Patients' Preferences for Second-line Pharmacological Agents in Type 2 Diabetes

by

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ABSTRACT

The second-line antihyperglycemic agents (AHAs) for Type 2 Diabetes Mellitus (T2DM) have a wide variety of treatment attributes, including treatment benefits, side effects, and various treatment processes, such as dosage form, mode of administration, etc. Identifying what T2DM patients preferred while selecting the second-line AHAs, including sodium-glucose cotransporter-2 inhibitors (SGLT-2is) and glucagon-like peptide-1 receptor agonists (GLP-1 RAs), is important. The purposes of this thesis were to rank the importance of the attributes of second-line AHAs and determine the patients' preferences for SGLT-2is and GLP-1 RAs.

The thesis was conducted in two steps using two stated preference methods. First, a cross-sectional, web-based survey was used to rank the important attributes of second-line AHAs using the best-worst scaling (BWS) method. A balanced incomplete block design (BIBD) was used to generate choice sets. Patients diagnosed with T2DM, aged 19 years or older, and were proficient in English were recruited through Qualtrics^{XM}. The BWS data were analyzed using the count analysis method, and the standardized BWS score was calculated for each attribute. Second, another cross-sectional, web-based survey was used to determine the patients' preferences for SGLT-2is and GLP-1 RAs using a discrete choice experiment (DCE). Six attributes (i.e., how do you take the medication, the chance of reaching target HbA1c (long-term blood glucose level) in 6 months, % reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to cardiovascular diseases), the chance of gastrointestinal side effects (i.e., nausea, vomiting, and diarrhea), the chance of genital infection and out-of-pocket cost per month) and their level for SGLT-2is and GLP-1 RAs from the literature review were confirmed and consolidated with the results from in-depth interviews with T2DM patients, and the BWS results. An orthogonal and balanced design was used to draw a subset of all combinations randomly. A total of 36 choice sets were generated and divided into four blocks. Each block comprised nine choice sets that were used to develop a self-administered questionnaire survey. Patients diagnosed with T2DM, 19 years or

older, and were proficient in English were recruited through Qualtrics^{XM}. Multinomial logit (MNL) and mixed logit (ML) analyses were conducted to examine patients' preferences and preference heterogeneity. Subgroup analyses were used to explore the preference heterogeneity across three variables, including gender, T2DM experience, and SGLT-2is or GLP-1 RA experience. The patients' willingness-to-pay (WTP) for all attributes and available SGLT-2is and GLP-1 RAs in the market were calculated from the estimated coefficients in the ML model.

A total of 99 T2DM patients completed the BWS survey questionnaire. Among 16 important attributes of second-line AHAs, reducing blood glucose and reducing the risk of cardiovascular diseases had the highest standardized BWS scores of 0.48 and 0.39, respectively. While the reaction at the injection site and route of administration attributes had the lowest standardized BWS scores of -0.52 and -0.31, respectively. Thus, T2DM patients ranked reducing blood glucose and reducing cardiovascular diseases as the most important attributes while selecting second-line medications.

A total of 176 T2DM patients completed the DCE survey questionnaire. The MNL analyses showed that reaching target Hb1c, reducing the risk of a major adverse cardiovascular event (MACE), gastrointestinal side-effect, genital infection, out-of-pocket cost, and all levels of route and frequency of administration (except for injectable, once a day) were significant attributes while selecting SGLT-2is and GLP-1 RAs. Similarly, the ML analyses confirmed the significance for all attributes, except for the two levels, injectable, once a day and injectable, once a week, of the route and frequency of administration attribute while selecting SGLT-2is and GLP-1 RAs. The ML model also showed preference heterogeneity for all attributes. Subgroup analyses indicated that treatment-related GI side effects and genital infection were not important for male T2DM patients or patients with lesser experience with T2DM, or patients who had experienced SGLT-2is or GLP-1 RAs. T2DM patients were willing to pay approximately $6 per month and $4 per month for a 1% increase in the chance of reaching the HbA1c target and for a 1% increase in reducing the risk of MACE, respectively. Similarly, they were willing to pay approximately $8 and $12 to avoid 1%

of GI side effects and 1% of genital infection, respectively. Among four different ways of taking medications, the T2DM patients were willing to pay the highest of $486 per month for oral, once-a-day medication and the lowest of $176 per month for injectable, twice-a-day medication. For different SGLT-2is and GLP-1 RAs, T2DM patients were willing to pay the highest of $1518 per month for oral, once-a-day GLP-1 RAs and the lowest of $1124 per month injectable, twice-a-day GLP-1 RAs. The result suggested that T2DM patients valued all SGLT-2is and GLP-1 RAs higher than their current wholesale acquisition costs (WAC).

The findings of this thesis could be used to inform clinicians about what attributes are important when selecting appropriate second-line medications for T2DM patients.

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List of Abbreviations

T2DM	Type 2 Diabetes Mellitus
AHAs	Antihyperglycemic Agents
SGLT-2is	Sodium-Glucose Cotransporter-2 Inhibitors
GLP-1 RAs	Glucagon-Like Peptide-1 Receptor Agonists
WTP	Willingness to Pay

Chapter 1

Introduction

1.1 Background

Diabetes Mellitus (DM) is a chronic and metabolic disease in which the body cannot properly regulate blood glucose levels. People with diabetes have high blood glucose level that increases the risk of cardiovascular disease, hypertension, obesity, cataracts, and nonalcoholic fatty liver disease.[1] Eventually, DM can cause serious health problems such as heart disease, vision loss, and kidney disease. It affects millions of people around the world.[1-3] According to the National Diabetes Statistics Report 2020 of the Centers for Disease Control and Prevention (CDC), over 34.2 million people, which is 10.5% of the whole U.S. population, had DM in 2018. There are three major types of DM, including type 1, type 2, and gestational diabetes. Approximately 90-95% of DM patients had type 2 DM (T2DM). [4] T2DM is characterized by the progressive loss of insulin secretion and (or) insulin resistance on target tissues that causes hyperglycemia, including metabolic alteration, cell death, and inflammation. Thus, controlling the blood glucose, assessed by an HbA1C test, is fundamental to T2DM management.[5] Various studies showed that controlling blood glucose decreased microvascular complications due to short and long terms of hyperglycemia, thus reducing related morbidity and mortality.[5-7]

Besides lifestyle changes, diet modification, increasing physical activities, and weight control, pharmacological treatments are recommended to control blood glucose levels and complications for T2DM.[8] Among various pharmacological T2DM treatments, metformin has been effective, safe, inexpensive, and reduces cardiovascular risks and deaths. [6] American Diabetes Association (ADA) recommends metformin as the first-line treatment for T2DM in addition to lifestyle changes.[9] However, due to the progressive nature of DM, metformin alone may not maintain blood glucose levels. If the goal of maintaining glycemic target is not achieved within three months of the initial treatment, second-line antihyperglycemic agents (AHAs) should be added. These second-line AHAs mainly include four old pharmacological groups, i.e., sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, and insulin, and two newer groups, i.e., sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor

agonists (GLP-1 RAs). Table 1-1 shows the six groups of AHAs and examples of medications within each group available in the U.S.

Table 1-1. Second-line antihyperglycemic agents (AHAs).

Group	Medications
Sulfonylureas	Glyburide (DiaBeta®, Glynase®), Glipizide (Glucotrol®) and Glimepiride (Amaryl®)
Thiazolidinediones	Osiglitazone (Avandia®) and Pioglitazone (Actos®)
DPP-4 inhibitors	Sitagliptin (Januvia®), Saxagliptin (Onglyza®) and Linagliptin (Tradjenta®)
GLP-1 agonists	Exenatide (Byetta®, Bydureon®), Liraglutide (Victoza®) and Semaglutide (Ozempic®)
SGLT2 inhibitors	Canagliflozin (Invokana®), Dapagliflozin (Farxiga®) and Empagliflozin (Jardiance®)
Insulin	Insulin with different duration of action are available: Novolog® Mix 70/30 (insulin aspart/insulin aspart protamine) Novolin® 70/30 (insulin isophane/insulin regular) Humalog® Mix 75/25 (insulin lispro/insulin lispro protamine) Humulin® N (insulin isophane/insulin regular) Tresiba® (insulin degludec) Novolog®, Penfill® (Insulin aspart)

In addition to the antihyperglycemic effect, many clinical studies identified that SGLT-2is and GLP-1 RAs provided better cardiovascular (CV) and renal outcomes than other second-line AHAs.[10-13] In the review of these clinical studies, Lo et al. found that SGLT-2is significantly reduced the risk ratio (RR) of major adverse cardiovascular events (MACE), i.e., cardiovascular death, stroke, or myocardial infarction by 7%, reduced CV death by 11%, reduced RR for heart failure hospitalizations by 29%, and lowered RR for all-cause mortality by 0.9.[14] Similarly, another study reported that GLP-1 RAs reduced hazard ratio (HR) for MACE by 12%, for all-cause mortality by 12%, and for hospital admission from heart failure by 9%. GLP-1 RAs also improved a broad composite kidney outcome, e.g., progression to end-stage kidney disease or death attributable to kidney causes, by 7% and had no increase in the risk of severe hypoglycemia, pancreatitis, or pancreatic cancer.[15] A recent systematic review also indicated the benefits of SGLT-2is and GLP-1 RAs, which were the reduction of body weight up to 3.43 kg, reduction of systolic blood pressure (SBP) up to 4.92 mmHg, and diastolic blood pressure (DBP) up to 2.00 mmHg, and reduction of total cholesterol up to 0.28 mmol/L in 24 weeks.[16] Based on such additional benefits of the decrease in cardiovascular and renal risks, ADA and the European Association for the Study of Diabetes (EASD) updated their treatment guidelines for T2DM among the high-risk population. They recommended using SGLT-2is and GLP-1 RAs as preferred second-line AHAs. [17]

1.2 Rationale

The American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) developed the comprehensive T2DM management algorithm.[18] One of the principles in this algorithm is to individualize the choice of diabetes therapies. Specifically, AACE recommended the choice of diabetes therapies should be based on attributes specific to both patients and medications, such as efficacy, risk of inducing hypoglycemia, risk of weight gain, cost, and safety or risk reduction in heart, kidney, or liver disease.[18] ADA recommended that patients' preferences of DM treatments should be considered while selecting the appropriate medications.[17] A recent large retrospective cohort study also showed that the selection of medications should be based on a person's characteristics, such as gender, age, BMI, the extent of hyperglycemia, comorbidities, and the benefits and adverse effects of each class of second-line

medications for T2DM.[19]

Despite AACE, ACE, and ADA recommendations, incorporating patients' preferences of second-line AHAs in treatment decisions remains a challenge for various reasons. First, all second-line AHAs have a wide variety of treatment attributes, including benefits (e.g., decreasing HbA1c level, weight loss), risks (e.g., side effect, adverse event), route of administration, and frequency of administration.[20, 21] For example, sulfonylureas and insulin medications had higher efficacy in terms of reducing HbA1c in comparison to other AHAs. Still, at the same time, they had various side effects, e.g., increasing the risk of hypoglycemia and gaining weight. GLP-1 RAs and SGLT-2is were associated with the low risks of hypoglycemia and weight loss, but GLP-1 RAs caused nausea, and SGLT-2is increased the risks of genitourinary and urinary tract infections.[16] Both GLP-1 RAs and SGLT-2is decreased cardiovascular and renal risks, but their costs were higher than the costs of drugs in other classes.[22] A recent study reported that the median retail prices for a one-year supply of these two drug groups across Medicare Part D prescription drug plans in 2019 ranged from $3,600 to $11,304, and the average beneficiary could spend at least $1,000 annually for an SGLT-2is and higher than $1,500 for a GLP-1 RA.[23] Clinicians, therefore, are challenged to balance the benefits, risks, and costs of these treatments. Second, although there are several preference studies on T2DM patients' preference for AHAs [24-40], none of them determined the patients' willingness to pay (WTPs) for newer second-line AHAs, GLP-1 RAs, and SGLT-2is. These studies identified a wide range of important treatment attributes, including blood glucose control, quality of life, heart function, method of delivery, mode of administration, dose frequency, the requirement of a blood test, treatment-related cost, weight gain, gastrointestinal side effects, injection site reaction, heart attack risk, and water retention.[41, 42] Other important attributes of SGLT-2is and GLP-1 RAs, such as reducing cardiovascular events or reducing hospitalization due to heart failure, were not included. Similarly, preference studies within diabetes care used WTP to quantify treatment benefits and risks or to estimate the potential effect of more convenient dosing on adherence [30, 37, 43]; however, such estimation has not been used to evaluate the attributes of the new AHAs. Therefore, it is critical to assess the importance of the attributes of new second-line AHAs, including SGLT-2is and GLP-1 RAs, for T2DM patients.

The goal of this study was to determine patients' preferences for the second-line AHAs. To achieve

the goal, this study included two steps. First, patients' priorities on all second-line AHAs' various attributes were examined using the best-worst scaling (BWS) method. The important attributes associated with SGLT-2is and GLP-1 RAs in the first step were used to identify the patients' preferences of these two drug groups in the second step of the study by using a discrete choice experiment (DCE).

1.3 Specific aims

Specific Aim 1: Rank the importance of the attributes of second-line AHAs for T2DM. BWS object case (Case 1) method was used to rank a comprehensive list of the attributes of the second-line AHAs, including sulfonylureas, SGLT-2is, thiazolidinediones, GLP-1 RAs, DPP-4 inhibitors, and insulin, based on the importance of these attributes to T2DM patients.

Specific Aim 2: Determine patients' preferences for SGLT-2is and GLP-1 RAs using discrete choice experiment (DCE). DCE was used to determine patients' willingness-to-pay (WTPs) for the attributes and SGLT-2is and GLP-1 RAs. These WTPs reflected the valuation of the SGLT-2is and GLP-1 RAs from patients' perspectives.

1.4 Significance of the study

This was the first study to empirically examine the relative importance of attributes from all six groups of the second-line AHAs. The BWS object case allowed a comprehensive list of the treatment attributes without a significant cognitive burden in this study.[44] The study findings helped to rank the important attributes for the second-line AHAs from the patient's perspective. Clinicians could use these findings to discuss with patients and better understand patients' needs while selecting the second-line AHAs. In other words, they could use the study findings to engage patients in their treatment decision-making process, leading to improved patient adherence and outcomes.[45] Similarly, this was the first study that examines the patients' preferences and their WTPs for each medication of SGLT-2is and GLP-1 RAs. The relative importance of the benefits, risks, and other important attributes of the SGLT-2is and GLP-1 RAs and how patients' tradeoff these attributes would guide clinicians to engage their patients in their treatment decision-making.

Also, various professional organizations, e.g., ADA, AACE, ACE, and EASD, could use the study findings to develop clinical practice recommendations. For instance, AACE and ACE could adopt

the results to improve their consensus statement on the comprehensive T2DM management algorithm. The findings would support a founding principle of the algorithm—the choice of T2DM therapies must be individualized based on attributes specific to both patients and the medications.

Chapter 2

Literature Review

2.1 Diabetes Mellitus (DM)

DM is a set of metabolic diseases due to insufficient production of β-cell hormones (i.e., pancreatic islet dysfunction), or insulin insensitivity of the normally insulin-sensitive peripheral tissues, responding improperly the insulin produced (i.e., peripheral insulin resistance). [46] It is characterized by an elevated concentration of blood glucose level for a long duration of time. [47] As per World Health Organization's (WHO) criteria, diagnostic tests for DM include the measurement of fasting plasma glucose level ≥126 mg/dL (7.0 mmol/L), 2-hour plasma glucose level ≥200 mg/dL (11.1 mmol/L) after a 75-g oral glucose load, and a glycated hemoglobin level of ≥6.5% or a random blood glucose level ≥200 mg/dL (11.1 mmol/L) in the presence of signs and symptoms of diabetes. [1] The presence of impaired glucose tolerance and/or impaired fasting glucose and/or A1c value between 5.7% and 6.4% are defined as prediabetes. [48] Patients with prediabetes are individuals whose glucose levels do not meet the criteria for diabetes but too high for normal consideration and usually associated with obesity, dyslipidemia with high triglycerides and/or low HDL cholesterol, and hypertension. [48] The signs and symptoms of DM include glycosuria (glucose excreted through urine), polyuria (frequent urination), polydipsia (increased thirst), polyphagia (increased hunger), diabetic retinopathy (blurred vision), frequent infections, extremity numbness or tingling, fatigue, and weight loss. [1, 48] Diabetes is often associated with long-term microvascular and macrovascular complications that result in damage and sometimes failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels. [49, 50]

As per the American Diabetes Association (ADA), diabetes can be classified into four categories [48]

1. Type 1 DM (T1DM); diabetes due to autoimmune β-cell destruction that leads to absolute insulin deficiency

2. Type 2 DM (T2DM); diabetes due to a progressive loss of adequate β-cell insulin

secretion

3. Gestational DM; diabetes diagnosed in the second or third trimester of pregnancy

4. Specific types of diabetes due to other causes such as neonatal diabetes or drug-or chemical-induced diabetes, e.g., glucocorticoid use or after organ transplantation

Although the classification of diabetes is used to determine treatments, some individuals at the time of diagnosis cannot be identified as having T1DM or T2DM.

T1DM is characterized by insufficient insulin production due to the loss of the pancreatic β-cells. It is an autoimmune disorder in which the body's immune system attacks the β- cells in the pancreas, the cells that produce insulin. Thus, it eliminates insulin production, which could occur because of a combination of β -cell loss and dysfunction. T1DM was referred to as insulin-dependent diabetes mellitus (IDDM) or juvenile diabetes due to its frequent onset in childhood. However, T1DM can occur in any age group, and a significant proportion is diagnosed among young children. [48, 51] Despite extensive research, the nature of the autoimmune abnormalities and destruction of the β-cells is still unclear. [47, 51] Based on the National Health Interview Survey (NHIS) data, the prevalence rate for T1DM was 0.5% of the adult population in the US for the years of 2016/17. [52]

Similarly, the prevalence rate in the same years for T2DM was 8.5% of US adults and accounted for more than 90% of all DM types. [52] Such a high prevalence rate might be due to various genetic, environmental, and lifestyle factors that result in the progressive loss of β-cell mass and function, causing insulin resistance and insulin deficiency, thus increasing hyperglycemia in T2DM. [47] Compared to T1DM, insulin is relatively deficient in T2DM. Therefore it was previously referred as "noninsulin-dependent diabetes or adult-onset diabetes. [48] Many patients with T2DM were overweight or obese and had an increased risk of insulin resistance. [53] In many cases, T2DM remained undiagnosed for extended periods because hyperglycemia developed gradually and did not cause severe complications to be noticed. [48] Thus, many patients had a late diagnosis of T2DM with a higher hyperglycemia value that required a combination of therapy.

Gestational DM is the condition of hyperglycemia diagnosed for the first time during pregnancy (gestation). Generally, gestational DM indicates an underlying β-cell dysfunction marked as an increased risk for T2DM in women after delivery. [48] Most women with gestational DM tended to have this β-cell dysfunction related to chronic insulin resistance or lower insulin secretion for the degree of insulin resistance. However, they might also have autoimmune β-cell dysfunction.

Also, there are different types of diabetes besides T1DM, T2DM, and gestational DM due to various causes such as cystic fibrosis-related diabetes, which is a common secondary complication of cystic fibrosis. [47, 48] Post-transplantation DM (PTDM) is a specific DM type in which individuals develop new-onset diabetes following transplants. [48] Monogenic diabetes syndromes are monogenic defects that cause β-cell dysfunction in neonatal diabetes and Maturity-Onset Diabetes of the Young (MODY). Pancreatic diabetes is another type of special diabetes due to structural and functional losses of glucose-normalizing insulin secretion.

2.2 Pharmacological treatments for T2DM

The management of diabetes treatment includes lifestyle intervention such as diet, physical activity, etc., and pharmacological therapies. [17] We will focus on the pharmacological treatments for T2DM in this review. These treatments focus on glycemic control by maintaining blood glucose levels within a normal range in order to reduce the risk of diabetes-related complications. Lowering A1c to the normal range showed a reduction in macrovascular and microvascular complications, cardiovascular diseases, and all-cause mortality. [5-7] For many non-pregnant adults, the A1c had to be lower than 7% (53 mmol/mol). Based on patients' preferences, lowering A1c level to less than 6.5% was also acceptable if it was achieved safely without significant hypoglycemia or other adverse effects. [5] Therefore, the recommended A1c goal for many non-pregnant, non-elderly adults was <7%. [5, 54]

Initial Therapy

Metformin is the preferred initial pharmacologic agent for T2DM unless there are contraindications along with combination with lifestyle modification. [18, 54] Its glucose-lowering effect results from decreased hepatic glucose production and increased glucose utilization. [55] Metformin is an effective, safe, inexpensive treatment that reduces the risk of

cardiovascular events and death. [6] It reduces A1c by 1.5% and fasting blood glucose by approximately 20%. It has neither an adverse cardiovascular effect nor lipid-lowering activity. [56] Nausea, abdominal discomfort, and diarrhea are the most common side effect, which may subside as the body gets used to the metformin. If metformin and lifestyle changes are not enough to control the blood sugar level, other medications can be added.

Combination Therapy (Second-line drugs)

Due to the progressive nature of diabetes, metformin alone may not able to maintain blood glucose levels. If the goal of maintaining glycemic target is not achieved within three months of the initial treatment or depending on the patients' hyperglycemic condition, a second-line treatment from six different groups of AHAs is recommended to combine with metformin. [9, 57] ADA/EASD preferred second-line drug classes for T2DM are sulfonylurea, thiazolidinedione, DPP-4 inhibitor, SGLT-2is , GLP-1 RA, and insulin. The choice of treatment to be added to metformin is based on the drug-specific characteristics and the patients-specific factors, including comorbidity conditions, e.g., cardiovascular disease, renal disease, the necessity of weight loss, etc. Insulin and GLP-1 RAs are the second-line AHAs available in injectable dosage form, except semaglutide that is available for both oral and injectable dosage forms.

Table 2-1 summarizes the drug-specific characteristics of the second-line AHAs that should also be considered while making such a selection. Sulfonylurea (SU), Thiazolidinediones (TZD), DPP-4 inhibitors, and insulin are older second-line drugs. SU increased insulin secretion and enhanced insulin activity by inhibiting an adenosine triphosphate–dependent potassium channel, which resulted in cell membrane depolarization and led to calcium influx and release of stored insulin from secretory granules within the cell. [58] SU such as glimepiride, glipizide, or glyburide could reduce A1c level in patients with T2DM by approximately 1.0% to 1.25%, compared to placebo and persisted for their effects at least two years. [59] Possible side effects of SU included low blood sugar and weight gain. Many observational studies also claim SU might increase CV risk. [59] TZD could lower the blood glucose level by activating the peroxisome proliferator-activated receptor (PPAR)-γ, thus fostering insulin sensitivity in skeletal muscle, liver, and adipose tissue. [57] TZD such as pioglitazone, rosiglitazone resulted in

significant A1c reductions of 0.5% to 1.5%; however, it was associated with fluid retention that caused weight gain, peripheral edema, and heart failure. [57] DPP-4is reduced the activity of serum DPP-4, which increased the availability of endogenous incretins, stimulated insulin secretion and inhibited glucagon release from pancreatic α-cells, suppressed gastric emptying, and reduced appetite and food intake. [60] In a meta-analysis of 80 clinical trials, DPP-4is lowered A1c 0.6% to 1.1%. [61] Different DPP-4is such as alogliptin, linagliptin, sitagliptin, or saxagliptin had different routes of elimination. Other significant benefits of DPP-4is included neutral to change in body weight, modest systolic and diastolic blood-pressure-lowering effects, and low risk of hypoglycemia. [68] The only potential risk of DPP-4is was pancreatitis. [57] Insulin helped the rapid onset of blood glucose level; however, it also required frequent monitoring of blood glucose in order to prevent hypoglycemia. There are various types of insulin, including rapid-acting treatments (e.g., lispro, aspart), short-acting treatments (e.g., human regular), and intermediate-acting treatments (e.g., Human isophane). [57] ADA recommended basal insulin combined with metformin as a step-up therapy from monotherapy or initial dual therapy for T2DM patients with A1c level >9% and hyperglycemia. [5]

SGLT-2is and GLP-1 RAs are newer second-line AHAs. SGLT-2is decreased the reabsorption rate of filtered renal glucose and promoted urinary glucose excretion, thus reducing hyperglycemia. [57] In a meta-analysis of 34 clinical trials, SGLT-2is were associated with a mean reduction in A1c of −0.69% (95% CI, −0.75 to −0.62), body weight by -2.1 kg (95% CI, −2.3 to −2.0), and systolic blood pressure by −3.9 mm Hg (95% CI, −4.6 to −3.3) in comparison to placebo. [62] EMPA-REG OUTCOME trial showed the cardiovascular outcomes for SGLT-2is by comparing with placebo, empagliflozin could reduce risks in MACE, cardiovascular mortality, all-cause mortality, and heart failure-related hospitalization for T2DM patients with cardiovascular diseases. [63] Canagliflozin and dapagliflozin could lower hypoglycemia risk and promote weight reduction, but their adverse effects included genitourinary infection, polyuria, and rarely diabetic ketoacidosis. [57] GLP-1 RAs, synthetics analog to the native human GLP-1, could stimulate the GLP-1 receptor, thus enhancing insulin release and decreasing glucagon secretion from the pancreas. [57] A review article indicated that all six GLP-1 RAs could reduce A1c ranging from -0.3% to -1.9%. [64] All GLP-1 RAs are administered by injection, except semaglutide, which is available in both oral and injection forms. [65] Liraglutide Effect and

Table 2-1. Characteristics of the second-line antihyperglycemic drug classes for T2DM. [17, 57]

Class (Route of Administration)	Drugs	Mechanism of Action	Advantage	Disadvantage	Cost
Sulfonylurea (Oral)	Glimepiride Glipizide Glyburide	• Increase insulin secretion	• Extensive experience • Relatively higher HbA1c efficacy	• Hypoglycemia • Increase weight	Low
Thiazolidinediones (Oral)	Pioglitazone Rosiglitazone	• Increase insulin sensitivity	• Relatively higher HbA1c efficacy • Rare hypoglycemia	• Increase weight • Edema / Heart failure	Low
DPP-4is (Oral)	Alogliptin Sitagliptin Linagliptin Saxagliptin	• Increase insulin secretion • Decrease glucagon secretion	• Rare hypoglycemia • Well tolerated	• Rarely angioedema/urticaria • Neutral in weight change	High

Sodium–Glucose Cotransporter-2 Inhibitor (Oral)	Canagliflozin Dapagliflozin Empagliflozin	• Blocks glucose reabsorption in the kidney	• Rare hypoglycemia • Decrease weight • Decrease blood pressure • Associated lower CVD event rate and mortality	• Genitourinary infections • Polyuria • Increase risk of diabetic ketoacidosis	High
Glucagon-Like Peptide-1 receptor agonist (Subcutaneous Injection)	Exenatide Dulaglutide Liraglutide Semaglutide*	• Increase insulin secretion • Decrease glucagon secretion • Slow gastric emptying	• Rare hypoglycemia • Decrease weight • Decrease CV risk factors • Associated with lower CVD event rate and mortality	• GI side effects such as nausea, vomiting • Increase heart rate • Injection site infection • Required training	High

Insulin (Subcutaneous Injection)	Insulin Aspart Insulin Lispro Insulin glargine	• Work as human insulin	• Highest efficacy of lowing blood sugar	• Higher risk of hypoglycemia • Injection site infection • Required training	High

*Semaglutide is available in both oral and injectable dosage form

Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial and long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6) trial demonstrated a reduced risk in MACE. [10, 11] Other benefits of GLP-1 RAs for T2DM patients included a low risk of hypoglycemia, weight reduction, lower CVD event rate, and mortality in patients with CVD. However, GLP-1 RAs' side effects had GI disorder, such as nausea, vomiting and diarrhea, and pancreatitis. [57]

2.3 Economics of T2DM medications

In 2019, the world prevalence of DM was approximately half a billion people, with 31 million people living in the US. [66] Without sufficient action, these numbers would increase by 51% in 2045. ADA also confirmed a high prevalence of diabetes in the US, with an annual growth of 700,000 people. [67] Uncontrolled diabetes could lead to several macrovascular (cardiovascular and cerebrovascular) and microvascular (nephropathy, diabetic foot, and retinopathy) complications, which reduced the quality of life and increased premature mortality considerable healthcare expenditures. [67, 68] An economic study in the US estimated that the total estimated cost of DM in 2017 was $327 billion, of which $237 billion represented direct healthcare expenditures attributed to DM. [67] The costs associated with medications were approximately $102 billion, of which $31 billion were AHAs' costs. Specifically, the treatment costs for T2DM had recently increased as the newer AHAs, including SGLT-2is and GLP-1 RAs, were expensive in comparison to other agents. [69] A recent study reported that the median retail price for one-year supply for these two drug groups across Medicare Part D prescription drug plan in 2019 ranged from $3,600 to $ 11,304. An average beneficiary could spend at least $1,000 annually for SGLT-2is and greater than $1,500 for GLP-1 RAs, making these medications unaffordable for hundreds of thousands of T2DM patients. [23] In addition, while people with private health insurance needed to spend a significant out-of-pocket amount for their diabetes treatments, two million adults with diabetes in the US had no health insurance coverage. [70] Since patients had to pay a large amount of cost-sharing for T2DM medications, the costs of these medications would impact their decisions of treatment initiation, adherence, and continuation of treatment. [71]

Cost-effectiveness analysis (CEA) with quality-adjusted life year (QALY) has been used as a tool to assess the value of drugs and healthcare services in order to help patients access needed

medicines and healthcare. The newer AHAs, including GLP-1 RAs and SGLT-2is, were more cost-effective than insulin, TZDS, and sulfonylurea. [69, 72, 73] The results of these studies showed GLP-1 RAs tended to be more cost-effective than SGLT-2is. [72] However, a systematic review indicated that approximately 85% of the cost-effectiveness analyses (CEAs) were based on a payer perspective and funded by the pharmaceutical industry. [72] Despite the wide use of CEA with QALYs for assessing the value of drugs, it remains controversial. [74] Since the QALY metric is a single-dimensional and generic health measure, the value assessments using CEA with QALYs fail to capture important elements of value. In addition, the QALY generally neither addresses the heterogeneity of patient preferences nor engages patients, who are increasingly taking on an active role in US healthcare. [75, 76] Therefore, it is important to determine patients' preferences and WTP for AHAs and incorporate it into the value assessment of these treatments.

2.4 Patient preference

Patient preference is important and increasingly used in the medical decision-making process. It is the individual's evaluation of dimensions of health outcomes such as a patients' value for a specific component or attribute, either in absolute terms or in relation to another attribute. [77, 78] US Food and Drug Administration (FDA) defined patient's preference as the "relative desirability or acceptability to patients of specified alternatives or choices among outcomes or other attributes that differ among alternative health interventions". [79] The relative importance is identified by choices that are traded off with one or more desirable outcomes, such as a change in A1c level or lower cost in order to obtain a more desirable composite outcome. Thus, patients' preferences reflect what patients prioritize while selecting their treatment, what treatment attributes are important to patients, and how patients make tradeoffs between treatment attributes. A patient's preference can primarily be estimated by two methods: preference exploration (qualitative) and elicitation (quantitative) methods. [80] The preference exploration method involves qualitative methods of collecting descriptive data through participation or observation and examining participants' subjective experiences and decisions. It is designed to gain an understanding of patients' thoughts, feelings, and experiences. Preference elicitation involves the quantitative method of patient-preference, a structure with predefined data to be collected, and response options limited to permit statistical analysis. [79] This review focuses on only preference elicitation, which

will be used to design this study.

Patient's preferences can be elicited through two different methods, stated preference, and revealed preference methods. The stated preference methods elicit subjects' preference for hypothetical options in an experimental framework, whereas the revealed preference methods are based on observed data relating to individuals' actual behavior. [78] Therefore, revealed preference data indicate what individuals do under the actual condition and lack the information why they do it. However, the stated preference methods allow researchers to ensure statistical variability to estimate individual features. [78] They have been used for many years to elicit information on preferences in various fields, including transportation, marketing, environmental, and resource economics. Recently, there is a growing interest among healthcare decision-makers using stated-preference methods to quantify preference in health economics, health technology assessment, benefit-risk assessments, and health service search. [81] The objective of stated-preference studies is to acquire information about tradeoff preferences among treatment outcomes, prioritization of clinical decision criteria, likely uptake or adherence to healthcare products, and acceptability of healthcare services or policies. There are several stated preference methods. This review includes only best-worst scaling (BWS) and discrete choice experiment (DCE), which are frequently used to elicit the patient's preference. They will be used in this study.

2.4.1 Best-Worst Scaling (BWS)

BWS is a stated preference elicitation method rooted in random utility theory. [82, 83] The statistical model of BWS assumes that a given pair's relative choice probability is proportional to the distance between the two attributes levels on a latent utility-scale. [82] BWS explores how participants make best and worst (or most important and least important) choices from the set of three or more choices. [82] Such a choice set in healthcare could be a list of interventions, treatments, medications, or comparable characteristics. The key assumption in BWS is that the worst estimates are equal to the minus best estimates. In BWS, individuals select the greatest value choices relative to other given choices, which provide the information that matters most to individuals. BWS also evaluates the overall impact of attributes on the same scale, instead of being evaluated separately from the additional utility gained/taken away by other attributes. [82] There are three types of BWS, including object case (case 1), profile case (case 2), and multi-profile case

(case 3). [84] In the BWS object case, individuals are asked to choose the best and worst from a set of objects. In the BWS profile case, individuals evaluate several profiles of objects described by combinations of attributes/features and choose the best and worst feature/attribute levels within each presented profile. [84] The multi-profile case is similar to classical DCE, where individuals choose the best and the worst designed profiles (choice alternatives) from three or more alternatives. [84] A BWS assumes that individuals make reliable and valid choices of the two most extreme objectives/items in a set. Both "best" and "worst" information is collected in BWS is the key advantage of BWS that provides information about both top-ranked and bottom-ranked items in a set. [85]

Many researchers have utilized the BWS object case since it is relatively easy to implement and analyze data through simple analysis methods such as best-minus-worst scores. [85] Such a methodology can include a large number of items or attributes of interest. Various studies used the BWS object case to rank the importance or prioritization of healthcare and medications' attributes. [86-88] For instance, one study used the BWS object case to prioritize general aspects of reflux treatments among the parents to identify important attributes of treatments, which were later used in multi-profile case of BWS to identify parent's preference for treatment attributes of Vesicoureteral Reflux (VUR). [88]

2.4.2 Discrete Choice Experiment (DCE)

Discrete choice experiment (DCE) is an attribute-based survey method based on a random utility theory (RUT). RUT assumes that a person has a "utility" for each choice alternative. [89, 90] DCE is used to estimate individual preference, assuming that individuals make a rational decision. [90] The relative preference for object A over object B is determined based on the relative frequency in which object A is preferred over object B with some degrees of error. DCE elicits people's preferences for goods and services based on their choices over different hypothetical situations with different levels of characteristics of that goods or services. [91] Instead of ranking or rating different features, DCE compares hypothetical alternatives and asks participants to choose among them. [92] Thus, the participants are forced to make tradeoffs between attributes and their levels, allowing them to determine the relative importance of attributes. [81]

DCE method is increasingly used in health literature to address a broad range of health policy-related concerns. [93, 94] While DCE was introduced to value patient experience, their applications are now much broader in health economics. A systematic review identified DCE's wide application, which is used to explore patient or consumer experience, tradeoffs between health outcomes and patients' experience factors, and health professionals' preferences for treatments and screenings. [95] DCE is also used to measure a wide range of outcomes, including WTP, utility score, probability score, odd ratio, and other outcomes such as choice shares, maximum acceptable risk, and relative importance. [95]

2.5 Patients' Preferences and WTP for T2DM medications

Patients' preferences for diabetes are complex due to the chronic nature of the disease, the extensive range of medication options & its related benefits, risk and treatment process, and time horizon of health outcomes. [43] Earlier two reviews summarized patients' preferences for T2DM medications. [42, 43] One systematic review included ten studies conducted in the US, Sweden, Denmark, and the UK from 2007 to 2012. These studies had different methods, including DCE, time tradeoff method, conjoint analysis, survey question with Likert-type rating scale, and standard gamble, to assess patients' preferences for non-insulin diabetes medications. [43] This review divided the attributes of medications into three categories: treatment benefit, treatment burden, and side effect. [43] The treatment benefits included glycemic control, weight loss or control, blood pressure control, heart function, and a factor associated with quality of life such as life expectancy, avoidance of diabetes complications, and ability to possess a driver's license. The review also identified gastrointestinal effects such as nausea and upset stomach, hypoglycemia, injection site reactions, weight gain, water retention, and increased risk of heart attack as attributes associated with the treatment side effect. [43] In contrast, the method of delivery and mode of administration, dose frequency and flexibility, required blood glucose and laboratory testing, treatment-related cost, and treatment intensity were identified as attributes related to the treatment burden. [43] Although this review identified various attributes of non-insulin diabetes medications, an important second-line AHAs' attributes, i.e., basal insulin, were not examined. A scoping review conducted a novel quality assessment (PREFS) for preference studies and cataloging the preference elicitation method. [42] This review identified ten out of 61 studies using a DCE. These

studies were conducted in 22 different countries, and the majority of them (N=27) were from the US. In this review, basal insulin and other AHAs were included, but these medications' important attributes were not discussed.

Several DCE studies that elicited preferences among T2DM patients were published after the study periods covered in those two reviews. [24-39] Some studies compared the specific medications such as dulaglutide, semaglutide, and liraglutide, [24, 27, 28] while one study compared the injectable exenatide (Byetta®), oral glucose-lowering medicines, and hypothetical new treatments. [26] One study did not mention the treatment comparison. [32] The majority of these studies used online or web-based surveys to collect data. [24-26, 28-33, 35, 36, 38, 39] Three studies used the in-person method. [27, 34, 37] Their sample sizes ranged from 100 to 1,114. [24-39] The number of attributes included in these studies ranged from five to ten. Table 2-2 summarizes the attributes included in these DCE studies. [24-39] These attributes could be categorized into three groups, including treatment benefits, side effects and treatment processes as discussed in the previous systematic review. [43] The attributes related to the treatment benefits included glycemic control, which assesses treatment efficacy in reducing HbA1c or reduction blood glucose or sugar, weight change or control, cardiovascular risk reduction such as a reduction in a heart attack or stroke, reduction in a macrovascular and microvascular event, change in life expectancy, change or decrease in blood pressure, stable blood glucose, long term effectiveness of medication and additional healthy life year. Glycemic control or medication efficacy was the most frequently used among these treatment benefit attributes [24, 25, 27-33, 35-39], followed by weight loss or change [24, 26-31, 33-35, 37-39] among these studies. The attributes related to the treatment side effects included gastrointestinal side effects related to nausea, vomiting, and diarrhea, hypoglycemia in different forms such as mild & moderate to severe forms, injection site reaction, urogenital infection including urinary tract infection as well as genital infection, and some adverse events such as the chance of heart failure, risk of cancer, and death. The incidence of gastrointestinal side effects such as nausea, vomiting, or diarrhea [24-34, 36-39] and hypoglycemia incidence [25-33, 36-38] was the most frequently used among the attributes related to the treatment side effects. These most used attributes for the treatment benefits and side effects coincided with the attributes from a previous systematic review of patients' preferences for non-insulin medications. [43]

Beside treatment benefits and side effects, medications have different treatment processes or characteristic, such as dosage form, dose frequency, route of administration which can have impact on quality of life, treatment adherence and disease outcomes. Also, patients might have difference preference for different characteristic of treatment. A systematic review on patients' preference examined the significance of these treatment characteristics which were grouped as treatment process attributes. This review study confirmed that treatment process attributes have a quantifiable impact on patients' preference and WTP for the treatment, even when treatment benefit and side effect were the primary concern. [96] Thus, most DCE studies for T2DM medications included treatment process attributes such as cost of medication, mode of administration, dosing frequency, needle size, storage, instruction to use, requirement of additional medicines, and blood glucose monitoring. [24-39] The cost of the medication was frequently used among the attributes related to the treatment process. [25, 26, 30-32, 35, 37-39] The results of the studies conducted outside the US were mixed due to various reasons, including different treatment attributes and populations. For instance, dosing frequency and type of delivery system were the most important characteristics in a study from Japan. [27] T2DM patients in Singapore were willing to trade the risk of higher urinary and genital tract infections for more effective medication. [39]

Among these 16 DCE studies, three studies were conducted in the US. [30-32] The first study specifically focused on T2DM patients' preferences for reducing pill burden and dosing frequency. [30] This study asked patients who were on oral AHAs to complete an online survey. The study attributes included reduction in average glucose, daily dosing schedule, the chance of mild to moderate stomach, hypoglycemic event, weight change within the first six months of treatment, the additional chance of congestive heart failure, and out-of-pocket cost. Among these attributes, the reduction in average glucose was the most important attribute. The reduction in daily-dosing schedule was relatively more important than the increases in the chance of mild to moderate stomach problems, weight change. This study also determined patients' WTPs for reducing pill burden and dosing frequency. The second study elicited preferences for alternative route of administration for oral AHAs among patients with different characteristics. [31] T2DM patients taking no or only one oral AHA, and no injectable therapies were asked to complete a web-enabled DCE survey. The study attributes included the same attributes as the first study did. The results

showed that the change in dosing schedule was less important than the out-of-pocket cost, which was the most important attribute. Among all patients, 67% preferred weekly dosing over a daily dosing schedule. The once-weekly dosing might provide additional incentive for younger patients and patients not currently on treatment to adhere to AHAs. Another study assessed the treatment preferences and WTP of T2DM patients by educational attainment. [32] T2DM patients were asked to complete an online DCE survey. The study consisted of six attributes, including A1c decrease, stable blood glucose, low blood glucose, nausea, treatment burden, and out-of-pocket cost. The results showed that patients with better education were more willing to pay. Although this study did not examine only oral AHAs, some potential benefits of new AHAs, as such SGLT-2is and GLP-1 RAs were excluded.

There is, therefore, no study focusing on patients' preferences and WTPs for SGLT-2is and GLP-1 RAs in the US. It is necessary to assess important treatment attributes from all six groups of second-line AHAs, based on patients' perspectives. Understanding patients' preferences and WTPs for T2DM medications can inform clinicians, payers, and policymakers and subsequently improve patient access to the second-line AHAs, adherence, outcomes, and quality of life.

Table 2-2. Summary of treatment-related attributes from patients' preference studies for T2DM medications using DCE methodology after 2013. [24-39]

Author	Year	Sample Size	Treatment-related attributes		
			Benefit	Side effects	Treatment Process
Brooks et al. [24]	2019	161	Glycemic Control (HbA1c change) Cardiovascular risk reduction Weight loss/change	Gastrointestinal effects	Method of administration
Donnan et al. [25]	2020	502	Glycemic control (HbA1c) Macrovascular events (Reduction in heart attack, stroke or death from cardiovascular diseases)	Risk of minor side effects (e.g., Weight gain, stomach upset, skin rash, low energy Hypoglycemia	Cost

			Microvascular events (Reduction in eye, kidney and nerve damage)	Risk of a serious side effect	
			Change in Life expectancy		
			Weight loss/change	Gastrointestinal effects (Nausea)	Dosing Frequency
				Injection site reactions/nodules	Needle size
Fifer et al. [26]	2018	171		Hypoglycemia	Storage
					Mode of administration
					Cost
					Instructions to use
			Glycemic control (HbA1c)	Gastrointestinal effects (Frequency of nausea)	Dosing frequency
Gelhorn et al. [27]	2016	182			
			Weight loss/change	Hypoglycemia (Frequency of low blood sugar event)	Mode of administration

Gelhorn et al. [28]	2015	243	Glycemic control (HbA1c)	Gastrointestinal effects (Frequency of nausea)	Dosing frequency
			Weight loss/change	Hypoglycemia (Frequency of low blood sugar event)	Mode of administration
Gelhorn et al. [29]	2013	100	Glycemic control (HbA1c)	Urogenital infection side effects	
			Weight loss/change	Gastrointestinal (GI) effect (nausea side effects)	
			Change in blood pressure	Hypoglycemia	
			Cardiovascular risk reduction		
Hauber et al. [30]	2013	1114	Glycemic control (reduction in Avg glucose)	Gastrointestinal (GI) effect	Dosing frequency
			Weight loss/control	Hypoglycemia (event)	Cost
				Chance of Heart Failure	
Hauber et al. [31]	2015	923	Glycemic control (reduction	Gastrointestinal (GI) effect	Dosing frequency

			in Avg glucose)		
			Weight loss/change	Hypoglycemia (event)	Cost
				Chance of Heart Failure	
Janssen et al. [32]	2017	552	Glycemic control (HbA1c)	Hypoglycemia	Additional medicine
			Stable blood glucose	Gastrointestinal (GI) effect (nausea)	Cost
Mansfield et al. [33]	2017	875	Glycemic control (HbA1c)	Hypoglycemia	Mode of administration
			Cardiovascular risk reduction	Gastrointestinal (GI) effect	Dosing frequency
			Weight loss/change		
Marchesini et al. [34]	2019	662	Weight loss/change	Urogenital infection	Mode of Administration
				Gastrointestinal (GI) effect (Nausea)	Dosing frequency
Mohamed et al. [35]	2013	400	Glycemic control (HbA1c) for once a day treatment	Mild to moderate hypoglycemia	Dosing frequency in the morning

			Glycemic control (HbA1c) for twice a day treatment	One severe hypoglycemia per year	Dosing frequency in morning and evening
			Weight loss/change		Cost
Mol et al. [36]	2015	226	Glycemic control (HbA1c)	Gastrointestinal (GI) effect (nausea, vomiting, or diarrhea)	
			Cardiovascular risk reduction	Hypoglycemia	
			Weight loss/change	Risk of Cancer	
Morillas et al. [37]	2015	330	Glycemic control (HbA1c)	Hypoglycemia	Mode of administration
			Weight loss/change	Gastrointestinal (GI) effect (Nausea)	Blood glucose monitoring
			Cardiovascular risk reduction		Cost
Mühlbacher et al. [38]	2016	626	Glycemic control (HbA1c)	Hypoglycemia	Additional healthy life years (AHY)

			Weight loss/control	Risk of genital infection	Cost
				Risk of urinary tract infection	
				Gastrointestinal (GI) effect	
			Years of medication effectiveness	Risk of gastrointestinal problems	Cost
Ozdemir et al. [39]	2020	160	Weight loss/change	Urogenital infection	
				Chance of heart failure	
				Number of people death	

Chapter 3

Methods

This study was completed in two steps. First, based on patients' priorities ranking of treatment attributes for second-line antihyperglycemic agents (AHAs) was determined using the best-worst scaling (BWS) method. Patients' priorities for the attributes of second-line AHAs would inform the important attributes associated with SGLT-2is and GLP-1 RAs. In the second step, patients' preferences for GLP-1 RAs and SGLT-2is and their WTPs for each attribute and each medication were determined using a DCE.

3.1 Methods for aim 1 (Rank the importance of the attributes of second-line AHAs)

3.1.1 Study Design

A cross-sectional, web-based BWS questionnaire survey was used to rank the importance of the attributes for all second-line AHAs based on patients' priorities. BWS object case (Case 1) was selected in this study since it could incorporate a large number of attributes and had a minimal cognitive burden to participants.[44, 97]

3.1.2 Samples

Qualtrics^{XM}, a commercial survey sampling and administration company, was contracted to recruit samples for this study. Qualtrics^{XM} aggregated panels of voluntary survey participants from market research who were recruited through email, social media, or website recruiting ads. Patients diagnosed with T2DM, 19 years or older, and proficient in English were included in this study. The literature provides no guidance for determining a minimal sample size for BWS application suggesting that the complexity of the analysis of the BWS prohibited the specific method for such calculations.[84, 98] Also, a recent systematic review indicated that previous BWS studies with significant results used a wide range of sample sizes from 16 to 5,026.[83] For this study, a sample size around 100 T2DM patients was considered to be sufficient to analyze the data for BWS score balanced with feasibility of recruitment and available resources.[99]

3.1.3 Selection of attributes

The ISPOR good research practices for conjoint analysis were used to guide the elicitation of the second-line AHAs' attributes that were important to patients.[100] Based on the current guidelines for the management of T2DM, these medications included SU, TZD, DPP-4is, SGLT-2is, GLP-1 RAs, and insulin.[17, 18, 101, 102] First, a literature review was conducted to obtain the attributes, e.g., benefits, risks, and treatment process, such as route of administration. These attributes were used to guide in-depth interviews with five purposively selected T2DM patients from Baptist Health in Montgomery, AL. Based on the literature review and patient interviews, 22 attributes were identified. Among them, "diabetic retinopathy", "skin rashes", "increased risk of pancreatitis", "increased quality of life (QoL)", and "increased life expectancy" were excluded from the final list of attributes of second-line AHAs in consultation with a clinical pharmacist, who had provided DM care for over a decade, for various reasons. First, diabetic retinopathy (DR) is a rare event and was only observed in the SUSTAIN clinical trial. A study confirmed that such early worsening of DR was associated with the rapidity and magnitude of improvement of glycemic control with insulin.[103] Also, the skin rash was only observed if patients were allergic to any drugs, and in such conditions, those drugs would be discontinued for use. Similarly, the risk of pancreatitis was rare among GLP-1 RAs and DPP4i. A study showed there was no increased risk of pancreatitis.[104] The increased life expectancy and decreasing all-cause mortality were similar; hence only "decreasing all-cause mortality" was kept in the final list of attributes. Similarly, the increased quality of life (QoL) was not selected because QoL itself is patient-reported outcomes that measure patients' physical, functional, mental, and social health conditions.[105] This is a difference from the objective of this study which is to capture patients' desirability and acceptability for treatment benefit, risk, and process. Thus, the final list of 16 attributes associated with six groups of second-line AHAs was confirmed, as showed in table 3.1.

Table 3-1. List of attributes of second-line AHAs.

Attributes	Descriptions	Category
Reduce blood glucose	The medication reduces the blood glucose level in your body	Treatment Benefit
Require regular self-monitoring of blood glucose level	The uses of medication require regular monitoring of your blood glucose level	Treatment Process

Reduce the risk of cardiovascular diseases	The medication can reduce cardiovascular diseases or risks such as heart attack, stroke, or death	Treatment Benefit
Reduce the risk of kidney diseases	The medication can reduce kidney-related complications or protect kidneys	Treatment Benefit
Reduce (slightly) blood pressure	The medication can slightly reduce blood pressure	Treatment Benefit
Reduce the risk of hospitalization for heart failure	The medication can reduce hospital admission due to heart failure	Treatment Benefit
Out-of-pocket cost	Cost of medication you pay out of your own pocket (e.g., copayment or whole amount)	Treatment Process
Increases the risk of diabetic ketoacidosis	The medication increases the risk of breaking down fats too fast making the blood more acidic that leads to diabetic coma or death	Treatment side-effect
Dosing Frequency	Number of times or how often you take the medication	Treatment Process
Gastrointestinal side-effects	The medication can cause gastrointestinal side effects such as nausea, vomiting, and diarrhea	Treatment side-effect
Increases risk of blood glucose lower than normal	The medication can make blood glucose level lower than normal, causing some symptoms, e.g., feeling shaky, sweating, chill, clamminess, confusion, fast heartbeat, lightheaded, etc.	Treatment side-effect
Reaction at injection site	The medication causes injection site reaction e.g. rashes, burning sensation, or nodules	Treatment side-effect
Route of administration	How you take the medication, such as oral or injection	Treatment Process
Increases the risk of urinary tract and genital infection	The medication can increase the risk of genital infection and urinary tract infection	Treatment side-effect
Weight change	The medication can change body weight	Treatment Benefit / Treatment side-effect
Reduce the all-cause death rate	The medication can reduce the death rate from any cause	Treatment Benefit

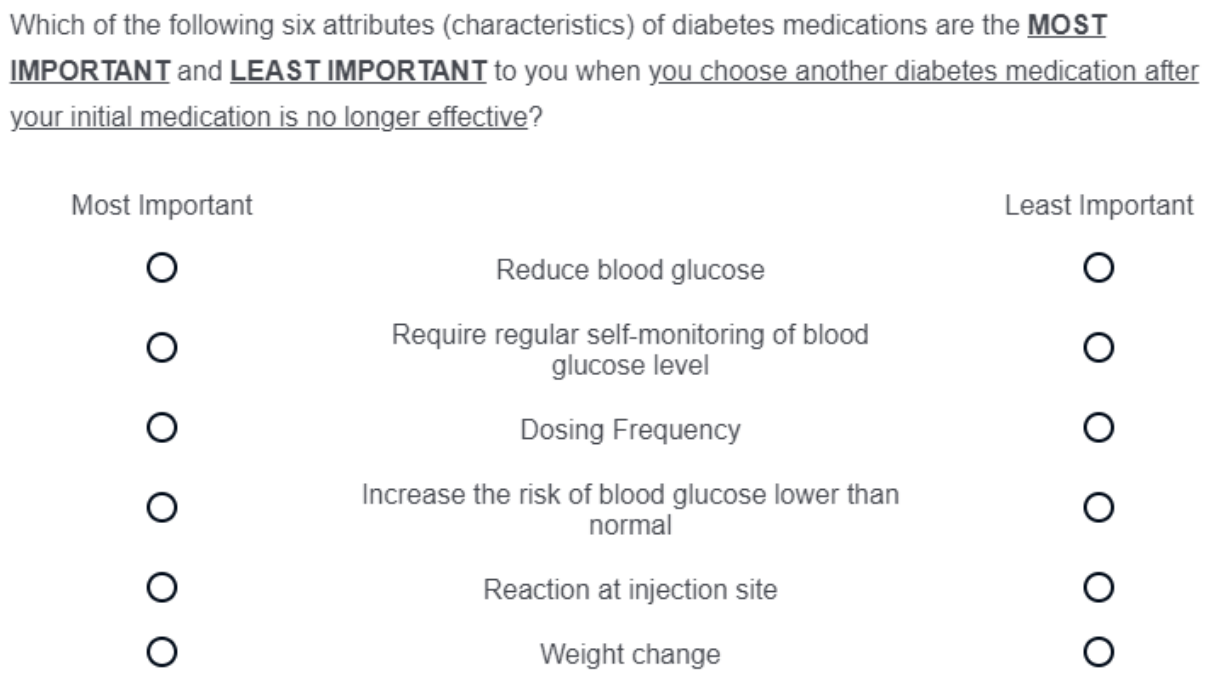
3.1.4 Instrument Development

A self-administered, web-based questionnaire survey was developed from the list of attributes. However, it was a cognitive challenge and burden for the participants if they were asked to consider all the attributes simultaneously. Thus, a balanced incomplete block design (BIBD) was used to generate choice sets included in the questionnaire survey.[106] This design is called balanced because each attribute appeared the same number of times, and any two attributes appeared together with the same number of times. Thus, BIBD ensured an equal probability of selection from each attribute. Computer software package R with library (crossdes) was utilized to create BIBD. The function "find.BIB" was used to generate a block design with "v" number of attributes, "b" number of blocks, and "k" number of elements per block/choice set. A total of 16 choice sets were generated by design to ensure that each attribute was presented six times in total and was viewed with each other twice to fulfill the criteria of BIBD. The design was divided into two versions of eight-choice set and each participant was presented with a randomly assigned version of eight-choice set to reduce the burden on the participants. Each choice set included six attributes along with the description for all attributes in each choice set. The participants were asked to choose the most and least important attributes when they chose another diabetes medication after their initial medication was no longer effective. The detailed instruction about the situation, and explained example choice set, and an additional explanation for all attributes in the survey were provided to participants for a better understanding of the BWS survey questionnaire. One repeated set was added in each survey block to validate their responses. Figure 3 shows an example of one choice set.

The questionnaire survey consisted of four sections (see Appendix I). The initial part of the survey instrument consisted of a screening portion to select patients who agreed to participate in the study based on their age and T2DM diagnosis. In the second part, questions were asked for patients' characteristics (e.g., age, gender, income, health insurance) and T2DM-related experience. Another section consisted of nine BWS choice sets, followed by a single open-ended question for patients' comments on the survey. Two experts from in the field of value assessment and clinical research, were asked to review and check the face validity of the questionnaire survey. The questionnaire survey was converted to a web-based survey using the Qualtrics^{XM} platform. The

survey was pilot tested with 16 patients through the Qualtrics^{XM} panel. The completion time and responses were recorded and assessed. The average time of completion was 10 minutes, and no change was made. Thus, the responses from the pilot study were retained in the final analysis.

Figure 3-1. An example of a BWS choice set.



Description:

Reduce blood glucose : The medication can reduce blood glucose level

Require regular self-monitoring of blood glucose level: The uses of medication require regular monitoring of your blood glucose level

Dosing Frequency: Number of times or how often you take the medication

Increase the risk of blood glucose lower than normal: The medication can make blood glucose level lower than normal, causing some symptoms, e.g., feeling shaky, sweating, chill, clamminess, confusion, fast heartbeat, lightheaded, etc.

Reaction at injection site: The medication causes injection site reaction e.g. rashes, burning sensation, or nodules

Weight change: The medication can change body weight

3.1.5 Data collection

The final survey was launched through the national, online Qualtrics^{XM} panel in March 2021. The initial page of the survey consisted of the consent information, followed by the screening questions for age and diagnosis with T2DM before proceeding further in the survey. Patients, who were unwilling to participate in this study or did not pass the screening questions, were asked to sign off from the survey. For the quality data collection, Qualtrics^{XM} excluded all the participants who completed the survey in less than one-third of the median completion time of the pilot test to warrant the consideration of thoughtful and complete responses. Upon the successful completion of the survey, the participants were remunerated from Qualtrics^{XM}. Auburn University Institutional Review Board (IRB) determined this study was exempt from human subject review (IRB 21-035 EX 2101). Consent from participants was asked in the first step of the survey. All of the participants were instructed that they could quit at any time, and their responses would remain anonymous.

3.1.6 Data analysis

Descriptive analyses were conducted for the participants' characteristics and DM-related experiences. The BWS data were analyzed using the count analysis method, and the standardized BWS score was calculated for each attribute in MS Excel. The values of "+1", "-1", and "0" were assigned to the most important attribute, the least important attribute, and other attributes that were not chosen, respectively. Then, all assigned scores of each attribute in the questionnaire survey were summed and divided by the number of times the attribute was present in the whole survey to calculate the standardized BWS score. The standardized BWS score ranged from -1.0 to +1.0, with a 0 indicating no salience and scores toward ±1.0 indicating increasing salience. In this study, a larger positive BWS score indicated a more important attribute, and a larger negative BWS score indicated a less important attribute. Based on the BWS scores, all attributes were ranked to reflect the importance of the attributes of the second-line AHAs or patients' priorities of these attributes.

3.2 Methods for aim 2 (Determine patients' preferences for SGLT-2is and GLP-1 receptor agonists)

3.2.1 Study Design

A cross-sectional, web-based DCE questionnaire survey was used to determine the patients' preferences for SGLT-2is and GLP-1 RAs. This study followed a user's DCE guide and two reports from the ISPOR Good Research Practices Task Force to design this study. [107]

3.2.2 Samples

Patients aged 19 years or older, diagnosed with T2DM, and proficient in English were recruited through a national, online Qualtrics^{XM} Panel. Qualtrics^{XM} aggregated panels of voluntary survey participants from market research who were recruited through email, social media, or website recruiting ads. This study followed a published practical guide to determine the sample size.[108] Initial coefficients were estimated from a pilot study described later in the instrument development section. The significance level was set at 0.05, while the statistical power level was 80%. We applied R code to calculate the sample size (see Appendix III) and found 39 was the minimum sample size for the significant attributes if we asked each patient to respond to 36 choice sets. In other words, a total of 1,404 responses were needed to test the hypothesis with enough power. Since we asked each patient to respond to nine choice sets in this study, at least a total of 156 patients was required for this study.

3.2.3 Selection of attributes and levels

A study review showed that DCE studies on patients' preferences included 4 to 12 attributes, and the most common number of attributes was six.[42] Benefits and risks associated with SGLT-2is and GLP-1 RAs were obtained from the literature.[14, 16, 109-112] These attributes of SGLT-2is and GLP-1 RAs from the literature review were confirmed and consolidated with the results from an in-depth interview with T2DM patients at Baptist Health, and the BWS results from the first aim. Table 3-2 summarizes the descriptions of selected attributes and their levels that were later used to generate DCE choice sets.

This study included a total of seven attributes, i.e., how do you take the medication, the chance of

reaching target HbA1c (long-term blood glucose level) in 6 months, % reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to cardiovascular diseases), chances of gastrointestinal side effects (i.e., nausea, vomiting, and diarrhea), the occurrence of diabetic ketoacidosis (e.g., vomiting, weight loss, loss of consciousness), chances of genital infection and out-of-pocket cost. DCE should sufficiently vary the relevant attribute levels for modeling, and an extreme range of attribute levels was recommended for DCE. [113] This study identified the extreme ranges of attribute levels from the literature review. These levels of attributes were equally spaced for designing purposes. Table 3-3 shows the list of attributes and their level included in this study.

The reduction of blood glucose attribute was selected since patients in the interview mentioned it, and the results of the BWS study also identified it as the most important attribute. A systematic review for SGLT-2is and GLP-1RAs confirmed that reducing blood glucose, i.e., improving HbA1c, was the primary outcome of these medications [16] and ADA also recommended achieving HbA1c target <7% among T2DM patients. [114] SGLT-2is and GLP-1 RAs had different strengths for achieving HbA1c target <7%, with the range of 18.5% to 87.4% of patients achieving target HbA1c <7% in 6 months. [110, 112] Thus, the three levels of these attributes, including 0%, 50%, and 90%, of the patients achieving target HbA1c <7% in 6 months attribute were chosen. Similarly, treatment guideline and systematic review for SGLT-2is and GLP-1 RAs indicated that reducing cardiovascular disease risk was an important outcome and should be considered while selecting second-line medications for T2DM patients. [17, 109] Reducing the risk of cardiovascular diseases was also the second most important attribute in earlier BWS study. Other attributes, including the reduction of all-cause death rate and the risk of hospitalization for heart failure, were also associated with cardiovascular benefits for SGLT-2is and GLP-1RAs. Many studies combined all these three outcomes as a component of 3-point or 4-point major adverse cardiovascular events (MACE). [109, 111] Reducing the risk of MACE for SGLT-2is and GLP-1 RAs ranged from 0.6% to 39%, which was used to determine the three levels of this attribute. [10, 111, 115]

Three attributes of treatment-related side effects, gastrointestinal side effects, genital infection, and diabetic ketoacidosis, were selected for this study. Recent systematic review and meta-analysis of GLP-1RAs and SGLT-2is also indicated these events were the most frequent and significant side

effects.[111] Although these attributes were ranked lower in the BWS study, T2DM patients showed their concern regarding gastrointestinal side effects of GLP-1 RAs and genital infection due to SGLT-2is during the patients' interviews. The FDA product prescription label was used to confirm the levels of these side effects for each product. For these medications, the percentage of incidence for the gastrointestinal side effects ranged from 2.3% to 25.0%, and the percentage of incidence for genital infection side effect ranged from very rare to 12.2%. The three levels of both GI side effects and genital infection were included to develop the final survey. However, the incidence of diabetic ketoacidosis (DKA) was very rare from the usage of these medications and reported among a few SGLT-2is.[62] Two levels for the occurrence of diabetic ketoacidosis, i.e., rare or none, were included in the survey instrument.

The next attribute was the route and frequency of administration of medication. All SGLT-2is were available in tablet and taken once a day, whereas most GLP-1 RAs were available in injectable form, except oral simaglutide. Also, the frequencies of administration of GLP-1RAs include once a day, twice a day and once a week. Thus, we combined the route and frequency of administration as a single attribute with four levels to ensure that our hypothetical products reflected the route and frequency of administration for existing SGLT-2is and GLP-1 RAs. The last attribute was the monthly out-of-pocket cost of the medication since this study intended to examine patient's WTP for SGLT-2is and GLP-1 RA. The most recent wholesale acquisition costs (WAC) of these SGLT-2is and GLP-1 RAs, ranging from approximately $314 to $915, were obtained from RED BOOK in March 2021.[116] Three levels of this attribute were chosen. Table 3-2 summarizes the selected attributes of SGLT-2is and GLP-1 RAs from the literature.

Table 3-2. Summary of selected SGLT-2is and GLP-1RAs attributes.

AHAs	Route and frequency of administration	Efficacy/Side effects	References
SGLP-2 inhibitors			
Canagliflozin (Invokana®)	Oral 100 mg and up to 300 mg	**Reaching target HbA1c in 6 months**: 971 out of 2016 (avg. 48.16)	[12, 110, 116-118]

	Once a day	**Risk reduction of MACE:** 14.60 (24.00, 4.00) **GI side effect:** Nausea 1.6% placebo, 2.1% Invokana 100 mg, 2.3% Invokana 300 mg **Occurrence of diabetic ketoacidosis:** Rare (0.76 per1000 patient-years) **Genital Infection** Female 2.8% placebo, 10.6% Invokana 100 mg, 11.6% Invokana 300 mg Male 0.7% placebo, 4.2% Invokana 100 mg, 3.8% Invokana 300 mg **Wholesale Acquisition Cost for 1 month** $550.97	
Dapagliflozin (Farxiga®)	Oral 5 mg and up to 10 mg Once a day	**Reaching target HbA1c in 6 months**: 105 out of 265 (avg. 39.62) **Risk reduction of MACE**: 16.00 (26.00, 4.60) **GI side effect:** Nausea 2.4% placebo, 2.8% Farxiga 5 mg, 2.5%, Farxiga 10 mg **Occurrence of diabetic ketoacidosis:**	[13, 110, 116, 117]

		Not reported **Genital Infection** Female 1.5% placebo, 8.4% Farxiga 5 mg, 6.9% Farxiga 10 mg Male 0.3% placebo, 2.8% Farxiga 5 mg, 2.7%, Farxiga 10 mg **Wholesale Acquisition Cost for 1 month** $540.24	
Empagliflozin (Jardiance®)	Oral 10 mg and up to 25 mg Once a day	**Reaching target HbA1c in 6 months**: 293 out of 871 (avg. 33.64) **Risk reduction of MACE**: 13.50 (24.60, 0.70) **GI side effect:** Nausea 1.4% placebo, 2.3% Jardiance 10 mg, 1.1%, Jardiance 25 mg **Occurrence of diabetic ketoacidosis:** Rare (0.6 per1000 patient-years) **Genital Infection: -** Female 1.5% placebo, 5.4% Jardiance 10 mg, 6.4%, Jardiance 25 mg Male 0.4% placebo, 3.1% Farxiga 5 mg, 1.6%, Farxiga 10 mg **Wholesale Acquisition Cost**	[110, 116, 117, 119]

		for 1 month $556.16	
Ertugliflozin (Steglatro®)	Oral 5 mg and up to 15 mg Once a day	**Reaching target HbA1c in 6 months**: 237 out of 720 (avg. 33.01) **Risk reduction of MACE**: 3.00 (15.00, 11.00) **GI side effect: -** **Occurrence of diabetic ketoacidosis:** Not reported **Genital Infection: -** Female 3.0% placebo, 9.1% Steglatro 5mg, 12.2% Steglatro 15 mg Male 0.4% placebo, 3.7% Steglatro 5mg, 4.2% Steglatro 15 mg **Wholesale Acquisition Cost for 1 month** $313.90	[110, 116, 117, 120, 121]
GLP-1 RA			
Exenatide (Byetta®)	Subcutaneous 5 mcg Twice a day	**Reaching target HbA1c in 6 months**: 266 out of 571(avg. 46.58) **Risk reduction of MACE**: 6.80 (14.70, -1.80) **Occurrence of diabetic ketoacidosis:**	[112, 116, 117]

		Not reported **GI side effect:** Nausea 0% placebo, 8% Byetta 5 mcg BID Vomiting 0% placebo, 4% Byetta 5 mcg BID **Genital Infection:** Not reported **Wholesale Acquisition Cost for 1 month** $767.75	
Exenatide (Bydureon®)	Subcutaneous 2 mg Once a week	**Reaching target HbA1c in 6 months**: 670 out of 1241(avg. 53.99) **Risk reduction of MACE**: 6.80 (14.70, -1.80) **GI side effect:** Nausea 11.3 % Bydureon 2mg OQ Diarrhea 10.9% Bydureon 2mg OQ **Genital Infection: -** **Wholesale Acquisition Cost for 1 month** $842.64	[112, 116, 117, 122]
Dulaglutide (Trulicity®)	Subcutaneous 0.75 mg and up to 1.5 mg Once a week	**Reaching target HbA1c in 6 months**: 757 out of 1164(avg. 65.03) **Risk reduction of MACE**: 10.40 (19.20, 0.60)	[112, 115, 117]

		GI side effect: Nausea 5.3% placebo, 12.4% Trulicity 0.75, 21.1% Trulicity 1.5 mg **Genital Infection: -** **Wholesale Acquisition Cost for 1 month** $914.72	
Albiglutide (Tanzeum®)	Subcutaneous 30 mg and up to 50 mg Once a week	**Reaching target HbA1c in 6 months**: 390.4 out of 1668 (avg. 23.4) **Risk reduction of MACE**: 13.00 (22.00, 3.00) **GI side effect:** Nausea 9.6% placebo, 11.1% Tanzeum, Diarrhea 10.5% placebo, 13.1% Tanzeum, **Genital Infection: -** **Wholesale Acquisition Cost for 1 month** Not recorded	[15, 117, 123]
Liraglutide (Victoza®, Saxenda®)	Subcutaneous 0.6 mg for 1st week then 1.2 mg up to 1.8 mg Once a day	**Reaching target HbA1c in 6 months**: 1478 out of 2372 (avg. 62.31) **Risk reduction of MACE**: 12.30 (20.70, 3.00) **GI side effect:** Nausea 5 placebo, 18%	[11, 112, 116, 117]

		Liraglutide 1.2 mg, 20.0% Liraglutide 1.8 mg **Genital Infection: -** **Wholesale Acquisition Cost for 1 month** $680.32 Victoza, $541.86 Saxenda	
Semaglutide (Ozempic®, SC)	Subcutaneous 0.25 mg QW for 4 weeks then 0.5 mg up to 1 mg Once a week	**Reaching target HbA1c in 6 months**: 1686 out of 2451 (avg. 68.79) **Risk reduction of MACE**: 23.00 (39.00, 3.00) **GI side effect:** Nausea 6.1% placebo, 15.8% Ozempic 0.5 mg, 20.3% Ozempic 1 mg Vomiting 2.3 % placebo, 5.0 % Ozempic 0.5 mg, 9.2% Ozempic 1 mg Diarrhea 1.9% placebo, 8.5% Ozempic 0.5 mg, 8.8% Ozempic 1 mg **Genital Infection: -** **Wholesale Acquisition Cost for 1 month** $887.09	[10, 112, 116, 117]
Semaglutide (Rybelsus®, oral)	Oral 3 mg OD for 30 days then 7 mg up to 14 mg Once a day	**Reaching target HbA1c in 6 months**: 407 out of 636 (avg. 63.99) **Risk reduction of MACE**: 23.00 (39.00, 3.00)	[112, 116, 117]

		GI side effect: Nausea 6.0% placebo, 11.0% Rybelsus 7 mg, 20.0% Rybelsus 14 mg Diarrhea 4.0% placebo, 9.0% Rybelsus 7 mg, 10% Rybelsus 14 mg **Genital Infection: -** **Wholesale Acquisition Cost for 1 month** $829.36	
Lixisenatide (Adlyxin®)	Subcutaneous 10 mcg OD for 14 days then 20 mcg Once a day	**Reaching target HbA1c in 6 months**: 979 out of 2373 (avg. 41.26) **Risk reduction of MACE**: 1.80 (10.50, -15.70) **GI side effect:** Nausea 6.0% placebo, 25.0% Adlyxin Vomiting 2.0% placebo, 10% Adlyxin Diarrhea 6.0% placebo, 8.0% Adlyxin **Genital Infection: -** **Wholesale Acquisition Cost for 1 month** $674.76	[112, 116, 117, 124]

Table 3-3. Selected attributes and levels for DCE survey instrument

Attributes	Description	Level
How do you take the medication?	Determine the route of administration such as oral or injectable and how often the medications are taken such as once a day or twice a day or once a week.	• Tablet, once a day • Injectable, once a day • Injectable, twice a day • Injectable, one a week
Chance of reaching target HbA1c (long-term blood glucose level) in 6 months	A normal HbA1c is 4% to 6%, but people with diabetes have a higher-than-normal HbA1c (up to 12% or more). The goal of diabetes treatment is usually to get the HbA1c to be under 7%. - Higher chance of reaching target HbA1c (long-term blood glucose level)is better	• 10 out of 100 (10%) patients reach target HbA1c • 50 out of 100 (50%) patients reach target HbA1c • 90 out of 100 (90%) patients reach target HbA1c
% reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to cardiovascular diseases)	Some type 2 diabetes medications can reduce the risk of these major adverse cardiovascular events, while other medications may not have any effects on this cardiovascular risk. - Higher % reduction in the risk of major adverse cardiovascular events is better	• No reduction in the risk of these cardiovascular events • 20% reduction in the risk of these cardiovascular events • 40% reduction in the risk of these cardiovascular event
Chances of gastrointestinal side effects (i.e., nausea, vomiting and diarrhea)	Gastrointestinal side effects are the common side effects of some type 2 diabetes medications, and their side effects vary among medications. - Lower chances of gastrointestinal side effects is better	• 1 out of 100 (1%) patient experiences GI side effects • 15 out of 100 (15%) patients experiences GI side effects • 30 out of 100 (30%) patients experience GI side effects

Occurrence of diabetic ketoacidosis (e.g., vomiting, weight loss, loss of consciousness)	Incidents of diabetic ketoacidosis are rare among type 2 diabetes medications and observed among very few people out of thousands of patients; however, it is a serious and life-threatening complication. - No diabetic ketoacidosis is better	• None • Rare
Chances of genital infection	Some type 2 diabetes medications increase the risk of genital infections. - Lower the chances of genital infection is better	• No patient (0%) experience genital infection • 8 out of 100 (8%) patients experience genital infection • 16 out of 100 (16%) patients experience genital infection
Out-of-Pocket Cost per month	Cost that patient pay out from their own pocket (e.g., copayment or whole amount) for type 2 diabetes medication. - Lower out-of-pocket cost is better	• $0 • $500 • $1000

3.2.4 Instrument Development

A self-administered, web-based questionnaire survey was developed from the list of attributes and their levels. From a total of seven attributes and their levels, it was not feasible to present all possible 1944 (4x3x3x3x3x3x2) combinations of choice sets to the study participants. Therefore, an orthogonal and balanced design was used to randomly draw a subset of all combinations using Ngene® software. A total of 36 choice sets were generated and divided into four blocks. Each block comprised nine choice sets that were used to develop a self-administered survey questionnaire for four versions. Thus, each participant was presented with a randomly assigned one version of nine choice sets. Each choice set contained three unlabeled alternatives, including two hypothetical treatments with different levels of attributes and an opt-out alternative, as shown in Figure 3-2. Patients were asked to choose a preferred alternative.

The questionnaire survey primarily consisted of four sections (see Appendix II). The initial part of the survey instrument consisted of a screening portion to select patients who agreed to participate in the study based on their age and T2DM diagnosis. In the second part, questions were asked for patients' characteristics (e.g., age, gender, income, health insurance) and T2DM-related experience. The third section consisted of DCE choice sets. At the initial portion of the DCE survey, detailed instruction about the situation, the description of attributes and the meanings of their value, and one example of DCE choice sets were provided to understand the DCE survey questionnaire better. One extra choice set, which contained a dominant alternative (e.g., highest chance of reaching target HbA1c, lowest GI side effect, and lowest cost), was added for a validity check. Patients who understood the DCE choice sets and the instruction of the survey were expected to choose the dominant alternative of this choice set. Nine DCE choice sets were included in this section. In each choice set, patients were asked to consider three unlabeled alternatives described by the study attributes and their levels and choose one of these alternatives. Finally, a single open-ended question for the patient's experience of taking the survey was included.

The DCE expert who had extensive experience in value assessment research was asked to check the face validity of the survey. All expert's comments were used to modify the survey. The attribute blood glucose (HbA1c) change was modified to chances of reaching target HbA1c (long-term

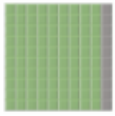
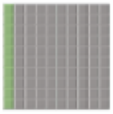
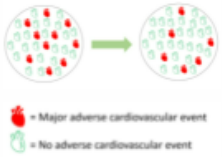
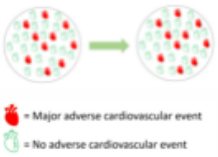
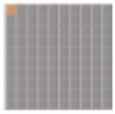
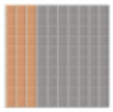
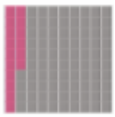
blood glucose level) in 6 months and cardiovascular risk reduction to % reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to cardiovascular diseases) for better understanding to patients. The statistical graphs were updated for clear differentiation between the levels and easy identification. Subsequently, the modified survey instrument was pilot-tested with 32 participants through the Qualtrics^{XM} panel. A multinomial logit (MNL) model was developed to identify the prior parameters and preliminarily checked the significance of the attributes. Based on the results of this pilot study and consultation with the clinical expert in DM care, the "occurrence of diabetic ketoacidosis" attribute was dropped from the main study. Thus, a total of six attributes, including how do you take the medication, the chance of reaching target HbA1c (long-term blood glucose level) in 6 months, % reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to cardiovascular diseases), chances of gastrointestinal side effects (i.e., nausea, vomiting, and diarrhea), chances of genital infection and out-of-pocket cost attributes were kept in the main survey.

A Bayesian D-efficient design was used to generate choice sets in the main survey. The Bayesian D-efficient design algorithm entailed an iterative procedure that compared statistical efficiency among various designs using Ngene® software. The statistical efficiency was computed from the 500 Halton draws of prior parameters from the pilot study results. 36 unique unlabeled choice sets were generated for the final main survey. The questionnaire survey was developed. Similar to the survey in the pilot study, this survey consisted of four sections, including the initial part of the survey instrument, questions about patients' characteristics (e.g., age, gender, income, health insurance) and their T2DM-related experience, DCE choice sets, and an open-ended question about patient's experience with the survey. At the initial portion of the DCE survey, detailed instruction about the situation, the description of attributes and the meanings of their value, and one example of DCE choice sets were provided to understand the DCE survey questionnaire better. One extra choice set, which contained a dominant alternative (e.g., highest chance of reaching target HbA1c, lowest GI side effect, and lowest cost), was added for a validity check. Ten DCE choice sets were included in this section. In each choice set, patients were asked to consider three unlabeled alternatives described by the study attributes and their levels and choose one of these alternatives. Finally, a single open-ended question for the patient's experience of taking the survey was included. Figure 3-2 shows an example of a choice set. See the survey instrument in Appendix

II for more detail.

Figure 3-2. An example of a DCE choice set

Q.1 Which of the following medication you would prefer based on the attributes (characteristics) presented after your initial medication (e.g., metformin) alone does not help you achieve your treatment goal? Choose by clicking one of the buttons below:

Attributes	Medication A	Medication B	Neither medication A nor medication B
How do you take the medication	Injectable, once a week 	Injectable, twice a day 	Neither medication A nor medication B
Chance of reaching target HbA1c (long-term blood glucose level) in 6 months	90 out of 100 (90%) patients reach target HbA1c 	10 out of 100 (10%) patients reach target HbA1c 	
% reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to cardiovascular diseases)	40% reduction in the risk of these cardiovascular events 	No reduction in the risk of these cardiovascular events 	
Chance of gastrointestinal (GI) side effects (i.e., nausea, vomiting, and diarrhea)	1 out of 100 (1%) patient experiences GI side effects 	30 out of 100 (30%) patients experience GI side effects 	
Chance of genital infection	No patient (0%) experiences genital infection	16 out of 100 (16%) patients experience genital infection 	
Out-of-Pocket Cost per month	$0	$1,000	

Which medication do you choose? (pick only one medication option)

- ○ I choose Medication A
- ○ I choose Medication B
- ○ I choose neither Medication A nor Medication B

3.2.5 Data collection

The final survey was launch through the national, online Qualtrics^{XM} panel in May 2021. The initial page of the survey consisted of the consent information, followed by the screening questions for age and diagnosis with T2DM before proceeding further in the survey. Patients, who were not willing to participate in this study or did not pass the screening questions, were asked to sign off from the survey. For the quality data collection, Qualtrics^{XM} excluded all the participants who completed the survey in less than one-third of the median completion time of the pilot test. Upon the successful completion of the survey, the participants were remunerated from Qualtrics^{XM}. Auburn University Institutional Review Board (IRB) determined this study was exempt from human subject review (IRB 21-035 EX 2101). Consent from the participant was requested during the screening. All participants were informed that they could quit at any time, and their responses would remain anonymous.

3.2.6 Data analysis

All data, except the responses to open-ended questions, were converted into numeric values for data analyses. Data were checked. Descriptive analyses were conducted to clean the data. All the patients, who responded correctly in the validity choice set, were included in further analyses.

Descriptive analyses for patients' characteristics and experiences with T2DM were conducted. Based on Random Utility Theory, patients' responses for each choice set were observed and analyzed in DCE. All attributes were treated as continuous variables for the better simulation of incremental changes in attributes and calculation of WTPs, except the attribute "how do you take the medication" which was treated as a categorical variable. Effect coding was applied to this categorical attribute. Among the four levels of this attribute, "oral, once a day" was used as the reference level. A multinomial logit (MNL) model was developed to determine the following patient's utility function (U_{nsj}) that a patients i assigns to an alternative j in a choice set:

$U_{nsj} = V_{nsj} + \varepsilon_{nsj}$; $V_{nsj} = \sum_{k=1}^{K} \beta_k X_{nsjk}$

where n = patient, s = choice set, j = alternative, k = attribute, X_{nsjk} = the full vector of observed attributes relating to individual n and alternative j on the choice set s, β_k= the coefficient or the

mean attribute weight of attribute k, and ε = an error term.

For this study, MNL model can be explained in terms of utility function as:

$$U_{nsj} = \beta_0 + \beta_1 Dose1_{nsj} + \beta_2 Dose2_{nsj} + \beta_3 Dose3_{nsj} + \beta_4 Hba1c_{nsj} + \beta_5 Mace_{nsj} + \beta_6 GI_{nsj} + \beta_7 Genital_{nsj} + \beta_8 Cost_{nsj} + \varepsilon_{nsj}$$

where β_0 is the constant reflecting patients' preferences for using medication relative to no medication. β_1, β_2, and β_3 are the coefficients of the effect codes (Dose1, Dose2, and Dose3, respectively) of the route and frequency of administration attribute. Dose1, Dose2, and Dose3 are -1 for the oral, once a day, reference level. For the injectable, once a day, Dose1 is 1; otherwise 0. For the injectable, twice a day, Dose2 is 1; otherwise 0. For the injectable, twice a week, Dose3 is 1; otherwise 0. β_4, β_5, β_6, β_7, and β_8 are the coefficients or the mean attribute weights of the chance of reaching target HbA1c (HbA1c), % reduction in the risk of major adverse cardiovascular events (Mace), chances of gastrointestinal side effects (GI), chances of a genital infection (Genital), and out-of-pocket cost per month (Cost), respectively, and ε_{nsj} is an error term. Each coefficient indicated the relative importance of each attribute, and the sign of the coefficient reflected whether the attribute had a positive or negative effect on the utility. The level of statistical significance was set at 0.05.

A mixed logit (ML) model was developed. The ML model captured the main effects as well as the distribution of each attribute level. The utility function (U_{nsj}) of the ML model was:

$$U_{nsj} = \sum_{k=1}^{K} \beta_{nk} X_{nsjk} + \varepsilon_{nsj}$$

where n = patient, s = choice set, j = alternative, k = attribute, X_{nsjk} = the full vector of observed attributes relating to individual n and alternative j on the choice set s, β_{nk} = the vector of individual-specific coefficients of attribute k, and ε = an error term. The level of statistical significance was be set at 0.05 for all analyses.

For this study, the ML model can be explained in terms of utility function as:

$$U_{nsjk} = \beta'_0 + \beta'_{1n} Dose1_{nsjk} + \beta'_{2n} Dose2_{nsjk} + \beta'_{3n} Dose3_{nsjk} + \beta'_{4n} Hba1c_{nsjk} + \beta'_{5n} Mace_{nsjk} + \beta'_{6n} GI_{nsjk} + \beta'_{7n} Genital_{nsjk} + \beta'_{8n} Cost_{nsjk} + \varepsilon_{nsj}$$

This can be explained in a similar way to MNL except for β_{nk} which is individual-specific coefficients of attributes.

The ML model identified the attributes for which there was significant preference heterogeneity but did not explain the heterogeneity. This study performed three subgroup analyses to examine the preference heterogeneity. First, our study had a slightly higher number of female patients. Also, clinical studies had confirmed that female T2DM patients experienced higher genital infection while using SGLT-2is.[111] The preferences between male and female T2DM patients might be different. Similarly, patients in our study had a wide range of T2DM experiences, with a median value of 10 years. Patients having T2DM for a more extended time might develop multiple comorbidities and take multiple medications for those conditions.[125] This group of patients might have a different preference while selecting the medications for their diabetes than the patients who just developed diabetes or had diabetes for a short duration. Also, patients with SGLT-2is or GLP-1 RAs experience might have direct experience of benefits and risks of these medications and have different preferences from patients who never used SGLT-2is or GLP-1RAs.

DCE also allowed the estimation of tradeoffs that the patients made between the study attributes (marginal rate of substitution) and cost attribute. Marginal WTPs of the attributes were calculated by taking the mean coefficients of attributes to the mean coefficient of cost attribute. Each of them represented the patient's WTP for a one-unit change of each attribute.[107] Krinsky and Robb's method was used to estimate 95 % confidence intervals of WTPs of the attributes.[126] Finally, WTPs for existing SGLT-2is and GLP-1 RAs in the real-world market were calculated by multiplying the marginal WTP for each medication with the difference between attribute levels, which were obtained from clinical literature, to reflect the value for each medication from the patient perspective.

Chapter 4

Results

This chapter includes the results of the first and second aims. Patient demographic data and their experience with T2DM are described for both aims. Ranking of attributes for six second-line antihyperglycemic medication groups based on T2DM patients' priorities and patients' preferences and their WTPs for the SGLT-2is and GLP-1 RAs are then reported for the first and second aims, respectively.

4.1 Aim 1: Rank the importance of the attributes of second-line AHAs

4.1.1 Participant characteristics:

Table 4-1 shows the characteristics of 113 eligible T2DM patients who agreed to participate in the survey after reading the consent information letter. The majority of these participants were white, non-Hispanic (89.38%), male (58.41%), and aged 65 or above (53.10%) with an average age of 59.67 (SD=15.12) years. The average BMI of these participants was 28.70 (SD=7.29). The majority of them were either overweight (35.40%) or obese (34.51%), according to the Centers for Disease Control and Prevention (CDC) guideline. Most of the participants were married (74.34%), and approximately half retired (50.44%). A total of 58 participants (51.33%) had Medicare for health insurance. High blood pressure (N=63) was most frequently reported among multiple co-morbidities. Many of these patients reported their health status as "good" (38.94%) or "fair" (24.78%). The average number of years that the patients had been diagnosed with T2DM was approximately 11 years. The majority of patients knew their current HbA1c values. They reported that their HbA1c ranged between 5.2% to 15%, with an average value of 7.74%. Most patients confirmed their experiences with metformin (N=98); however, experiences with GLP-1 RAs (N= 25-31) or SGLT-2is (N= 23-29) were minimal.

After excluding the participants, who responded inconsistently with the repeated BWS question, responses from 99 participants were included in further analyses. Table 4-1 shows the characteristic of these participants. The majority of these participants were white, non-Hispanic (88.89%), male (60.61%), and aged 65+ (51.52%) with an average age of 59.35 (SD= 15.18) years.

The average BMI of these participants was 28.40 (SD=7.12), while approximately two-thirds of these participants were overweight (34.34%) or obese (33.33%). They reported their health status as "good" (38.38%) or "fair" (24.24%). Most of these participants were married (75.76%). Approximately half of them retired (49.49%) and had Medicare (49.49%) for health insurance. Among all co-morbidities, high blood pressure (N = 63) was most frequently reported. The majority of patients have either a 4-year college degree (26.26%) or graduate or professional degrees (34.34%). The average number of years that the patients had been diagnosed with T2DM was approximately 11 years. The majority of patients know their current HbA1c value ranges between 5.2% to 15%, with an average value of 7.81%. Although each patient used multiple medications, most of them had experience using metformin (N=85) for managing their T2DM. Only a few patients (N = 20-28) had experience with GLP-1 RAs or SGLT-2is. Similarly, increasing thirst (N=63) or frequent urination (N=60) were frequently reported as T2DM symptoms.

All characteristics, except gender and education, and T2DM related experiences of patients, who had invalid BWS responses, were similar to those of the patients who responded to the BWS correctly. Patients with invalid responses were mostly female (57.14%) and had technical or vocational training (35.71%).

Table 4-1. Participant characteristics and T2DM experiences for Aim 1

Characteristic	Full Cohort (n=113)	Final Analysis Cohort (n=99)	Invalid BWS Responses Cohort (n=14)
Age in years, mean (SD, range)	59.67 (15.12, 19-84)	59.35 (15.18, 19-84)	61.93 (14.45, 34-77)
Age groups in years, N (%)			
19-44	25 (22.12)	22 (22.22)	3 (21.43)
45-64	28 (24.78)	26 (26.26)	2 (14.29)
≥ 65	60 (53.10)	51 (51.52)	9 (64.29)
Body Mass Index, mean (SD, range)	28.70 (7.29, 15.41-49.48)	28.40 (7.12, 15.41-49.48)	30.50 (8.22, 16.72-49.12)
Body Mass Index (CDC cluster), N (%)			

Underweight (BMI < 18.5)	9 (7.96)	8 (8.08)	1 (7.14)
Normal weight (BMI 18.5 - <25)	25 (22.12)	24 (24.24)	1 (7.14)
Overweight (BMI 25 - <30)	40 (35.40)	34 (34.34)	6 (42.86)
Obesity (BMI >= 30)	39 (34.51)	33 (33.33)	6 (42.86)
Gender, N (%)			
Male	66 (58.41)	60 (60.61)	6 (42.86)
Female	47 (41.59)	39 (39.39)	8 (57.14)
Race, N (%)			
American Indian / Alaska Native	1 (0.88)	1 (1.01)	0 (0.00)
Asian / Native Hawaiian / Other Pacific Islander	3 (2.65)	3 (3.03)	0 (0.00)
Black or African American	5 (4.42)	4 (4.04)	1 (7.14)
Hispanic American	3 (2.65)	3 (3.03)	0 (0.00)
White non-Hispanic / Caucasian	101 (89.38)	88 (88.89)	13 (92.86)
Multiple ethnicity / Others	0 (0)	0 (0)	0 (0.00)
Marital Status, N (%)			
Single	7 (6.19)	6 (6.06)	1 (7.14)
Married	84 (74.34)	75 (75.76)	9 (64.29)
Divorced or separated	9 (7.96)	6 (6.06)	3 (21.43)
Widowed	12 (10.62)	11 (11.11)	1 (7.14)
Other / Domestic Partner	1 (0.88)	1 (1.01)	0 (0.00)
Education , N (%)			
Less than high school	1 (0.88)	1 (1.01)	0 (0.00)
High school or equivalence (e.g., GED)	25 (22.12)	24 (24.24)	1 (7.14)
Technical / vocational training	12 (10.62)	7 (7.07)	5 (35.71)
2-year college degree (Associate's degree)	9 (7.96)	7 (7.07)	2 (14.29)
4-year college degree (e.g., BA, BS)	28 (24.78)	26 (26.26)	2 (14.29)
Graduate or professional degree (e.g., MBA, MS, MD, PhD)	38 (33.63)	34 (34.34)	4 (28.57)
Employment Status N (%)			
Employed full-time	34 (30.09)	30 (30.30)	4 (28.57)

Employed part-time	13 (11.50)	12 (12.12)	1 (7.14)
Self-employed	2 (1.77)	2 (2.02)	0 (0.00)
Stay-at-home spouse	4 (3.54)	4 (4.04)	0 (0.00)
Student	0 (0.00)	0 (0.00)	0 (0.00)
Retired	57 (50.44)	49 (49.49)	8 (57.14)
Unemployed	3 (2.65)	2 (2.02)	1 (7.14)
Health Insurance, N (%)			
No insurance	4 (3.54)	4 (4.04)	0 (0.00)
Private insurance	32 (28.32)	29 (29.29)	3 (21.43)
Medicaid	11 (9.73)	11 (11.11)	0 (0.00)
Medicare	58 (51.33)	49 (49.49)	9 (64.29)
Veterans' Health Insurance	7 (6.19)	5 (5.05)	2 (14.29)
Others	1 (0.88)	1 (1.01)	0 (0.00)
Medical Conditions*			
None	12	11	1
High blood pressure	73	63	10
Heart disease	21	19	2
High blood lipid levels	43	36	7
Cancer	7	7	0
Ulcer or stomach diseases	6	5	1
Blood diseases	2	2	0
Kidney diseases	4	4	0
Lung diseases	9	8	1
Liver diseases	3	3	0
Osteoarthritis	20	17	3
Rheumatoid arthritis	11	11	0
Back Pain	31	26	5
Depression	20	17	3
Others	12	11	1
Health status			
Excellent	12 (10.68)	11 (11.11)	1 (7.14)
Very good	21 (18.58)	18 (18.18)	3 (21.43)
Good	44 (38.94)	38 (38.38)	6 (42.86)
Fair	28 (24.78)	24 (24.24)	4 (28.57)

Poor	8 (7.08)	8 (8.08)	0 (0.00)
Number of years of T2DM diagnosis, mean (SD, range)	11.23 (9.02, 1-54)	11.35 (9.27, 1-54)	10.23 (6.90, 1-23)
Current HbA1c value			
Know	82 (72.57)	71 (71.71)	11 (78.57)
Do not know	30 (26.55)	27 (27.27)	3 (21.43)
Prefer not to answer	1 (0.88)	1 (1.01)	0 (0.0)
Mean HbA1c (SD, range)	7.74 (2.22, 5.2-15)	7.81 (2.31, 5.2-15)	7.27 (1.42, 5.8 -10)
Experience with antihyperglycemic medication[a]			
Metformin			
Experienced	98	85	13
Do not know	15	14	1
Exenatide			
Experienced	30	27	3
Do not know	80	70	10
Dulaglutide			
Experienced	31	26	5
Do not know	79	71	8
Liraglutide			
Experienced	28	24	4
Do not know	82	73	9
Semaglutide			
Experienced	30	27	3
Do not know	80	70	10
Albiglutide			
Experienced	23	20	3
Do not know	87	77	10
Lixisenatide			
Experienced	25	22	3
Do not know	85	75	10
Canagliflozin			
Experienced	29	25	4
Do not know	81	72	9
Dapagliflozin			

Experienced	28	23	5
Do not know	82	74	8
Empagliflozin			
Experienced	31	28	3
Do not know	80	70	10
Ertugliflozin			
Experienced	23	20	3
Do not know	87	77	10
T2DM symptoms*			
Increased thirst	68	63	5
Frequent urination	65	60	5
Increased hunger	36	32	4
Fatigue	53	48	5
Blurred vision	42	37	5
Slow-healing sores	29	26	3
Frequent infections	10	8	2
Numbness or tingling in the hands or feet	41	38	3
Areas of darkened skin usually in the armpits and neck	10	9	1
Other	6	5	1

*Patients had multiple options to choose

[a]Patients had multiple non-compulsory options to choose

4.1.2 Ranking of attributes:

Table 4-2 shows the frequencies and standardized BWS scores for the attributes of second-line T2DM medications, ranked in ascending order of BWS scores. Among all 16 attributes, the reducing blood glucose (0.48) attribute had the highest standardized BWS score. This attribute was cited as the most important attribute 155 times and the least important attribute 11 times. It was followed by the risk of cardiovascular diseases (0.39), the risk of kidney diseases (0.26), the all-cause death rate (0.25), and the reductions of the risk of hospitalization for heart failure (0.24) attributes. These attributes were cited as the most important attribute (ranging from 139 to 85) more frequently than the least important attribute (ranging from 13 to 22).

The standardized BWS scores of the gastrointestinal side-effects (-0.06), requiring regular self-monitoring of blood glucose level (-0.04), reducing (slightly) blood pressure (-0.03), and increasing the risk of the urinary tract and genital infection (-0.02) attributes were slightly less than zero. Similarly, the standardized BWS scores of the increased risk of blood glucose lower than normal (0.02) and increase the risk of diabetic ketoacidosis (0.02) attributes were slightly above zero. The numbers of times in which these attributes were cited as the least important attribute were about the same as the numbers of times they were cited as the most important attribute.

Among all 16 attributes, the reaction at injection site attribute was the most frequently cited as the least important attribute and had the least BWS score (-0.52). This attribute was cited as the most important attribute only three times and the least important attribute 157 times. It was followed by the route of administration (-0.31), dosing frequency (-0.29), weight change (-0.22), and out-of-pocket cost (-0.18) attributes. These attributes were cited as the least important attribute (ranging from 78 to 108) more frequently than the most important attribute (ranging from 12 to 31).

Table 4-2. Frequency and the standardized score of T2DM medication attributes.

Attributes of T2DM medications	Number of times chosen		Standardized BWS Score[b]
	Most Important (Best)	Least Important (Worst)	
Reduce blood glucose	155	11	0.48
Reduce the risk of cardiovascular diseases	139	22	0.39
Reduce the risk of kidney diseases	93	15	0.26
Reduce the all-cause death rate	86	13	0.25
Reduce the risk of hospitalization for heart failure	85	13	0.24
Increase the risk of diabetic ketoacidosis	27	21	0.02
Increase the risk of blood glucose lower than normal	34	29	0.02
Increase the risk of urinary tract and genital infection	12	17	-0.02
Reduce (slightly) blood pressure	34	42	-0.03
Require regular self-monitoring of blood glucose level	42	54	-0.04
Gastrointestinal side-effects	8	25	-0.06
Out-of-pocket cost	31	84	-0.18
Weight change	12	78	-0.22
Dosing Frequency	16	103	-0.29
Route of administration	15	108	-0.31
Reaction at injection site	3	157	-0.52

[b]Difference between the count of chosen as most important and count of chosen as least important, divided by the number of times attribute was available to be selected per experimental design (for this design, (number of participants*(number of repetition of attributes /number of blocks)). Standardized scores indicate the salience of an attribute on a scale from –1.0 to +1.0. Scores toward +1.0 indicate higher importance, scores toward –1 indicate the least important attributes of T2DM medications.

4.2 Aim 2: Determine patients' preferences for SGLT-2is and GLP-1 RAs

4.2.1 Participant characteristics:

A total of 242 participants initiated the survey. After reading the consent information letter, 176 agreed to participate in the survey, completed the DCE questions, and correctly responded to the validity choice set. Table 4-3 shows the characteristics and DM-related experience of these participants. The majority of them were White, Non-Hispanic (86.93%), female (54.55%), and aged 65 or above (48.86%) with an average age of 60.36 (SD=13.74) years. The average BMI of these participants was 32.61 (SD=8.57), and the majority of them were obese (61.93%). Most of the participants reported they were married (59.09%), and almost half retired (48.86%). Nearly half of them reported a yearly household income of $50,000 or higher. Nearly two-thirds of total patients (74.44%) had an education level higher than high school, and half of the total population (49.53%) had Medicare for health insurance. High blood pressure (N=111) and high blood lipid level (N=76) were the most common comorbidities for these T2DM patients. The average number of years that the patients had been diagnosed with T2DM was approximately 13 years. The majority of patients knew their latest HbA1c values. Their HbA1c values ranged between 5% to 15%, with an average value of 7.43%. The most frequently reported T2DM symptoms were increases thirst (N =112), fatigue (N=110), and frequent urination (N =107). The majority of the patients did not have experiences (47.16%) of taking SGLT-2is or GLP-1 RAs for their T2DM. Among the available SGLT-2is & GLP-1 RA, the highest number of patients experienced dulaglutide (Trulicity®) (N= 39), followed by empagliflozin (Jardiance®) (N= 24).

Table 4-3. Participant characteristics and T2DM experiences for Aim 2. (N=176)

Characteristic	
Age in years, mean (SD, range)	60.36 (13.74, 19-87)
Age groups in years, N (%)	
19-44	27 (15.34)
45-64	63 (35.80)
≥ 65	86 (48.86)

Body Mass Index, mean (SD, range)	32.61 (8.57, 10.20-66.94)
Body Mass Index (CDC cluster), N (%)	
Underweight (BMI < 18.5)	5 (2.84)
Normal weight (BMI 18.5 - <25)	24 (13.64)
Overweight (BMI 25 - <30)	38 (21.59)
Obesity (BMI >= 30)	109 (61.93)
Gender, N (%)	
Female	96 (54.55)
Male	80 (45.45)
Race, N(%)	
American Indian / Alaska Native	1 (0.57)
Asian / Native Hawaiian / Other Pacific Islander	3 (1.70)
Black or African American	6 (3.41)
Hispanic American	12 (6.82)
White non-Hispanic / Caucasian	153 (86.93)
Multiple ethnicity / Others	1 (0.57)
Marital Status	
Single	24 (13.64)
Married	104 (59.09)
Divorced or separated	29 (16.48)
Widowed	16 (9.09)
Other	3 (1.71)
Household Income	
$100,000 or more per year	28 (15.91)
$75,000 to $99,999 per year	24 (13.64)
$50,000 to $74,999 per year	34 (19.32)
$25,000 to $49,999 per year	45 (25.57)
Less than $25,000 per year	34 (19.32)
Prefer not to answer	11 (6.25)

Education	
High school or less than high school	45 (25.57)
Technical / vocational training	21 (11.93)
2-year college degree (Associate's degree)	30 (17.05)
4-year college degree (e.g., BA, BS)	40 (22.73)
Graduate or professional degree (e.g., MBA, MS, MD, PhD)	40 (22.73)
Employment Status, N (%)	
Employed full-time	48 (27.27)
Employed part-time	12 (6.82)
Self-employed	6 (3.41)
Stay-at-home spouse	6 (3.41)
Student	0 (0.00)
Retired	86 (48.86)
Unemployed	18 (10.23)
Health Insurance , N (%)	
I do not have health insurance	3 (1.70)
Private insurance	50 (28.41)
Medicaid	22 (12.50)
Medicare	87 (49.53)
Veterans' Health Insurance	8 (4.55)
Others	6 (3.41)
Medical Conditions*, N	
High blood pressure	111
High blood lipid levels	76
Back Pain	51
Depression	40
Osteoarthritis	34
Heart disease	27
Lung diseases	15

Kidney diseases	14
Rheumatoid arthritis	13
Cancer	9
Ulcer or stomach diseases	9
Liver diseases	7
Blood diseases	2
None of above	15
Other	17
Health status, N (%)	
Excellent	9 (5.11)
Very good	27 (15.34)
Good	65 (36.93)
Fair	64 (36.36)
Poor	11 (6.25)
Number of years of T2DM diagnosis, mean (SD, median, range)	12.63 (9.18, 10, 1- 45)
Current HbA1c value, N (%)	
Know	136 (77.27)
Do not know	38 (21.59)
Prefer not to answer	2 (1.14)
Mean % of HbA1c (SD, range)	7.43 (1.78, 5-15)
Antihyperglycemic medication Experience*, N	
Dulaglutide (Trulicity®)	39
Exenatide (Byetta® Bydureon®)	24
Empagliflozin (Jardiance®)	24
Semaglutide (Ozempic® Rybelsus®)	21
Liraglutide (Victoza® Saxenda®)	15
Albiglutide (Tanzeum®)	11
Canagliflozin (Invokana®)	11
Dapagliflozin (Farxiga®)	10

Ertugliflozin (Steglatro®)	8
Lixisenatide (Adlyxin®)	5
None of above	83
Do not know	5
T2DM symptoms*, N	
Increased thirst	112
Fatigue	110
Frequent urination	107
Numbness or tingling in the hands or feet	79
Blurred vision	51
Increased hunger	42
Slow-healing sores	40
Frequent infections	16
Areas of darkened skin usually in the armpits and neck	12
Other	1

*Each patient had multiple options

Other medical conditions include anxiety, hypothyroidism, PTSD, psoriatic arthritis, gout, multiple sclerosis, sjogren's syndrome, sleep apnea

Other T2DM symptoms include neuropathy

4.2.2 Preference weights of attributes levels

The four versions of the questionnaire survey were evenly spread among 176 T2DM patients. This represented 4,752 observations (176 participants x 9 choice sets/participant x 3 alternatives/choice set). From the responses to the open-ended question regarding their experiences with the survey, many participants found the survey was easy to understand and interesting. Approximately 25% of all DCE observations chose the opt-out alternative, while about 40% and 35% chose the first and second alternatives, respectively, in the choice sets.

Table 4-4 shows the estimated coefficients of all study attributes and their p-values of the MNL model. The estimated coefficients of all attributes had expected signs. They were statistically significant (P <0.05), except for one level of the how do you take the medication attribute

(injectable, once a week, *P =0.368)*. The coefficient (β_0) of the constant was 0.83421 (*P* <0.001). Using oral, once a day as the reference attribute, the coefficients of the injectable, once a day (β_1), injectable, twice (β_2), and injectable, once a week (β_3) were -0.21193 (*P* =0.038), -0.49014 (*P <0.001*), and -0.09761 (*P* =0.368), respectively. The coefficients of the reaching target HbA1c in 6 months (β_4) and reduction in the risk of major adverse cardiovascular events (β_5) attributes were 0.01102 (*P <0.001*) and 0.01028 (*P <0.001*), respectively. At the same time, the coefficients of gastrointestinal side effects (β_6), genital infection (β_7), out-of-pocket cost per month (β_8) attributes were -0.01431 (*P <0.001*), -0.00189 (*P <0.001*), and 0.00148 (*P <0.001*), respectively.

Table 4-4. Multinomial logistic model: coefficient estimates and p-values. (N = 176)

Attributes (Level)	Coefficient Estimate	*P* Value
Constant[a]	0.83421	0.00000*
Reaching target HbA1c (long-term blood glucose level) in 6 months	0.01102	0.00000*
Reduction in the risk of major adverse cardiovascular events	0.01028	0.00000*
Gastrointestinal side effects	-0.01431	0.00000*
Genital Infection	-0.00189	0.00020*
Out-of-Pocket Cost per month	-0.00148	0.00000*
How do you take the medication		
Tablet, once a day (ref.)	n/a	n/a
Injectable, once a day (DOSE1)	-0.21193	0.03800*
Injectable, twice a day (DOSE2)	-0.49014	0.00000*
Injectable, once a week (DOSE3)	-0.09761	0.36830
Log-likelihood of model	-1513.04000	
AIC	3044.10000	

*p<0.05

Table 4-5 shows the estimated coefficients of all the study attributes, standard deviations, and their respective *P*-values of the ML model. The estimated coefficients of all attributes had expected

signs, and all of them were significant (P < 0.05), except the two levels of the attribute—how do you take the medication (injectable, once a day and injectable, once a week). Using oral, once a day as a reference level, the coefficients of injectable, once a day (β'_1), injectable, twice (β'_2), and injectable, once a week (β'_3) were -0.178962 (*P*=0.164), -0.78850 (*P <0.001*), and -0.27143 (*P*=0.052), respectively. The coefficients of the reaching target HbA1c in 6 months (β'_4) and reduction in the risk of major adverse cardiovascular events (β'_5) attributes were 0.01523 (*P <0.001*) and of 0.01104 (*P <0.001*), respectively. The coefficients of gastrointestinal side effects (β'_6), genital infection (β'_7), out-of-pocket cost per month (β'_8) attributes were -0.01926 (*P <0.001*), -0.03037 (*P <0.001*), and -0.00286 (*P <0.001*), respectively. The estimated standard deviations of all attributes were statistically significant (*P <0.001*).

Table 4-5 Mixed logistic model: coefficient and standard deviation estimates. (N = 176)

Attributes (Level)	Coefficient Estimate	*P* Value	Standard Deviation	*P* Value
Constant[a]	1.78962	0.00000*	1.89393	0.00000*
Reaching target HbA1c (long-term blood glucose level) in 6 months	0.01523	0.00000*	0.01001	0.00000*
Reduction in the risk of major adverse cardiovascular events	0.01104	0.00060*	0.01763	0.00070*
Gastrointestinal side effects	-0.01926	0.00010*	0.03057	0.00000*
Genital Infection	-0.03037	0.00030*	0.04448	0.00090*
Out-of-Pocket Cost per month	-0.00286	0.00000*	0.00086	0.00000*
How do you take the medication				
Tablet, once a day (ref.)	n/a	n/a	n/a	n/a
Injectable, once a day	-0.17587	0.16400	-	-
Injectable, twice a day	-0.78850	0.00000*	-	-
Injectable, once a week	-0.27143	0.05200	-	-
Log likelihood of model	-1277.80027			
AIC	2585.60000			
McFadden Pseudo R^2	0.26572			

*p<0.05

4.2.3 Subgroup analyses

Subgroup analyses in this study were performed to explore the preference heterogeneity across three variables, including gender, T2DM experience, and SGLT-2is or GLP-1 RAs experience. Table 4-6 shows the subgroup analyses based on gender. For male T2DM patients, only the coefficients of reaching target HbA1c in 6 months (β_4=0.01682, *P <0.001*) and out-of-pocket cost per month (β_8=-0.00226, *P <0.001*) attributes were significant, and the standard deviations for all attributes were also significant ($P < 0.05$). On the other hand, the coefficients of all attributes were significant ($P < 0.001$) for female T2DM patients, and only standard deviations of the GI side effects, genital infection, and out-of-pocket cost attributes were significant ($P < 0.05$).

Table 4-7 shows the subgroup analyses based on the experience with T2DM. For patients who had T2DM for 10 or more years, the coefficients of all attributes were significant ($P < 0.05$), and the standard deviations of all attributes, except the GI side effects and genital infection attributes, were significant ($P < 0.05$). Similarly, the coefficients of reaching target HbA1c in 6 months (β_4=0.01250, *P <0.001*), reduction in the risk of major adverse cardiovascular events (β_5=0.01218, *P*=0.015) and out-of-pocket cost per month (β_8=-0.00171, *P <0.001*) attributes were only significant, and the standard deviations of all attributes, except the reaching target HbA1c in 6 months attribute, were significant ($P < 0.05$) for patients, who had T2DM for less than 10 years.

Table 4-8 illustrates the subgroup analyses patients' preferences based on experience with SGLT-2is or GLP-1 RAs. The coefficients of all attributes were significant ($P < 0.05$), and the standard deviations of all attributes, except the reduction in the risk of MACE and genital infection attributes, were significant ($P < 0.05$) for patients who never used SGLT-2is or GLP-1 RAs. On the other hand, the coefficients of the reaching target HbA1c in 6 months (β_4=0.01259, $P < 0.001$) and out-of-pocket cost per month (β_8=-0.00247, $P < 0.001$) attributes were significant. Still, the only standard deviation of the reaching target HbA1c in 6 months was not significant (*P*=0.099) for patients who had SGLT-2is or GLP-1 RAs experience.

Table 4-6. Mixed logit model stratified on gender.

Attributes (Level)	Female (n=96)				Male (n=80)			
	Coefficient Estimate	*P* Value	Standard Deviation	*P* Value	Coefficient Estimate	*P* Value	Standard Deviation	*P* Value
Constant	1.77983	0.00000*	1.58932	0.00000*	2.21980	0.00010*	2.33183	0.00000*
Reaching target HbA1c (long-term blood glucose level) in 6 months	0.01256	0.00000*	0.00729	0.09410	0.01682	0.00000*	0.00892	0.02700*
Reduction in the risk of major adverse cardiovascular events	0.01434	0.00060*	0.00820	0.50940	0.00741	0.14080	0.02277	0.00140*
Gastrointestinal side effects	-0.02547	0.00010*	0.03201	0.00050*	-0.00990	0.20870	0.02598	0.00900*
Genital Infection	-0.03834	0.00030*	0.05531	0.00190*	-0.01826	0.18000	0.04168	0.04730*
Out-of-Pocket Cost per month	-0.00360	0.00000*	0.00117	0.00000*	-0.00226	0.00000*	0.00088	0.00000*
How do you take the medication								
Tablet, once a day (ref.)	n/a	n/a	-	-	n/a	n/a	-	-
Injectable, once a day	-0.41954	0.16400	-	-	0.11292	0.52210	-	-
Injectable, twice a day	-0.88608	0.00000*	-	-	-0.73100	0.00380*	-	-
Injectable, once a week	-0.21641	0.05200	-	-	-0.28638	0.20970	-	-
Log likelihood of model	-696.96304				-556.21928			
AIC	1423.90000				1142.40000			
McFadden Pseudo R^2	0.26574				0.29682			

*p<0.05

Table 4-7. Mixed logit model stratified on T2DM experience.

Attributes (Level)	Less than 10 years (n=75)				10 years or more (n=101)			
	Coefficient Estimate	*P* Value	Standard Deviation	*P* Value	Coefficient Estimate	*P* Value	Standard Deviation	*P* Value
Constant	2.58951	0.00000*	2.65117	0.00000*	1.43449	0.00000*	1.80093	0.00000*
Reaching target HbA1c (long-term blood glucose level) in 6 months	0.01250	0.00000*	0.00629	0.15840	0.01799	0.0000*	0.01060	0.00040*
Reduction in the risk of major adverse cardiovascular events	0.01218	0.01510*	0.02012	0.00730*	0.01334	0.00230*	0.01589	0.01590*
Gastrointestinal side effects	-0.00715	0.33920	0.02956	0.00410*	-0.03216	0.00000*	0.01181	0.49240
Genital Infection	-0.02640	0.06460	0.06258	0.00430*	-0.02923	0.00810*	0.02595	0.40990
Out-of-Pocket Cost per month	-0.00171	0.00000*	0.00053	0.00020*	-0.00364	0.0000*	0.00105	0.00000*
How do you take the medication								
Tablet, once a day (ref.)	n/a	n/a	-	-	n/a	n/a	-	-
Injectable, once a day	-0.26646	0.12540	-	-	-0.00470	0.98140	-	-
Injectable, twice a day	-0.62753	0.00530*	-	-	-0.86431	0.00000*	-	-
Injectable, once a week	-0.36004	0.12020	-	-	-0.10348	0.58210	-	-
Log likelihood of model	-550.140020				-708.76547			
AIC	1130.30000				1447.50000			
McFadden Pseudo R^2	0.25813				0.29027			

*p<0.05

Table 4-8. Mixed logit model stratified on experience with SGLT-2is and GLP-1 RAs.

Attributes (Level)	Experience (n=88)				No experience (n=88)			
	Coefficient Estimate	*P* Value	Standard Deviation	*P* Value	Coefficient Estimate	*P* Value	Standard Deviation	*P* Value
Constant	2.32044	0.00000*	1.77655	0.00000*	1.71620	0.00010*	2.08416	0.00000*
Reaching target HbA1c (long-term blood glucose level) in 6 months	0.01259	0.00000*	0.00658	0.09980	0.02034	0.00000*	0.01502	0.00030*
Reduction in the risk of major adverse cardiovascular events	0.00614	0.18360	0.02207	0.0009*	0.01855	0.00030*	0.00985	0.52820
Gastrointestinal side effects	-0.01276	0.05440	0.02714	0.00150*	-0.02797	0.00070*	0.03368	0.00040*
Genital Infection	-0.01504	0.25770	0.05914	0.00030*	-0.05386	0.00000*	0.00191	0.98280
Out-of-Pocket Cost per month	-0.00247	0.00000*	0.00095	0.00000*	-0.00465	0.00000*	0.00155	0.00000*
How do you take the medication								
Tablet, once a day (ref.)	n/a	n/a	-	-	n/a	n/a	-	-
Injectable, once a day	0.13078	0.45650	-	-	-0.55664	0.00610*	-	-
Injectable, twice a day	-0.74963	0.00070*	-	-	-1.04356	0.00000*	-	-
Injectable, once a week	-0.14193	0.50980	-	-	-0.45620	0.02110*	-	-
Log likelihood of model	-636.52031				-599.05635			
AIC	1303.00000				1228.10000			
McFadden Pseudo R^2	0.26845				0.31151			

*p<0.05

4.2.4 Patients' willingness-to-pay for SGLT-2is and GLP-1 RAs' attributes and medications

Table 4-9 shows T2DM patients' WTPs for all attributes. The results showed that the patients were willing to pay approximately $6 per month if the use of SGLT-2is or GLP-1 RAs could increase the chance of reaching the HbA1c target by 1%. They were willing to pay approximately $4 per month if the medication could reduce the risk of MACE by 1%. Similarly, the T2DM patients were willing to pay approximately $8 and $12 to avoid 1% of GI side effects and genital infection, respectively. Among different ways of taking medication, the T2DM patients were willing to pay the highest (approximately $486 per month) for oral, once day medication and lowest (approximately $176 per month) for injectable, twice a day medication. However, the patients were willing to pay $417 and $379 for injectable, once a day and injectable, once a week medication, respectively.

Table 4-9. Willingness-to-pay (WTP) for the attributes of AHAs.

Attributes	Average WTP per month (95% confidence interval) ($)
Constant	697.36 ((-782.32) – 2604.58)
Reaching target HbA1c (long-term blood glucose level) in 6 months	6.04 ((-1.65) – 17.85)
Reduction in the risk of major adverse cardiovascular events	4.29 ((-9.84) – 20.95)
Gastrointestinal side effects	-7.52 ((-37.56) – 16.42)
Genital Infection	-12.07 ((-56.25) – 22.76)
How do you take the medication	
Tablet, once a day[a]	485.82 (270.37 – 1053.48)
Injectable, once a day[b]	416.68 (231.90 – 903.55)
Injectable, twice a day	175.84

	(97.86 – 381.31)
Injectable, once a week[b]	379.12 (210.99 – 822.09)

[a]Reference level
[b]Non-significant attribute's levels in comparison to reference level

Table 4-10 shows the T2DM patients' WTPs for SGLT-2is and GLP-1 RAs. The average WTP per month for these medications ranged from approximately $1124 to $1518. They were willing to pay the highest (approximately $1518 per month) for oral semaglutide (Rybelsus®), followed by injectable semaglutide (Ozempic®) at approximately $1438 per month. Semaglutide was the only GLP-1 RA available in both oral and injectable forms. For other injectable GLP-1 RAs, the patients were willing to pay $1393 per month for liraglutide (Victoza®, Saxenda®), $1347 per month for exenatide (Bydureon®), $1335 for dulaglutide (Trulicity®), $1175 per month for albiglutide (Tanzeum®), $1168 per month for lixisenatide (Adlyxin®), and $1123.68 per month for exenatide (Byetta®). Similarly, for SGLT-2is, patients were willing to pay approximately $1385 per month for canagliflozin (Invokana®), followed by $1369 per month for dapagliflozin (Farxiga®), $1350 per month for empagliflozin (Jardiance®) and $1241 per month for ertugliflozin (Steglatro®).

Table 4-10. Willingness-to-pay (WTP) for antihyperglycemic agents (AHAs).

AHAs	Average WTP per month 95% confidence interval ($)
Exenatide (Byetta®)	1123.68 ((-377.41) – 3351.37)
Exenatide (Bydureon®)	1346.90 ((-188.73) – 3778.77)
Dulaglutide (Trulicity®)	1334.82 ((-295.66) – 3784.06)
Liraglutide (Victoza®, Saxenda®)	1392.90 ((-232.83) – 3873.94)
Semaglutide (Ozempic®, SC)	1438.16 ((-226.26) – 4017.32)
Semaglutide (Rybelsus®, Oral)	1518.12 ((-127.44) – 4167.42)

Albiglutide (Tanzeum®)	1175.16 ((-354.26) – 3440.17)
Lixisenatide (Adlyxin®)	1167.57 ((-417.66) – 3529.98)
Canagliflozin (Invokana®)	1385.33 ((-179.30) – 3835.51)
Dapagliflozin (Farxiga®)	1368.83 ((-166.46) – 3780.69)
Empagliflozin (Jardiance®)	1349.86 ((-156.89) – 3736.09)
Ertugliflozin (Steglatro®)	1240.76 ((-156.89) – 3736.09)

Table 4-11 shows the comparison of WTPs per month for SGLT-2is and GLP-1 RAs with their current wholesale acquisition costs (WACs) per month calculated from the Red Book in March 2021 except for albiglutide (Tanzeum®). The WAC value for albiglutide (Tanzeum®) was not reported in Red Book while accessing the data. Among, 13 medications, ertugliflozin (Steglatro®) has the lowest WAC of approximately $314 per month with average WTP of $1241 per month which is 295% more than its WAC value. Whereas dulaglutide (Trulicity®) had the highest WAC of $915 per month while patients' WTP was $ 1335 per month which is 46% more than its WAC value.

Table 4-11. Comparison of WTPs and WACs for SGLT-2is and GLP-1 RAs.

AHAs	Group	Average WTP per month	WAC per month ($)	Difference of WTP from WAC (%)
Exenatide (Byetta®)	GLP-1 RAs	1123.68	767.75	46.36
Lixisenatide (Adlyxin®)	GLP-1 RAs	1167.57	674.76	73.04
Albiglutide (Tanzeum®)	GLP-1 RAs	1175.16	N/A	-
Ertugliflozin (Steglatro®)	SGLT-2is	1240.76	313.90	295.27

Dulaglutide (Trulicity®)	GLP-1 RAs	1334.82	914.72	45.93
Exenatide (Bydureon®)	GLP-1 RAs	1346.90	842.64	59.84
Empagliflozin (Jardiance®)	SGLT-2is	1349.86	556.16	142.71
Dapagliflozin (Farxiga®)	SGLT-2is	1368.83	540.24	153.37
Canagliflozin (Invokana®)	SGLT-2is	1385.33	550.97	151.43
Liraglutide (Victoza®)	GLP-1 RAs	1392.90	680.32	104.74
Liraglutide (Saxenda®)	GLP-1 RAs	1392.90	541.86	157.06
Semaglutide (Ozempic®, SC)	GLP-1 RAs	1438.16	887.08	62.12
Semaglutide (Rybelsus®, Oral)	GLP-1 RAs	1518.12	829.36	82.77

Chapter 5

Discussions

This study used stated preference methods to determine the treatment attributes that were important for patients while selecting the second-line AHAs. This was accomplished through two aims. In the first aim, the ranking of important attributes of second-line AHAs was identified. The important attributes of these medications were ranked based on patients' priorities using the BWS object case method. These findings, along with the literature review, interviews with T2DM patients, and consultation with a clinical expert, were used to identify the study attributes for the newer second-line AHAs, SGLT-2is, and GLP-1 RAs, in the second aim. Patients' preferences and WTPs for SGLT-2is and GLP-1 RAs were determined using the DCE method.

5.1 Aim 1: Rank the importance of the attributes of second-line AHAs

BWS object case is one of the patient-centered methods to assess the relative importance of attributes.[82] The BWS object case has various advantages over other stated preference methods, including the relative ease of answering BWS questions for participants and less restrictive than DCE questions to include the numbers of attributes.[44] The BWS object case also provides better information for both top-ranked and bottom-ranked items since information about "best" and "worst" items is collected from the given set of items.[85] Various previous studies used the BWS object case to rank the importance of attributes and elicit patients' priorities in different disease states.[87, 127, 128] For this study, the BWS object case was applied to rank the importance of 16 attributes for second-line T2DM medications based on patients' priorities.

This study used an online panel to recruit T2DM patients to elicit their priorities while selecting second-line T2DM medications. Out of 113 T2DM patients, 14 incorrectly answered the repeated BWS question, and they were not included in the main analysis. Most of the characteristics of the participants, who failed to answer the repeated BWS questionnaire correctly, were similar to those who answered them correctly. However, it is noteworthy that many of these participants were female and had education at the technical or vocational training level.

Based on the standardized BWS scores, we found that the reduction of blood glucose was ranked as the most important attribute. It was followed by other attributes, including the reduction of the

risk of cardiovascular disease, the risk of kidney disease, all-cause death rate, and the risk reduction of hospitalization for heart failure. These attributes were cited as the most important attribute significantly more frequently than as the least important attribute. The reaction at the injection site attribute had the least BWS score and was therefore ranked last among the list of 16 attributes, followed by the route of administration and dosing frequency. All these attributes were cited as the least important attribute significantly more often than the most important attribute, thus resulting in lower standardized BWS scores. The result of the least important attribute should not be interpreted as they were not important to patients at all, but they were relatively less important than other attributes.

The reduction of blood glucose in clinical contexts is referred to HbA1c reduction and is mostly used to inform medical management and treatment decision for T2DM. Intuitively, patients would consider reducing blood glucose as the most important attribute while choosing second-line T2DM medications. In a recent study, Crossnohere et al. compared the preferences of patients and the general public for treatment outcomes of type 2 diabetes using both BWS and rating approaches.[129] They found similar results that T2DM patients valued the highest for treatment outcome HbA1c or the reduction of blood glucose. However, our study used a more comprehensive list of attributes, including treatment benefits, side effects, route of administration, and dosing frequency of second-line T2DM medications, instead of focusing on treatment outcomes only.

The other treatment benefit attributes, including the risk reduction of cardiovascular diseases, reduction of the all-cause death rate, and the risk of hospitalization for heart failure, were also ranked high based on patients' priorities. One of the reasons could be that the study participants were concerned about diabetes-related cardiovascular diseases since diabetes was a major risk factor for cardiovascular disease.[57, 130] Another reason could be many participants in this study had high co-morbidities such as hypertension and hyperlipidemia, and they tended to be concerned about the cardiovascular risk. A study among Japanese T2DM patients also confirmed that the risk reduction of cardiovascular disease was the most important attribute while selecting GLP-1 RA.[24]

This study found that the route of administration and dosing frequency was ranked relatively low. However, these attributes were found to be significantly important for T2DM patients in previous

studies.[27, 28, 33, 34] There were several reasons for the difference in these results. First, the previous studies used DCEs with a different and limited number of attributes, including the route and frequency of administration that might be relatively important to the participants. Second, while the route and dosing frequency was ranked low in this BWS study, they could still be important to the patients. Possible reasons could be that the BWS object case included only the study attributes without their levels, and the patients' priorities were based on the attributes alone. On the other hand, other studies had both attributes and their levels.

The study had some limitations. First, the results might be subject to selection biases due to using an online panel for patient recruitment. The T2DM patients, who did not use online technology, might be omitted from this study. The second limitation was that BWS assumed that preferences were similar across individuals and used group means to present the results. Also, there might be potential heterogeneity for patients' priority, which was not explored in this study due to the limited sample size.

5.2 Aim 2: Determine patients' preferences for SGLT-2is and GLP-1 RAs

In addition to the literature review and the consultation with a clinical expert, the findings of the BWS study (aim 1) were used to guide the selection of the attributes for this aim 2. This method was similar to a previous study that developed survey instruments in augmentative and alternative communication (AAC) provision for children.[131] In this study, patients' preferences and WTPs for SGLT-2is and GLP-1 RAs were investigated using a DCE. Approximately 73% of 242 participants completed the survey and correctly responded to the validity choice set. This represented 1,584 observations. These responses reflected that these patients tended to understand the DCE choice sets well. This could result from the information about the attributes and their effects on T2DM provided in the survey.

We conducted the MNL analysis to examine patients' preferences. We confirmed all the attributes were significant, except for one level of the how you take the medication (injectable, once a day) attribute. However, MNL assumptions might not hold if the individual responses varied consistently, leading to bias results. Thus, the ML model was developed to examine patients' preferences. The ML model assumed preference varied randomly and accounted for the preference heterogeneity among the attributes. In the ML model, all of the attributes were statistically significant, except the two levels of the how do you take the medication attribute, i.e., injectable, once a day, and injectable, once a week. The positive sign and statistically significant coefficient of the constant in the ML model were intuitive since it indicated T2DM patients preferred the newer second-line T2DM medications to no second-line treatment. The results were consistent with the previous studies on T2DM patients' preferences in which patients preferred improvement in each attribute.[24, 27, 28, 30, 32-34, 36, 40] The chance of reaching target HbA1c in 6 months and % reduction in the risk of MACE were significant attributes and had positive coefficients in the ML model. These results suggested that T2DM patients preferred the SGLT-2is and GLP-1 RAs with a higher chance of reaching target HbA1C in 6 months and a higher % reduction in the risk of MACE. The chance of gastrointestinal side effects, the chance of genital infection, and out-of-pocket cost per month were also significant attributes but had negative coefficients, suggesting that patients preferred lower gastrointestinal side effects, the chance of genital infection and out-of-pocket cost per month or to avoid the SGLT-2is and GLP-1 RAs with these attributes. Also, the

results of the coefficients of the route and frequency administration were sensible since patients preferred to avoid injectable, twice a day medication.

The importance of these attributes from the coefficients of the ML model could not be compared directly since their measurements were not the same. However, the relative changes of these coefficients for one level change of each attribute could be compared to reflect the relative preference across attributes. For instance, reducing every 1% chance of genital infection was approximately two times more important to the patients than every 1% increase in reaching target HbA1c in 6 months or nearly three times more important to the patient than increasing every 1% reduction in the risk of MACE. Thus, the patient traded off between these treatment benefits, risks, and process attribute when using SGLT-2is and GLP-1 RAs. The significance of these attributes in our studies for patients' preferences could be compared; however, the coefficients of these attributes could not be compared with the results of the previous studies [24, 27, 28, 30, 32-34, 36, 40] because the set of attributes and their levels were different. Even though this set of attributes might have some common attributes, they were presented by different levels. We considered all attributes as continuous variables for our study, except for the route and frequency of administration, which was a categorical variable, and effect coding was used to run the ML model.

Due to the effect coding, the patients' preferences for the route and frequency of administration of SGLT-2is and GLP-1 RAs could be compared directly. The results of the ML model confirmed that T2DM patients preferred most to avoid injectable, twice a day medication since it was significantly different from the oral, once a day medication and had a large negative coefficient value. For another level of the route and frequency of administration attribute, injectable, once a day and injectable, once a week were not significantly different from the oral, once a day. In other words, the findings confirmed T2DM preferred indifferently among the oral, once a day medication and injectable, once a day medication, or injectable, once a week medication. These findings of our study were consistent with previous studies that indicated the route and frequency of administration were significant while determining the T2DM patients' preferences. [27, 28, 33, 34] However, these studies used the route of administration and frequency of administration as separate attributes. Our study combined the route and frequency of administration as one attribute to ensure our hypothetical products reflected the route and frequency of administration for existing SGLT-2is and GLP-1 RAs. Boye et al. also combined the route and frequency of administration.

They explored why patients preferred once-daily oral medication over once-weekly injectable medication and found that patients were already taking oral medication and could add another oral medication that better fitted in their schedule. They were concerned about using injectable medication.[132]

The ML model results confirmed that treatment benefit attributes of SGLT-2is and GLP-1 RAs for reaching target HbA1c in 6 months and reducing the risk of MACE (i.e., heart attack, stroke, and death due to cardiovascular diseases) had a positive and significant effect on the patients' preferences. Also, T2DM patients in this study had an average HbA1c of 7.43%, and many patients had comorbidities of hypertension and hyperlipidemia, making them more vulnerable to heart attack, stroke, and even death due to these cardiovascular diseases. Thus, achieving the target HbA1c < 7% and reducing the risk of MACE for these patients were important and would improve their health conditions. Similarly, many clinical studies confirmed that SGLT-2is and GLP-1 RAs had different odds of achieving target HbA1c and reducing the risk of MACE to a different level.[109, 110, 112] Patients would prefer the medications with higher odds of reaching the target HbA1c level and reducing the risk of MACE. Our finding was consistent with the previous studies on patients' preferences for T2DM medication.[24, 31, 40] In a study of patients' preferences of GLP-1 RA treatments of T2DM in Japan, Brooks et al. confirmed that the reduction in cardiovascular risk and reduction in HbA1c were the key drivers for the selection of GLP-1 RAs.[24]

For the results of significant treatment side effect attributes—chance of gastrointestinal side effect (i.e., nausea, vomiting, and diarrhea) and the chance of genital infection, intuitively T2DM patients preferred to avoid the medications that caused GI side effects or genital infections. Our study showed that patients were willing to trade off the benefits, e.g., reaching target HbA1c in 6 months and reducing the risk of MACE of the second-line T2DM medications with certain levels of the side effects of these medications. These findings were consistent with previous preference studies for T2DM medications.[33, 39] For instance, Mansfield et al. explored the patients' preferences for attributes of T2DM medications. They found that German patients demonstrated the significant and greatest preference for a lower risk of GI problems.[33] Also, Ozdemir et al. showed the significance of genital infection while selecting SGLT-2is and DPP4i to quantify patients' maximum acceptable risk of genital infection in exchange for benefits.[39] This study found that

patients were willing to trade a higher risk of genital infection for more effective medication.[39] However, we also observed the preference heterogeneity for all the attributes included in the ML model that explained patients with different characteristics and experiences with T2DM could have different preferences while trading off these attributes.

The preference heterogeneity was examined further for all attributes based on gender, the number of years of experience with T2DM, and experience with SGLT-2is and GLP-1 RAs using subgroup analyses. In all three sub-group analyses based on gender, experience with T2DM, and experience with SGLT-2is and GLP-1 RAs, it was intuitive that reaching target HbA1c in 6 months and out-of-pocket cost per month were significant for patients' preferences. However, the findings from the subgroup analysis based on gender indicated the reduction of risk of MACE, GI side effects, and genital infection were not significant for the preferences of male T2DM patients but significant to female T2DM patients. One of the reasons for the genital infection was that female T2DM patients had a higher incidence of genital infection than male T2DM patients.[111] Thus, female patients might prefer to avoid genital infection. Similarly, a study showed that women were more susceptible to short- and long-term cardiovascular complications.[133] Hence, the reduction of risk of MACE attribute might have been more important to female T2DM patients than to male patients. These findings were different from the findings of a previous study, indicating that male and female T2DM patients had no difference in their preferences for any attributes.[33] Such difference in our study might be due to genital infection attributes that were not included in the previous study but had a significant effect on our study. Also, the previous study was conducted in Germany and Spain, T2DM patients of different geographical locations might have different importance and preference. However, it was unclear why female and male patients viewed the GI side effect differently in this study.

Interestingly, while all study attributes were significant for the preferences of patients who had T2DM for 10 or more years, GI and genital infection side effects were not significant attributes for patients with less than 10 years of having T2DM. One of the reasons was that the patients with a long time experience of T2DM tended to develop various co-morbidities and preferred to avoid any additional drug-related side effects or adverse events that could lead to more health problems or complications.[125] For the patients who had the experience of using SGLT-2is or GLP-1 RAs, the reduction in risk of MACE, GI side effects, and genital infection had no significant effect on

their preferences, compared to patients who did not have any experience of using SGLT-2is and GLP-1 RAs. One reason could be the patients who experienced SGLT-2is or GLP-1 RAs might not be concerned about risk reduction of MACE, genital infection, and GI side effects because, as a result of using SGLT-2is or GLP-1 RAs, they knew they were at a lower MACE risk. Also, they might have some experiences with genital infection and GI side effects, and they knew how to cope with them. On the other hand, these attributes were important to patients who never used SGLT-2is and GLP-1 RAs since they expected the risk reduction of MACE, and they might be skeptical for the GI and genital infection side effects.

To our knowledge, this was the first study examining patients' WTPs for SGLT-2is and GLP-1 RAs in the U.S. The WTPs were the maximum amount of money that patients were willing to forfeit to obtain some benefits from specific attributes. They reflected the intrinsic value of SGLT-2is and GLP-1 RAs to the patients. The T2DM patients in this study valued overall SGLT-2is and GLP-1 RAs relatively high since they were willing to pay approximately $697 a month for SGLT-2is or GLP-1 RAs. However, any attribute that increased the patients' utility would raise their WTPs. For instance, the patients would be willing to pay $6 more if SGLT-2is or GLP-1 RAs increased, reaching target HbA1c in 6 months by 1%. Similarly, any attribute that decreased the patients' utility would lower their WTPs. For instance, patients would be willing to pay approximately $12 less for every 1% genital infection caused by SGLT-2is or GLP-1 RAs. Similarly, among the various ways of taking medications, these T2DM patients were willing to pay approximately $486 more for oral, once a day medication. Intuitively, patients were more comfortable with oral medication and as it was convenient to use once a day and easy to accommodate in their daily schedule. They were willing to pay the same amount for the injectable, once a day or injectable, once a week medications. On the other hand, the patients were willing to pay significantly lower if they needed to inject the medication twice a day. Our results were similar to the study results in Spain and Portugal, which assessed patients' and physicians' preferences and the monthly WTPs of T2DM treatments.[37] The study showed that T2DM patients were willing to pay higher to avoid side effects such as nausea than for a 1% increase in HbA1c.[37] Also, similar results were found in a study by Hauber et al. that examined the patients' WTPs among T2DM patients and showed patients were willing to pay more for oral and less frequent dosing medications. [30]

It is noteworthy that the WTPs of SGLT-2is and GLP-1 RAs in this study did not imply their prices, but they reflected how T2DM patients relatively valued these medications. Our results showed patients' WTPs for GLP-1 RAs varied widely from $1124 per month for exenatide (Byetta®) to $1518 per month for oral semaglutide (Rybelsus®), while patients' WTPs for SGLT-2is medications were comparatively uniform and ranged from $1241 for ertugliflozin (Steglatro®) to $1385 for canagliflozin (Invokana®). One of the reasons for the lower variation of WTPs for these SGLT-2is was that these medications had comparable benefits and side effects. Also, all of them were administered orally once a day and had minimal GI side effects.

When these WTPs for SGLT-2is and GLP-1 RAs were sorted and compared with each other, both top portion with low WTPs and bottom portion of high WTPs were for the GLP-1 RAs, as shown in Table 5-1. Our results showed patients were willing to pay the lowest of $1124 per month for exenatide (Byetta®), followed by $1168 per month for lixisenatide (Adlyxin®). One of the reasons patients were willing to pay the lowest for exenatide (Byetta®) might be its route and frequency of administration. Exenatide (Byetta®) is the only medications among all SGLT-2is and GLP-1 RAs administered injectable twice a day which patients preferred to pay lowest among the available route and frequency of administration. Patients were willing to pay lower for lixisenatide (Adlyxin®) because it has lower efficacy of reaching target HbA1c and reducing the risk of MACE in comparison to other GLP-1 RAs. Whereas patients were willing to pay the highest of $1518 per month for oral semaglutide (Rybelsus®) followed by $1438 per month for injectable semaglutide (Ozempic®). Patients were willing to pay the highest for oral semaglutide (Rybelsus®) because it is the only GLP-1 RAs administered orally, once a day which patients preferred the most and were willing to pay the highest among four different types of the route and frequency of administration. Similarly, both oral semaglutide (Rybelsus®) and injectable semaglutide (Ozempic®) had the highest efficacy of reaching target HbA1c and reducing the risk of MACE in comparison to other SGLT-2is and GLP-1 RAs.[112]

Interestingly, patients were willing to pay neither high nor low for all SGLT-2is, as they were in the middle range. Although, patients were willing to pay more for SGLT-2is as they were administered orally once a day, unlike liraglutide (Victoza®, Saxenda®) which was administered injectable once a day. However, patients were willing to pay less for SGLT-2is than liraglutide (Victoza®, Saxenda®) because they had lower efficacy of reaching target HbA1c in comparison to

liraglutide.[110] Also, patients were willing to pay less for SGLT-2is because SGLT-2is had shown an increased risk of genital infection in contrast to GLP 1 RAs [16]

However, to determine whether the market prices of these medications were congruent with the patient valuation, these WTPs for the SGLT-2is and GLP-1 RAs were compared with their current WACs calculated from the Red Book in March 2021. WACs is the manufacturer's published list price for drug products to wholesalers which reflect the value for medications from pharmaceutical companies' perspective. Interestingly, patients valued all these medications higher than their WACs. Among all SGLT-2is and GLP-1 RAs, patients valued ertugliflozin (Steglatro®) of 295% higher than its current market price and valued dulaglutide (Trulicity®) of just 46% higher than its current market price although their WTPs were comparable. Such huge difference in valuation might occur because patients valued these groups of medication differently than the pharmaceutical companies. Patients valued the highest for the oral, once a day medications such as ertugliflozin (Steglatro®), dapagliflozin (Farxiga®), canagliflozin (Invokana®), empagliflozin (Jardiance®) and semaglutide (Rybelsus®) while pharmaceutical companies valued the highest for the injectable, once a week medication such as dxenatide (Bydureon®), semaglutide (Ozempic®) and dulaglutide (Trulicity®) as their WACs were higher than other once a day medications. This might be the reason patients valued oral, once a day semaglutide (Rybelsus®) higher over injectable, once a week semaglutide (Ozempic®) but pharmaceutical companies valued higher for injectable, once a week semaglutide (Ozempic®) than oral, once a day semaglutide (Rybelsus®). Similarly, patients valued the exenatide (Byetta®) the lowest among all SGLT-2is and GLP-1 RAs but it has higher WACs than oral, once a day and injectable, once a day medication. Overall, patients valued the oral, once a day SGLT-2is higher than short-acting, injectable GLP-1 RAs. It is noteworthy that the patients' WTPs for SGLT-2is and GLP-1 RAs from DCE were derived from the attributes out-of-pocket cost per month the patients were willing to forfeit to obtain the hypothetical SGLT-2is or GLP-1 RAs. The patients were asked to trade off the cost that they were willing to pay from their pocket with only selected benefits and risks of treatments in the study. Such value for attributes was used to determine the patients' WTPs for SGLT-2is or GLP-1 RAs.

The study result should be interpreted cautiously in light of several limitation. First, the samples were recruited from an online panel and may not be representative of the U.S. population. The second limitation was patients stated their preferences from hypothetical medication choices and

their stated preferences might not reflect their real choices, where patients made decisions with emotion, financial and clinical consequences. However, this study generated hypothetical medication choices based on real-world medication attributes and their levels. The third limitation was that continuous coding was used for the probability of treatment changes and linearity was assumed for the per unit change in attribute's utility. This assumption might not hold true for all the levels of attributes. However, the continuous coding facilitated the simulation of the incremental changes in the attributes and permitted the estimations of the marginal rate of substitutions for non-cost attributes and the calculation of WTPs of these attributes.

Future Research

This study included only some attributes, e.g., target Hb1c, reducing the risk of MACE, GI side-effect, genital infection, out-of-pocket cost, that were important to T2DM patients. However, other treatment attributes should be explored further. For instance, dose timing could also have a significant impact on patients' preferences. Some GLP-1 RAs, such as exenatide (Byetta®) and lixisenatide (Adlyxin®), need to be administered 60 minutes before meals, while other GLP-1 RAs have flexible dose timing.[134] Patients may have different preferences for these medications. Future research should also collect patients' experiences with T2DM treatment-related side effects or adverse events, e.g., GI side effects and genital infection, in addition to other patient's characteristics, e.g., household income. The impact of these characteristics and experiences on patients' preferences and heterogeneity of preference of the T2DM treatments should be explored.

Conclusion

This study confirmed reducing blood glucose and reducing cardiovascular diseases are most important attributes while selecting second-line medications. It also provides the ranking of all the attributes of second-line T2DM medications based on their importance from the patient perspective that helps to guide physicians while making a shared decision with patients for selecting an appropriate medication. The decision about diabetes treatment requires a tradeoff among many attributes. This study revealed that T2DM patients valued reaching target Hb1c, reducing the risk of a major adverse cardiovascular event (MACE), gastrointestinal side-effect, genital infection, out-of-pocket cost, and route and frequency of administration while selecting preferred medications among SGLT-2is and GLP-1 RAs. However, preference heterogeneity

existed. Male T2DM patients or patients with lesser experience with T2DM or patients who had experienced SGLT-2is or GLP-1 RAs were less bothered with treatment-related GI side effects and genital infection. Also, T2DM patients were willing to pay highest for oral, once a day GLP-1 RAs and lowest for injectable, twice a day GLP-1 RAs. However, the patients' WTPs for SGLT-2is and GLP-1 RAs varied based on their attributes. This study's results can help clinicians engage their patients in the decision of SGLT-2is and GLP-1 RAs for better outcomes.

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Appendix 1. Aim 1 Survey Instrument

Survey on Diabetes Medications

Start of Block: Default Question Block

Q1.0 Dear Participant,

My name is Bidur Banjara. I am currently a graduate student at the Department of Health Outcomes Research & Policy, Harrison School of Pharmacy, Auburn University. I am reaching out to you through QualtricsTM to invite you to participate in a research project that explores patients' priorities for type 2 diabetes medications. I conduct this survey for my thesis work under the supervision of Dr. Surachat Ngorsuraches. I hope you will participate in this study.

As part of my research, I am interested in finding out how patients prioritize different characteristics of the second-line medications for Type 2 Diabetes Miletus (T2DM). This survey is anonymous. It will take approximately 12-15 minutes to complete the survey. The questionnaire in this survey includes 1) Demographic questions, 2) Questions related to your experience with diabetes, and 3) A series of questions in which you will be asked to choose the most and least important T2DM medication attributes (characteristics).

It is entirely up to you to decide whether or not to take part in this study. There is not any risk associated with this study. All your information will be confidential and will not be shared with anyone. There are no immediate benefits to you from the study, but the long-term benefit would be developing patients' choices to inform treatment decisions.

If you change your mind about participating in this study, you can withdraw at any time during the study. Your participation is fully voluntary. Your decision about whether not to participate or stop participating will not jeopardize your future relations with Auburn University or the Department of Health Outcomes Research & Policy. Upon completing the survey, your panel provider will compensate you as per the agreement for your valuable time and information.

Your privacy will be protected. Any data obtained in connection with this study will remain anonymous. We are highly concerned about your privacy. The data you provide will be utilized as per Auburn University Institutional Review Board (IRB) for the Protection of Human Subjects in Research guideline. Information collected through your participation may be used in the thesis to fulfill an educational requirement and will be published in professional journals in aggregate form. The Auburn University Institutional Review Board has approved this project with protocol # 21-035 EX 2101, Banjara.

If you have questions about this study, *please* contact Mr. Bidur Banajra at bzb0081@auburn.edu or Dr. Surachat Ngorsuraches at surachat@auburn.edu.

If you have questions about your rights as a research participant, you may contact the Auburn University Office of Research Compliance or the Institutional Review Board by phone (334)-844-5966 or e-mail IRBadmin@auburn.edu or IRBChair@auburn.edu.

HAVING READ THE INFORMATION PROVIDED, YOU MUST DECIDE WHETHER OR NOT YOU WISH TO PARTICIPATE IN THIS RESEARCH STUDY. YOUR ACCEPTANCE TO CONSENT AND CLICKING ARROW WILL TAKE TO THE SURVEY AND CONSIDERED AS INFORMED CONSENT.

- ○ Yes, I consent to participate (1)
- ○ No, I do not consent to participate (2)

Skip To: End of Block If Q1.0 = No, I do not consent to participate

Page Break

Q1.1 Are you 19 years of age or older?

- ○ Yes (1)
- ○ No (2)

Skip To: Q5.2 If Q1.1 = No

Page Break

Q1.2 Have you ever been diagnosed with type 2 diabetes?

- ○ Yes (1)
- ○ No (2)

Skip To: Q5.2 If Q1.2 = No

Q2.0. **Section A: Demographics Questions**

Q2.1 How do you identify your gender?

- ○ Female (1)
- ○ Male (2)
- ○ Prefer not to answer (3)

Q2.2 What year were you born?

_____

Q2.3 What is your weight?

_____

Q2.4 What is your height?

- ○ Feet _____
- ○ Inch _____

Page Break

Q2.5 Which of the following **best** describes your race/ethnicity?

- ○ American Indian / Alaska Native (1)
- ○ Asian / Native Hawaiian / Other Pacific Islander (2)
- ○ Black or African American (3)
- ○ Hispanic American (4)
- ○ White non-Hispanic / Caucasian (5)
- ○ Multiple ethnicity / Others (Please indicate) (6)

_____

- ○ Prefer not to answer (7)

Q2.6 What is your marital status?

- ○ Single (1)
- ○ Married (2)
- ○ Divorced or separated (3)
- ○ Widowed (4)
- ○ Other (Please indicate) (5) _____
- ○ Prefer not to answer (6)

Q2.7 What is the **highest** degree or level of education you have completed? (Check only one answer)

- ○ Less than high school (1)
- ○ High school or equivalence (e.g., GED) (2)
- ○ Technical / vocational training (3)
- ○ 2-year college degree (Associate's degree) (4)
- ○ 4-year college degree (e.g., BA, BS) (5)
- ○ Graduate or professional degree (e.g., MBA, MS, MD, PhD) (6)

Q2.8 Which of the following **best** describes your employment status? (Check only one answer)

- ○ Employed full-time (1)
- ○ Employed part-time (2)
- ○ Self-employed (3)
- ○ Stay-at-home spouse (4)
- ○ Student (5)
- ○ Retired (6)
- ○ Unemployed (7)

Q2.9 What is your **primary** health insurance? (Check only one answer)

- ○ I do not have health insurance (1)
- ○ Private Insurance (2)
- ○ Medicaid (3)
- ○ Medicare (4)
- ○ Veterans Health Insurance (5)
- ○ Others (Please indicate) (6) _____

Q2.10 Besides diabetes, what are the other medical conditions do you have? (Check all that apply)

- ☐ None (1)
- ☐ High blood pressure (2)
- ☐ Heart diseases (3)
- ☐ High blood lipid levels e.g., cholesterol, triglyceride (4)
- ☐ Cancer (5)
- ☐ Ulcer or stomach diseases (6)
- ☐ Blood diseases (7)
- ☐ Kidney diseases (8)

- [ ] Lung diseases (9)
- [ ] Liver diseases (10)
- [ ] Osteoarthritis (11)
- [ ] Rheumatoid arthritis (12)
- [ ] Back pain (13)
- [ ] Depression (14)
- [ ] Others (Please specify) (15)

Page Break

Q2.11 In general, how would you rate your overall health now?

- ○ Excellent (1)
- ○ Very good (2)
- ○ Good (3)
- ○ Fair (4)
- ○ Poor (5)

Page Break

Q3.0 **Section B: Your Experience with Type 2 Diabetes Miletus (T2DM)**

Q3.1 How many years ago were you diagnosed with type 2 diabetes?

_____

Q3.2 Do you know your HbA1c value?

- ○ Yes (1)
- ○ No (2)
- ○ Prefer not to answer (3)

Display This Question:

If Q3.2 = Yes

Q3.3 If YES, what is your recent HbA1c value ?

_____

Page Break

Q3.4 Your experiences with antidiabetic medication/s.

	Did you **previously** use this medication? (1)	Do you **currently** use this medication? (2)	Don't know (3)
Metformin (25)	☐	☐	☐
Exenatide (Byetta®, Bydureon®) (2)	☐	☐	☐
Dulaglutide (Trulicity®) (3)	☐	☐	☐
Liraglutide (Victoza®, Saxenda®) (4)	☐	☐	☐
Semaglutide (Ozempic®, Rybelsus®) (5)	☐	☐	☐
Albiglutide (Tanzeum®) (6)	☐	☐	☐
Lixisenatide (Adlyxin®) (7)	☐	☐	☐
Canagliflozin (Invokana®) (8)	☐	☐	☐
Dapagliflozin (Farxiga®) (9)	☐	☐	☐

Empagliflozin (Jardiance®) (10)	☐	☐	☐
Ertugliflozin (Steglatro®) (11)	☐	☐	☐
Other antidiabetic medication, please specify (26)	☐	☐	☐
Other antidiabetic medication, please specify (32)	☐	☐	☐

Page Break

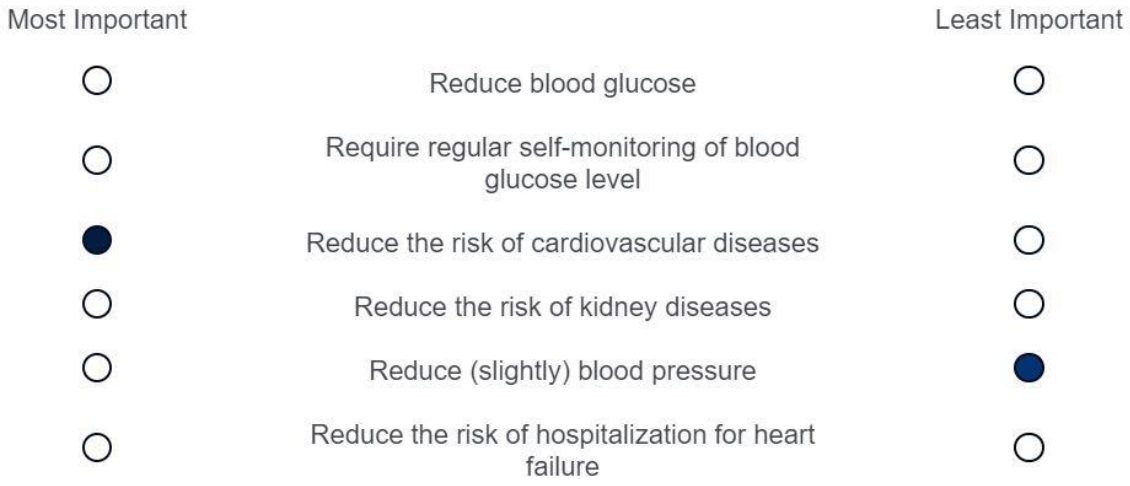
Q3.5 Which of the following T2DM symptoms have you ever had? (Check all that apply)

- [ ] Increased thirst (1)
- [ ] Frequent urination (2)
- [ ] Increased hunger (3)
- [ ] Fatigue (4)
- [ ] Blurred vision (5)
- [ ] Slow-healing sores (6)
- [ ] Frequent infections (7)
- [ ] Numbness or tingling in the hands or feet (8)
- [ ] Areas of darkened skin, usually in the armpits and neck (9)
- [ ] Other, please specify (10) _____
- [ ] Other, please specify (11) _____

Page Break

Q4.0 **Section C : Your opinion on the attributes (characteristics) of Type 2 Diabetes Mellitus (T2DM) medications**

For the upcoming nine sets of six attributes or characteristics of T2DM medications, please imagine that you are deciding to choose another medication for your diabetes after your initial medication is no longer effective. Then, consider the attributes or characteristics within each set and select the **MOST IMPORTANT** and the **LEAST IMPORTANT** attributes for you. Please see the example below.



Description:

Reduce blood glucose: The medication reduces the blood glucose level in your body

Require regular self-monitoring of blood glucose level: The uses of medication require regular monitoring of your blood glucose level

Reduce the risk of cardiovascular diseases: The medication can reduce cardiovascular diseases or risks such as heart attack, stroke, or death

Reduce the risk of kidney diseases: The medication can reduce kidney-related complications or protect kidneys

Reduce (slightly) blood pressure: The medication can slightly reduce blood pressure

Reduce the risk of hospitalization for heart failure: The medication can reduce hospital admission due to heart failure

Page Break

X→

Q4.1 Which of the following six attributes (characteristics) of diabetes medications are the **MOST IMPORTANT** and **LEAST IMPORTANT** to you when you choose another diabetes medication after your initial medication is no longer effective?

Most Important		Least Important
○	Reduce blood glucose	○
○	Reduce the risk of hospitalization for heart failure	○
○	Out-of-pocket cost	○
○	Gastrointestinal side-effects	○
○	Weight change	○
○	Reduce the all-cause death rate	○

Description:

Reduce blood glucose: The medication can reduce blood glucose level

Reduce the risk of hospitalization for heart failure: The medication can reduce hospital admission due to heart failure

Out-of-pocket cost: Cost of medication you pay out of your own pocket (e.g., copayment or whole amount)

Gastrointestinal side-effects: The medication can cause gastrointestinal side effects such as nausea, vomiting, and diarrhea

Weight change: The medication can change body weight

Reduce the all-cause death rate: The medication can reduce the death rate from any cause

Page Break

Q4.2 Which of the following six attributes (characteristics) of diabetes medications are the **MOST IMPORTANT** and **LEAST IMPORTANT** to you when you choose another diabetes medication after your initial medication is no longer effective?

Most Important		Least Important
○	Reduce (slightly) blood pressure	○
○	Out-of-pocket cost	○
○	Increase the risk of diabetic ketoacidosis	○
○	Dosing Frequency	○
○	Increase the risk of urinary tract and genital infection	○
○	Weight change	○

Description:

Reduce (slightly) blood pressure: The medication can slightly reduce blood pressure

Out-of-pocket cost: Cost of medication you pay out of your own pocket (e.g., copayment or whole amount)

Increase the risk of diabetic ketoacidosis: The medication increases the risk of breaking down fats too fast making the blood more acidic that leads to diabetic coma or death

Dosing Frequency: Number of times or how often you take the medication

Increase the risk of urinary tract and genital infection: The medication can increase the risk of genital infection and urinary tract infection

Weight change: The medication can change body weight

Page Break

X→

Q4.3 Which of the following six attributes (characteristics) of diabetes medications are the **MOST IMPORTANT** and **LEAST IMPORTANT** to you when you choose another diabetes medication after your initial medication is no longer effective?

Most Important		Least Important
○	Reduce blood glucose	○
○	Reduce the risk of kidney diseases	○
○	Reduce (slightly) blood pressure	○
○	Gastrointestinal side-effects	○
○	Increase the risk of blood glucose lower than normal	○
○	Increase the risk of urinary tract and genital infection	○

Description:

Reduce blood glucose: The medication can reduce blood glucose level

Reduce the risk of kidney diseases: The medication can reduce kidney-related complications or protect kidneys

Reduce (slightly) blood pressure: The medication can slightly reduce blood pressure

Gastrointestinal side-effects: The medication can cause gastrointestinal side effects such as nausea, vomiting, and diarrhea

Increase the risk of blood glucose lower than normal: The medication can make blood glucose level lower than normal, causing some symptoms, e.g., feeling shaky, sweating, chill, clamminess, confusion, fast heartbeat, lightheaded, etc.

Increase the risk of urinary tract and genital infection: The medication can increase the risk of genital infection and urinary tract infection

Page Break

Q4.4 Which of the following six attributes (characteristics) of diabetes medications are the **MOST IMPORTANT** and **LEAST IMPORTANT** to you when you choose another diabetes medication after your initial medication is no longer effective?

Most Important		Least Important
○	Reduce blood glucose	○
○	Require regular self-monitoring of blood glucose level	○
○	Reduce (slightly) blood pressure	○
○	Increase the risk of diabetic ketoacidosis	○
○	Route of administration	○
○	Reduce the all-cause death rate	○

Description:
Reduce blood glucose: The medication can reduce blood glucose level
Require regular self-monitoring of blood glucose level: The uses of medication require regular monitoring of your blood glucose level
Reduce (slightly) blood pressure: The medication can slightly reduce blood pressure
Increase the risk of diabetic ketoacidosis: The medication increases the risk of breaking down fats too fast, making blood more acidic that lead to diabetic coma or death
Route of administration: How you take the medication, such as oral or injection
Reduce the all-cause death rate: The medication can reduce the death rate from any cause

Page Break

Q4.5 Which of the following six attributes (characteristics) of diabetes medications are the **MOST IMPORTANT** and **LEAST IMPORTANT** to you when you choose another diabetes medication after your initial medication is no longer effective?

Most Important		Least Important
○	Reduce the risk of kidney diseases	○
○	Reduce the risk of hospitalization for heart failure	○
○	Increase the risk of diabetic ketoacidosis	○
○	Dosing Frequency	○
○	Increase the risk of blood glucose lower than normal	○
○	Reduce the all-cause death rate	○

Description:

Reduce the risk of kidney diseases: The medication can reduce kidney-related complications or protect kidneys

Reduce the risk of hospitalization for heart failure: The medication can reduce hospital admission due to heart failure

Increase the risk of diabetic ketoacidosis: The medication increases the risk of breaking down fats too fast, making blood more acidic that lead to diabetic coma or death

Dosing Frequency: Number of times or how often you take the medication

Increase the risk of blood glucose lower than normal: The medication can make blood glucose level lower than normal, causing some symptoms, e.g., feeling shaky, sweating, chill, clamminess, confusion, fast heartbeat, lightheaded, etc.

Reduce the all-cause death rate: The medication can reduce the death rate from any cause

Page Break

Q4.6 Which of the following six attributes (characteristics) of diabetes medications are the **MOST IMPORTANT** and **LEAST IMPORTANT** to you when you choose another diabetes medication after your initial medication is no longer effective?

Most Important		Least Important
○	Require regular self-monitoring of blood glucose level	○
○	Reduce the risk of cardiovascular diseases	○
○	Reduce (slightly) blood pressure	○
○	Reduce the risk of hospitalization for heart failure	○
○	Out-of-pocket cost	○
○	Increase the risk of blood glucose lower than normal	○

Description:

Require regular self-monitoring of blood glucose level: The uses of medication require regular monitoring of your blood glucose level

Reduce the risk of cardiovascular diseases: The medication can reduce cardiovascular diseases or risk, e.g., heart attack, stroke, or death.

Reduce (slightly) blood pressure: The medication can slightly reduce blood pressure

Reduce the risk of hospitalization for heart failure: The medication can reduce hospital admission due to heart failure

Out-of-pocket cost: Cost of medication you pay out of your own pocket (e.g., copayment or whole amount)

Increase the risk of blood glucose lower than normal: The medication can make blood glucose level lower than normal, causing some symptoms, e.g., feeling shaky, sweating, chill, clamminess, confusion, fast heartbeat, lightheaded, etc.

Page Break

Q4.7 Which of the following six attributes (characteristics) of diabetes medications are the **MOST IMPORTANT** and **LEAST IMPORTANT** to you when you choose another diabetes medication after your initial medication is no longer effective?

Most Important		Least Important
○	Reduce blood glucose	○
○	Require regular self-monitoring of blood glucose level	○
○	Dosing Frequency	○
○	Increase the risk of blood glucose lower than normal	○
○	Reaction at injection site	○
○	Weight change	○

Description:

Reduce blood glucose: The medication can reduce blood glucose level

Require regular self-monitoring of blood glucose level: The uses of medication require regular monitoring of your blood glucose level

Dosing Frequency: Number of times or how often you take the medication

Increase the risk of blood glucose lower than normal: The medication can make blood glucose level lower than normal, causing some symptoms, e.g., feeling shaky, sweating, chill, clamminess, confusion, fast heartbeat, lightheaded, etc.

Reaction at injection site: The medication causes injection site reaction e.g. rashes, burning sensation, or nodules

Weight change: The medication can change body weight

Page Break

Q4.8 Which of the following six attributes (characteristics) of diabetes medications are the **MOST IMPORTANT** and **LEAST IMPORTANT** to you when you choose another diabetes medication after your initial medication is no longer effective?

Most Important		Least Important
○	Require regular self-monitoring of blood glucose level	○
○	Reduce the risk of cardiovascular diseases	○
○	Dosing Frequency	○
○	Gastrointestinal side-effects	○
○	Increase the risk of urinary tract and genital infection	○
○	Reduce the all-cause death rate	○

Description:

Require regular self-monitoring of blood glucose level: The uses of medication require regular monitoring of your blood glucose level

Reduce the risk of cardiovascular diseases : The medication can reduce cardiovascular diseases or risk, e.g., heart attack, stroke, or death.

Dosing Frequency: Number of times or how often you take the medication

Gastrointestinal side-effects: The medication can cause gastrointestinal side effects such as nausea, vomiting, and diarrhea

Increase the risk of urinary tract and genital infection: The medication can increase risk of genital infection and urinary tract infection

Reduce the all-cause death rate: The medication can reduce the death rate from any cause

Page Break

Q4.9 Which of the following six attributes (characteristics) of diabetes medications are the **MOST IMPORTANT** and **LEAST IMPORTANT** to you when you choose another diabetes medication after your initial medication is no longer effective?

Most Important		Least Important
○	Reduce (slightly) blood pressure	○
○	Out-of-pocket cost	○
○	Increase the risk of diabetic ketoacidosis	○
○	Dosing Frequency	○
○	Increase the risk of urinary tract and genital infection	○
○	Weight change	○

Description:

Reduce (slightly) blood pressure: The medication can slightly reduce blood pressure

Out-of-pocket cost: Cost of medication you pay out of your own pocket (e.g., copayment or whole amount)

Increase the risk of diabetic ketoacidosis: The medication increases the risk of breaking down fats too fast making the blood more acidic that leads to diabetic coma or death

Dosing Frequency: Number of times or how often you take the medication

Increase the risk of urinary tract and genital infection: The medication can increase the risk of genital infection and urinary tract infection

Weight change: The medication can increase or decrease body weight

Page Break

Q5.1
Last question, how was your experience taking this survey? Please describe your feedback or comment on the overall survey questionnaire.

_____

_____

Q5.2 Thank you for your participation!

End of Block: Default Question Block

Appendix II. Aim 2 Survey Instrument

Initial Screening Questions

Dear Participant,

My name is Bidur Banjara. I am currently a graduate student at the Department of Health Outcomes Research & Policy, Harrison School of Pharmacy, Auburn University. I am inviting you to participate in a research project that explores patients' preferences for type 2 diabetes medications. I am conducting this project with the help of Dr. Surachat Ngorsuraches. I hope you will participate in this study.

As part of my research, I am interested in finding out what patients prefer for different characteristics of the newer second-line medications for Type 2 Diabetes Miletus (T2DM). It will take approximately 10-15 minutes to complete the survey. The questionnaire in this survey includes 1) Demographic questions, 2) Questions related to your experience with diabetes, and 3) A series of questions in which you will be asked to compare 2 hypothetical medications based on their different characteristics (attributes) and choose your preferred medication.

It is entirely up to you to decide whether to take part in this study. There is not any risk associated with this study. There are no immediate benefits to you from the study, but the long-term benefit would be developing patients' choices to inform treatment decisions. If you change your mind about participating in this study, you can withdraw at any time during the study. Your participation is fully voluntary. Your decision about whether or not to participate or stop participating will not jeopardize your future relation with Auburn University. Upon completing the survey, your panel provider will compensate you as per the agreement for your valuable time and information.

Your privacy will be protected. All your information will be confidential and will not be shared with anyone. Any data obtained in connection with this study will remain anonymous. The data you provide will be utilized as per Auburn University Institutional Review Board (IRB) for the Protection of Human Subjects in Research guideline. Information collected through your participation may be used in the thesis to fulfill an educational requirement and will be published in professional journals in aggregate form. The Auburn University Institutional Review Board has approved this project with protocol #21-035 EX 2101, Banjara.

If you have questions about this study, *please* contact Mr. Bidur Banajra at bzb0081@auburn.edu or Dr. Surachat Ngorsurachesat surachat@auburn.edu.

If you have questions about your rights as a research participant, you may contact the Auburn University Office of Research Compliance or the Institutional Review Board by phone (334)-844-5966 or e-mail IRBadmin@auburn.edu or IRBChair@auburn.edu. **HAVING READ THE INFORMATION PROVIDED, YOU MUST DECIDE WHETHER OR NOT YOU WISH TO PARTICIPATE IN THIS RESEARCH STUDY. YOUR ACCEPTANCE TO CONSENT AND CLICKING "NEXT" WILL TAKE INTO THE SURVEY AND CONSIDERED AS INFORMED CONSENT.**

- ○ Yes, I consent to participate
- ○ No, I do not consent to participate

Are you 19 years of age or older?

- ○ Yes
- ○ No

Have you ever been diagnosed with type 2 diabetes?

- ○ Yes
- ○ No

Demographic and Experience Questions

SECTION A: Demographics Questions

How do you identify your gender?

- ○ Female
- ○ Male
- ○ Prefer not to answer

What year were you born?

[ ] YYYY

What is your weight?

[ ] Pounds (lbs)

What is your height?

Feet

Inch

Which of the following **best** describes your race/ethnicity?

- ○ American Indian / Alaska Native
- ○ Asian / Native Hawaiian / Other Pacific Islander
- ○ Black or African American
- ○ Hispanic American
- ○ White non-Hispanic / Caucasian
- ○ Multiple ethnicity / Others (Please indicate)
- ○ Prefer not to answer

What is your marital status?

- ○ Single
- ○ Married
- ○ Divorced or separated
- ○ Widowed
- ○ Other (Please indicate)
- ○ Prefer not to answer

What is your total **annual household income**?

- ○ $100,000 or more per year
- ○ $75,000 to $99,999 per year
- ○ $50,000 to $74,999 per year
- ○ $25,000 to $49,999 per year
- ○ Less than $25,000 per year
- Prefer not to answer

What is the **highest** degree or level of education you have completed? (Check only one answer)

- ○ Less than high school
- ○ High school or equivalence (e.g., GED)
- ○ Technical / vocational training
- ○ 2-year college degree (Associate's degree) ○

4-year college degree (e.g., BA, BS)

- ○ Graduate or professional degree (e.g., MBA, MS, MD, PhD)

Which of the following **best** describes your employment status? (Check only one answer)

- ○ Employed full-time
- ○ Employed part-time
- ○ Self-employed
- ○ Stay-at-home spouse ○

Student

- ○ Retired
- ○ Unemployed

What is your **primary** health insurance? (Check only one answer)

- ○ I do not have health insurance ○

Private Insurance

- ○ Medicaid
- ○ Medicare
- ○ Veterans Health Insurance
- ○ [ ] Others (Please indicate)

Besides diabetes, what are the other medical conditions do you have? (Check all that apply)

- ☐ None
- ☐ High blood pressure
- ☐ Heart diseases
- ☐ High blood lipid levels e.g., cholesterol, triglyceride ☐

Cancer

- ☐ Ulcer or stomach diseases

- [ ] Blood diseases
- [ ] Kidney diseases
- [ ] Lung diseases
- [ ] Liver diseases
- [ ] Osteoarthritis
- [ ] Rheumatoid arthritis
- [ ] Back pain
- [ ] Depression
- [ ] _____ Others (Please specify)

In general, how would you rate your overall health now?

- ○ Excellent
- ○ Very good
- ○ Good
- ○ Fair
- ○ Poor

SECTION B: Your Experience with Type 2 Diabetes Miletus (T2DM)

How many years ago were you diagnosed with type 2 diabetes?

_____ year/s ago

Do you know your HbA1c value?

- ○ Yes
- ○ No
- ○ Prefer not to answer

If YES, what is your recent HbA1c value ?

☐ % mmol/L

Do you have experience of using any of the following antidiabetic medications? (Check all that apply)

☐ Exenatide (Byetta®, Bydureon®) ☐ Dulaglutide (Trulicity®)
☐ Liraglutide (Victoza®, Saxenda®)
☐ Semaglutide (Ozempic®, Rybelsus®)
☐ Albiglutide (Tanzeum®)
☐ Lixisenatide (Adlyxin®)
☐ Canagliflozin (Invokana®)
☐ Dapagliflozin (Farxiga®)
☐ Empagliflozin (Jardiance®)
☐ Ertugliflozin (Steglatro®)
☐ None of above
☐ Do not know
☐ Prefer not to answer

Which of the following T2DM symptoms have you ever had? (Check all that apply)

☐ Increased thirst ☐ Frequent urination ☐ Increased hunger ☐ Fatigue
☐ Blurred vision
☐ Slow-healing sores
☐ Frequent infections
☐ Numbness or tingling in the hands or feet
☐ Areas of darkened skin, usually in the armpits and neck
☐ ☐ Other, please specify

DCE Survey - Version 1

Section C: Your preference of Diabetes Mellitus (DM) treatments

In this section, we would like to learn about your opinion for new medications **after your initial medication (e.g., metformin) alone does not help you achieve your treatment goal**. Please read the descriptions of the following medication attributes (characteristics) carefully. We will describe type medications by these attributes (characteristics).

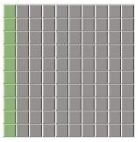
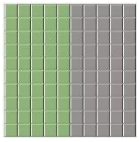
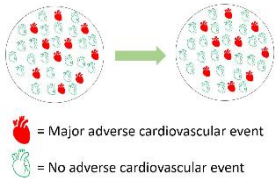
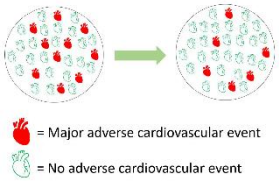
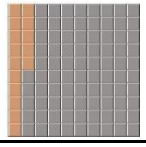
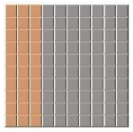
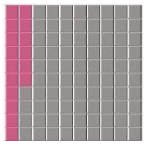
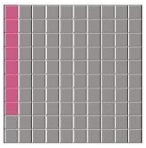
Attributes	Descriptions

How do you take the medication	Determine the route of administration such as oral or injectable and how often the medications are taken such as once a day or twice a day or once a week.
Chance of reaching target HbA1c (long-term blood glucose level) in 6 months	Measure the benefit of type 2 diabetes medications. Diabetes medications lower your blood glucose. HbA1c is a test of your blood glucose that is done at the doctor's office. It is an average of your blood glucose over the last 3 months. A normal HbA1c is 4% to 6%, but people with diabetes have a higher-than-normal HbA1c (up to 12% or more). The goal of diabetes treatment is usually to get the HbA1c to be under 7%. **Higher chance of reaching target HbA1c (long-term blood glucose level) is better**
% reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to cardiovascular diseases)	People with type 2 diabetes have four times higher risk of having heart attack and 2-4 times higher risk of having stroke. Some type 2 diabetes medications can reduce the risk of these major adverse cardiovascular events, while other medications may not have any effects on this cardiovascular risk. **Higher % reduction in the risk of major adverse cardiovascular events is better**
Chance of gastrointestinal (GI) side effects (i.e., nausea, vomiting, and diarrhea)	Gastrointestinal side effects are the common side effects of some type 2 diabetes medications, and their side effects vary among medications. **Lower chances of gastrointestinal side effects is better**
Chance of genital infection	Some type 2 diabetes medications increase the risk of genital infections. **Lower the chances of genital infection is better**

Out-of-Pocket Cost per month	• Cost you pay out from your own pocket (e.g., copayment or whole amount) fortype 2 • diabetes medication. **Lower out-of-pocket cost is better**

For the next ten questions, you will be asked to carefully consider three medication options: (1) Medication A, (2) Medication B, and (3) Neither Medication A nor Medication B, described in each table and choose your **PREFERRED MEDICATION** option **after your initial medication (e.g., metformin) alone does not help you achieve your treatment goal.**

EXAMPLE: After you compare the 3 medication options, if you decide to choose Medication B, then click on ☐ the option of Medication B, as shown below.

Attributes	Medication A	Medication B	Neither medication A nor medication B
How do you take the medication	Injectable, once a week 	Injectable, twice a day 	Neither medication A nor medication B
Chance of reaching target HbA1c (long-term blood glucose level) in 6 months	10 out of 100 (10%) patients reach target HbA1c 	50 out of 100 (50%) patients reach target HbA1c 	
% reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to cardiovascular diseases)	No reduction in the risk of these cardiovascular events 	40% reduction in the risk of these cardiovascular events 	
Chance of gastrointestinal (GI) side effects (i.e., nausea, vomiting, and diarrhea)	15 out of 100 (15%) patient experiences GI side effects 	30 out of 100 (30%) patients experience GI side effects 	
Chance of genital infection	16 out of 100 (16%) patients experience genital infection 	8 out of 100 (8%) patients experience genital infection 	
Out-of-Pocket Cost per month	$0	$1,000	

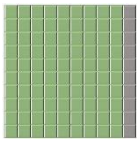
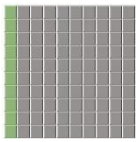
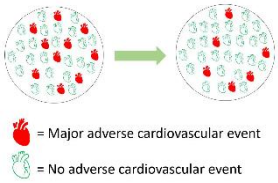
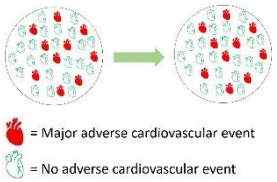
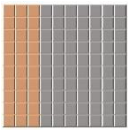
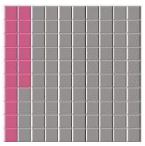
Which medication do you choose? (pick only one medication option)

☐ I choose Medication A

☐ I choose Medication B
☐ I choose neither Medication A nor Medication B

*This is just an example, click on NEXT to continue the survey.

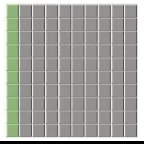
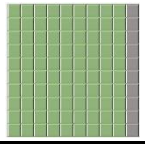
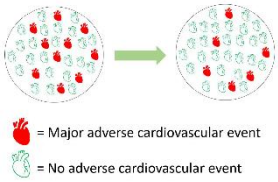
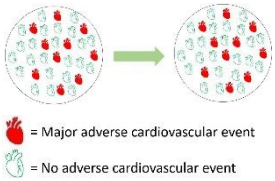
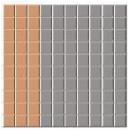
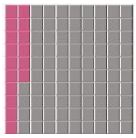
Q.1 Which of the following medication you would prefer based on the attributes (characteristics) presented **after your initial medication (e.g., metformin) alone does not help you achieve your treatment goal**? Choose by clicking one of the buttons below:

Attributes	Medication A	Medication B	Neither medication A nor medication B
How do you take the medication	Injectable, once a week 	Injectable, twice a day 	Neither medication A nor medication B
Chance of reaching target HbA1c (long-term blood glucose level) in 6 months	90 out of 100 (90%) patients reach target HbA1c 	10 out of 100 (10%) patients reach target HbA1c 	
% reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to cardiovascular diseases)	40% reduction in the risk of these cardiovascular events 	No reduction in the risk of these cardiovascular events 	
Chance of gastrointestinal (GI) side effects (i.e., nausea, vomiting, and diarrhea)	1 out of 100 (1%) patient experiences GI side effects 	30 out of 100 (30%) patients experience GI side effects 	
Chance of genital infection	No patient (0%) experiences genital infection	16 out of 100 (16%) patients experience genital infection 	
Out-of-Pocket Cost per month	$0	$1,000	

Which medication do you choose? (pick only one medication option)

○ I choose Medication A
○ I choose Medication B
○ I choose neither Medication A nor Medication B

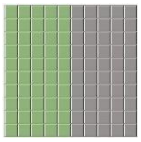
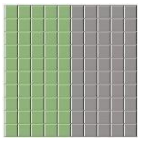
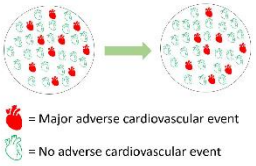
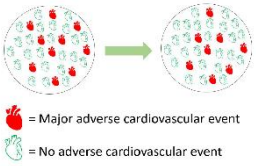
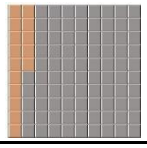
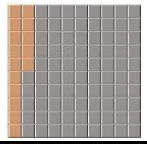
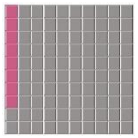
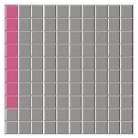
Q.2 Which of the following medication you would prefer based on the attributes (characteristics) presented **after your initial medication (e.g., metformin) alone does not help you achieve your treatment goal**? Choose by clicking one of the buttons below:

Attributes	Medication A	Medication B	Neither medication A nor medication B
How do you take the medication	Tablet, once a day 	Injectable, one a week 	Neither medication A nor medication B
Chance of reaching target HbA1c (long-term blood glucose level) in 6 months	10 out of 100 (10%) patients reach target HbA1c 	90 out of 100 (90%) patients reach target HbA1c 	
% reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to cardiovascular diseases)	40% reduction in the risk of these cardiovascular events 	No reduction in the risk of these cardiovascular events 	
Chance of gastrointestinal (GI) side effects (i.e., nausea, vomiting, and diarrhea)	1 out of 100 (1%) patient experiences GI side effects 	30 out of 100 (30%) patients experience GI side effects 	
Chance of genital infection	16 out of 100 (16%) patients experience genital infection 	No patient (0%) experiences genital infection	
Out-of-Pocket Cost per month	$0	$500	

Which medication do you choose? (pick only one medication option)

- ○ I choose Medication A
- ○ I choose Medication B
- ○ I choose neither Medication A nor Medication B

Q.3 Which of the following medication you would prefer based on the attributes (characteristics) presented **after your initial medication (e.g., metformin) alone does not help you achieve your treatment goal**? Choose by clicking one of the buttons below:

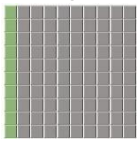
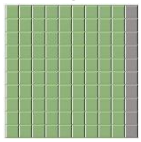
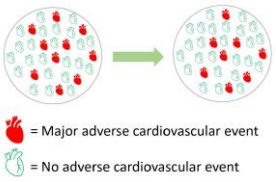
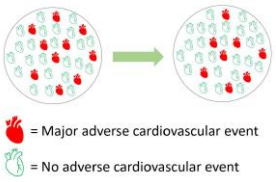
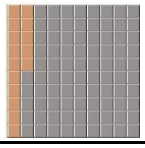
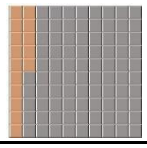
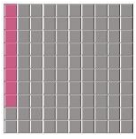
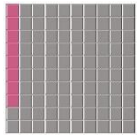
Attributes	Medication A	Medication B	Neither medication A nor medication B
How do you take the medication	Injectable, once a day 	Tablet, once a day 	Neither medication A nor medication B
Chance of reaching target HbA1c (long-term blood glucose level) in 6 months	50 out of 100 (50%) patients reach target HbA1c 	50 out of 100 (50%) patients reach target HbA1c 	
% reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to cardiovascular diseases)	20% reduction in the risk of these cardiovascular events 	20% reduction in the risk of these cardiovascular events 	
Chance of gastrointestinal (GI) side effects (i.e., nausea, vomiting, and diarrhea)	15 out of 100 (15%) patients experience GI side effects 	15 out of 100 (15%) patients experience GI side effects 	
Chance of genital infection	8 out of 100 (8%) patients experience genital infection 	8 out of 100 (8%) patients experience genital infection 	
Out-of-Pocket Cost per month	$ 1,000	$ 1,000	

Which medication do you choose? (pick only one medication option)

- ○ I choose Medication A
- ○ I choose Medication B
- ○ I choose neither Medication A nor Medication B

Q.4 Which of the following medication you would prefer based on the attributes (characteristics) presented **after your initial medication (e.g., metformin) alone does not help you achieve your treatment goal**? Choose by clicking one of the buttons below:

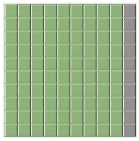
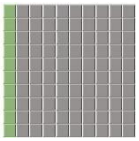
Attributes	Medication A	Medication B	Neither medication A nor medication B
How do you take the medication	Injectable, one a week 	Injectable, twice a day 	Neither medication A nor medication B
Chance of reaching target HbA1c (long-	10 out of 100 (10%) patients	90 out of 100 (90%) patients	

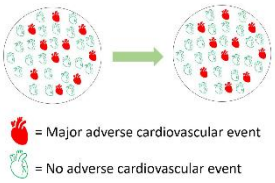
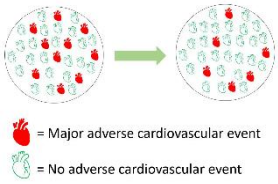
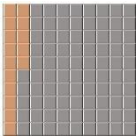
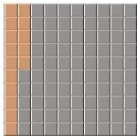
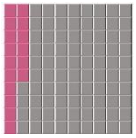
term blood glucose level) in 6 months	reach target HbA1c 	reach target HbA1c 
% reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to cardiovascular diseases)	20% reduction in the risk of these cardiovascular events 	20% reduction in the risk of these cardiovascular events 
Chances of gastrointestinal side effects(i.e., nausea, vomiting and diarrhea)	15 out of 100 (15%) patient experiences GI side effects 	15 out of 100 (15%) patient experiences GI side effects 
Chances of genital infection	8 out of 100 (8%) patients experience genital infection 	8 out of 100 (8%) patients experience genital infection 
Out-of-Pocket Cost per month	$ 1,000	$ 0

Which medication do you choose? (pick only one medication option)

- ○ I choose Medication A
- ○ I choose Medication B
- ○ I choose neither Medication A nor Medication B

Q.5 Which of the following medication you would prefer based on the attributes (characteristics) presented **after your initial medication (e.g., metformin) alone does not help you achieve your treatment goal**? Choose by clicking one of the buttons below:

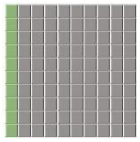
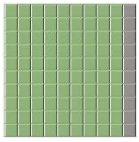
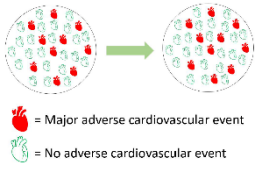
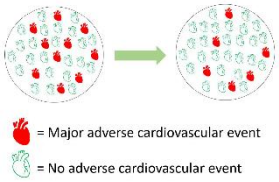
Attributes	Medication A	Medication B	Neither medication A nor medication B
How do you take the medication	Injectable, once a day 	Injectable, once a week 	Neither medication A nor medication B
Chance of reaching target HbA1c (long-term blood glucose level) in 6 months	90 out of 100 (90%) patients reach target HbA1c 	10 out of 100 (10%) patients reach target HbA1c 	
% reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to cardiovascular diseases)	No reduction in the risk of these cardiovascular events	40% reduction in the risk of these cardiovascular events	

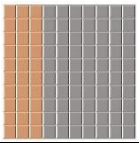
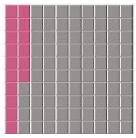
		
Chances of gastrointestinal (GI) sideeffects (i.e. nausea, vomiting and diarrhea)	15 out of 100 (15%) patients experience GI side effects 	15 out of 100 (15%) patients experience GI side effects 
Chances of genital infection	No patient (0%) experiences genital infection	16 out of 100 (16%) patients experience genital infection 
Out-of-Pocket Cost per month	$ 500	$ 500

Which medication do you choose? (pick only one medication option)

- ○ I choose Medication A
- ○ I choose Medication B
- ○ I choose neither Medication A nor Medication B

Q.6 Which of the following medication you would prefer based on the attributes (characteristics) presented **after your initial medication (e.g., metformin) alone does not help you achieve your treatment goal**? Choose by clicking one of the buttons below:

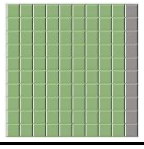
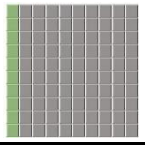
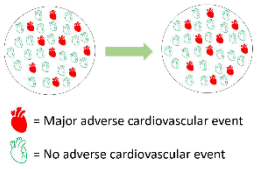
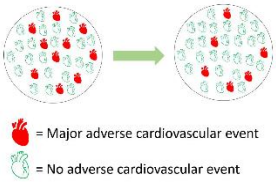
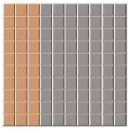
Attributes	Medication A	Medication B	Neither medication A nor medication B
How do you take the medication	Injectable, one a week 	Tablet, once a day 	Neither medication A nor medication B
Chance of reaching target HbA1c (long-term blood glucose level) in 6 months	10 out of 100 (10%) patients reach target HbA1c 	90 out of 100 patients (90%) reach target HbA1c 	
% reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to cardiovascular diseases)	No reduction in the risk of these cardiovascular events 	40% reduction in the risk of these cardiovascular events 	
Chance of gastrointestinal (GI) sideeffects (i.e., nausea, vomiting, and	1 out of 100 (1%) patient experiences GI side effects	30 out of 100 (30%) patients experience GI side effects	

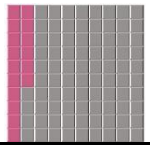
diarrhea)			
Chance of genital infection	16 out of 100 (16%) patients experience genital infection 	No patients (0%) experience genital infection	
Out-of-Pocket Cost per month	$ 500	$ 0	

Which medication do you choose? (pick only one medication option)

- ○ I choose Medication A
- ○ I choose Medication B
- ○ I choose neither Medication A nor Medication B

Q.7 Which of the following medication you would prefer based on the attributes (characteristics) presented **after your initial medication (e.g., metformin) alone does not help you achieve your treatment goal**? Choose by clicking one of the buttons below:

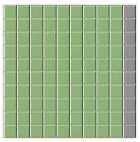
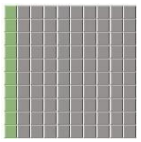
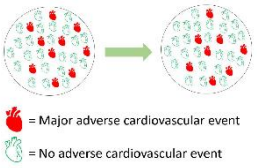
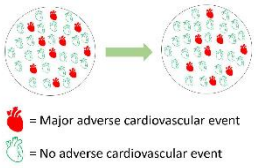
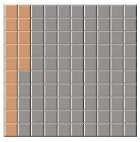
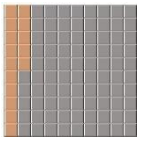
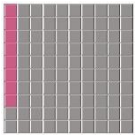
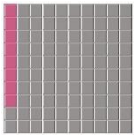
Attributes	Medication A	Medication B	Neither medication A nor medication B
How do you take the medication	Tablet, once a day 	Injectable, once a day 	Neither medication A nor medication B
Chance of reaching target HbA1c (long-term blood glucose level) in 6 months	90 out of 100 patients (90%) reach target HbA1c 	10 out of 100 patients (10%) reach target HbA1c 	
% reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to cardiovascular diseases)	No reduction in the risk of these cardiovascular events 	40% reduction in the risk of these cardiovascular events 	
Chances of gastrointestinal side effects (i.e. nausea, vomiting and diarrhea)	1 out of 100 (1%) patient experiences GI side effects 	30 out of 100 (30%) patient experiences GI side effects 	
Chances of genital infection	16 out of 100 (16%) patients experience genital infection	No patients (0%) experience genital infection	

			
Out-of-Pocket Cost per month	$ 1, 000	$ 0	

Which medication do you choose? (pick only one medication option)

- ○ I choose Medication A
- ○ I choose Medication B
- ○ I choose neither Medication A nor Medication B

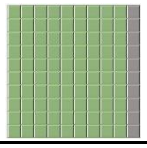
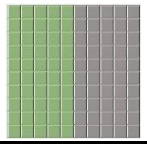
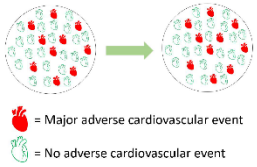
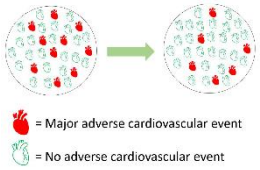
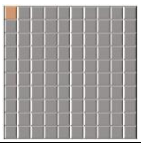
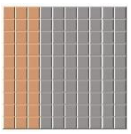
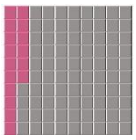
Q.8 Which of the following medication you would prefer based on the attributes (characteristics) presented **after your initial medication (e.g., metformin) alone does not help you achieve your treatment goal**? Choose by clicking one of the buttons below:

Attributes	Medication A	Medication B	Neither medication A nor medication B
How do you take the medication	Injectable, once a day 	Injectable, twice a day 	Neither medication A nor medication B
Chance of reaching target HbA1c (long-term blood glucose level) in 6 months	90 out of 100 patients (90%) reach target HbA1c 	10 out of 100 (10%) patients reach target HbA1c 	
% reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to cardiovascular diseases)	20% reduction in the risk of these cardiovascular events 	20% reduction in the risk of these cardiovascular events 	
Chance of gastrointestinal (GI) side effects (i.e., nausea, vomiting, and diarrhea)	15 out of 100 (15%) patient experiences GI side effects 	15 out of 100 (15%) patient experiences GI side effects 	
Chance of genital infection	8 out of 100 (8%) patients experience genital infection 	8 out of 100 (8%) patients experience genital infection 	
Out-of-Pocket Cost per month	$ 0	$ 1,000	

Which medication do you choose? (pick only one medication option)

○ I choose Medication A
○ I choose Medication B
○ I choose neither Medication A nor Medication B

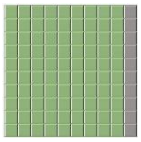
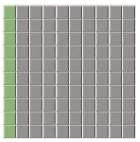
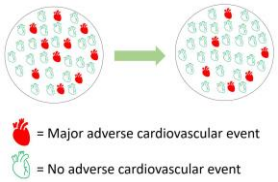
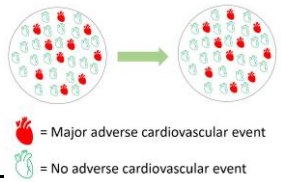
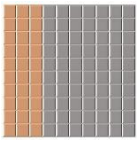
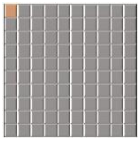
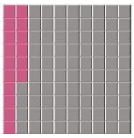
Q.9 Which of the following medication you would prefer based on the attributes (characteristics) presented **after your initial medication (e.g., metformin) alone does not help you achieve your treatment goal**? Choose by clicking one of the buttons below:

Attributes	Medication A	Medication B	Neither medication A nor medication B
How do you take the medication	Injectable, one a week 	Injectable, twice a day 	Neither medication A nor medication B
Chance of reaching target HbA1c (long-term blood glucose level) in 6 months	90 out of 100 (90%) patients reach target HbA1c 	50 out of 100 (50%) patients reach target HbA1c 	
% reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to cardiovascular diseases)	No reduction in the risk of these cardiovascular events 	40% reduction in the risk of these cardiovascular events 	
Chances of gastrointestinal side effects (i.e. nausea, vomiting and diarrhea)	1 out of 100 (1%) patient experiences GI side effects 	30 out of 100 (30%) patients experience GI side effects 	
Chances of genital infection	No patient (0%) experiences genital infection	16 out of 100 (16%) patients experience genital infection 	
Out-of-Pocket Cost per month	$ 0	$ 1,000	

Which medication do you choose? (pick only one medication option)

○ I choose Medication A
○ I choose Medication B
○ I choose neither Medication A nor Medication B

Q.10 Which of the following medication you would prefer based on the attributes (characteristics) presented **after your initial medication (e.g., metformin) alone does not help you achieve your treatment goal**? Choose by clicking one of the buttons below:

Attributes	Medication A	Medication B	Neither medication A nor medication B
How do you take the medication	Injectable, once a day 	Injectable, once a week 	Neither medication A nor medication B
Chance of reaching target HbA1c (long-term blood glucose level) in 6 months	90 out of 100 (90%) patients reach target HbA1c 	10 out of 100 (10%) patients reach target HbA1c 	
% reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to cardiovascular diseases)	40% reduction in the risk of these cardiovascular events 	No reduction in the risk of these cardiovascular events 	
Chance of gastrointestinal (GI) side effects (i.e., nausea, vomiting, and diarrhea)	30 out of 100 (30%) patients experience GI side effects 	1 out of 100 (1%) patient experiences GI side effects 	
Chance of genital infection	16 out of 100 (16%) patients experience genital infection 	No patients (0%) experience genital infection	
Out-of-Pocket Cost per month	$ 500	$ 0	

Which medication do you choose? (pick only one medication option)

- ○ I choose Medication A
- ○ I choose Medication B
- ○ I choose neither Medication A nor Medication B

DCE Survey - Version 2

Section C: Your preference of Diabetes Mellitus (DM) treatments

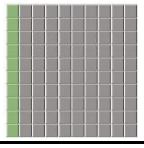
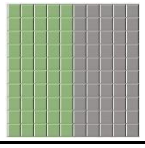
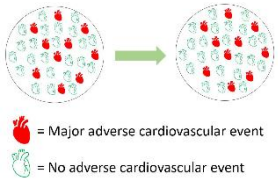
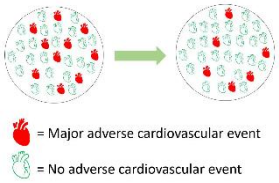
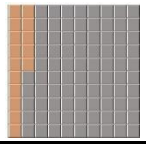
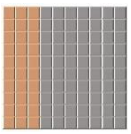
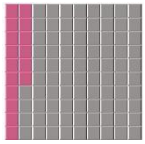
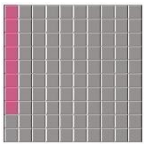
In this section, we would like to learn about your opinion for new medications **after your initial medication (e.g., metformin) alone does not help you achieve your treatment goal**. Please read the descriptions of the following medication attributes (characteristics) carefully. We will describe type medications by these attributes (characteristics).

Attributes	Descriptions

How do you take the medication	• Determine the route of administration such as oral or injectable and how often the medications are taken such as once a day or twice a day or once a week.
Chance of reaching target HbA1c (long-term blood glucose level) in 6 months	• Measure the benefit of type 2 diabetes medications. • Diabetes medications lower your blood glucose. HbA1c is a test of your blood glucose that is done at the doctor's office. It is an average of your blood glucose over the last 3 months. • A normal HbA1c is 4% to 6%, but people with diabetes have a higher-than-normal HbA1c (up to 12% or more). The goal of diabetes treatment is usually to get the HbA1c to be under 7%. • **Higher chance of reaching target HbA1c (long-term blood glucose level) is better**
% reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to cardiovascular diseases)	• People with type 2 diabetes have four times higher risk of having heart attack and 2-4 times higher risk of having stroke. • Some type 2 diabetes medications can reduce the risk of these major adverse cardiovascular events, while other medications may not have any effects on this cardiovascular risk. • **Higher % reduction in the risk of major adverse cardiovascular events is better**
Chance of gastrointestinal (GI) side effects (i.e., nausea, vomiting, and diarrhea)	• Gastrointestinal side effects are the common side effects of some type 2 diabetes medications, and their side effects vary among medications. • **Lower chances of gastrointestinal side effects is better**
Chance of genital infection	• Some type 2 diabetes medications increase the risk of genital infections. • **Lower the chances of genital infection is better**
Out-of-Pocket Cost per month	• Cost you pay out from your own pocket (e.g., copayment or whole amount) for type 2 diabetes medication. • **Lower out-of-pocket cost is better**

For the next ten questions, you will be asked to carefully consider three medication options: (1) Medication A, (2) Medication B, and (3) Neither Medication A nor Medication B, described in each table and choose your **PREFERRED MEDICATION** option **after your initial medication (e.g., metformin) alone does not help you achieve your treatment goal.**

EXAMPLE: After you compare the 3 medication options, if you decide to choose Medication B, then click on ☐ the option of Medication B, as shown below.

Attributes	Medication A	Medication B	Neither medication A nor medication B
How do you take the medication	Injectable, once a week 	Injectable, twice a day 	Neither medication A nor medication B
Chance of reaching target HbA1c (long-term blood glucose level) in 6 months	10 out of 100 (10%) patients reach target HbA1c 	50 out of 100 (50%) patients reach target HbA1c 	
% reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to cardiovascular diseases)	No reduction in the risk of these cardiovascular events 	40% reduction in the risk of these cardiovascular events 	
Chance of gastrointestinal (GI) side effects (i.e., nausea, vomiting, and diarrhea)	15 out of 100 (15%) patient experiences GI side effects 	30 out of 100 (30%) patients experience GI side effects 	
Chance of genital infection	16 out of 100 (16%) patients experience genital infection 	8 out of 100 (8%) patients experience genital infection 	
Out-of-Pocket Cost per month	$0	$1,000	

Which medication do you choose? (pick only one medication option)

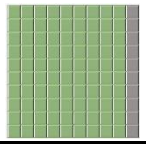
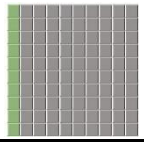
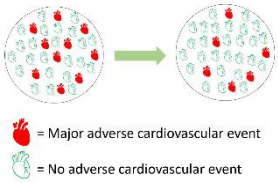
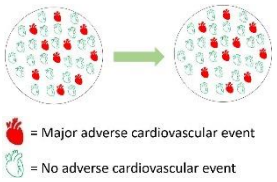
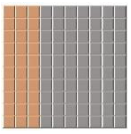
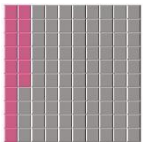
☐ I choose Medication A

☐ I choose Medication B

☐ I choose neither Medication A nor Medication B

*This is just an example, click on NEXT to continue the survey.

Q.1 Which of the following medication you would prefer based on the attributes (characteristics) presented **after your initial medication (e.g., metformin) alone does not help you achieve your treatment goal**? Choose by clicking one of the buttons below:

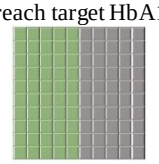
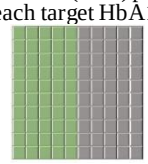
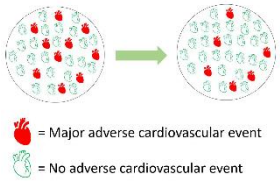
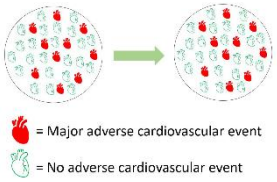
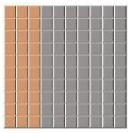
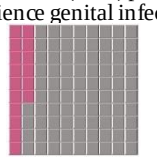
Attributes	Medication A	Medication B	Neither medication A nor medication B
How do you take the medication	Injectable, once a week 	Injectable, twice a day 	Neither medication A nor medication B
Chance of reaching target HbA1c (long-term blood glucose level) in 6 months	90 out of 100 (90%) patients reach target HbA1c 	10 out of 100 (10%) patients reach target HbA1c 	
% reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to cardiovascular diseases)	40% reduction in the risk of these cardiovascular events 	No reduction in the risk of these cardiovascular events 	
Chance of gastrointestinal (GI) side effects (i.e., nausea, vomiting, and diarrhea)	1 out of 100 (1%) patient experiences GI side effects 	30 out of 100 (30%) patients experience GI side effects 	
Chance of genital infection	No patient (0%) experiences genital infection	16 out of 100 (16%) patients experience genital infection 	
Out-of-Pocket Cost per month	$0	$1,000	

Which medication do you choose? (pick only one medication option)

- ○ I choose Medication A
- ○ I choose Medication B
- ○ I choose neither Medication A nor Medication B

Q.2 Which of the following medication you would prefer based on the attributes (characteristics) presented **after your initial medication (e.g., metformin) alone does not help you achieve your treatment goal**? Choose by clicking one of the buttons below:

Attributes	Medication A	Medication B	Neither medication A nor medication B
How do you take the medication	Injectable, twice a day	Tablet, once a day	Neither medication A nor medication B

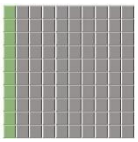
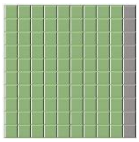
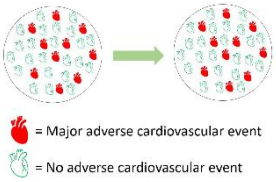
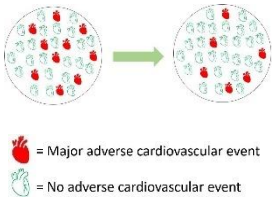
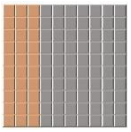
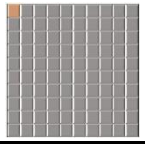
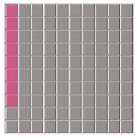
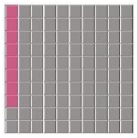
		
Chance of reaching target HbA1c (long-term blood glucose level) in 6 months	50 out of 100 (50%) patients reach target HbA1c 	50 out of 100 (50%) patients reach target HbA1c 
% reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to cardiovascular diseases)	40% reduction in the risk of these cardiovascular events 	No reduction in the risk of these cardiovascular events 
Chance of gastrointestinal (GI) side effects (i.e., nausea, vomiting, and diarrhea)	30 out of 100 (30%) patients experience GI side effects 	1 out of 100 (1%) patient experiences GI side effects 
Chance of genital infection	No patients (0%) experience genital infection	16 out of 100 (16%) patients experience genital infection 
Out-of-Pocket Cost per month	$ 1,000	$ 0

Which medication do you choose? (pick only one medication option)

- ○ I choose Medication A
- ○ I choose Medication B
- ○ I choose neither Medication A nor Medication B

Q.3 Which of the following medication you would prefer based on the attributes (characteristics) presented **after your initial medication (e.g., metformin) alone does not help you achieve your treatment goal**? Choose by clicking one of the buttons below:

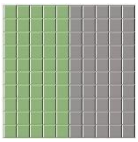
Attributes	Medication A	Medication B	Neither medication A nor medication B
How do you take the medication	Injectable, twice a day 	Tablet, once a day 	Neither medication A nor medication B
Chance of reaching target HbA1c (long-term blood glucose level) in 6 months	10 out of 100 (10%) patients reach target HbA1c	90 out of 100 (90%) patients reach target HbA1c	

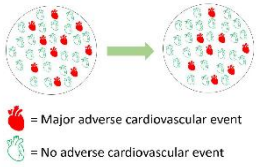
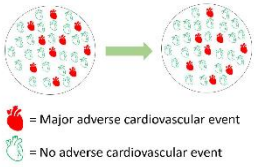
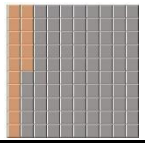
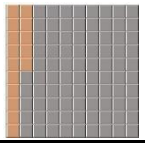
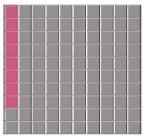
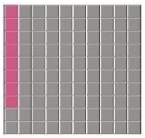
		
% reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to cardiovascular diseases)	No reduction in the risk of these cardiovascular events 	40% reduction in the risk of these cardiovascular events 
Chance of gastrointestinal (GI) side effects (i.e., nausea, vomiting, and diarrhea)	30 out of 100 (30%) patients experience GI side effects 	1 out of 100 (1%) patient experiences GI side effects 
Chance of genital infection	8 out of 100 (8%) patients experience genital infection 	8 out of 100 (8%) patients experience genital infection 
Out-of-Pocket Cost per month	$ 0	$ 1,000

Which medication do you choose? (pick only one medication option)

- ○ I choose Medication A
- ○ I choose Medication B
- ○ I choose neither Medication A nor Medication B

Q.4 Which of the following medication you would prefer based on the attributes (characteristics) presented **after your initial medication (e.g., metformin) alone does not help you achieve your treatment goal**? Choose by clicking one of the buttons below:

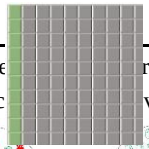
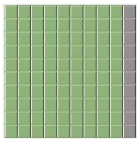
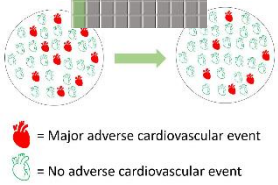
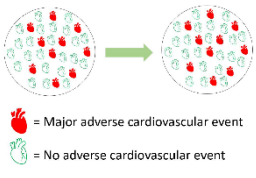
Attributes	Medication A	Medication B	Neither medication A nor medication B
How do you take the medication	Injectable, once a day 	Tablet, once a day 	Neither medication A nor medication B
Chance of reaching target HbA1c (long-term blood glucose level) in 6 months	50 out of 100 patients (50%) reach target HbA1c 	10 out of 100 (10%) patients reach target HbA1c 	
% reduction in the risk of major adverse cardiovascular events (i.e.,	20% reduction in the risk of these cardiovascular events	20% reduction in the risk of these cardiovascular events	

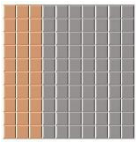
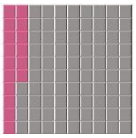
heart attack, stroke, and death due to cardiovascular diseases)			
Chances of gastrointestinal side effects(i.e. nausea, vomiting and diarrhea)	15 out of 100 (15%) patient experiences GI side effects 	15 out of 100 (15%) patient experiences GI side effects 	
Chances of genital infection	8 out of 100 (8%) patients experience genital infection 	8 out of 100 (8%) patients experience genital infection 	
Out-of-Pocket Cost per month	$ 1,000	$ 1,000	

Which medication do you choose? (pick only one medication option)

- ○ I choose Medication A
- ○ I choose Medication B
- ○ I choose neither Medication A nor Medication B

Q.5 Which of the following medication you would prefer based on the attributes (characteristics) presented **after your initial medication (e.g., metformin) alone does not help you achieve your treatment goal**? Choose by clicking one of the buttons below:

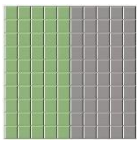
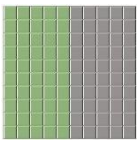
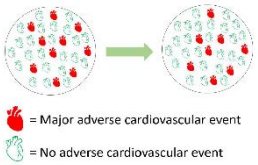
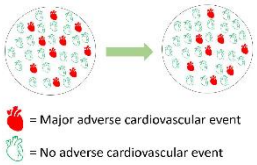
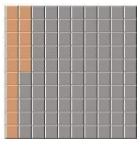
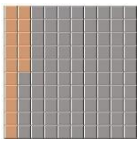
Attributes	Medication A	Medication B	Neither medication A nor medication B
How do you take the medication	Tablet, once a day 	Injectable, twice a day 	Neither medication A nor medication B
Chance of reaching target HbA1c (long-term blood glucose level) in 6 months	10 out of 100 (10%) patients reach target HbA1c 	90 out of 100 (90%) patients reach target HbA1c 	
% reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to cardiovascular diseases)	40% re risk of these c vents 	No reduction in the risk of these cardiovascular events 	
Chance of gastrointestinal (GI) side effects (i.e., nausea, vomiting, and	30 out of 100 (30%) patients experience GI side effects	1 out of 100 (1%) patient experiences GI side effects	

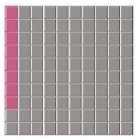
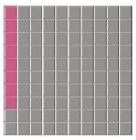
diarrhea)		
Chance of genital infection	No patient (0%) experiences genital infection	16 out of 100 (16%) patients experience genital infection 
Out-of-Pocket Cost per month	$ 0	$ 1,000

Which medication do you choose? (pick only one medication option)

- ○ I choose Medication A
- ○ I choose Medication B
- ○ I choose neither Medication A nor Medication B

Q.6 Which of the following medication you would prefer based on the attributes (characteristics) presented **after your initial medication (e.g., metformin) alone does not help you achieve your treatment goal**? Choose by clicking one of the buttons below:

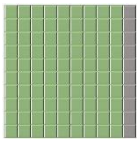
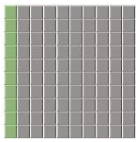
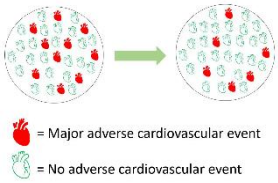
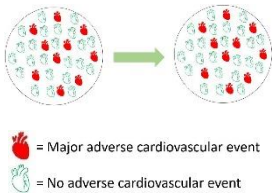
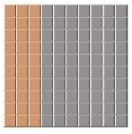
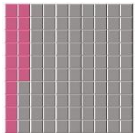
Attributes	Medication A	Medication B	Neither medication A nor medication B
How do you take the medication	Injectable, one a week 	Tablet, once a day 	Neither medication A nor medication B
Chance of reaching target HbA1c (long-term blood glucose level) in 6 months	50 out of 100 (50%) patients reach target HbA1c 	50 out of 100 (50%) patients reach target HbA1c 	
% reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to cardiovascular diseases)	20% reduction in the risk of these cardiovascular events 	20% reduction in the risk of these cardiovascular events 	
Chances of gastrointestinal side effects (i.e. nausea, vomiting and diarrhea)	15 out of 100 (15%) patients experience GI side effects 	15 out of 100 (15%) patients experience GI side effects 	
Chances of genital infection	8 out of 100 (8%) patients experience genital infection	8 out of 100 (8%) patients experience genital infection	

			
Out-of-Pocket Cost per month	$ 0	$ 1,000	

Which medication do you choose? (pick only one medication option)

- ○ I choose Medication A
- ○ I choose Medication B
- ○ I choose neither Medication A nor Medication B

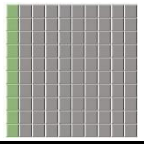
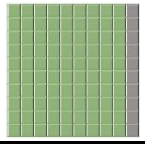
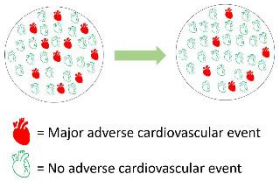
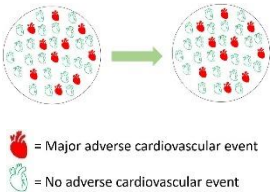
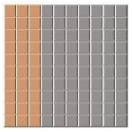
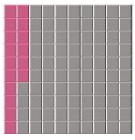
Q.7 Which of the following medication you would prefer based on the attributes (characteristics) presented **after your initial medication (e.g., metformin) alone does not help you achieve your treatment goal**? Choose by clicking one of the buttons below:

Attributes	Medication A	Medication B	Neither medication A nor medication B
How do you take the medication	Injectable, one a week 	Injectable, twice a day 	Neither medication A nor medication B
Chance of reaching target HbA1c (long-term blood glucose level) in 6 months	90 out of 100 (90%) patients reach target HbA1c 	10 out of 100 (10%) patients reach target HbA1c 	
% reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to cardiovascular diseases)	40% reduction in the risk of these cardiovascular events 	No reduction in the risk of these cardiovascular events 	
Chance of gastrointestinal (GI) side effects (i.e., nausea, vomiting, and diarrhea)	30 out of 100 (30%) patients experience GI side effects 	1 out of 100 (1%) patient experiences GI side effects 	
Chance of genital infection	16 out of 100 (16%) patients experience genital infection 	No patient (0%) experiences genital infection	
Out-of-Pocket Cost per month	$ 1,000	$ 0	

Which medication do you choose? (pick only one medication option)

○ I choose Medication A
○ I choose Medication B
○ I choose neither Medication A nor Medication B

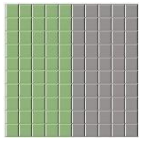
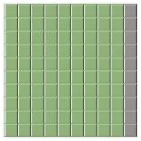
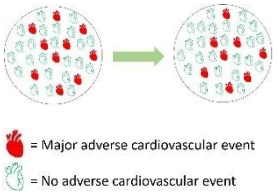
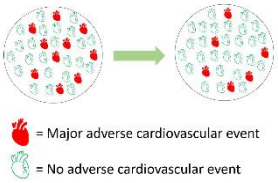
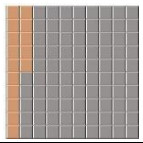
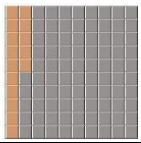
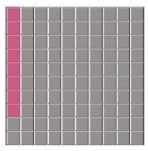
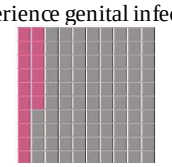
Q.8 Which of the following medication you would prefer based on the attributes (characteristics) presented **after your initial medication (e.g., metformin) alone does not help you achieve your treatment goal**? Choose by clicking one of the buttons below:

Attributes	Medication A	Medication B	Neither medication A nor medication B
How do you take the medication	Injectable, one a week 	Injectable, twice a day 	Neither medication A nor medication B
Chance of reaching target HbA1c (long-term blood glucose level) in 6 months	10 out of 100 (10%) patients reach target HbA1c 	90 out of 100 (90%) patients reach target HbA1c 	
% reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to cardiovascular diseases)	40% reduction in the risk of these cardiovascular events 	No reduction in the risk of these cardiovascular events 	
Chance of gastrointestinal (GI) side effects (i.e., nausea, vomiting, and diarrhea)	30 out of 100 (30%) patients experience GI side effects 	1 out of 100 (1%) patient experiences GI side effects 	
Chance of genital infection	No patient (0%) experiences genital infection	16 out of 100 (16%) patient experience genital infection 	
Out-of-Pocket Cost per month	$ 0	$ 1,000	

Which medication do you choose? (pick only one medication option)

○ I choose Medication A
○ I choose Medication B
○ I choose neither Medication A nor Medication B

Q.9 Which of the following medication you would prefer based on the attributes (characteristics) presented **after your initial medication (e.g., metformin) alone does not help you achieve your treatment goal**? Choose by clicking one of the buttons below:

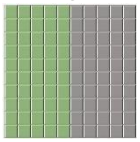
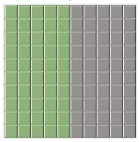
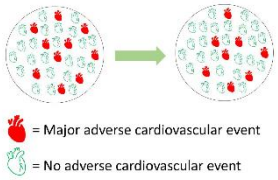
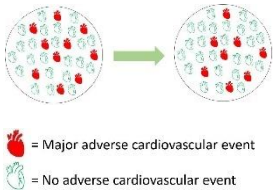
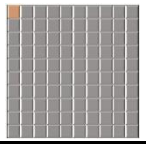
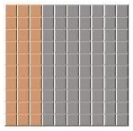
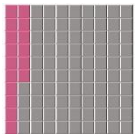
Attributes	Medication A	Medication B	Neither medication A nor medication B
How do you take the medication	Injectable, once a day 	Injectable, one a week 	Neither medication A nor medication B
Chance of reaching target HbA1c (long-term blood glucose level) in 6 months	50 out of 100 (50%) patients reach target HbA1c 	90 out of 100 (90%) patients reach target HbA1c 	
% reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to cardiovascular diseases)	20% reduction in the risk of these cardiovascular events 	40% reduction in the risk of these cardiovascular events 	
Chances of gastrointestinal (GI) side effects (i.e. nausea, vomiting and diarrhea)	15 out of 100 (15%) patients experience GI side effects 	15 out of 100 (15%) patients experience GI side effects 	
Chances of genital infection	No patients (0%) experience genital infection 	16 out of 100 (16%) patients experience genital infection 	
Out-of-Pocket Cost per month	$ 500	$ 500	

Which medication do you choose? (pick only one medication option)

- ○ I choose Medication A
- ○ I choose Medication B
- ○ I choose neither Medication A nor Medication B

Q. 10 Which of the following medication you would prefer based on the attributes (characteristics) presented **after your initial medication (e.g., metformin) alone does not help you achieve your treatment goal**? Choose by clicking one of the buttons below:

Attributes	Medication A	Medication B	Neither medication A nor medication B
How do you take the medication	Injectable, twice a day 	Injectable, once a day 	Neither medication A nor medication B
Chance of reaching target HbA1c	50 out of 100 (50%) patients	50 out of 100 (50%) patients	

(long-term blood glucose level) in 6 months	reach target HbA1c 	reach target HbA1c 
% reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to cardiovascular diseases)	20% reduction in the risk of these cardiovascular events 	20% reduction in the risk of these cardiovascular events 
Chance of gastrointestinal (GI) side effects (i.e., nausea, vomiting, and diarrhea)	1 out of 100 (1%) patient experiences GI side effects 	30 out of 100 (30%) patients experience GI side effects 
Chance of genital infection	No patient (0%) experiences genital infection	16 out of 100 (16%) patients experience genital infection 
Out-of-Pocket Cost per month	$ 1,000	$ 0

Which medication do you choose? (pick only one medication option)

- ○ I choose Medication A
- ○ I choose Medication B
- ○ I choose neither Medication A nor Medication B

DCE Survey - Version 3

Section C: Your preference of Diabetes Mellitus (DM) treatments

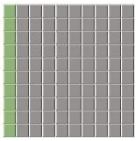
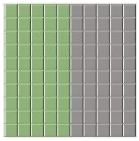
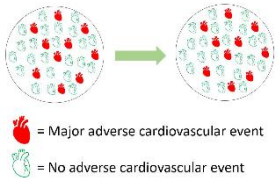
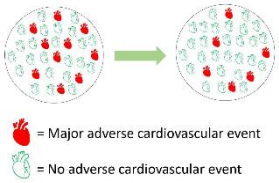
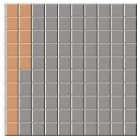
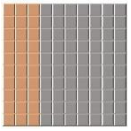
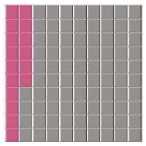
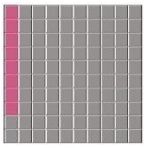
In this section, we would like to learn about your opinion for new medications **after your initial medication (e.g., metformin) alone does not help you achieve your treatment goal**. Please read the descriptions of the following medication attributes (characteristics) carefully. We will describe type medications by these attributes (characteristics).

Attributes	Descriptions
How do you take the medication	• Determine the route of administration such as oral or injectable and how often the medications are taken such as once a day or twice a day or once a week.

Chance of reaching target HbA1c (long-term blood glucose level) in 6 months	• Measure the benefit of type 2 diabetes medications. • Diabetes medications lower your blood glucose. HbA1c is a test of your blood glucose that is done at the doctor's office. It is an average of your blood glucose over the last 3 months. • A normal HbA1c is 4% to 6%, but people with diabetes have a higher-than-normal HbA1c (up to 12% or more). The goal of diabetes treatment is usually to get the HbA1c to be under 7%. • **Higher chance of reaching target HbA1c (long-term blood glucose level) is better**
% reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to cardiovascular diseases)	• People with type 2 diabetes have four times higher risk of having heart attack and 2-4 times higher risk of having stroke. • Some type 2 diabetes medications can reduce the risk of these major adverse cardiovascular events, while other medications may not have any effects on this cardiovascular risk. • **Higher % reduction in the risk of major adverse cardiovascular events is better**
Chance of gastrointestinal (GI) side effects (i.e., nausea, vomiting, and diarrhea)	• Gastrointestinal side effects are the common side effects of some type 2 diabetes medications, and their side effects vary among medications. • **Lower chances of gastrointestinal side effects is better**
Chance of genital infection	• Some type 2 diabetes medications increase the risk of genital infections. • **Lower the chances of genital infection is better**
Out-of-Pocket Cost per month	• • Cost you pay out from your own pocket (e.g., copayment or whole amount) for type 2 diabetes medication. **Lower out-of-pocket cost is better**

For the next ten questions, you will be asked to carefully consider three medication options: (1) Medication A, (2) Medication B, and (3) Neither Medication A nor Medication B, described in each table and choose your **PREFERRED MEDICATION** option **after your initial medication (e.g., metformin) alone does not help you achieve your treatment goal.**

EXAMPLE: After you compare the 3 medication options, if you decide to choose Medication B, then click on ☐ the option of Medication B, as shown below.

Attributes	Medication A	Medication B	Neither medication A nor medication B
How do you take the medication	Injectable, once a week 	Injectable, twice a day 	Neither medication A nor medication B
Chance of reaching target HbA1c (long-term blood glucose level) in 6 months	10 out of 100 (10%) patients reach target HbA1c 	50 out of 100 (50%) patients reach target HbA1c 	
% reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to cardiovascular diseases)	No reduction in the risk of these cardiovascular events 	40% reduction in the risk of these cardiovascular events 	
Chance of gastrointestinal (GI) side effects (i.e., nausea, vomiting, and diarrhea)	15 out of 100 (15%) patient experiences GI side effects 	30 out of 100 (30%) patients experience GI side effects 	
Chance of genital infection	16 out of 100 (16%) patients experience genital infection 	8 out of 100 (8%) patients experience genital infection 	
Out-of-Pocket Cost per month	$0	$1,000	

Which medication do you choose? (pick only one medication option)

☐ I choose Medication A

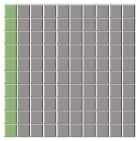
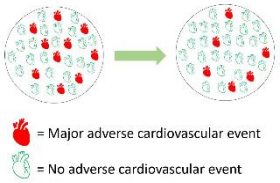
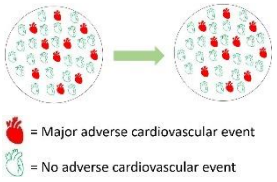
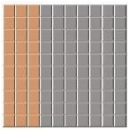
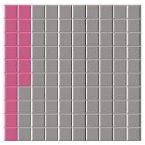
☐ I choose Medication B

☐ I choose neither Medication A nor Medication B

*This is just an example, click on NEXT to continue the survey.

Q.1 Which of the following medication you would prefer based on the attributes (characteristics) presented **after your initial medication (e.g., metformin) alone does not help you achieve your treatment goal**? Choose by clicking one of the buttons below:

Attributes	Medication A	Medication B	Neither medication A nor medication B
How do you take the medication	Injectable, once a week 	Injectable, twice a day 	Neither medication A nor medication B

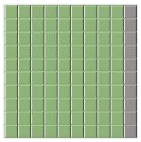
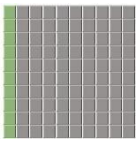
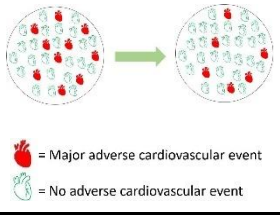
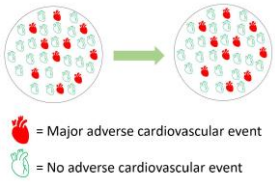
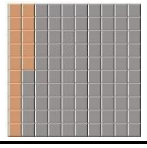
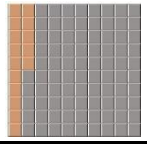
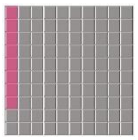
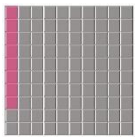
Chance of reaching target HbA1c (long-term blood glucose level) in 6 months	90 out of 100 (90%) patients reach target HbA1c 	10 out of 100 (10%) patients reach target HbA1c 
% reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to cardiovascular diseases)	40% reduction in the risk of these cardiovascular events 	No reduction in the risk of these cardiovascular events 
Chance of gastrointestinal (GI) side effects (i.e., nausea, vomiting, and diarrhea)	1 out of 100 (1%) patient experiences GI side effects 	30 out of 100 (30%) patients experience GI side effects 
Chance of genital infection	No patient (0%) experiences genital infection	16 out of 100 (16%) patients experience genital infection 
Out-of-Pocket Cost per month	$0	$1,000

Which medication do you choose? (pick only one medication option)

- ○ I choose Medication A
- ○ I choose Medication B
- ○ I choose neither Medication A nor Medication B

Q.2 Which of the following medication you would prefer based on the attributes (characteristics) presented **after your initial medication (e.g., metformin) alone does not help you achieve your treatment goal**? Choose by clicking one of the buttons below:

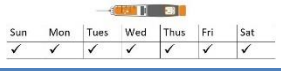
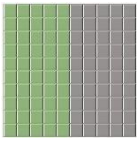
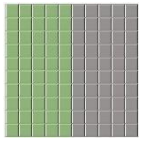
Attributes	Medication A	Medication B	Neither medication A nor medication B
How do you take the medication	Injectable, twice a day 	Injectable, once a day 	Neither medication A nor medication B
Chance of reaching target HbA1c (long-term blood glucose level) in 6 months	90 out of 100 (90%) patients reach target HbA1c	10 out of 100 (10%) patients reach target HbA1c	

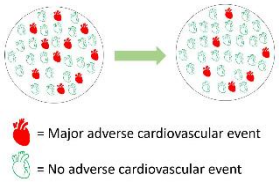
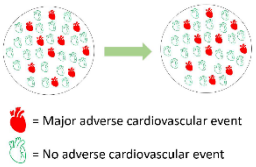
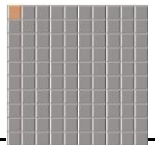
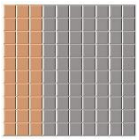
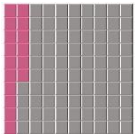
		
% reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to cardiovascular diseases)	40% reduction in the risk of these cardiovascular events 	No reduction in the risk of these cardiovascular events 
Chance of gastrointestinal (GI) side effects (i.e., nausea, vomiting, and diarrhea)	15 out of 100 (15%) patients experience GI side effects 	15 out of 100 (15%) patients experience GI side effects 
Chance of genital infection	8 out of 100 (8%) patients experience genital infection 	8 out of 100 (8%) patients experience genital infection 
Out-of-Pocket Cost per month	$ 1,000	$ 0

Which medication do you choose? (pick only one medication option)

- ○ I choose Medication A
- ○ I choose Medication B
- ○ I choose neither Medication A nor Medication B

Q.3 Which of the following medication you would prefer based on the attributes (characteristics) presented **after your initial medication (e.g., metformin) alone does not help you achieve your treatment goal**? Choose by clicking one of the buttons below:

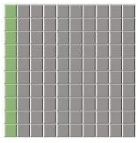
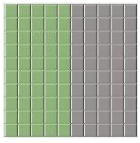
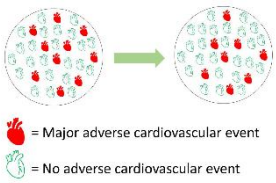
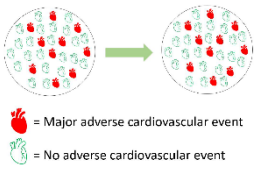
Attributes	Medication A	Medication B	Neither medication A nor medication B
How do you take the medication	Injectable, twice a day 	Injectable, once a day 	Neither medication A nor medication B
Chance of reaching target HbA1c (long-term blood glucose level) in 6 months	50 out of 100 (50%) patients reach target HbA1c 	50 out of 100 (50%) patients reach target HbA1c 	
% reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to cardiovascular diseases)	40% reduction in the risk of these cardiovascular events	No reduction in the risk of these cardiovascular events	

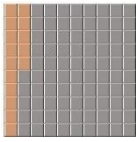
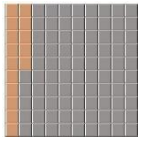
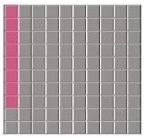
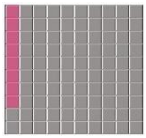
		
Chances of gastrointestinal side effects(i.e., nausea, vomiting and diarrhea)	1 out of 100 (1%) patient experiences GI side effects 	30 out of 100 (30%) patients experience GI side effects 
Chances of genital infection	No patients (0%) experience genital infection	16 out of 100 (16%) patients experience genital infection 
Out-of-Pocket Cost per month	$ 1,000	$ 0

Which medication do you choose? (pick only one medication option)

- ○ I choose Medication A
- ○ I choose Medication B
- ○ I choose neither Medication A nor Medication B

Q.4 Which of the following medication you would prefer based on the attributes (characteristics) presented **after your initial medication (e.g., metformin) alone does not help you achieve your treatment goal**? Choose by clicking one of the buttons below:

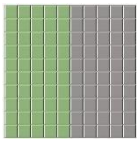
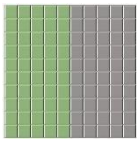
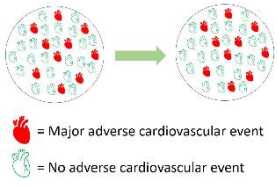
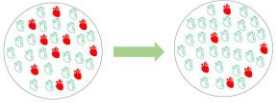
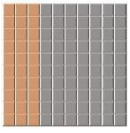
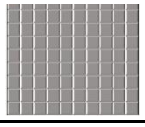
Attributes	Medication A	Medication B	Neither medication A nor medication B
How do you take the medication	Tablet, once a day 	Injectable, once a day 	Neither medication A nor medication B
Chance of reaching target HbA1c (long-term blood glucose level) in 6 months	10 out of 100 (10%) patients reach target HbA1c 	50 out of 100 (50%) patients reach target HbA1c 	
% reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to cardiovascular diseases)	20% reduction in the risk of these cardiovascular events 	No reduction in the risk of these cardiovascular events 	
Chances of gastrointestinal (GI) side effects (i.e. nausea, vomiting and	15 out of 100 (15%) patients	15 out of 100 (15%) patients	

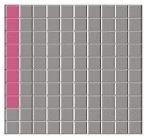
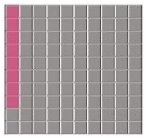
diarrhea)	experience GI side effects 	experience GI side effects 	
Chances of genital infection	8 out of 100 (8%) patients experience genital infection 	8 out of 100 (8%) patients experience genital infection 	
Out-of-Pocket Cost per month	$ 1,000	$ 1,000	

Which medication do you choose? (pick only one medication option)

- ○ I choose Medication A
- ○ I choose Medication B
- ○ I choose neither Medication A nor Medication B

Q.5 Which of the following medication you would prefer based on the attributes (characteristics) presented **after your initial medication (e.g., metformin) alone does not help you achieve your treatment goal**? Choose by clicking one of the buttons below:

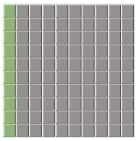
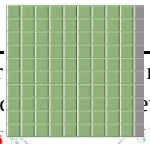
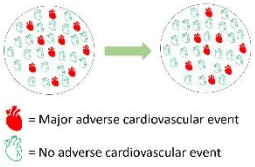
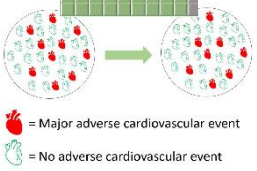
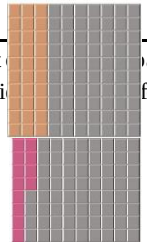
Attributes	Medication A	Medication B	Neither medication A nor medication B
How do you take the medication	Tablet, once a day 	Injectable, twice a day 	Neither medication A nor medication B
Chance of reaching target HbA1c (long-term blood glucose level) in 6 months	50 out of 100 patients (50%) reach target HbA1c 	50 out of 100 patients (50%) reach target HbA1c 	
% reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to cardiovascular diseases)	No reduction in the risk of these cardiovascular events 	40% reduction in the risk of these cardiovascular events 	
Chance of gastrointestinal (GI) side effects (i.e., nausea, vomiting, and diarrhea)	30 out of 100 (30%) patients experience GI side effects 		

Chance of genital infection	8 out of 100 (8%) patients experience genital infection 	8 out of 100 (8%) patients experience genital infection 	
Out-of-Pocket Cost per month	$ 500	$ 500	

Which medication do you choose? (pick only one medication option)

- ○ I choose Medication A
- ○ I choose Medication B
- ○ I choose neither Medication A nor Medication B

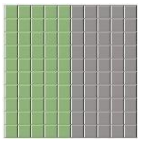
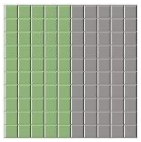
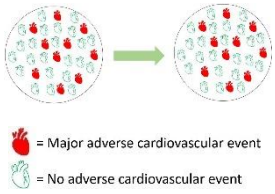
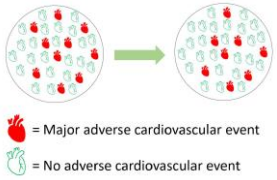
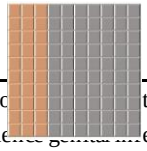
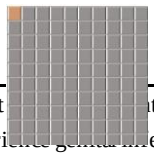
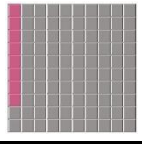
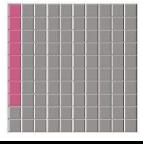
Q.6 Which of the following medication you would prefer based on the attributes (characteristics) presented **after your initial medication (e.g., metformin) alone does not help you achieve your treatment goal**? Choose by clicking one of the buttons below:

Attributes	Medication A	Medication B	Neither medication A nor medication B
How do you take the medication	Injectable, twice a day 	Injectable, once a day 	Neither medication A nor medication B
Chance of reaching target HbA1c (long-term blood glucose level) in 6 months	10 out of 100 patients (10%) reach target HbA1c 	90 out of 100 patients (90%) reach target HbA1c 	
% reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to cardiovascular diseases)	20% reduction in the risk of these cardiovascular events 	20% r risk of these (vents 	
Chances of gastrointestinal side effects (i.e. nausea, vomiting and diarrhea)	30 out of 100 (30%) patients experience GI side effects 	1 out of 100 (1%) patient experiences GI side effects 	
Chances of genital infection	16 out atients experi fection	No patients (0%) experience genital infection	
Out-of-Pocket Cost per month	$ 500	$ 500	

Which medication do you choose? (pick only one medication option)

- ○ I choose Medication A
- ○ I choose Medication B
- ○ I choose neither Medication A nor Medication B

Q.7 Which of the following medication you would prefer based on the attributes (characteristics) presented **after your initial medication (e.g., metformin) alone does not help you achieve your treatment goal**? Choose by clicking one of the buttons below:

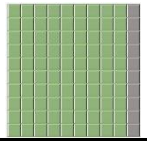
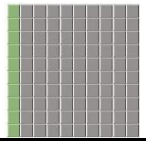
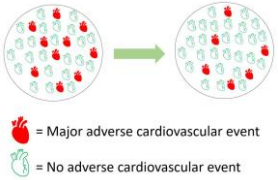
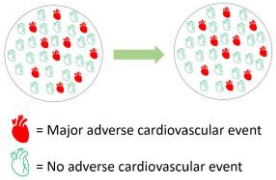
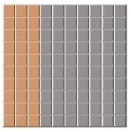
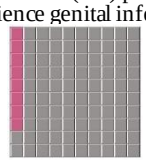
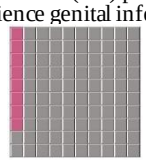
Attributes	Medication A	Medication B	Neither medication A nor medication B
How do you take the medication	Tablet, once a day 	Injectable, once a day 	Neither medication A nor medication B
Chance of reaching target HbA1c (long-term blood glucose level) in 6 months	50 out of 100 (50%) patients reach target HbA1c 	50 out of 100 (50%) patients reach target HbA1c 	
% reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to cardiovascular diseases)	No reduction in the risk of these cardiovascular events 	20% reduction in the risk of these cardiovascular events 	
Chance of gastrointestinal (GI) side effects (i.e., nausea, vomiting, and diarrhea)	30 out of 100 (30%) patients experience GI side effects 	experiences GI side effects 	
Chance of genital infection	8 out of [illegible] patients experience genital infection 	8 out of [illegible] patients experience genital infection 	
Out-of-Pocket Cost per month	$ 500	$ 1,000	

Which medication do you choose? (pick only one medication option)

- ○ I choose Medication A
- ○ I choose Medication B

○ I choose neither Medication A nor Medication B

Q.8 Which of the following medication you would prefer based on the attributes (characteristics) presented **after your initial medication (e.g., metformin) alone does not help you achieve your treatment goal**? Choose by clicking one of the buttons below:

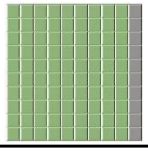
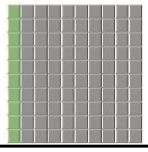
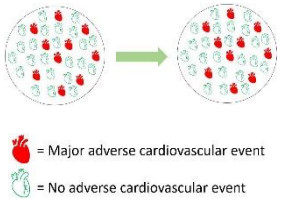
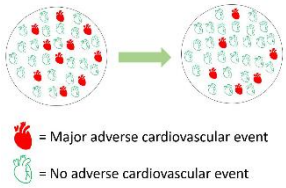
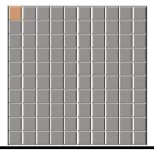
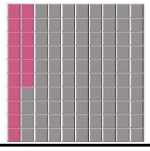
Attributes	Medication A	Medication B	Neither medication A nor medication B
How do you take the medication	Injectable, once a day 	Tablet, once a day 	Neither medication A nor medication B
Chance of reaching target HbA1c (long-term blood glucose level) in 6 months	90 out of 100 (90%) patients reach target HbA1c 	10 out of 100 (10%) patients reach target HbA1c 	
% reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to cardiovascular diseases)	40% reduction in the risk of these cardiovascular events 	No reduction in the risk of these cardiovascular events 	
Chances of gastrointestinal side effects (i.e. nausea, vomiting and diarrhea)	1 out of 100 (1%) patient experiences GI side effects 	30 out of 100 (30%) patients experience GI side effects 	
Chances of genital infection	8 out of 100 (8%) patients experience genital infection 	8 out of 100 (8%) patients experience genital infection 	
Out-of-Pocket Cost per month	$ 500	$ 500	

Which medication do you choose? (pick only one medication option)

○ I choose Medication A
○ I choose Medication B
○ I choose neither Medication A nor Medication B

Q.9 Which of the following medication you would prefer based on the attributes (characteristics) presented **after your initial medication (e.g., metformin) alone does not help you achieve your treatment goal**? Choose by clicking one of the buttons below:

Attributes	Medication A	Medication B	Neither medication A nor

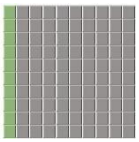
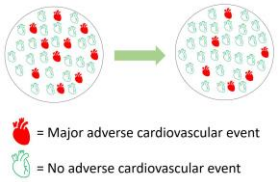
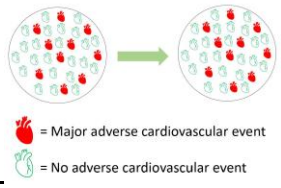
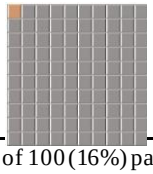
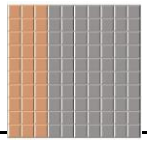
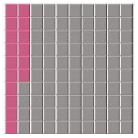
			medication
How do you take the	Injectable, twice a 	Injectable, once a 	Neither medication A nor medication B
Chance of reaching target HbA1c (long-term blood glucose level) in 6	90 out of 100 (90%) patients reach target 	10 out of 100 (10%) patients reach target 	
% reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to	No reduction in the risk of these cardiovascular 	40% reduction in the risk of these cardiovascular 	
Chance of gastrointestinal (GI) side effects (i.e., nausea, vomiting, and diarrhea)	30 out of 100 (30%) patients 	1 out of 100 (1%) patients experiences GI side 	
Chance of genital	16 out of 100 (16%) patients 	No patient (0%) experiences	
Out-of-Pocket Cost per	$	$	

Which medication do you choose? (pick only one medication option)

- ○ I choose Medication A
- ○ I choose Medication B
- ○ I choose neither Medication A nor Medication B

Q.10 Which of the following medication you would prefer based on the attributes (characteristics) presented **after your initial medication (e.g., metformin) alone does not help you achieve your treatment goal**? Choose by clicking one of the buttons below:

Attributes	Medication A	Medication B	Neither medication A nor medication B
How do you take the medication	Injectable, once a day 	Injectable, once a week 	Neither medication A nor medication B
Chance of reaching target HbA1c (long-term blood glucose level) in 6 months	10 out of 100 (10%) patients reach target HbA1c	90 out of 100 patients (90%) reach target HbA1c	

		
% reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to cardiovascular diseases)	40% reduction in the risk of these cardiovascular events 	No reduction in the risk of these cardiovascular events 
Chance of gastrointestinal (GI) side effects (i.e., nausea, vomiting, and diarrhea)	1 out of 100 (1%) patients experiences GI side effects 	30 out of 100 (30%) patients experience GI side effects 
Chance of genital infection	16 out of 100 (16%) patients experience genital infection 	No patient (0%) experiences genital infection
Out-of-Pocket Cost per month	$ 0	$ 500

Which medication do you choose? (pick only one medication option)

- ○ I choose Medication A
- ○ I choose Medication B
- ○ I choose neither Medication A nor Medication B

DCE Survey - Version 4

Section C: Your preference of Diabetes Mellitus (DM) treatments

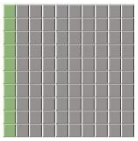
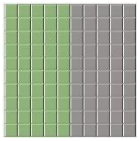
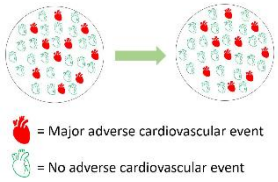
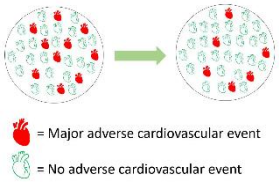
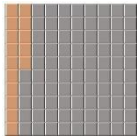
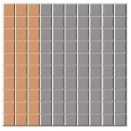
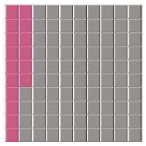
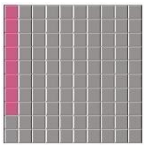
In this section, we would like to learn about your opinion for new medications **after your initial medication (e.g., metformin) alone does not help you achieve your treatment goal**. Please read the descriptions of the following medication attributes (characteristics) carefully. We will describe type medications by these attributes (characteristics).

Attributes	Descriptions
How do you take the medication	• Determine the route of administration such as oral or injectable and how often the medications are taken such as once a day or twice a day or once a week.

Chance of reaching target HbA1c (long-term blood glucose level) in 6 months	• Measure the benefit of type 2 diabetes medications. • Diabetes medications lower your blood glucose. HbA1c is a test of your blood glucose that is done at the doctor's office. It is an average of your blood glucose over the last 3 months. • A normal HbA1c is 4% to 6%, but people with diabetes have a higher-than-normal HbA1c (up to 12% or more). The goal of diabetes treatment is usually to get the HbA1c to be under 7%. • **Higher chance of reaching target HbA1c (long-term blood glucose level) is better**
% reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to cardiovascular diseases)	• People with type 2 diabetes have four times higher risk of having heart attack and 2-4 times higher risk of having stroke. • Some type 2 diabetes medications can reduce the risk of these major adverse cardiovascular events, while other medications may not have any effects on this cardiovascular risk. • **Higher % reduction in the risk of major adverse cardiovascular events is better**
Chance of gastrointestinal (GI) side effects (i.e., nausea, vomiting, and diarrhea)	• Gastrointestinal side effects are the common side effects of some type 2 diabetes medications, and their side effects vary among medications. • **Lower chances of gastrointestinal side effects is better**
Chance of genital infection	• Some type 2 diabetes medications increase the risk of genital infections. • **Lower the chances of genital infection is better**
Out-of-Pocket Cost per month	• • Cost you pay out from your own pocket (e.g., copayment or whole amount) for type 2 diabetes medication. **Lower out-of-pocket cost is better**

For the next ten questions, you will be asked to carefully consider three medication options: (1) Medication A, (2) Medication B, and (3) Neither Medication A nor Medication B, described in each table and choose your **PREFERRED MEDICATION** option **after your initial medication (e.g., metformin) alone does not help you achieve your treatment goal.**

EXAMPLE: After you compare the 3 medication options, if you decide to choose Medication B, then click on ☐ the option of Medication B, as shown below.

Attributes	Medication A	Medication B	Neither medication A nor medication B
How do you take the medication	Injectable, once a week 	Injectable, twice a day 	Neither medication A nor medication B
Chance of reaching target HbA1c (long-term blood glucose level) in 6 months	10 out of 100 (10%) patients reach target HbA1c 	50 out of 100 (50%) patients reach target HbA1c 	
% reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to cardiovascular diseases)	No reduction in the risk of these cardiovascular events 	40% reduction in the risk of these cardiovascular events 	
Chance of gastrointestinal (GI) side effects (i.e., nausea, vomiting, and diarrhea)	15 out of 100 (15%) patient experiences GI side effects 	30 out of 100 (30%) patients experience GI side effects 	
Chance of genital infection	16 out of 100 (16%) patients experience genital infection 	8 out of 100 (8%) patients experience genital infection 	
Out-of-Pocket Cost per month	$0	$1,000	

Which medication do you choose? (pick only one medication option)

☐ I choose Medication A

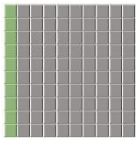
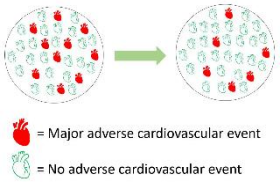
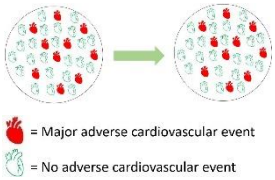
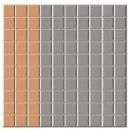
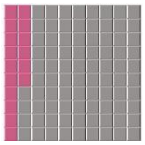
☐ I choose Medication B

☐ I choose neither Medication A nor Medication B

*This is just an example, click on the arrow sign for the next question.

Q.1 Which of the following medication you would prefer based on the attributes (characteristics) presented **after your initial medication (e.g., metformin) alone does not help you achieve your treatment goal**? Choose by clicking one of the buttons below:

Attributes	Medication A	Medication B	Neither medication A nor medication B
How do you take the medication	Injectable, once a week 	Injectable, twice a day 	Neither medication A nor medication B

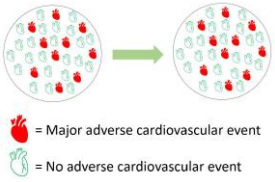
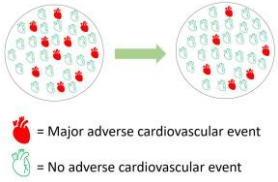
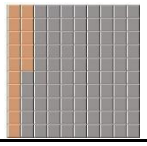
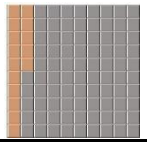
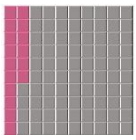
Chance of reaching target HbA1c (long-term blood glucose level) in 6 months	90 out of 100 (90%) patients reach target HbA1c 	10 out of 100 (10%) patients reach target HbA1c 	
% reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to cardiovascular diseases)	40% reduction in the risk of these cardiovascular events 	No reduction in the risk of these cardiovascular events 	
Chance of gastrointestinal (GI) side effects (i.e., nausea, vomiting, and diarrhea)	1 out of 100 (1%) patient experiences GI side effects 	30 out of 100 (30%) patients experience GI side effects 	
Chance of genital infection	No patient (0%) experiences genital infection	16 out of 100 (16%) patients experience genital infection 	
Out-of-Pocket Cost per month	$0	$1,000	

Which medication do you choose? (pick only one medication option)

- ○ I choose Medication A
- ○ I choose Medication B
- ○ I choose neither Medication A nor Medication B

Q.2 Which of the following medication you would prefer based on the attributes (characteristics) presented **after your initial medication (e.g., metformin) alone does not help you achieve your treatment goal**? Choose by clicking one of the buttons below:

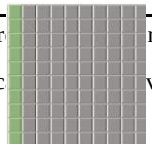
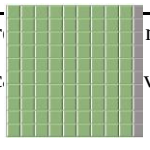
Attributes	Medication A	Medication B	Neither medication A nor medication B
How do you take the medication	Injectable, once a week 	Injectable, once a day 	Neither medication A nor medication B
Chance of reaching target HbA1c (long-term blood glucose level) in 6 months	50 out of 100 (50%) patients reach target HbA1c	50 out of 100 (50%) patients reach target HbA1c	

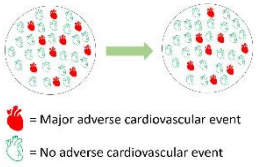
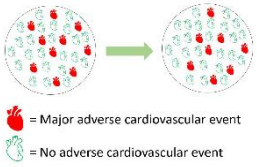
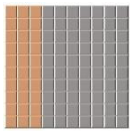
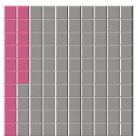
% reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to cardiovascular diseases)	No reduction in the risk of these cardiovascular events 	40% reduction in the risk of these cardiovascular events 
Chances of gastrointestinal side effects(i.e., nausea, vomiting and diarrhea)	15 out of 100 (15%) patient experience GI side effects 	15 out of 100 (15%) patient experience GI side effects 
Chances of genital infection	No patients (0%) experience genital infection	16 out of 100 (16%) patient experience genital infection 
Out-of-Pocket Cost per month	$ 500	$ 500

Which medication do you choose? (pick only one medication option)

- ○ I choose Medication A
- ○ I choose Medication B
- ○ I choose neither Medication A nor Medication B

Q.3 hich of the following medication you would prefer based on the attributes (characteristics) presented **after your initial medication (e.g., metformin) alone does not help you achieve your treatment goal**? Choose by clicking one of the buttons below:

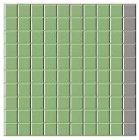
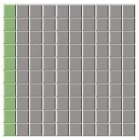
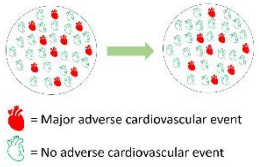
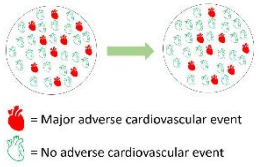
Attributes	Medication A	Medication B	Neither medication A nor medication B
How do you take the medication	Injectable, once a week 	Tablet, once a day 	Neither medication A nor medication B
Chance of reaching target HbA1c (long-term blood glucose level) in 6 months	10 out of 100 (10%) patients reach target HbA1c	90 out of 100 (90%) patients reach target HbA1c	
% reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to cardiovascular diseases)	20% r risk of these c vents 	20% r risk of these c vents 	

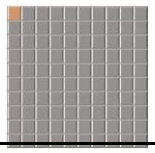
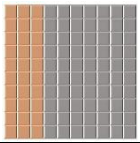
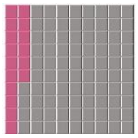
		
Chances of gastrointestinal side effects(i.e., nausea, vomiting and diarrhea)	30 out of 100 (30%) patients experience GI side effects 	1 out of 100 (1%) patient experiences GI side effects 
Chances of genital infection	16 out of 100 (16%) patient experience genital infection 	No patients (0%) experience genital infection
Out-of-Pocket Cost per month	$ 500	$ 0

Which medication do you choose? (pick only one medication option)

- ○ I choose Medication A
- ○ I choose Medication B
- ○ I choose neither Medication A nor Medication B

Q.4 Which of the following medication you would prefer based on the attributes (characteristics) presented **after your initial medication (e.g., metformin) alone does not help you achieve your treatment goal**? Choose by clicking one of the buttons below:

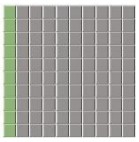
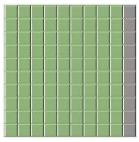
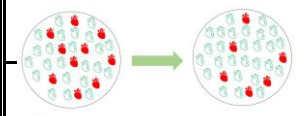
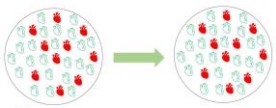
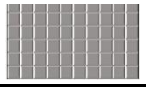
Attributes	Medication A	Medication B	Neither medication A nor medication B
How do you take the medication	Injectable, once a day 	Injectable, twice a day 	Neither medication A nor medication B
Chance of reaching target HbA1c (long-term blood glucose level) in 6 months	90 out of 100 (90%) patients reach target HbA1c 	10 out of 100 (10%) patients reach target HbA1c 	
% reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to cardiovascular diseases)	20% reduction in the risk of these cardiovascular events 	20% reduction in the risk of these cardiovascular events 	
Chances of gastrointestinal (GI) sideeffects (i.e. nausea, vomiting and diarrhea)	1 out of 100 (1%) patient experiences GI side effects	30 out of 100 (30%) patients experience GI side effects	

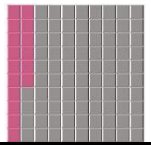
			
Chances of genital infection	No patient (0%) experiences genital infection	16 out of 100 (16%) patients experience genital infection 	
Out-of-Pocket Cost per month	$ 500	$ 500	

Which medication do you choose? (pick only one medication option)

- ○ I choose Medication A
- ○ I choose Medication B
- ○ I choose neither Medication A nor Medication B

Q.5 Which of the following medication you would prefer based on the attributes (characteristics) presented **after your initial medication (e.g., metformin) alone does not help you achieve your treatment goal**? Choose by clicking one of the buttons below:

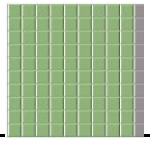
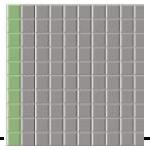
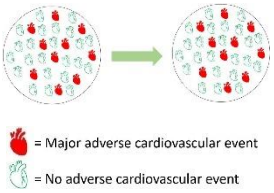
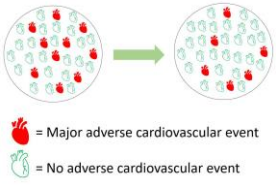
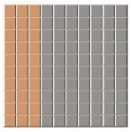
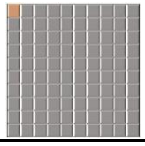
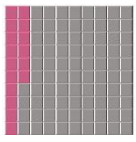
Attributes	Medication A	Medication B	Neither medication A nor medication B
How do you take the medication	Injectable, twice a day 	Injectable, one a week 	Neither medication A nor medication B
Chance of reaching target HbA1c (long-term blood glucose level) in 6 months	10 out of 100 (10%) patients reach target HbA1c 	90 out of 100 (90%) patients reach target HbA1c 	
% reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to cardiovascular diseases)	40% reduction in the risk of these cardiovascular events 	No reduction in the risk of these cardiovascular events 	
Chance of gastrointestinal (GI) side effects (i.e., nausea, vomiting, and diarrhea)			
Chance of genital infection	No patients (0%) experiences genital infection	16 out of 100 (16%) patients experience genital infection	

			
Out-of-Pocket Cost per month	$ 0	$ 500	

Which medication do you choose? (pick only one medication option)

- ○ I choose Medication A
- ○ I choose Medication B
- ○ I choose neither Medication A nor Medication B

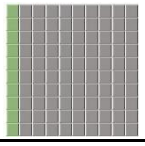
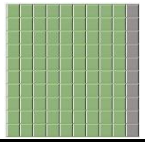
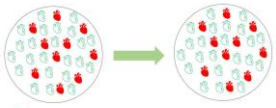
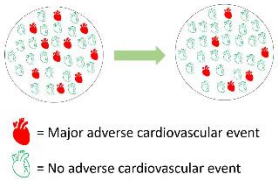
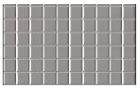
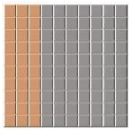
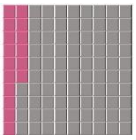
Q.6 Which of the following medication you would prefer based on the attributes (characteristics) presented **after your initial medication (e.g., metformin) alone does not help you achieve your treatment goal**? Choose by clicking one of the buttons below:

Attributes	Medication A	Medication B	Neither medication A nor medication B
How do you take the medication	Injectable, twice a day 	Injectable, once a week 	Neither medication A nor medication B
Chance of reaching target HbA1c (long-term blood glucose level) in 6 months	90 out of 100 patients (90%) reach target HbA1c 	10 out of 100 patients (10%) reach target HbA1c 	
% reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to cardiovascular diseases)	No reduction in the risk of these cardiovascular events 	40% reduction in the risk of these cardiovascular events 	
Chances of gastrointestinal side effects (i.e. nausea, vomiting and diarrhea)	30 out of 100 (30%) patient experiences GI side effects 	1 out of 100 (1%) patient experiences GI side effects 	
Chances of genital infection	No patients (0%) experience genital infection	16 out of 100 (16%) patients experience genital infection 	
Out-of-Pocket Cost per month	$ 0	$ 1,000	

Which medication do you choose? (pick only one medication option)

○ I choose Medication A
○ I choose Medication B
○ I choose neither Medication A nor Medication B

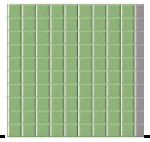
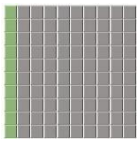
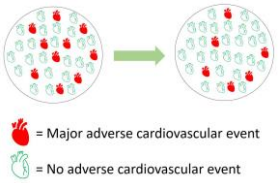
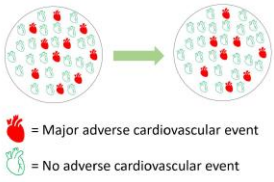
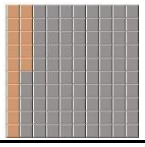
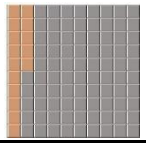
Q.7 Which of the following medication you would prefer based on the attributes (characteristics) presented **after your initial medication (e.g., metformin) alone does not help you achieve your treatment goal**? Choose by clicking one of the buttons below:

Attributes	Medication A	Medication B	Neither medication A nor medication B
How do you take the medication	Tablet, once a day 	Injectable, one a week 	Neither medication A nor medication B
Chance of reaching target HbA1c (long-term blood glucose level) in 6 months	10 out of 100 patients (10%) reach target HbA1c 	90 out of 100 patients (90%) reach target HbA1c 	
% reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to cardiovascular diseases)	No reduction in the risk of these cardiovascular events 	40% reduction in the risk of these cardiovascular events 	
Chance of gastrointestinal (GI) side effects (i.e., nausea, vomiting, and diarrhea)		30 out of 100 (30%) patient experience GI side effects 	
Chance of genital infection	16 out of 100 (16%) patients experience genital infection 	No patients (0%) experience genital infection	
Out-of-Pocket Cost per month	$ 0	$ 1,000	

Which medication do you choose? (pick only one medication option)

○ I choose Medication A
○ I choose Medication B
○ I choose neither Medication A nor Medication B

Q.8 Which of the following medication you would prefer based on the attributes (characteristics) presented **after your initial medication (e.g., metformin) alone does not help you achieve your treatment goal**? Choose by clicking one of the buttons below:

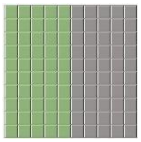
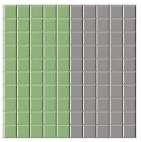
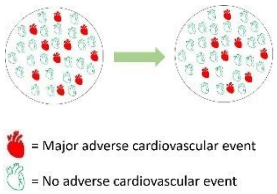
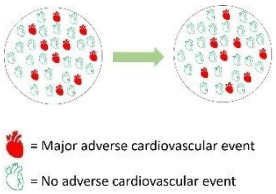
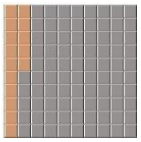
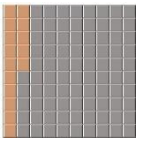
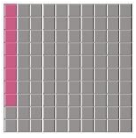
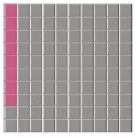
Attributes	Medication A	Medication B	Neither medication A nor medication B
How do you take the medication	Tablet, once a day 	Injectable, once a day 	Neither medication A nor medication B
Chance of reaching target HbA1c (long-term blood glucose level) in 6 months	90 out of 100 (90%) patients reach target HbA1c 	10 out of 100 (10%) patients reach target HbA1c 	
% reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to cardiovascular diseases)	40% reduction in the risk of these cardiovascular events 	20% reduction in the risk of these cardiovascular events 	
Chances of gastrointestinal side effects (i.e. nausea, vomiting and diarrhea)	15 out of 100 (15%) patients experience GI side effects 	15 out of 100 (15%) patients experience GI side effects 	
Chances of genital infection	16 out of 100 (16%) experience genital infection 	No patient (0%) experiences genital infection	
Out-of-Pocket Cost per month	$ 500	$ 500	

Which medication do you choose? (pick only one medication option)

- ○ I choose Medication A
- ○ I choose Medication B
- ○ I choose neither Medication A nor Medication B

Q.9 Which of the following medication you would prefer based on the attributes (characteristics) presented **after your initial medication (e.g., metformin) alone does not help you achieve your treatment goal**? Choose by clicking one of the buttons below:

Attributes	Medication A	Medication B	Neither medication A nor medication B
How do you take the medication	Tablet, once a day	Injectable, twice a day 	Neither medication A nor medication B

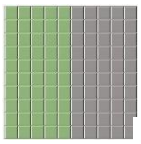
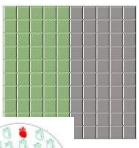
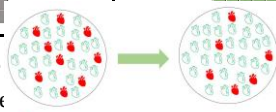
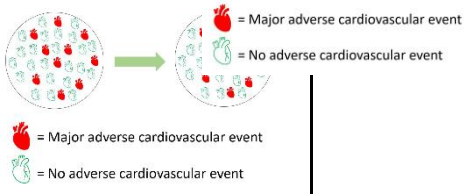
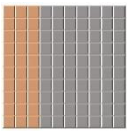
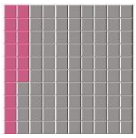
			
Chance of reaching target HbA1c (long-term blood glucose level) in 6 months	50 out of 100 (50%) patients reach target HbA1c 	50 out of 100 (50%) patients reach target HbA1c 	
% reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to cardiovascular diseases)	20% reduction in the risk of these cardiovascular events 	20% reduction in the risk of these cardiovascular events 	
Chance of gastrointestinal (GI) side effects (i.e., nausea, vomiting, and diarrhea)	15 out of 100 (15%) patients experience GI side effects 	15 out of 100 (15%) patients experience GI side effects 	
Chance of genital infection	8 out of 100 (8%) patients who experience genital infection 	8 out of 100 (8%) patients who experience genital infection 	
Out-of-Pocket Cost per month	$ 1,000	$ 0	

Which medication do you choose? (pick only one medication option)

- ○ I choose Medication A
- ○ I choose Medication B
- ○ I choose neither Medication A nor Medication B

Q.10 Which of the following medication you would prefer based on the attributes (characteristics) presented **after your initial medication (e.g., metformin) alone does not help you achieve your treatment goal**? Choose by clicking one of the buttons below:

Attributes	Medication A	Medication B	Neither medication A nor medication B
How do you take the medication	Injectable, one a week 	Tablet, once a day 	Neither medication A nor medication B
Chance of reaching target HbA1c (long-term blood glucose level) in 6	50 out of 100 (50%) patients reach target HbA1c	50 out of 100 (50%) patients reach target HbA1c	

months		
% reduction in the risk of major adverse cardiovascular events (i.e., heart attack, stroke, and death due to cardiovascular diseases)	No reduction in the these cardiovascular e   	in the risk of these events
Chance of gastrointestinal (GI) side effects (i.e., nausea, vomiting, and diarrhea)	1 out of 100 (1%) patient experiences GI side effects 	30 out of 100 (30%) patients experience GI side effects 
Chance of genital infection	16 out of 100 (16%) patients experience genital infection 	No patients (0%) experience genital infection
Out-of-Pocket Cost per month	$ 1,000	$ 0

Which medication do you choose? (pick only one medication option)

- ○ I choose Medication A
- ○ I choose Medication B
- ○ I choose neither Medication A nor Medication B

Patients review on questionnaire

Last question, how was your experience taking this survey? Please describe your feedback or comment on the overall survey questionnaire.

Appendix III

R Code for sample size calculation for Aim 2

```
> #step1 Significance Level (??)
> test_alpha=0.05
> z_one_minus_alpha<-qnorm(1-test_alpha)
> #step2 Statistical Power Level (1?????)
> test_beta=0.2
> z_one_minus_beta<-qnorm(1-test_beta)
> > #Step3 Statistical Model Used in the DCE Analysis
> parameters<-c(0.4790 , -0.3031 , -0.4576 , 0.0284 , 0.0060 , 0.0099 , -0.0091 , 0.0067 , 0.0185 , -0.00096)
> ncoefficients=10
> nalts=3
> nchoices=36
> # load the design information
> design<-as.matrix(read.table("C:/Users/brban/Desktop/PilotDCE/BDpilot.txt",header=FALSE));
> #compute the information matrix
> # initialize a matrix of size ncoefficients by ncoefficients filled with zeros.
> info_mat=matrix(rep(0,ncoefficients*ncoefficients), ncoefficients, ncoefficients)
> # compute exp(design matrix times initial parameter values)
> exputilities=exp(design%*%parameters)
> # loop over all choice sets
> for (k_set in 1:nchoices) {
+   # select alternatives in the choice set
+   alternatives=((k_set-1)*nalts+1) : (k_set*nalts)
+   # obtain vector of choice shares within the choice set
+   p_set=exputilities[alternatives]/sum(exputilities[alternatives])
+   # also put these probabilities on the diagonal of a matrix that only contains zeros
+   p_diag=diag(p_set)
+   # compute middle term P-pp'
+   middle_term<-p_diag-p_set%o%p_set
+   # pre- and postmultiply with the Xs from the design matrix for the alternatives in this choice set
+   full_term<-t(design[alternatives,])%*%middle_term%*%design[alternatives,]
+   # Add contribution of this choice set to the information matrix
+   info_mat<-info_mat+full_term
```

```
+ } # end of loop over choice sets
> #get the inverse of the information matrix (i.e., gets the variance-covariance matrix)
> sigma_beta<-solve(info_mat,diag(ncoefficients))
>
> # Use the parameter values as effect size. Other values can be used here.
> effectsize<-parameters
> # formula for sample size calculation is n>[(z_(beta)+z_(1-alpha))*sqrt(S??)/delta]^2
> N<-((z_one_minus_beta+z_one_minus_alpha)*sqrt(diag(sigma_beta))/abs(effectsize))^2
> # Display results (required sample size for each coefficient)
N [1]    27.918549    38.880488    15.396747  3826.886391    10.787581    15.547742
 [7]    35.408081 36571.821317    27.750473     2.814411
```