduction in risk
Risk of minor side effects (e.g. weight gain, stomach upset, skin rash, low energy)	40 out of 100 people	0 out of 100 people
Number of severe hypoglycemic (low blood sugar) episodes over 10 years	40 out of 100 people	40 out of 100 people
Risk of serious but rare side effects over a 10 year period	4 out of 100 people	4 out of 100 people
Reduction in life expectancy	Increase in life expectancy by 1.5 years	Increase in life expectancy by 1.5 years
	Q7_Random11 Select	Q7_Random11 Select

Option C

No medication therapy

Choosing to not manage blood glucose means:

* Cost: **$0**

* Drop in blood glucose: **0%**

* Risk of diabetes complications: **no reduction in your risk** of complications from diabetes (e.g. heart attack, stroke, kidney failure, loss of eye sight and nerve pain)

* Risk for a minor or major side effects: **0%**

* Life expectancy: about **6 years less** than the general population.

Q7_Random11

Select

0% 100%

Q7_Random12

Imagine you are a 55 year old individual with type 2 diabetes. You have tried metformin (an oral diabetes medication) but you have not been able to get your blood sugar levels under control. You need to add an additional diabetes therapy. Consider the options below and select the one you would prefer based on the characteristics presented.
Choose by clicking one of the buttons below:

(14 of 14)

	Option A	Option B
Monthly cost	$150	$30
Expected decrease in A1C%	2.0% reduction	1.0% reduction
Reduction in heart attack, stroke, or death from cardiovascular diseases.	A 40% reduction in risk	No reduction in risk
Reduction in eye, kidney and nerve damage	A 40% reduction in risk	No reduction in risk
Risk of minor side effects (e.g. weight gain, stomach upset, skin rash, low energy)	0 out of 100 people	20 out of 100 people
Number of severe hypoglycemic (low blood sugar) episodes over 10 years	20 out of 100 people	0 out of 100 people
Risk of serious but rare side effects over a 10 year period	0 out of 100 people	4 out of 100 people
Reduction in life expectancy	Increase in life expectancy by 3 years	Increase in life expectancy by 1.5 years
	Q7_Random12 Select	Q7_Random12 Select

Option C

No medication therapy

Choosing to not manage blood glucose means:

* Cost: **$0**

* Drop in blood glucose: **0%**

* Risk of diabetes complications: **no reduction in your risk** of complications from diabetes (e.g. heart attack, stroke, kidney failure, loss of eye sight and nerve pain)

* Risk for a minor or major side effects: **0%**

* Life expectancy: about **6 years less** than the general population.

Q7_Random12

Select

0% 100%

QFinal

The next few questions of this survey relate to the length of time a medication has been on the market and used by the general population.

Would you prefer a medication that has been on the market:

QFinal=1 ○ 5 Years

QFinal=2 ○ 10 Years

QFinal2

Would you prefer a medication that has been on the market for:

QFinal2=1 ○ 6 Months

QFinal2=2 ○ 5 Years

QFinal3

Would you prefer a medication that has been on the market:

QFinal3=1 ○ 6 Months

QFinal3=2 ○ 10 Years

Q2

Background Questions

The final few questions will provide some background information on your diabetes experience.

What is your gender?

- Q2=1 ◯ Male
- Q2=2 ◯ Female

Q3a

What is your current marital status?

- Q3a=1 ◯ Single
- Q3a=2 ◯ Married / Common Law
- Q3a=3 ◯ Divorced / Separated
- Q3a=4 ◯ Widowed
- Q3a=5 ◯ Other

Q4a

What is your current employment status?

- Q4a=1 ◯ Student
- Q4a=2 ◯ Employed
- Q4a=3 ◯ Unemployed and seeking employment
- Q4a=4 ◯ Unemployed
- Q4a=5 ◯ Retired

Q5a

What is the highest level of education that you have completed?

- Q5a=1 ◯ Did not complete high school
- Q5a=2 ◯ Graduated high school
- Q5a=3 ◯ Trade/Technical/vocational training

Q5a=4 ◯ Some College/University

Q5a=5 ◯ Bachelor's degree

Q5a=6 ◯ Professional degree

Q5a=7 ◯ Graduate degree

Q6a

How long have you known that you have diabetes?

Q6a=1 ◯ Less than a year

Q6a=2 ◯ 1-2 years

Q6a=3 ◯ 3-5 years

Q6a=4 ◯ 6-10 years

Q6a=5 ◯ Greater than 10 years

Q7a

How many (if any) different oral diabetes medications have you used?

Q7a=1 ◯ None

Q7a=2 ◯ 1 oral medication

Q7a=3 ◯ 2 oral medications

Q7a=4 ◯ 3 oral medications

Q7a=5 ◯ More than 3 oral medications

Q7a=6 ◯ I am not sure

Q8a

Have you ever used a medication by injection (eg.insulin, Trulicity, Byetta, Bydureon, Victoza, etc.) to manage your diabetes at home?

Q8a=1 ◯ Yes

Q8a=2 ◯ No

Q9

Do you have any heart or stroke related conditions? Please select any of the following that apply to you.

Q9_1 ☐ No heart or stroke related conditions

Q9_2 ☐ High blood pressure

Q9_3 ☐ High cholesterol

Q9_4 ☐ Angina

Q9_5 ☐ Heart arrhythmia

Q9_6 ☐ History of heart attack

Q9_7 ☐ History of stroke

Q9_8 ☐ Q9_8_other Other, please specify

Q9a

Do you have any other chronic conditions besides diabetes or heart disease? Check all that apply.

Q9a_1 ☐ None

Q9a_2 ☐ Osteoporosis

Q9a_3 ☐ Asthma or COPD

Q9a_4 ☐ Osteoarthritis

Q9a_5 ☐ Rheumatoid Arthritis

Q9a_6 ☐ Anxiety or Depression

Q9a_7 ☐ Other mental health conditions (Bipolar, schizophrenia, etc.)

Q9a_8 ☐ Multiple Sclerosis

Q9a_9 ☐ Chronic pain

Q9a_10 ☐ Obesity

Q9a_11 ☐ Cancer

Q9a_12 ☐ Q9a_12_other Other, please specify

Q10a

What would you estimate your annual household income is before taxes?

Q10a=1 ○ Less than $25,000

Q10a=2 ○ $25,000 to $49,999

Q10a=3 ○ $50,000 to $74,999

Q10a=4 ○ $75,000 to $99,999

Q10a=5 ○ $100,000 or more


0%
100%

Terminate1

Note:

When respondents take the survey in regular mode this page will not be displayed. Respondents will be redirected to the link below:

http://endlinks.researchnow.com/d/?status=1&rnid=
[Script] **&study=** [Script]

0% 100%

TerminateDisqualified

Note:

When respondents take the survey in regular mode this page will not be displayed. Respondents will be redirected to the link below:

http://endlinks.researchnow.com/d/?status=2&rnid=
[Script] **&study=** [Script]

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0% 100%

TerminateOverQuota

Note:

When respondents take the survey in regular mode this page will not be displayed. Respondents will be redirected to the link below:

http://endlinks.researchnow.com/d/?status=3&rnid=
[Script] **&study=** [Script]

0% 100%