

**The comparative effects of metabolic surgery, SGLT2i, or GLP-1RA in patients with obesity and type 2 diabetes: A retrospective cohort study**

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**Short title:** Compare metabolic surgery, SGLT2i, and GLP1RA

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## **Highlights**

Beneficial weight loss and metabolic outcomes at 12-month were observed in metabolic surgery, GLP-1RA, and SGLT2i groups.

Metabolic surgery had the most remarkable effects on clinical outcomes but incurred the greatest 1-year medical costs, mainly due to surgery and related hospitalization.

Despite greater medical expenditures, metabolic surgery may be of higher values in achieving glycemic control, weight loss, and kidney protection.

## Abstract

**Background:** New antidiabetic agents (sodium-glucose cotransporter-2 inhibitor [SGLT2i] and glucagon-like peptide-1 receptor agonist [GLP-1RA]) and metabolic surgery have protective effects on metabolic syndromes.

**Objectives:** To compare the changes of metabolic parameters and costs among patients with obesity and type 2 diabetes undergoing metabolic surgery and initiating new antidiabetic agents over 12 months.

**Setting:** Hong Kong Hospital Authority database from 2006 to 2017.

**Methods:** This is a population-wide retrospective cohort study consisting of 2,616 patients (1,810 SGLT2i, 528 GLP-1RA, 278 metabolic surgery). Inverse probability treatment weighting of propensity score was applied to balance baseline covariates of patients with obesity and type 2 diabetes who underwent metabolic surgery, or initiated SGLT2i or GLP-1RA. Metabolic parameters and direct medical costs were measured and compared from baseline to 12 months in bariatric surgery, SGLT2i, and GLP-1RA groups.

**Results:** Patients in all 3 groups had improved metabolic parameters over a 12-month period. Patients with metabolic surgery achieved significantly better outcomes in BMI (-5.39, -0.56, -0.40 kg/m<sup>2</sup>, p<0.001), % total weight loss (15.16%, 1.34%, 1.63%, p<0.001), systolic (-2.21, -0.59, 1.28 mmHg, p<0.001) and diastolic (-1.16, 0.50, -0.13 mmHg, p<0.001) blood pressure, HbA1c (-1.80%, -0.77%, -0.80%, p<0.001), triglycerides (-0.64, -0.11, -0.09 mmol/L, p<0.001), and estimated glomerular filtration rate (3.08, -1.37, -0.41 ml/min/1.73m<sup>2</sup>, p<0.001) after 12-month compared with patients with SGLT2i and GLP1-RA. Although the metabolic surgery group incurred the greatest direct medical costs (US\$33,551, US\$10,945, US\$10,627, p<0.001), largely due to the surgery itself, the total monthly direct medical expenditure of metabolic surgery group became lower than that of SGLT2i and GLP1RA groups at 7 months.

**Conclusions:** Beneficial weight loss and metabolic outcomes at 12-months were observed in all 3 groups, among which the metabolic surgery group showed the most remarkable effects but incurred the greatest medical costs. However, studies with a longer follow-up period are warranted to show long-term outcomes.

**Keywords:** Metabolic surgery; New antidiabetic agents; Obesity; Cohort study; Type 2 diabetes

## **Introduction**

Sodium-glucose co-transporter 2 inhibitor (SGLT2i) and glucagon-like peptide-1 receptor agonist (GLP-1RA) are new types of antidiabetic agents. There are several types of SGLT2i and GLP-1RA drugs, which have prominent beneficial effects among patients with type 2 diabetes in glycaemic control, and cardiovascular and renal disease prevention <sup>(1-5)</sup>. Several well-designed placebo-controlled randomized trials have demonstrated that patients on SGLT2i and GLP-1RA had significant and sustainable improvement in glucose levels <sup>(1,3)</sup>. Findings from a systematic review of 97 randomized controlled trials showed that a favourable weight reduction of 2.01 kg and 1.32 kg, along with significant lowered HbA1c, was achieved in patients with SGLT2i or GLP-1RA over 12 weeks, respectively <sup>(6)</sup>. In addition, both SGLT2i and GLP1-RA had robust and consistent reno- and cardio- protective effects <sup>(3-5, 7-9)</sup>.

Metabolic surgery has been included as one of antidiabetic interventions for the treatment of type 2 diabetes and obesity, according to the latest American Diabetes Association (ADA) guidelines <sup>(10)</sup>. Despite increased expenditures <sup>(11, 12)</sup>, higher risks of suicide and non-fatal self-harm (even though the absolute risks were low) <sup>(13)</sup>, and re-operations due to complications or weight regain <sup>(14)</sup>, the effects of metabolic surgery on weight reduction, diabetes remission, and renal protection have been widely confirmed <sup>(15-17)</sup>. As reported by multiple trials and cohort studies, metabolic surgery showed superior effects in weight and glycaemic control over conventional therapies in both the short and long term <sup>(18-21)</sup>.

To-date, extrapolation of clinical outcomes exerted by these newer drug classes to patients with type 2 diabetes and obesity was uncertain given the absence of head-to-head comparisons between pharmacological and non-pharmacological treatments such as

metabolic surgery. Although pooled evidence from randomized controlled trials comparing metabolic surgery and non-surgical therapies is available<sup>(22)</sup>, the effectiveness and costs among metabolic surgery, SGLT2i and GLP-1RA in patients with obesity and type 2 diabetes has rarely been compared<sup>(23)</sup>. In this respect, a population-based analysis has been conducted to critically assess the effects of SGLT2i, GLP-1RA and metabolic surgery on a comprehensive set of clinical outcomes and direct medical costs over a 12-month period.

## **Materials/Subjects and Methods**

### *Study Design and Data Source Description*

A population-based retrospective cohort of patients with diabetes mellitus who used Hong Kong Hospital Authority (HA) services during January 1, 2006 to December 31, 2017 was extracted. HA database has been extensively used for conducting high-quality large population-based studies<sup>(24-26)</sup>. The diagnosis of diabetes mellitus was identified by the International Classification of Primary Care, Version 2 (ICPC-2) codes T89/T90 or International Statistical Classification of Diseases and Related Health Problems, 9th Revision, Clinical Modification (ICD-9-CM) codes 250.x. The database links to various individual patient-level information on the healthcare service utilization, metabolic surgeries (defined by ICD-9-CM procedure codes displayed in Supplementary Table 1), dispensing of new antidiabetic agents (including name, dosage and quantity), serial readings of anthropometric and laboratory tests, and presence of comorbidities as recorded by the ICD-9-CM or ICPC-2 diagnosis codes.

Eligible patients were those with type 2 diabetes and obesity (defined by body mass index [BMI]  $\geq 30 \text{ kg/m}^2$ ) and receiving one of the following drugs: 1) SGLT2i, 2) GLP-1RA, or 3) prescribed metabolic surgery. The index date of patients in the SGLT2i or GLP-1RA groups

was defined as the date of initiating SGLT2i or GLP-1RA, whereas the index date of patients in the metabolic surgery group was defined as the date of first metabolic surgery (further dates would refer to revisional surgeries). Patients who were aged <18 years, had BMI <30 kg/m<sup>2</sup>, diagnosed with type 1 or gestational diabetes, or did not use any new antidiabetic agents were excluded. Patients who had been co-administered the treatments under study at the index date (i.e. receiving any two or three of SGLT2i, GLP-1RA, and metabolic surgery in the same month) were also excluded from the study. In addition, patients who were lost to follow-up after the index date, or had histories of end-stage renal disease or cancers were excluded. Patients were followed up from the index date to 12 months.

### *Outcome Measures*

The primary outcomes were the changes in anthropometric and metabolic readings from baseline to 12 months. Measured parameters included BMI, HbA1c, systolic and diastolic blood pressure (SBP and DBP), total cholesterol (TC) to high-density lipoprotein cholesterol (HDL-C) ratio, low-density lipoprotein cholesterol (LDL-C), triglycerides, percentage of total weight loss (%TWL), and estimated glomerular filtration rate (eGFR). The secondary outcomes were 12-month cumulative direct medical costs, incurred by healthcare service utilization, new antidiabetic agents or metabolic surgery. Costs of healthcare service utilization were calculated as the frequency of healthcare services use multiplied by the corresponding unit costs sourced from the Hong Kong Government Gazette<sup>(27)</sup>. Costs of new antidiabetic agents were estimated from the reference price list by drug classes<sup>(28)</sup>. The unit costs are displayed in Supplementary Table 2. In addition, diabetes remission rates were measured for each group over the 12-month follow up. Diabetes remission was defined as maintaining a HbA1c level of <6.5% for at least 3 months without usual glucose-lowering pharmacotherapy<sup>(29)</sup>.



### *Baseline Covariates*

Baseline covariates of patients included age, sex, clinical characteristics, and history of cardiovascular disease and severe hypoglycaemia. Clinical characteristics included BMI, HbA1c, SBP and DBP, TC/HDL-C ratio, LDL-C, and triglycerides, eGFR, Charlson comorbidity index (CCI), duration of diabetes, and ever having used insulin, anti-hypertensive and lipid-lowering drugs. The eGFR was estimated by the serum creatinine from blood tests based on the Modification of Diet in Renal Disease Study formula and adjusted for a Chinese population.

### *Statistical Analysis*

Multiple imputation by chained equations (MICE)<sup>(30)</sup> was performed to address missing data. The missing values at the baseline were imputed by random chained equation using other known baseline covariates<sup>(31)</sup> for five iterations<sup>(32)</sup> in order to generate five complete imputed datasets. Results of the model parameters were then combined to a single estimate by applying Rubin's combination rules<sup>(30)</sup>.

To adjust for confounding, inverse probability treatment weighting (IPTW) of propensity scores was applied to balance the baseline covariates in the 3 treatment groups. Multinomial logistic regression models were fitted, where the indicator variables of treatment groups were the dependent variables and the baseline covariates were the independent variables. The propensity score, which is the predicted probability of patients receiving a certain treatment, was calculated based on the baseline covariates of patients. Patients with similar propensity scores were considered to have similar characteristics. The time between the initiation of new antidiabetic agents and the index date was accounted for when calculating propensity scores

for each patient<sup>(33)</sup>. IPTW was calculated from propensity scores and applied throughout the study. The balance of baseline covariates between the groups were assessed using univariate linear, binary logistic or multinomial logistic regression, as appropriate. A standardized mean difference (SMD) less than 0.2 indicated optimal balance. Baseline characteristics of each group were presented by means with standard errors (SE) for continuous variables, and numbers with percentages for categorical variables.

Clinical and cost outcomes were compared at baseline and 12-months by paired t-test within the same treatment group, and were also compared across the 3 groups using one-way analysis of variance test. The incidence rate ratios (IRR) calculated by negative binomial regression models were used to compare the usage of each type of healthcare service among groups. Sensitivity analyses were carried out for patients with sleeve gastrectomy, for patients with baseline insulin use, and for patients using exenatide or liraglutide.

All statistical analyses were performed using Stata version 13.0 (StataCorp LP, College Station, Texas). All significance tests were two-tailed and P values <.05 were taken to indicate statistical significance.

## **Results**

The flowchart of the study is outlined in Figure 1. A total of 2616 eligible patients (1,810 SGLT2i, 528 GLP-1RA, 278 metabolic surgery) were included in the analysis. Among the SGLT2i cohort, 1434 (54.8%), 1148 (43.9%), and 37 (1.4%) of patients took dapagliflozin, empagliflozin, and canagliflozin, respectively; whereas in the GLP-1RA group, 157 (29.7%), 322 (61.0%), and 49 (9.2%) used exenatide, liraglutide, and lixisenatide, respectively. There

were 239 (86.0%), 32 (11.5%), and 7 (2.5%) patients with laparoscopic sleeve gastrectomy, laparoscopic gastric bypass, and laparoscopic gastric banding in the metabolic surgery group.

### *Patient characteristics*

The baseline characteristics of patients in each group after weighting is displayed in Table 1. Most of the baseline covariates were well balanced across the 3 groups, except age. The mean age of SGL2i, GLP-1RA and bariatric surgery patients were 53.4 (SE 0.2), 52.7 (SE 0.2), and 48.7 (SE 0.6), respectively. The prescribing durations of patients in the SGLT2i and GLP-1RA groups were 274 (95%CI: 269 - 279) days and 200 (95%CI: 190 - 211) days, respectively. The data completion rates at baseline and 12-months are shown in Supplementary Table 3. Details of baseline characteristics of each group before weighting are listed in Supplementary Table 4.

### *Paired comparison of clinical outcome at baseline and 12-month follow-up*

Patients in all 3 groups had a significant decrease in BMI, TC/HDL-C ratio, triglycerides, %TWL, and HbA1c. Patients in the metabolic surgery group had significantly higher %TWL (15.16%, 1.34% and 1.63%,  $p<0.001$ ) and a greater reduction in BMI ( $-5.39\text{kg/m}^2$ ,  $-0.56\text{kg/m}^2$ ,  $-0.40\text{kg/m}^2$ ,  $p<0.001$ ), TC/HDL-C ratio ( $-0.20$ ,  $-0.08$ ,  $-0.12$ ,  $p<0.001$ ), triglycerides ( $-0.64\text{mmol/L}$ ,  $-0.11\text{mmol/L}$ ,  $-0.09\text{mmol/L}$ ,  $p<0.001$ ), and HbA1c ( $-1.80\%$ ,  $-0.77\%$ ,  $-0.80\%$ ,  $p<0.001$ ) than patients in the SGLT2i and GLP-1RA groups. Neither SGLT2i nor GLP-1RA patients saw significant improvement in blood pressure, while patients in the metabolic surgery group experienced a significant reduction in systolic blood pressure of 2.21 mmHg ( $p=0.012$ ) and diastolic blood pressure of 1.16 mmHg ( $p<0.001$ ). In addition, eGFR increased significantly in the metabolic surgery group ( $3.08\text{ mL/min/1.73m}^2$ ,  $p<0.001$ ), but decreased significantly in the SGLT2i ( $-1.37\text{ mL/min/1.73m}^2$ ,  $p<0.001$ ) group.

However, significant changes in LDL-C were not observed in the metabolic surgery group, whereas the parameter significantly dropped in SGLT2i and GLP-1RA groups. (Figure 2; Supplemental Table 5)

Patients in the metabolic surgery group had the highest diabetes remission rates over the 12 months, with a total of 13 (4.68%), 135 (48.56%), 78 (28.06%), and 110 (39.57%) patients achieving diabetes remission at 3, 6, 9, and 12 months, respectively. In comparison, less than 5% of patients in the SGLT2i or GLP1RA groups achieved diabetes remission across 12 months (Supplemental Table 6).

#### *Direct medical costs in 12-month follow-up*

Figure 3 depicts the mean monthly and cumulative direct medical costs for each group over a 12-month period. Patients in the SGLT2i and GLP-1RA groups incurred similar expenditure on antidiabetic drugs (US\$8,580 and US\$8,184) and healthcare service use (US\$2,364 and US\$2,443), with a total spending of US\$10,944 and US\$10,627 over 12 months, respectively. Though the drug costs of the metabolic surgery group were the lowest over time, patients who underwent metabolic surgery had the highest cumulative healthcare service use costs (US\$33,551) and cumulative total direct medical costs (US\$30,213) over 12 months (Table 2). Of note, the monthly direct medical expenditures of the metabolic surgery group decreased sharply at 2 months and were lower than the other two groups from 7 months onwards.

#### *Healthcare service utilization*

Inpatient services were most frequently used by patients in the metabolic surgery group, with a mean of 7 hospitalization admissions that accounted for a length of stay of 19 days in 12

months (Supplemental Table 7). The metabolic surgery group had 0.322 and 0.376 times the incidence rate of hospital admissions compared to SGLT2i and GLP-1RA groups over the study period, respectively. Furthermore, patients with SGLT2i (IRR 0.294,  $p < 0.001$ ) and GLP-1RA (IRR 0.409,  $p < 0.001$ ) used allied health professionals' services less frequently than patients with metabolic surgery. The use of accident and emergency services was rare among all groups ( $< 2$ ) over the 12-month period. The SGLT2i group had the lowest frequency of outpatient visits compared with metabolic surgery and GLP-1RA groups, with an IRR of 0.719 ( $p = 0.002$ ) and 0.767 ( $p < 0.001$ ), respectively. (Supplemental Table 8)

### *Sensitivity analysis*

Results on patients with laparoscopic sleeve gastrectomy, patients with insulin at baseline, and patients using exenatide or liraglutide, are displayed in Supplemental Table 9. Sleeve gastrectomy significantly improved most metabolic parameters, such as BMI, SBP, LDL-C, etc., except DBP. Cumulative direct medical costs reached US\$32,459 at 12 months, largely driven by hospitalizations. Metabolic surgery had greater effect on clinical parameters but higher medical costs than in the other two groups in patients using insulin at baseline. Also, higher direct medical costs were incurred among patients on insulin at baseline (~70% of patients). Mean dosages were 10.26 mg/day and 0.76 mg/day for patients using exenatide and liraglutide, respectively. Exenatide and liraglutide showed similar effects and significantly lowered BMI, HbA1c, and LDL-C levels over 12 months. However, patients with exenatide incurred more health care service use costs (US\$2,610 vs. US\$2,504) and drug costs (US\$8,470 vs. US\$7,951) than patients on liraglutide. The 12-month cumulative direct medical costs of patients on exenatide and those of patients on liraglutide were US\$11,081 and US\$10,455, respectively.

## Discussion

Although the effects of metabolic surgery and conventional medical therapy have been widely compared <sup>(22)</sup>, head-to-head comparisons between metabolic surgery and new antidiabetic medications have rarely been made <sup>(23)</sup>. This population-based cohort study assessed changes in clinical parameters, use of healthcare services, and costs among patients with type 2 diabetes and obesity who started on new antidiabetic drugs or received metabolic surgery. The findings of this study indicated that the clinical outcomes of patients in all 3 groups improved to varying degrees. Among all 3 groups, the metabolic surgery group showed superior effects in weight reduction, glycaemic control, and renal protection, at the cost of incurring the greatest medical expenditure.

Our results were consistent with the findings of previous studies that either new antidiabetic drugs or metabolic surgery were beneficial in weight management and glycaemic control. The finding that greater BMI reduction was achieved in the metabolic surgery group was observed in multiple randomized controlled trials that compared the effectiveness of metabolic surgery and medical therapies <sup>(22)</sup>. Furthermore, systematic reviews focused on patients with type 2 diabetes on different dosages of SGLT2i<sup>(34)</sup> and GLP-1RA<sup>(35)</sup> also found that body weight dropped significantly after 12-20 weeks' of treatment. As for glycaemic control, the HbA1c levels of SGLT2i and GLP-1RA groups decreased significantly over 12 months, and the magnitude of declining HbA1c fell within the within the ranges produced by meta-analyses <sup>(36, 37)</sup>. However, bariatric surgery was deemed to be the most efficacious treatment in lowering HbA1c levels both in this study and in other published evidence. For example, a randomized controlled trial found that 28 out of 31 patients (90%) with gastric bypass achieved diabetes remission after 1-year follow-up, while no such outcome occurred in patients in the exenatide or placebo groups <sup>(38)</sup>.

Significantly higher cumulative direct medical costs of metabolic surgery compared with SGLT2i and GLP-1RA were maintained at 12-months, primarily driven by longer stays in hospital and costs associated with metabolic surgery and re-operations. Notably, within a 12-month time horizon, patients with metabolic surgery incurred the lowest monthly direct medical costs from 7 months onwards. However, reduction or discontinuation of glucose-lowering drugs after surgery failed to offset the direct medical costs associated with hospitalization and surgery, and thus, the 12-month cumulative medical costs of the metabolic surgery group were significantly higher than those of SGLT2i and GLP-1RA groups. This finding indicated that metabolic surgery was not cost-saving at 12-month post-surgery when compared with intensifying SGLT2i or GLP1-RA. However, metabolic surgery may be cost-effective in the longer term ( $\geq 5$  years) compared with the willingness-to-pay threshold of the jurisdiction <sup>(39)</sup>.

This study had several limitations. Firstly, the current study assessed the clinical and financial impact of 3 treatments limited to within a 12-month period. Secondly, although matching weights based on the propensity-score balanced the measured baseline characteristics of patients in the 3 groups, a few characteristics, including age, was not balanced at baseline. Moreover, unmeasured or residual confounding factors such as smoking and drinking habits that may potentially have influenced the treatment-outcome associations were not included in the analysis. Thirdly, only direct medical costs were considered in this study. Indirect costs such as productivity loss due to absence from work were not measured. Fourthly, variability in dosage, brand, and adjustment of medications were not taken into account. Although patients were identified by prescription, the compliance of patients to medication was not available in our dataset. Lastly, over 80% of patients in the surgery group had sleeve

gastrectomy but only a minority (1.5%) underwent gastric banding, and thus, the results may not be generalisable to patients who underwent gastric banding or other metabolic procedures that were not involved in this study.

In conclusion, beneficial weight loss and metabolic outcomes at 12-months were observed in all 3 groups, among which metabolic surgery had the most significant effect but incurred the greatest medical costs. Studies with a longer follow-up period are warranted to show long-term outcomes.



## **List of Abbreviations**

ADA = American Diabetes Association

BMI = Body Mass Index

GLP-1RA = Glucagon-like peptide-1 receptor agonist

HA = Hospital Authority

ICD-9-CM = International Statistical Classification of Diseases and Related Health Problems,  
9th Revision, Clinical Modification

ICPC-2 = International Classification of Primary Care, Version 2

SE = Standard Error

SGLT2i = Sodium-glucose co-transporter 2 inhibitor

T2DM = Type 2 diabetes mellitus

MICE = Multiple imputation by chained equations

IPTW = inverse probability treatment weighting

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## **Competing Interests**

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### **Ethics approval and consent to participate**

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethics approval of this study was granted by the Institutional Review Board of the University of Hong Kong /Hospital Authority Hong Kong West Cluster (HKU/HA HKW IRB) (Ref No. UW 16-1018).

### **Authors Contribution statement**

CKHW had the original idea for the study, contributed to the development of the study, reviewed the literature, constructed the study design, conducted the statistical analysis, and act as guarantors for the study. CKHW and WTT wrote the first draft of the manuscript. KKCM provided critical input to the statistical analyses and design. EWYC, ICKW and CLKL provided critical input to the study design. SKHW, ETYT and EN provided critical input to the diagnosis, metabolic surgery and drug dispensing codes from the database. EHMT and CHA conducted the statistical analysis. All authors contributed to the interpretation of the analysis, critically reviewed and revised the manuscript, and approved the final manuscript as submitted. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

### **Data availability**

The data that support the findings of this study are available from the Central Panel on Administrative Assessment of External Data Requests, Hong Kong Hospital Authority Head Office but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Central Panel on Administrative Assessment of External Data Requests, Hong Kong Hospital Authority Head Office.

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## **Legends to Figures**

Figure 1. Enrolment of patients with type 2 diabetes initiating sodium glucose co-transporter-2 inhibitors (SGLT2i) or glucagon-like peptide-1 receptor agonists (GLP-1RA), or undergoing metabolic surgery

Figure 2. Paired comparison of clinical characteristics at baseline and 12-month follow-up for patients with type 2 diabetes initiating sodium glucose co-transporter-2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1RA) and those undergoing metabolic surgery

Figure 3. Mean monthly and cumulative costs associated with new antidiabetic agents, healthcare service and total direct medical costs for each month and each group over a 12-month period

Table 1. Baseline characteristics of patients initiating glucose-lowering medications of SGLT2i, GLP-1RA, or undergoing metabolic surgery after multiple imputation and inverse probability of treatment weighting for propensity scores

| Baseline characteristics                          | Total<br>(N =<br>2,616) | SGLT2i<br>(N =<br>1,810) | GLP-1RA<br>(N = 528) | Metabolic<br>Surgery<br>(N = 278) | Maximum<br>pairwise<br>ASMD |
|---|-------------------------|--------------------------|----------------------|-----------------------------------|-----------------------------|
| <b>Socio-Demographics</b>                         |                         |                          |                      |                                   |                             |
| Gender (%)  |                         |                          |                      |                                   | 0.03                        |
| Female  | 44.8%                   | 45.6%                    | 44.7%                | 43.9%                             |                             |
| Male  | 55.2%                   | 54.4%                    | 55.3%                | 56.1%                             |                             |
| Mean Age (SE), year                               | 51.7 (0.2)              | 53.4 (0.2)               | 52.7 (0.2)           | 48.7 (0.6)                        | 0.41*                       |
| Age group, (%)                                    |                         |                          |                      |                                   | 0.12                        |
| ≤60   | 75.0%                   | 72.7%                    | 74.7%                | 78.1%                             |                             |
| >60   | 25.0%                   | 27.3%                    | 25.3%                | 21.9%                             |                             |
| <b>Clinical Characteristics</b>                   |                         |                          |                      |                                   |                             |
| Mean SBP (SE), mmHg                               | 136.1 (0.6)             | 137.1 (0.5)              | 136.8 (1.1)          | 134.1 (1.9)                       | 0.20                        |
| Mean DBP (SE), mmHg                               | 79.3 (0.7)              | 79.4 (0.3)               | 79.8 (0.2)           | 78.7 (2.5)                        | 0.14                        |
| Mean BMI (SE), kg/m <sup>2</sup>                  | 35.4 (0.1)              | 35.1 (0.1)               | 35.4 (0.1)           | 35.8 (0.2)                        | 0.14                        |
| Mean LDL-C (SE), mmol/L                           | 2.3 (0.0)               | 2.3 (0.0)                | 2.3 (0.0)            | 2.4 (0.0)                         | 0.16                        |
| Mean TC/HDL-C Ratio                               | 4.3 (0.0)               | 4.3 (0.0)                | 4.3 (0.0)            | 4.4 (0.0)                         | 0.15                        |
| Mean triglyceride (SE), mmol/L                    | 2.1 (0.0)               | 2.1 (0.0)                | 2.1 (0.0)            | 2.1 (0.0)                         | 0.04                        |
| Mean hemoglobin A1c (SE), %                       | 9.0 (0.0)               | 8.9 (0.0)                | 8.9 (0.0)            | 9.2 (0.1)                         | 0.20                        |
| Mean eGFR (SE), mL/min/1.73m <sup>2</sup>         | 111.8 (0.5)             | 110.6 (0.6)              | 109.9 (0.7)          | 115.1 (1.4)                       | 0.13                        |
| Chronic Kidney Disease (by eGFR)                  |                         |                          |                      |                                   | 0.18                        |
| Stage 1 (≥90 mL/min/1.73m <sup>2</sup> )          | 72.0%                   | 76.1%                    | 71.3%                | 68.3%                             |                             |
| Stage 2 - 5 (<90 mL/min/1.73m <sup>2</sup> )      | 28.0%                   | 23.9%                    | 28.7%                | 31.7%                             |                             |
| Mean Charlson Comorbidity Index (SE) <sup>†</sup> | 4.3 (0.0)               | 4.4 (0.0)                | 4.3 (0.0)            | 4.2 (0.1)                         | 0.09                        |
| Charlson Comorbidity Index <sup>†</sup> , (%)     |                         |                          |                      |                                   | 0.19                        |
| 1-2   | 24.0%                   | 20.6%                    | 24.1%                | 27.8%                             |                             |
| 3   | 16.2%                   | 18.6%                    | 15.7%                | 14.2%                             |                             |
| 4 or above  | 59.7%                   | 60.7%                    | 60.3%                | 57.9%                             |                             |
| Mean duration of Diabetes (SE), year              | 7.6 (0.0)               | 7.9 (0.1)                | 7.8 (0.1)            | 7.1 (0.1)                         | 0.22*                       |
| Duration of Diabetes, year, (%)                   |                         |                          |                      |                                   | 0.16                        |
| <5 years  | 20.7%                   | 23.8%                    | 17.3%                | 20.9%                             |                             |
| ≥ 5 years   | 79.3%                   | 76.2%                    | 82.7%                | 79.1%                             |                             |
| <b>Treatment morbidity (%)</b>                    |                         |                          |                      |                                   |                             |
| Use of Insulin                                    | 73.1%                   | 71.4%                    | 70.4%                | 77.9%                             | 0.17                        |
| Use of anti-hypertensive drugs                    | 93.7%                   | 93.9%                    | 93.4%                | 93.7%                             | 0.02                        |
| Use of lipid lowering agent                       | 82.3%                   | 82.8%                    | 82.2%                | 81.9%                             | 0.02                        |
| <b>Disease status (%)</b>                         |                         |                          |                      |                                   |                             |
| Cardiovascular Disease                            | 27.1%                   | 25.6%                    | 24.2%                | 31.8%                             | 0.17                        |
| Severe hypoglycemia (1 year before baseline)      | 8.8%                    | 7.0%                     | 9.1%                 | 10.5%                             | 0.09                        |

SGLT2i = Sodium Glucose Co-transporter-2 Inhibitors; GLP-1RA = Glucagon-like Peptide-1 Receptor Agonists; BMI = Body Mass Index; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; LDL-C = Low Density

Lipoprotein - Cholesterol; TC = Total Cholesterol; HDL-C = High Density Lipoprotein - Cholesterol; eGFR = Estimated Glomerular Filtration Rate; ASMD = Absolute Standardized Mean Difference

Notes:

\* A standardized mean difference (SMD) less than 0.2 indicated optimal balance.

† The calculation of Charlson Index does not include Acquired Immune Deficiency Syndrome (AIDS).

Table 2. 12-month cumulative costs associated with health service and glucose-lowering drugs for each treatment group

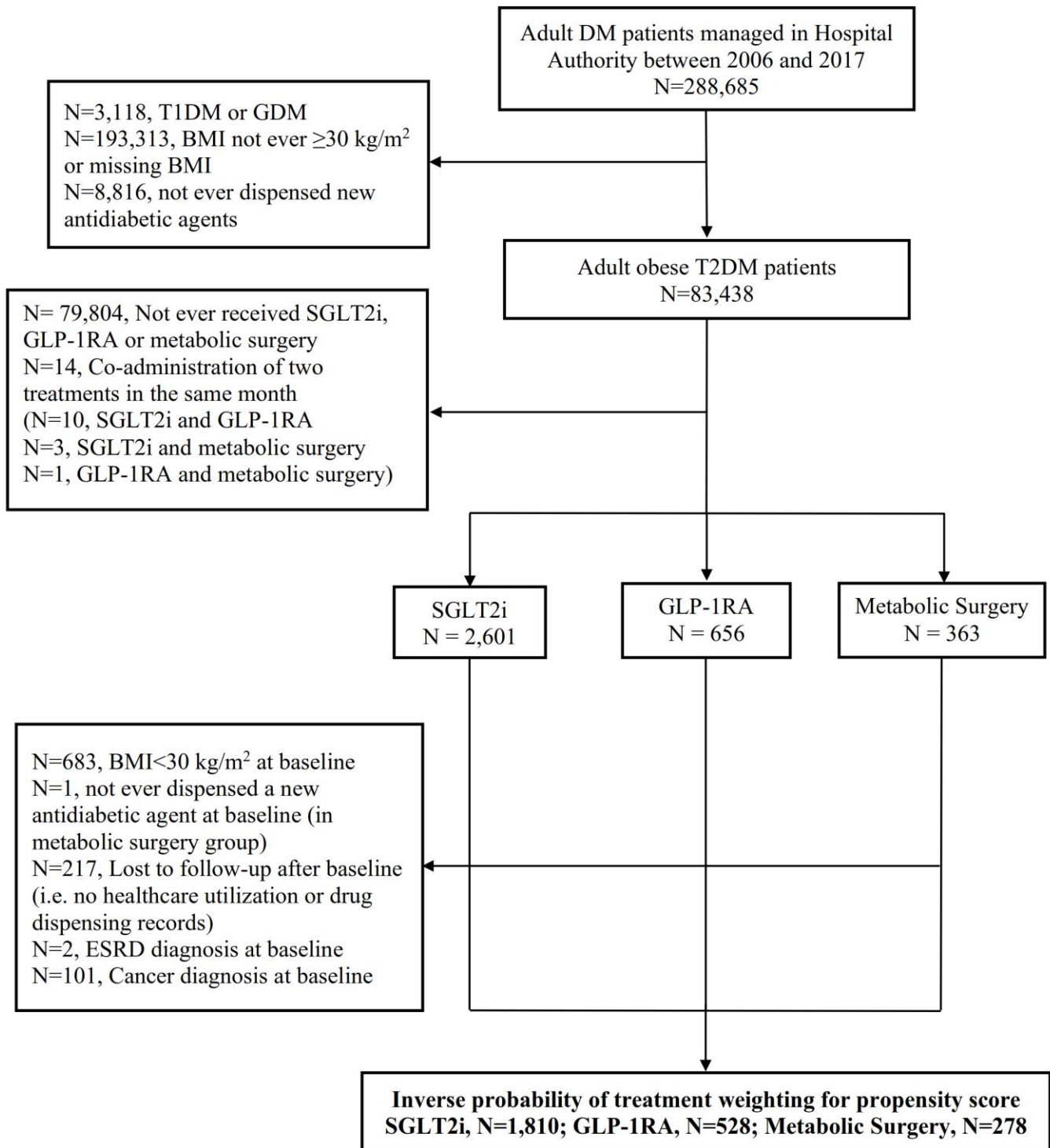
|  | SGLT2i<br>(N = 1,810) | GLP-1RA<br>(N = 528) | Metabolic Surgery<br>(N = 278) | P-value |
|--|-----------------------|----------------------|--------------------------------|---------|
| <b>Mean Health Service Cost (SE), US\$</b>       |                       |                      |                                |         |
| Hospitalization                                  | 1,377.61 (122.69)     | 1,309.13 (172.22)    | 12,995.89 (649.33)             | <0.001* |
| General Ward                                     | 1,241.18 (110.36)     | 1,170.58 (162.63)    | 8,472.48 (363.94)              | <0.001* |
| Intensive Care Unit                              | 85.84 (22.14)         | 48.47 (10.61)        | 3,659.03 (341.36)              | <0.001* |
| Coronary Care Unit                               | 51.46 (16.26)         | 88.60 (39.09)        | 0.00 (0.00)                    | 0.047*  |
| High Dependency Unit                             | 2.66 (1.33)           | 1.48 (1.00)          | 864.38 (186.00)                | <0.001* |
| Accident and Emergency                           | 86.23 (5.94)          | 77.14 (4.44)         | 71.78 (3.41)                   | 0.103   |
| Out-patient clinic                               | 864.30 (11.82)        | 1,014.54 (12.40)     | 1,519.92 (42.25)               | <0.001* |
| Specialist                                       | 822.38 (11.17)        | 959.90 (11.35)       | 1,462.86 (43.03)               | <0.001* |
| General  | 41.92 (2.97)          | 54.64 (3.82)         | 57.06 (2.24)                   | 0.001*  |
| Allied Health Professionals                      | 36.07 (1.90)          | 42.35 (2.14)         | 213.11 (3.80)                  | <0.001* |
| Total health service cost                        | 2,364.21 (127.71)     | 2,443.15 (176.46)    | 30,212.64 (658.47)             | <0.001* |
| <b>Mean Drug Cost (SE), US\$</b>                 |                       |                      |                                |         |
| Glucose-lowering medication cost                 | 8,580.43 (81.18)      | 8,184.08 (87.45)     | 3,338.99 (107.20)              | <0.001* |
| <b>Mean Total Direct Medical Cost (SE), US\$</b> |                       |                      |                                |         |
|  | 10,944.64 (157.68)    | 10,627.23 (203.69)   | 33,551.63 (658.03)             | <0.001* |

SGLT2i = Sodium Glucose Co-transporter-2 Inhibitors; GLP-1RA = Glucagon-like Peptide-1 Receptor Agonists; SE = Standard Error

Notes:

\* Significant at 0.05 level by one-way analysis of variance.

Figure 1. Enrolment of type 2 diabetes mellitus patients initiating sodium glucose co-transporter-2 inhibitors (SGLT2i) and glucagon - like peptide-1 receptor agonists (GLP-1RA) and those patients undergoing metabolic surgery



DM = Diabetes Mellitus; T1DM = Type 1 DM; GDM = Gestational DM; BMI = Body Mass Index; T2DM = Type 2 DM; SGLT2i = Sodium-glucose cotransporter 2 inhibitors; GLP-1RA = Glucagon-like peptide-1 receptor agonists; ESRD=End-stage renal disease

Figure 2. Paired comparison of clinical characteristics at baseline and 12-month follow-up for type 2 diabetes mellitus patients initiating sodium glucose co-transporter-2 inhibitors (SGLT2i), glucagon-like peptide-1 receptor agonists (GLP-1RA) and those patients undergoing metabolic surgery

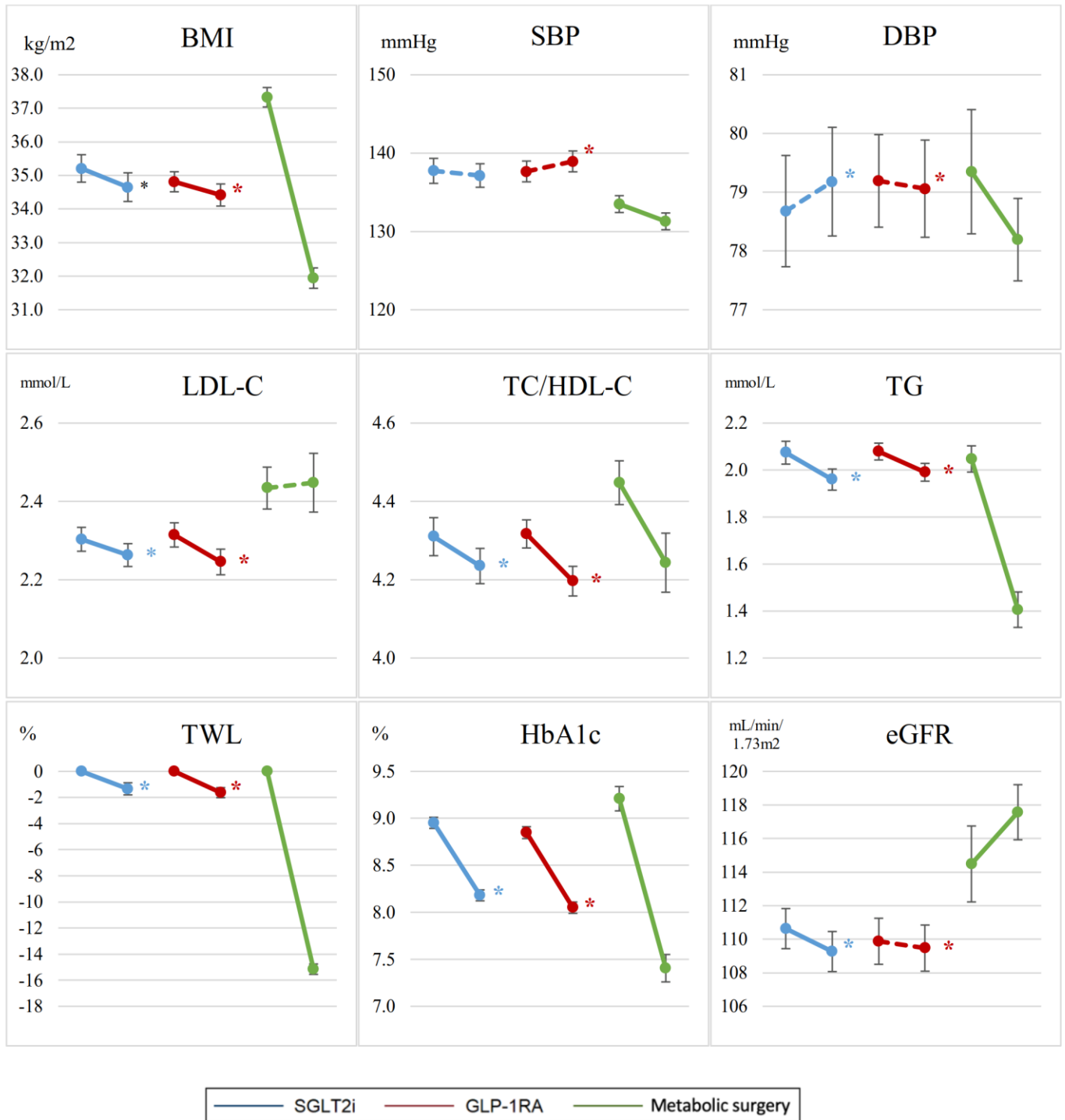
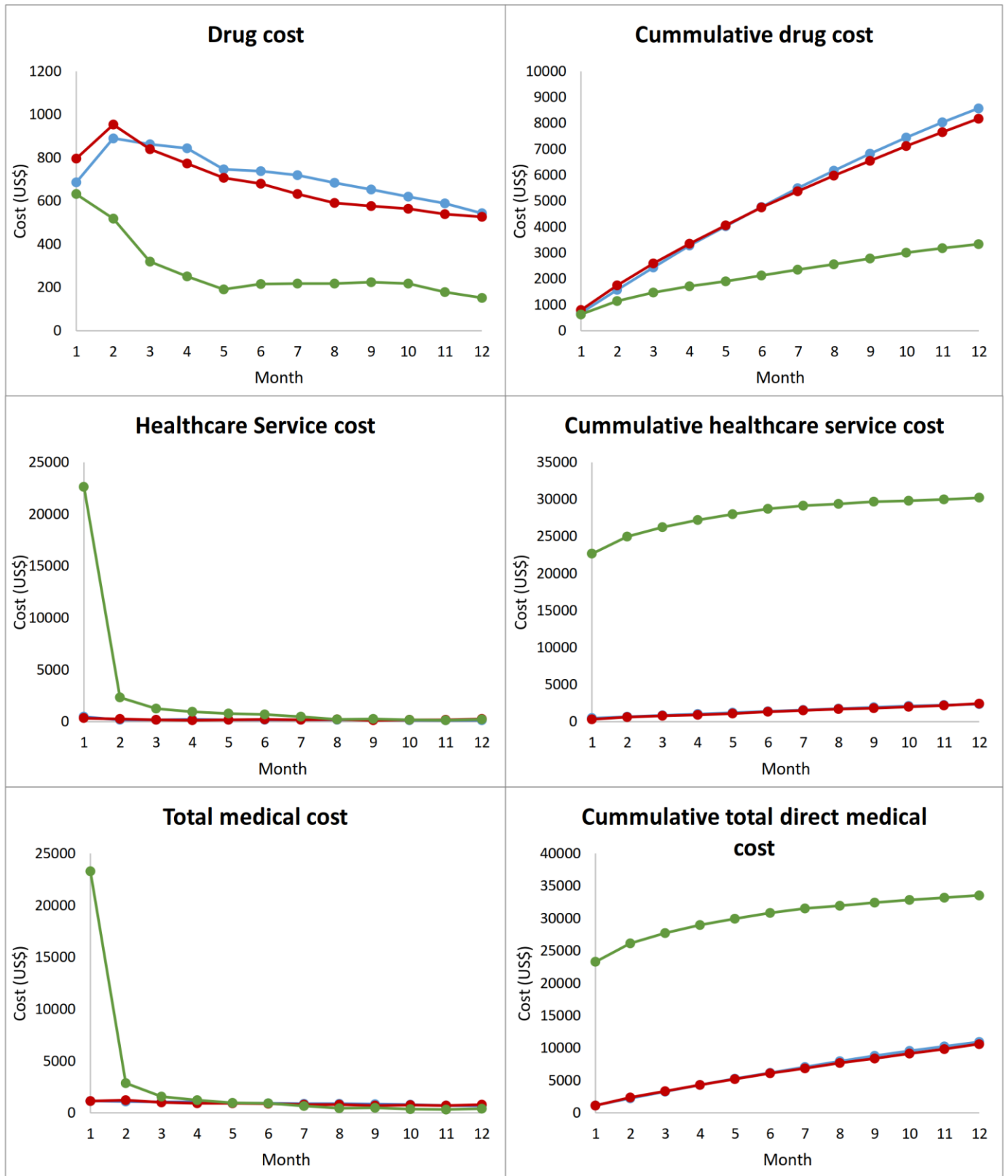


Figure 3. Mean monthly and cumulative costs associated with glucose-lowering drugs, healthcare service and total direct healthcare costs for each month and each group over a 12-month period



— SGLT2i — GLP-1RA — Metabolic surgery



Supplemental Table 1. Disease diagnosis and drug coding

| Code Type                   | Description                  | Diagnosis Code   |
|-----------------------------|------------------------------|--|
| ICD-9-CM                    | Hypoglycemia                 | 250.30-250.33; 250.80-250.83; 251.0-251.2; 270.3; 775.0; 775.6; 962.3  |
|                             | Acute myocardial infarction  | 410.00-410.92  |
|                             | Other ischemic heart disease | 411.0; 411.1; 411.81; 411.89; 412; 413.0; 413.1; 413.9; 414.00-414.07; 414.10-414.12; 414.19; 414.2-414.4; 414.8; 414.9  |
|                             | Congestive heart failure     | 428.0-428.9  |
|                             | Stroke                       | 430; 431; 432.0-432.9; 433.00-433.91; 434.00-434.91; 435.0-435.9; 436; 437.0-437.9; 438.0-438.9  |
|                             | Peripheral vascular disease  | 250.60-250.69; 440.2; 997.2; 997.6   |
|                             | End-stage renal disease      | 585; 586   |
| ICPC-2                      | Diabetes Mellitus            | T89; T90   |
|                             | Acute myocardial infarction  | K75  |
|                             | Other ischemic heart disease | K74; K76   |
|                             | Congestive heart failure     | K77  |
|                             | Stroke                       | K89; K90; K91  |
| Peripheral vascular disease | K92                          |  |
| BNF                         | ACEI/ARB                     | CAPT01; CAPT02; CAPT03; CAPT06; ENAL01; ENAL02; ENAL03; LISI01; LISI02; LISI03; PERI17; PERI28; PERI29; RAMI01; RAMI02; RAMI03; CAND01; CAND02; IRBE01; IRBE02; LOSA01; LOSA03; S00031; S00069; S00454; S00455; TELM01; TELM02; VALS02; VALS03; CO-D01; CO-D02; EXFO01; EXFO02; EXFO03; IRBE03; IRBE04; LOSA02; LOSA04; MICA01 |
|                             | Beta blocker                 | ATEN01; ATEN02; BISO01; BISO02; CARV01; CARV02; CARV03; CARV04; LODO02; LODO03; METO06; METO07; METO10; METO11; METO13; METO16; NADO01; PIND01; PROP04; PROP05; LODO02; LODO03   |
|                             | Calcium channel blocker      | AMLO01; AMLO02; DILT01; DILT02; DILT05; DILT06; DILT07; DILT08; FELO01; FELO02; FELO03; LACI01; LACI02; NIFE03; NIFE04; NIFE05; NIMO01; EXFO01; EXFO02; EXFO03   |

ICD-9-CM = International Statistical Classification of Diseases and Related Health Problems, 9th Revision, Clinical Modification; ICPC-2 = International Classification of Primary Care, Version 2; BNF = British National Formulary

Supplemental Table 2. Unit cost of healthcare services, metabolic surgery and glucose-lowering medication

| Items  | Cost (HK\$) <sup>§</sup> | Cost (US\$)      |
|--|--------------------------|------------------|
| <b>Healthcare services<sup>†</sup></b>                     |                          |                  |
| <b>Clinic visit</b>  |                          |                  |
| General outpatient clinic                                  | 445 per visit            | 57 per visit     |
| Specialist outpatient clinic                               | 1,190 per visit          | 153 per visit    |
| Accident and emergency                                     | 1,230 per visit          | 158 per visit    |
| <b>Allied health professionals</b>                         |                          |                  |
| Clinical Psychologist                                      | 550 per visit            | 71 per visit     |
| Dietitian  | 550 per visit            | 71 per visit     |
| Occupational Therapist                                     | 550 per visit            | 71 per visit     |
| Physiotherapist  | 550 per visit            | 71 per visit     |
| Smoking counselling and cessation centre                   | 550 per visit            | 71 per visit     |
| <b>Hospitalization</b>                                     |                          |                  |
| General ward   | 5,100 per day            | 654 per day      |
| Intensive care unit  | 24,400 per day           | 3,128 per day    |
| Cardiac care unit  | 24,400 per day           | 3,128 per day    |
| High dependency unit                                       | 13,650 per day           | 1,750 per day    |
| <b>Metabolic surgery and revision surgery<sup>‡</sup></b>  |                          |                  |
| Laparoscopic sleeve gastrectomy                            | 114,585                  | 14,690           |
| Laparoscopic adjustable gastric banding                    | 105,410                  | 13,514           |
| Laparoscopic gastric bypass                                | 119,585                  | 15,331           |
| Laparoscopic sleeve gastrectomy with duodenojejunal bypass | 162,910                  | 20,886           |
| Laparoscopic plication of greater curve of stomach         | 67,010                   | 8,591            |
| Duodeno-jejunoostomy                                       | 67,735                   | 8,684            |
| <b>Glucose-lowering medication<sup>¶</sup></b>             |                          |                  |
| Metformin  | --                       | 7 per 30 day     |
| Insulin  | --                       | 397.5 per 30 day |
| Sulfonylureas  | --                       | 12 per 30 day    |
| Pioglitazone   | --                       | 14.5 per 30 day  |
| Dipeptidyl peptidase 4 inhibitors                          | --                       | 285 per 30 day   |
| Sodium-glucose cotransporter 2 inhibitors                  | --                       | 437.5 per 30 day |
| Glucagon-like peptide-1 receptor agonists                  | --                       | 588 per 30 day   |

**Note:**

<sup>†</sup> Data source: 2017 Hong Kong SAR Government Gazette and Hospital Authority Ordinance (chapter 113): Public charges – non-eligible persons.

<sup>‡</sup> Data source: 2017 Hong Kong SAR Government Gazette and Hospital Authority Ordinance (chapter 113): Private charges (midpoint value); and personal communication with bariatric surgeons

<sup>§</sup> At a fixed exchange rate of 1 US= 7.80HK.

<sup>¶</sup> Data source: Tran, KL et al. Overview of Glucagon-Like Peptide-1 Receptor Agonists for the Treatment of Patients with Type 2 Diabetes. *Am Health Drug Benefits*. 2017; 10(4):178-188. (Midpoint costs of the cost range were used)

Supplementary Table 3. Data completion rates before multiple imputation and inverse probability of treatment weighting for propensity scores

| Time frame                              | At baseline          |                       |                      |                                   | At 12 months         |                       |                      |                                   |
|---|----------------------|-----------------------|----------------------|-----------------------------------|----------------------|-----------------------|----------------------|-----------------------------------|
| Factor                                  | Total<br>(N = 2,616) | SGLT2i<br>(N = 1,810) | GLP-1RA<br>(N = 528) | Metabolic<br>Surgery<br>(N = 278) | Total<br>(N = 2,616) | SGLT2i<br>(N = 1,810) | GLP-1RA<br>(N = 528) | Metabolic<br>Surgery<br>(N = 278) |
| <b>Socio-Demographic (% , n)</b>        |                      |                       |                      |                                   |                      |                       |                      |                                   |
| Gender                                  | 100.0% (2,616)       | 100.0% (1,810)        | 100.0% (528)         | 100.0% (278)                      | 100.0% (2,616)       | 100.0% (1,810)        | 100.0% (528)         | 100.0% (278)                      |
| Age                                     | 100.0% (2,616)       | 100.0% (1,810)        | 100.0% (528)         | 100.0% (278)                      | 100.0% (2,616)       | 100.0% (1,810)        | 100.0% (528)         | 100.0% (278)                      |
| <b>Clinical Characteristics (% , n)</b> |                      |                       |                      |                                   |                      |                       |                      |                                   |
| BMI                                     | 100.0% (2,616)       | 100.0% (1,810)        | 100.0% (528)         | 100.0% (278)                      | 55.1% (1,441)        | 49.4% (895)           | 63.8% (337)          | 75.2% (209)                       |
| SBP                                     | 69.1% (1,808)        | 70.9% (1,284)         | 60.0% (317)          | 74.5% (207)                       | 31.2% (816)          | 27.8% (504)           | 27.8% (147)          | 59.4% (165)                       |
| DBP                                     | 69.1% (1,808)        | 70.9% (1,284)         | 60.0% (317)          | 74.5% (207)                       | 31.2% (816)          | 27.8% (504)           | 27.8% (147)          | 59.4% (165)                       |
| LDL-C                                   | 99.8% (2,610)        | 99.7% (1,805)         | 100.0% (528)         | 99.6% (277)                       | 94.8% (2,479)        | 94.5% (1,710)         | 94.7% (500)          | 96.8% (269)                       |
| TC/HDL-C Ratio                          | 100.0% (2,615)       | 99.9% (1,809)         | 100.0% (528)         | 100.0% (278)                      | 95.9% (2,509)        | 95.6% (1,731)         | 96.0% (507)          | 97.5% (271)                       |
| Triglyceride                            | 99.9% (2,614)        | 99.9% (1,808)         | 100.0% (528)         | 100.0% (278)                      | 95.8% (2,507)        | 95.5% (1,729)         | 96.0% (507)          | 97.5% (271)                       |
| HbA1c                                   | 100.0% (2,615)       | 99.9% (1,809)         | 100.0% (528)         | 100.0% (278)                      | 99.6% (2,605)        | 99.6% (1,803)         | 99.4% (525)          | 99.6% (277)                       |
| Serum creatinine                        | 100.0% (2,616)       | 100.0% (1,810)        | 100.0% (528)         | 100.0% (278)                      | 99.5% (2,603)        | 99.4% (1,800)         | 99.4% (525)          | 100.0% (278)                      |
| Charlson's Index <sup>†</sup>           | 100.0% (2,615)       | 99.9% (1,809)         | 100.0% (528)         | 100.0% (278)                      | 100.0% (2,615)       | 99.9% (1,809)         | 100.0% (528)         | 100.0% (278)                      |
| Duration of Diabetes                    | 99.9% (2,614)        | 99.9% (1,808)         | 100.0% (528)         | 100.0% (278)                      | 99.9% (2,614)        | 99.9% (1,808)         | 100.0% (528)         | 100.0% (278)                      |
| <b>Treatment morbidity, (%)</b>         |                      |                       |                      |                                   |                      |                       |                      |                                   |
| Use of Insulin                          | 100.0% (2,616)       | 100.0% (1,810)        | 100.0% (528)         | 100.0% (278)                      | 100.0% (2,616)       | 100.0% (1,810)        | 100.0% (528)         | 100.0% (278)                      |
| Use of Oral anti-diabetic drugs         | 100.0% (2,616)       | 100.0% (1,810)        | 100.0% (528)         | 100.0% (278)                      | 100.0% (2,616)       | 100.0% (1,810)        | 100.0% (528)         | 100.0% (278)                      |
| Use of anti-hypertensive drugs          | 100.0% (2,616)       | 100.0% (1,810)        | 100.0% (528)         | 100.0% (278)                      | 100.0% (2,616)       | 100.0% (1,810)        | 100.0% (528)         | 100.0% (278)                      |
| Use of lipid drug                       | 100.0% (2,616)       | 100.0% (1,810)        | 100.0% (528)         | 100.0% (278)                      | 100.0% (2,616)       | 100.0% (1,810)        | 100.0% (528)         | 100.0% (278)                      |

SGLT2i = Sodium Glucose Co-transporter-2 Inhibitors; GLP-1RA = Glucagon-like Peptide-1 Receptor Agonists; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; BMI = Body Mass Index; HbA1c = Hemoglobin A1c; eGFR = Estimated Glomerular Filtration Rate; Urine ACR = Urine Albumin to Creatinine Ratio

Notes:

<sup>†</sup> The calculation of Charlson Index does not include Acquired Immune Deficiency Syndrome (AIDS).

Supplemental Table 4. Baseline characteristics of patients initiating glucose-lowering medications of SGLT2i, GLP-1RA, or undergoing metabolic surgery before multiple imputation and inverse probability of treatment weighting for propensity scores

| Baseline characteristics                          | Total<br>(N =<br>2,616) | SGLT2i<br>(N =<br>1,810) | GLP-1RA<br>(N = 528) | Metabolic<br>Surgery<br>(N = 278) | Maximum<br>pairwise<br>ASMD |
|---|-------------------------|--------------------------|----------------------|-----------------------------------|-----------------------------|
| <b>Socio-Demographics</b>                         |                         |                          |                      |                                   |                             |
| Gender (%)  |                         |                          |                      |                                   | 0.13                        |
| Female  | 45.9%                   | 46.0%                    | 42.2%                | 52.2%                             |                             |
| Male  | 54.1%                   | 54.0%                    | 57.8%                | 47.8%                             |                             |
| Age (mean±SE), year                               | 53.4 (0.2)              | 55.1 (0.3)               | 51.3 (0.5)           | 46.0 (0.6)                        | 0.83                        |
| Age group, (%)                                    |                         |                          |                      |                                   | 0.20                        |
| ≤60   | 72.4%                   | 67.4%                    | 79.0%                | 92.8%                             |                             |
| >60   | 27.6%                   | 32.6%                    | 21.0%                | 7.2%                              |                             |
| <b>Clinical Characteristics</b>                   |                         |                          |                      |                                   |                             |
| Mean BMI (SE), kg/m <sup>2</sup>                  | 35.0 (0.1)              | 34.5 (0.1)               | 35.2 (0.2)           | 38.5 (0.3)                        | 0.94                        |
| Mean SBP (SE), mmHg                               | 137.0 (0.4)             | 137.8 (0.5)              | 135.3 (1.3)          | 134.6 (1.3)                       | 0.17                        |
| Mean DBP (SE), mmHg                               | 79.4 (0.3)              | 79.6 (0.3)               | 79.2 (0.5)           | 78.9 (0.7)                        | 0.05                        |
| Mean LDL-C (SE), mmol/L                           | 2.3 (0.0)               | 2.2 (0.0)                | 2.4 (0.0)            | 2.4 (0.0)                         | 0.28                        |
| Mean TC/HDL-C Ratio (SE)                          | 4.3 (0.0)               | 4.2 (0.0)                | 4.4 (0.0)            | 4.4 (0.1)                         | 0.23                        |
| Mean triglyceride (SE), mmol/L                    | 2.0 (0.0)               | 2.0 (0.0)                | 2.1 (0.1)            | 2.0 (0.1)                         | 0.07                        |
| Mean hemoglobin A1c (SE), %                       | 8.9 (0.0)               | 9.1 (0.0)                | 9.1 (0.1)            | 7.7 (0.1)                         | 0.89                        |
| Mean eGFR (SE), mL/min/1.73m <sup>2</sup>         | 110.2 (0.6)             | 108.1 (0.7)              | 112.8 (1.5)          | 118.6 (2.4)                       | 0.33                        |
| Chronic Kidney Disease (by eGFR)                  |                         |                          |                      |                                   | 0.63                        |
| Stage 1 (≥90 mL/min/1.73m <sup>2</sup> )          | 74.2%                   | 73.4%                    | 74.8%                | 78.8%                             |                             |
| Stage 2 - 5 (<90 mL/min/1.73m <sup>2</sup> )      | 25.8%                   | 26.6%                    | 25.2%                | 21.2%                             |                             |
| Mean urine ACR (SE), µg/mg                        | 26.9 (1.5)              | 24.6 (1.7)               | 31.7 (3.7)           | 32.9 (5.9)                        | 0.13                        |
| Mean Charlson Comorbidity Index (SE) <sup>†</sup> | 4.5 (0.0)               | 4.7 (0.1)                | 3.9 (0.1)            | 3.8 (0.1)                         | 0.43                        |
| Charlson Comorbidity Index <sup>†</sup> , (%)     |                         |                          |                      |                                   | 0.38                        |

|  |           |           |           |           |      |
|--|-----------|-----------|-----------|-----------|------|
| 1-2  | 20.7%     | 16.5%     | 28.6%     | 32.7%     |      |
| 3  | 17.1%     | 17.5%     | 17.8%     | 13.7%     |      |
| 4 or above   | 62.2%     | 66.0%     | 53.6%     | 53.6%     |      |
| Mean duration of Diabetes (SE), year                                 | 7.9 (0.1) | 8.5 (0.1) | 7.2 (0.1) | 5.4 (0.2) | 1.05 |
| Duration of Diabetes, year, (%)                                      |           |           |           |           | 0.54 |
| <5 years   | 20.1%     | 15.9%     | 22.2%     | 43.5%     |      |
| ≥ 5 years  | 79.9%     | 84.1%     | 77.8%     | 56.5%     |      |
| Mean duration of first new antidiabetic agent to baseline (SE), year | 7.8 (0.1) | 8.5 (0.1) | 6.9 (0.1) | 4.8 (0.2) | 1.27 |
| <b>Treatment morbidity (%)</b>                                       |           |           |           |           |      |
| Use of Insulin   | 71.1%     | 68.4%     | 85.0%     | 62.2%     | 0.15 |
| Use of anti-hypertensive drugs                                       | 94.1%     | 94.4%     | 94.9%     | 91.0%     | 0.28 |
| Use of lipid lowering agent  | 83.3%     | 84.7%     | 83.3%     | 73.4%     | 0.04 |
| <b>Disease status (%)</b>  |           |           |           |           |      |
| Cardiovascular Disease   | 25.2%     | 29.0%     | 18.2%     | 13.3%     | 0.76 |
| Severe hypoglycemia (1 year before baseline)                         | 7.8%      | 7.1%      | 10.6%     | 7.6%      | 0.39 |

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SGLT2i = Sodium Glucose Co-transporter-2 Inhibitors; GLP-1RA = Glucagon-like Peptide-1 Receptor Agonists; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; BMI = Body Mass Index; HbA1c = Hemoglobin A1c; eGFR = Estimated Glomerular Filtration Rate; CI = Confidence Interval; SE = Standard Error; ASMD = Absolute Standardized Mean Difference

Notes:

† The calculation of Charlson Index does not include Acquired Immune Deficiency Syndrome (AIDS).

Supplemental Table 5. Comparisons of clinical outcomes at baseline and 12-month follow-up

|                                  |                   | Baseline | Baseline (with 12-month data) | 12-month Follow-Up | Paired difference | P-value for difference = 0 |
|----------------------------------|-------------------|----------|-------------------------------|--------------------|-------------------|----------------------------|
| Mean BMI (SE), kg/m <sup>2</sup> | SGLT2i            | 35.087   | 35.210                        | 34.652             | -0.557*           | <0.001*                    |
|                                  | GLP-1RA           | 35.369   | 34.813                        | 34.418             | -0.395*           | <0.001*                    |
|                                  | Metabolic surgery | 35.751   | 37.331                        | 31.941             | -5.390*           | <0.001*                    |
|                                  | P-value           | 0.002*   | <0.001*                       | <0.001*            | <0.001*           |                            |
| Mean SBP (SE), mmHg              | SGLT2i            | 137.352  | 137.733                       | 137.140            | -0.593            | 0.415                      |
|                                  | GLP-1RA           | 136.271  | 137.660                       | 138.943            | 1.283*            | 0.025*                     |
|                                  | Metabolic surgery | 136.560  | 133.493                       | 131.286            | -2.207*           | <0.001*                    |
|                                  | P-value           | 0.929    | <0.001*                       | <0.001*            | <0.001*           |                            |
| Mean DBP (SE), mmHg              | SGLT2i            | 79.719   | 78.180                        | 78.681             | 0.502             | 0.224                      |
|                                  | GLP-1RA           | 79.597   | 78.694                        | 78.561             | -0.132            | 0.689                      |
|                                  | Metabolic surgery | 79.194   | 78.850                        | 77.694             | -1.157*           | 0.022*                     |
|                                  | P-value           | 0.957    | 0.580                         | 0.152              | <0.001*           |                            |
| Mean LDL-C (SE), mmol/L          | SGLT2i            | 2.305    | 2.303                         | 2.263              | -0.040*           | <0.001*                    |
|                                  | GLP-1RA           | 2.312    | 2.314                         | 2.245              | -0.069*           | <0.001*                    |
|                                  | Metabolic surgery | 2.418    | 2.434                         | 2.448              | 0.014             | 0.525                      |
|                                  | P-value           | <0.001*  | <0.001*                       | <0.001*            | <0.001*           |                            |
| Mean TC/HDL-C ratio (SE)         | SGLT2i            | 4.300    | 4.310                         | 4.235              | -0.075*           | <0.001*                    |
|                                  | GLP-1RA           | 4.313    | 4.317                         | 4.196              | -0.121*           | <0.001*                    |
|                                  | Metabolic surgery | 4.433    | 4.448                         | 4.243              | -0.204*           | <0.001*                    |
|                                  | P-value           | <0.001*  | <0.001*                       | 0.393              | <0.001*           |                            |
| Mean triglyceride (SE), mmol/L   | SGLT2i            | 2.080    | 2.074                         | 1.960              | -0.114*           | <0.001*                    |

|  |                   |         |         |         |          |         |
|--|-------------------|---------|---------|---------|----------|---------|
|  | GLP-1RA           | 2.080   | 2.079   | 1.991   | -0.088*  | <0.001* |
|  | Metabolic surgery | 2.126   | 2.047   | 1.406   | -0.642*  | <0.001* |
|  | P-value           | 0.535   | 0.791   | <0.001* | <0.001*  |         |
| Mean percentage of total weight loss (SE), % | SGLT2i            | 0.000   | 0.000   | -1.337  | -1.337*  | <0.001* |
|  | GLP-1RA           | 0.000   | 0.000   | -1.629  | -1.629*  | <0.001* |
|  | Metabolic surgery | 0.000   | 0.000   | -15.155 | -15.155* | <0.001* |
|  | P-value           | NA      | NA      | <0.001* | <0.001*  |         |
| Mean HbA1c (SE), %                           | SGLT2i            | 8.948   | 8.952   | 8.181   | -0.771*  | <0.001* |
|  | GLP-1RA           | 8.849   | 8.848   | 8.050   | -0.799*  | <0.001* |
|  | Metabolic surgery | 9.208   | 9.209   | 7.406   | -1.804*  | <0.001* |
|  | P-value           | <0.001* | <0.001* | <0.001* | <0.001*  |         |
| Mean eGFR (SE), mL/min/1.73m <sup>2</sup>    | SGLT2i            | 110.604 | 110.629 | 109.264 | -1.366*  | <0.001* |
|  | GLP-1RA           | 110.028 | 109.874 | 109.468 | -0.406   | 0.152   |
|  | Metabolic surgery | 114.483 | 114.483 | 117.566 | 3.083*   | <0.001* |
|  | P-value           | <0.001* | <0.001* | <0.001* | <0.001*  |         |

SGLT2i = Sodium Glucose Co-transporter-2 Inhibitors; GLP-1RA = Glucagon-like Peptide-1 Receptor Agonists; BMI = Body Mass Index; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; LDL-C = Low Density Lipoprotein - Cholesterol; TC = Total Cholesterol; HDL-C = High Density Lipoprotein - Cholesterol; HbA1c = Hemoglobin A1c; eGFR = Estimated Glomerular Filtration Rate

Notes:

\* Significant difference at 0.05 level

Supplemental Table 6. Diabetes remission

| <b>Groups</b>                    | <b>3 months</b> | <b>6 months</b> | <b>9 months</b> | <b>12 months</b> |
|----------------------------------|-----------------|-----------------|-----------------|------------------|
| <b>SGLT2i (N=1810)</b>           | 4 (0.22%)       | 32 (1.77%)      | 74 (4.09%)      | 42 (2.32%)       |
| <b>GLP1RA (N=528)</b>            | 0 (0.00%)       | 26 (4.92%)      | 22 (4.17%)      | 21 (3.98%)       |
| <b>Metabolic surgery (N=278)</b> | 13 (4.68%)      | 135 (48.56%)    | 78 (28.06%)     | 110 (39.57%)     |

SGLT2i = Sodium Glucose Co-transporter-2 Inhibitors; GLP-1RA = Glucagon-like Peptide-1 Receptor Agonists



Supplemental Table 7. The incidence of service uses of patients initiating medications of SGLT2i, GLP1-RA or metabolic surgery after multiple imputation and inverse probability of treatment weighting for propensity scores

| Frequency after baseline                 | SGLT2i |                |        |         |                        |                    |                                     |
|--|--------|----------------|--------|---------|------------------------|--------------------|-------------------------------------|
|  | Mean   | 95% CI         | Median | Range   | Total number of events | Total person-years | Event rate (cases/100 person-years) |
| <b>Hospitalization</b>                   |        |                |        |         |                        |                    |                                     |
| Admission                                | 0.833  | (0.743, 0.923) | 0      | 0 - 44  | 2189                   | 2781.96            | 78.67                               |
| Overnight Hospitalization, night         | 2.546  | (2.116, 2.975) | 0      | 0 - 208 | 6689                   | 2781.96            | 240.44                              |
| Accident and Emergency                   | 0.748  | (0.661, 0.835) | 0      | 0 - 42  | 1966                   | 2781.96            | 70.65                               |
| Outpatient clinic                        | 8.856  | (8.549, 9.163) | 7      | 0 - 85  | 23270                  | 2781.96            | 836.46                              |
| Specialist                               | 7.776  | (7.530, 8.023) | 6      | 0 - 78  | 20433                  | 2781.96            | 734.50                              |
| General                                  | 1.079  | (0.930, 1.229) | 0      | 0 - 63  | 2836                   | 2781.96            | 101.96                              |
| Allied health professionals              | 0.726  | (0.655, 0.797) | 0      | 0 - 16  | 1908                   | 2781.96            | 68.58                               |
| <b>Frequency after baseline - 1 year</b> |        |                |        |         |                        |                    |                                     |
| <b>Hospitalization</b>                   |        |                |        |         |                        |                    |                                     |
| Admission                                | 0.512  | (0.453, 0.570) | 0      | 0 - 15  | 1345                   | 1993.21            | 67.49                               |
| Overnight Hospitalization, night         | 1.943  | (1.606, 2.281) | 0      | 0 - 134 | 5106                   | 1993.21            | 256.18                              |
| Accident and Emergency                   | 0.546  | (0.472, 0.619) | 0      | 0 - 41  | 1434                   | 1993.21            | 71.95                               |
| Outpatient clinic                        | 6.111  | (5.927, 6.294) | 5      | 0 - 61  | 16056                  | 1993.21            | 805.55                              |
| Specialist                               | 5.375  | (5.232, 5.518) | 4      | 0 - 54  | 14124                  | 1993.21            | 708.59                              |
| General                                  | 0.735  | (0.633, 0.838) | 0      | 0 - 54  | 1933                   | 1993.21            | 96.96                               |
| Allied health professionals              | 0.508  | (0.456, 0.560) | 0      | 0 - 12  | 1335                   | 1993.21            | 66.97                               |

| Frequency after baseline          | GLP1-RA |                  |        |           |                        |                    |                                     |
|-----------------------------------|---------|------------------|--------|-----------|------------------------|--------------------|-------------------------------------|
|                                   | Mean    | 95% CI           | Median | Range     | Total number of events | Total person-years | Event rate (cases/100 person-years) |
| Hospitalization                   |         |                  |        |           |                        |                    |                                     |
| Admission                         | 1.753   | (1.609, 1.898)   | 0      | 0 - 32    | 4553                   | 5239.48            | 86.90                               |
| Overnight Hospitalization, night  | 7.718   | (5.350, 10.087)  | 0      | 0 - 1,233 | 20043                  | 5239.48            | 382.53                              |
| Accident and Emergency            | 1.289   | (1.182, 1.397)   | 0      | 0 - 28    | 3348                   | 5239.48            | 63.90                               |
| Outpatient clinic                 | 19.280  | (18.465, 20.096) | 13     | 0 - 231   | 50067                  | 5239.48            | 955.57                              |
| Specialist                        | 16.421  | (15.791, 17.051) | 12     | 0 - 119   | 42641                  | 5239.48            | 813.84                              |
| General                           | 2.860   | (2.451, 3.268)   | 0      | 0 - 172   | 7426                   | 5239.48            | 141.73                              |
| Allied health professionals       | 1.675   | (1.523, 1.827)   | 0      | 0 - 40    | 4349                   | 5239.48            | 83.01                               |
| Frequency after baseline - 1 year |         |                  |        |           |                        |                    |                                     |
| Hospitalization                   |         |                  |        |           |                        |                    |                                     |
| Admission                         | 0.408   | (0.362, 0.454)   | 0      | 0 - 12    | 1059                   | 2104.52            | 50.34                               |
| Overnight Hospitalization, night  | 1.835   | (1.344, 2.325)   | 0      | 0 - 240   | 4764                   | 2104.52            | 226.36                              |
| Accident and Emergency            | 0.488   | (0.433, 0.543)   | 0      | 0 - 26    | 1268                   | 2104.52            | 60.24                               |
| Outpatient clinic                 | 7.232   | (7.025, 7.440)   | 6      | 0 - 52    | 18781                  | 2104.52            | 892.41                              |
| Specialist                        | 6.274   | (6.128, 6.419)   | 5      | 0 - 26    | 16292                  | 2104.52            | 774.13                              |
| General                           | 0.959   | (0.827, 1.090)   | 0      | 0 - 41    | 2489                   | 2104.52            | 118.27                              |
| Allied health professionals       | 0.597   | (0.537, 0.656)   | 0      | 0 - 12    | 1549                   | 2104.52            | 73.61                               |

| Metabolic surgery                        |        |                  |        |         |                        |                    |                                     |
|--|--------|------------------|--------|---------|------------------------|--------------------|-------------------------------------|
| Frequency after baseline                 | Mean   | 95% CI           | Median | Range   | Total number of events | Total person-years | Event rate (cases/100 person-years) |
| <b>Hospitalization</b>                   |        |                  |        |         |                        |                    |                                     |
| Admission                                | 6.533  | (5.922, 7.144)   | 5      | 0 - 50  | 15483                  | 7489.53            | 206.73                              |
| Overnight Hospitalization, night         | 19.236 | (17.157, 21.315) | 10     | 0 - 352 | 45592                  | 7489.53            | 608.74                              |
| Accident and Emergency                   | 1.816  | (1.688, 1.945)   | 1      | 0 - 31  | 4305                   | 7489.53            | 57.48                               |
| Outpatient clinic                        | 31.610 | (30.503, 32.717) | 29     | 0 - 260 | 74919                  | 7489.53            | 1000.32                             |
| Specialist                               | 27.813 | (26.869, 28.758) | 25     | 0 - 144 | 65921                  | 7489.53            | 880.18                              |
| General                                  | 3.796  | (3.321, 4.272)   | 1      | 0 - 147 | 8998                   | 7489.53            | 120.14                              |
| Allied health professionals              | 5.505  | (5.215, 5.794)   | 4      | 0 - 44  | 13047                  | 7489.53            | 174.20                              |
| <b>Frequency after baseline - 1 year</b> |        |                  |        |         |                        |                    |                                     |
| Frequency after baseline - 1 year        | Mean   | 95% CI           | Median | Range   | Total number of events | Total person-years | Event rate (cases/100 person-years) |
| <b>Hospitalization</b>                   |        |                  |        |         |                        |                    |                                     |
| Admission                                | 3.084  | (2.859, 3.310)   | 3      | 0 - 13  | 7310                   | 2143.62            | 341.03                              |
| Overnight Hospitalization, night         | 14.619 | (13.373, 15.864) | 7      | 0 - 180 | 34648                  | 2143.62            | 1616.32                             |
| Accident and Emergency                   | 0.454  | (0.409, 0.499)   | 0      | 0 - 7   | 1077                   | 2143.62            | 50.23                               |
| Outpatient clinic                        | 10.562 | (9.890, 11.234)  | 10     | 0 - 28  | 25034                  | 2143.62            | 1167.83                             |
| Specialist                               | 9.561  | (8.845, 10.277)  | 9      | 0 - 27  | 22661                  | 2143.62            | 1057.14                             |
| General                                  | 1.001  | (0.923, 1.079)   | 0      | 0 - 10  | 2373                   | 2143.62            | 110.69                              |
| Allied health professionals              | 3.002  | (2.895, 3.108)   | 3      | 0 - 12  | 7114                   | 2143.62            | 331.87                              |

SGLT2i = Sodium Glucose Co-transporter-2 Inhibitors; GLP-1RA = Glucagon-like Peptide-1 Receptor Agonists; CI = Confidence Interval

Supplemental Table 8. Negative binomial regressions of patients initiating SGLT2i or GLP1-RA compared to that of metabolic surgery on the service uses adjusted for baseline characteristics after multiple imputation and inverse probability of treatment weighting for propensity scores

|                                  | SGLT2i (vs Metabolic surgery) |                |         | GLP1-RA (vs Metabolic surgery) |                |         | SGLT2i (vs GLP1A) |                |         |
|----------------------------------|-------------------------------|----------------|---------|--------------------------------|----------------|---------|-------------------|----------------|---------|
|                                  | IRR                           | 95% CI         | P-value | IRR                            | 95% CI         | P-value | IRR               | 95% CI         | P-value |
| Hospitalization                  |                               |                |         |                                |                |         |                   |                |         |
| Admission                        | 0.322                         | (0.293, 0.353) | <0.001* | 0.376                          | (0.342, 0.414) | <0.001* | 0.855             | (0.783, 0.934) | <0.001* |
| Overnight Hospitalization, night | 0.213                         | (0.187, 0.242) | <0.001* | 0.259                          | (0.226, 0.298) | <0.001* | 0.820             | (0.724, 0.930) | 0.002*  |
| Accident and Emergency           | 1.226                         | (1.060, 1.417) | 0.009*  | 1.130                          | (0.977, 1.307) | 0.094   | 1.085             | (0.985, 1.195) | 0.098   |
| Outpatient clinic                | 0.719                         | (0.618, 0.837) | 0.002*  | 0.937                          | (0.805, 1.091) | 0.326   | 0.767             | (0.736, 0.800) | <0.001* |
| Specialist                       | 0.688                         | (0.579, 0.819) | 0.003*  | 0.897                          | (0.754, 1.067) | 0.168   | 0.767             | (0.735, 0.801) | <0.001* |
| General                          | 1.066                         | (0.924, 1.230) | 0.383   | 1.367                          | (1.189, 1.572) | <0.001* | 0.780             | (0.682, 0.891) | <0.001* |
| Allied health professionals      | 0.294                         | (0.257, 0.336) | <0.001* | 0.409                          | (0.354, 0.473) | <0.001* | 0.719             | (0.646, 0.799) | <0.001* |

SGLT2i = Sodium Glucose Co-transporter-2 Inhibitors; GLP-1RA = Glucagon-like Peptide-1 Receptor Agonists; IRR = Incidence Rate Ratio; CI = Confidence Interval

Notes:

\* Significant at 0.05 level by multivariable negative binomial regression

Supplemental Table 9 Subgroup analysis

a) Patients with sleeve gastrectomy

| Clinical parameter                           | Baseline      | Baseline (with 12-month data) | 12-month Follow-Up | Paired difference | P-value |
|--|---------------|-------------------------------|--------------------|-------------------|---------|
| Mean BMI (SE), kg/m <sup>2</sup>             | 35.59 (0.15)  | 37.32 (0.15)                  | 31.86 (0.16)       | -5.46 (0.09)      | <0.001* |
| Mean SBP (SE), mmHg                          | 136.72 (3.78) | 133.17 (0.66)                 | 131.57 (0.61)      | -1.61 (0.59)      | 0.014*  |
| Mean DBP (SE), mmHg                          | 78.74 (2.73)  | 78.76 (0.57)                  | 77.71 (0.39)       | -1.05 (0.51)      | 0.081   |
| Mean LDL-C (SE), mmol/L                      | 2.39 (0.03)   | 2.41 (0.03)                   | 2.47 (0.04)        | 0.06 (0.02)       | 0.010*  |
| Mean TC/HDL-C ratio (SE)                     | 4.42 (0.03)   | 4.42 (0.03)                   | 4.30 (0.04)        | -0.13 (0.03)      | <0.001* |
| Mean triglyceride (SE), mmol/L               | 2.14 (0.04)   | 2.04 (0.05)                   | 1.44 (0.02)        | -0.60 (0.04)      | <0.001* |
| Mean percentage of total weight loss (SE), % | 0.00 (0.00)   | 0.00 (0.00)                   | -15.56 (0.22)      | -15.56 (0.22)     | <0.001* |
| Mean HbA1c (SE), %                           | 9.22 (0.06)   | 9.23 (0.06)                   | 7.47 (0.07)        | -1.76 (0.05)      | <0.001* |
| Mean eGFR (SE), mL/min/1.73m <sup>2</sup>    | 110.14 (0.98) | 110.14 (0.98)                 | 113.94 (0.83)      | 3.80 (0.77)       | <0.001* |

| Cost items                                   | Mean cost (SE), US\$       |
|--|----------------------------|
|  | Sleeve gastrectomy (N=239) |
| <b>Healthcare services</b>                   | 29120.20 (682.92)          |
| <b>Hospitalization</b>                       | 12208.25 (682.67)          |
| General wards                                | 7653.21 (280.65)           |
| Intensive care units                         | 3579.96 (351.24)           |
| Coronary care units                          | 0.00 (0.00)                |
| High dependency units                        | 975.08 (210.83)            |
| <b>Accident and Emergency</b>                | 71.88 (3.32)               |
| <b>General outpatient clinic services</b>    | 52.47 (2.29)               |
| <b>Specialist outpatient clinic services</b> | 1469.59 (30.94)            |
| <b>Allied health professional services</b>   | 223.35 (3.89)              |
| <b>Drug</b>                                  | 3338.33 (82.57)            |
| <b>Total direct medical costs</b>            | 32458.62 (685.25)          |

SGLT2i = Sodium Glucose Co-transporter-2 Inhibitors; GLP-1RA = Glucagon-like Peptide-1 Receptor Agonists; BMI = Body Mass Index; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; LDL-C = Low Density Lipoprotein - Cholesterol; TC = Total Cholesterol; HDL-C = High Density Lipoprotein - Cholesterol; HbA1c = Hemoglobin A1c; eGFR = Estimated Glomerular Filtration Rate

Notes: \* Significant difference at 0.05 level

## b) Patients with insulin at baseline

| Baseline characteristics                          | Total<br>(N = 1859) | SGLIT2i<br>(N=1237) | GLP1RA<br>(N=449) | Metabolic<br>surgery<br>(N=173) | Maximum<br>pairwise<br>ASMD |
|---|---------------------|---------------------|-------------------|---------------------------------|-----------------------------|
| <b>Socio-Demographics</b>                         |                     |                     |                   |                                 |                             |
| Gender (%)  |                     |                     |                   |                                 | 0.06                        |
| Female  | 46.5%               | 48.1%               | 46.2%             | 45.1%                           |                             |
| Male  | 53.5%               | 51.9%               | 53.8%             | 54.9%                           |                             |
| Mean Age (SE), year                               | 52.3 (0.2)          | 53.8 (0.3)          | 54 (0.2)          | 49.2 (0.4)                      | 0.44*                       |
| Age group, (%)                                    |                     |                     |                   |                                 | 0.10                        |
| ≤60   | 75.0%               | 72.0%               | 73.0%             | 76.8%                           |                             |
| >60   | 25.0%               | 28.0%               | 27.0%             | 23.2%                           |                             |
| <b>Clinical Characteristics</b>                   |                     |                     |                   |                                 |                             |
| Mean SBP (SE), mmHg                               | 137 (1.5)           | 137.5 (0.5)         | 136.1 (1.1)       | 137.3 (4)                       | 0.08                        |
| Mean DBP (SE), mmHg                               | 78.9 (1)            | 79.1 (0.3)          | 78.7 (0.5)        | 79.1 (2.7)                      | 0.03                        |
| Mean BMI (SE), kg/m <sup>2</sup>                  | 34.9 (0.1)          | 34.9 (0.1)          | 34.8 (0.1)        | 35.1 (0.2)                      | 0.07                        |
| Mean LDL-C (SE), mmol/L                           | 2.3 (0)             | 2.3 (0)             | 2.3 (0)           | 2.4 (0)                         | 0.16                        |
| Mean TC/HDL-C Ratio                               | 4.4 (0)             | 4.3 (0)             | 4.3 (0)           | 4.5 (0)                         | 0.20                        |
| Mean triglyceride (SE), mmol/L                    | 2.2 (0)             | 2.1 (0)             | 2.2 (0)           | 2.2 (0)                         | 0.06                        |
| Mean hemoglobin A1c (SE), %                       | 9.3 (0)             | 9.1 (0)             | 9.3 (0)           | 9.6 (0.1)                       | 0.20                        |
| Mean eGFR (SE), mL/min/1.73m <sup>2</sup>         | 108.3 (0.6)         | 108.7 (0.7)         | 104.8 (0.8)       | 111.3 (1.4)                     | 0.27*                       |
| Chronic Kidney Disease (by eGFR)                  |                     |                     |                   |                                 | 0.22*                       |
| Stage 1 (≥90 mL/min/1.73m <sup>2</sup> )          | 68.0%               | 73.9%               | 66.2%             | 63.9%                           |                             |
| Stage 2 - 5 (<90 mL/min/1.73m <sup>2</sup> )      | 32.0%               | 26.1%               | 33.8%             | 36.1%                           |                             |
| Mean Charlson Comorbidity Index (SE) <sup>†</sup> | 4.5 (0)             | 4.6 (0.1)           | 4.6 (0.1)         | 4.4 (0.1)                       | 0.07                        |
| Charlson Comorbidity Index <sup>†</sup> , (%)     |                     |                     |                   |                                 | 0.14                        |
| 1-2   | 20.3%               | 18.3%               | 18.6%             | 24.0%                           |                             |
| 3   | 16.1%               | 17.7%               | 15.5%             | 15.3%                           |                             |
| 4 or above  | 63.5%               | 64.1%               | 65.9%             | 60.7%                           |                             |
| Mean duration of Diabetes (SE), year              | 8 (0)               | 8.3 (0.1)           | 8.1 (0.1)         | 7.7 (0.1)                       | 0.22*                       |
| Duration of Diabetes, year, (%)                   |                     |                     |                   |                                 | 0.15                        |
| <5 years  | 16.2%               | 18.9%               | 13.4%             | 16.3%                           |                             |
| ≥ 5 years   | 83.8%               | 81.1%               | 86.6%             | 83.7%                           |                             |
| <b>Treatment morbidity (%)</b>                    |                     |                     |                   |                                 |                             |
| Use of Insulin                                    | 100.0%              | 100.0%              | 100.0%            | 100.0%                          | NA                          |
| Use of anti-hypertensive drugs                    | 95.2%               | 95.0%               | 94.9%             | 95.7%                           | 0.04                        |
| Use of lipid lowering agent                       | 85.6%               | 84.4%               | 86.0%             | 86.4%                           | 0.06                        |
| <b>Disease status (%)</b>                         |                     |                     |                   |                                 |                             |
| Cardiovascular Disease                            | 29.6%               | 26.0%               | 26.0%             | 36.7%                           | 0.23*                       |
| Severe hypoglycemia (1 year before baseline)      | 10.4%               | 8.2%                | 10.1%             | 12.9%                           | 0.16                        |

Notes:

\* A standardized mean difference (SMD) less than 0.2 indicated optimal balance.

† The calculation of Charlson Index does not include Acquired Immune Deficiency Syndrome (AIDS).

|                                  |                   | Baseline      | Baseline (with 12-month data) | 12-month Follow-Up | Paired difference | P-value for difference = 0 |
|----------------------------------|-------------------|---------------|-------------------------------|--------------------|-------------------|----------------------------|
| Mean BMI (SE), kg/m <sup>2</sup> | SGLT2i            | 34.88 (0.11)  | 34.62 (0.22)                  | 34.16 (0.22)       | -0.46 (0.11)      | <0.001*                    |
|                                  | GLP-1RA           | 34.77 (0.10)  | 34.90 (0.21)                  | 34.79 (0.22)       | -0.10 (0.10)      | 0.313                      |
|                                  | Metabolic surgery | 35.10 (0.16)  | 36.94 (0.17)                  | 31.81 (0.18)       | -5.12 (0.09)      | <0.001*                    |
|                                  | P-value           | 0.210         | <0.001*                       | <0.001*            | <0.001*           |                            |
| Mean SBP (SE), mmHg              | SGLT2i            | 137.53 (0.54) | 138.17 (1.00)                 | 137.58 (0.93)      | -0.59 (0.87)      | 0.502                      |
|                                  | GLP-1RA           | 136.09 (1.13) | 136.63 (0.78)                 | 138.50 (0.80)      | 1.87 (0.79)       | 0.020*                     |
|                                  | Metabolic surgery | 137.28 (4.03) | 132.45 (0.55)                 | 131.90 (0.62)      | -0.54 (0.47)      | 0.252                      |
|                                  | P-value           | 0.906         | <0.001*                       | <0.001*            | 0.033             |                            |
| Mean DBP (SE), mmHg              | SGLT2i            | 79.06 (0.29)  | 77.61 (0.58)                  | 78.15 (0.56)       | 0.55 (0.42)       | 0.256                      |
|                                  | GLP-1RA           | 78.66 (0.49)  | 77.47 (0.50)                  | 77.31 (0.52)       | -0.16 (0.46)      | 0.726                      |
|                                  | Metabolic surgery | 79.08 (2.76)  | 78.35 (0.45)                  | 78.04 (0.36)       | -0.31 (0.33)      | 0.364                      |
|                                  | P-value           | 0.977         | 0.408                         | 0.425              | 0.339             |                            |
| Mean LDL-C (SE), mmol/L          | SGLT2i            | 2.28 (0.02)   | 2.29 (0.02)                   | 2.25 (0.02)        | -0.04 (0.01)      | 0.003*                     |
|                                  | GLP-1RA           | 2.27 (0.02)   | 2.27 (0.02)                   | 2.19 (0.02)        | -0.08 (0.01)      | <0.001*                    |
|                                  | Metabolic surgery | 2.44 (0.03)   | 2.46 (0.03)                   | 2.41 (0.04)        | -0.05 (0.03)      | 0.057                      |
|                                  | P-value           | <0.001*       | <0.001*                       | <0.001*            | 0.234             |                            |
| Mean TC/HDL-C ratio (SE)         | SGLT2i            | 4.30 (0.03)   | 4.31 (0.03)                   | 4.26 (0.03)        | -0.06 (0.02)      | <0.001*                    |
|                                  | GLP-1RA           | 4.31 (0.02)   | 4.32 (0.02)                   | 4.16 (0.02)        | -0.16 (0.02)      | <0.001*                    |
|                                  | Metabolic surgery | 4.49 (0.03)   | 4.51 (0.03)                   | 4.22 (0.04)        | -0.28 (0.03)      | <0.001*                    |
|                                  | P-value           | <0.001*       | <0.001*                       | 0.128              | <0.001*           |                            |
| Mean triglyceride (SE), mmol/L   | SGLT2i            | 2.10 (0.03)   | 2.09 (0.04)                   | 1.99 (0.03)        | -0.10 (0.03)      | <0.001*                    |
|                                  | GLP-1RA           | 2.19 (0.04)   | 2.20 (0.04)                   | 2.05 (0.03)        | -0.15 (0.03)      | <0.001*                    |
|                                  | Metabolic surgery | 2.20 (0.05)   | 2.09 (0.05)                   | 1.43 (0.02)        | -0.67 (0.04)      | <0.001*                    |
|                                  | P-value           | 0.161         | 0.121                         | <0.001*            | <0.001*           |                            |

|  |                   |             |             |               |               |         |
|--|-------------------|-------------|-------------|---------------|---------------|---------|
| Mean percentage of total weight loss (SE), % | SGLT2i            | 0.00 (0.00) | 0.00 (0.00) | -0.78 (0.26)  | -0.78 (0.26)  | 0.003*  |
|  | GLP-1RA           | 0.00 (0.00) | 0.00 (0.00) | -0.95 (0.23)  | -0.95 (0.23)  | <0.001* |
|  | Metabolic surgery | 0.00 (0.00) | 0.00 (0.00) | -14.73 (0.24) | -14.73 (0.24) | <0.001* |
|  | P-value           | NA          | NA          | <0.001*       | <0.001*       |         |

|                    |                   |             |             |             |              |         |
|--------------------|-------------------|-------------|-------------|-------------|--------------|---------|
| Mean HbA1c (SE), % | SGLT2i            | 9.14 (0.04) | 9.14 (0.04) | 8.36 (0.04) | -0.78 (0.03) | <0.001* |
|                    | GLP-1RA           | 9.27 (0.04) | 9.27 (0.04) | 8.41 (0.04) | -0.87 (0.03) | <0.001* |
|                    | Metabolic surgery | 9.58 (0.06) | 9.58 (0.06) | 7.68 (0.07) | -1.90 (0.06) | <0.001* |
|                    | P-value           | <0.001*     | <0.001*     | <0.001*     | <0.001*      |         |

|   |                   |               |               |               |              |         |
|---|-------------------|---------------|---------------|---------------|--------------|---------|
| Mean eGFR (SE), mL/min/1.73m <sup>2</sup> | SGLT2i            | 108.69 (0.71) | 108.76 (0.71) | 107.67 (0.73) | -1.09 (0.37) | 0.003*  |
|   | GLP-1RA           | 104.78 (0.81) | 104.75 (0.81) | 104.25 (0.81) | -0.49 (0.34) | 0.144   |
|   | Metabolic surgery | 111.28 (1.36) | 111.28 (1.36) | 115.81 (0.96) | 4.53 (0.88)  | <0.001* |
|   | P-value           | <0.001*       | <0.001*       | <0.001*       | <0.001*      |         |

| Cost items                                   | Mean cost (SE), US\$ |                   |                           |
|--|----------------------|-------------------|---------------------------|
|  | SGLT2i (N=1237)      | GLP1RA (N=449)    | Metabolic surgery (N=173) |
| <b>Healthcare services</b>                   | 2823.76 (175.78)     | 2886.40 (247.04)  |                           |
| <b>Hospitalization</b>                       | 1770.38 (151.99)     | 1726.97 (241.72)  | 13872.67 (778.41)         |
| General wards                                | 121.78 (31.40)       | 1565.68 (227.16)  | 8999.85 (400.60)          |
| Intensive care units                         | 45.44 (19.61)        | 63.48 (14.77)     | 3966.63 (354.84)          |
| Coronary care units                          | 0.00 (0.00)          | 95.69 (54.46)     | 0.00 (0.00)               |
| High dependency units                        | 3.50 (1.81)          | 2.12 (1.43)       | 906.20 (211.81)           |
| <b>Accident and Emergency</b>                | 103.11 (8.13)        | 80.12 (5.95)      | 74.09 (3.68)              |
| <b>General outpatient clinic services</b>    | 43.41 (3.87)         | 55.37 (4.42)      | 52.39 (2.57)              |
| <b>Specialist outpatient clinic services</b> | 865.79 (14.02)       | 973.90 (13.94)    | 1519.09 (31.40)           |
| <b>Allied health professional services</b>   | 41.07 (2.45)         | 50.04 (2.82)      | 198.19 (3.91)             |
| <b>Drug</b>                                  | 9775.46 (94.77)      | 9603.07 (94.92)   | 4180.09 (81.72)           |
| <b>Total direct medical costs</b>            | 12599.22 (203.89)    | 12489.48 (268.60) | 35301.60 (793.12)         |

SGLT2i = Sodium Glucose Co-transporter-2 Inhibitors; GLP-1RA = Glucagon-like Peptide-1 Receptor Agonists; BMI = Body Mass Index; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; LDL-C = Low Density Lipoprotein - Cholesterol; TC = Total Cholesterol; HDL-C = High Density Lipoprotein - Cholesterol; HbA1c = Hemoglobin A1c; eGFR = Estimated Glomerular Filtration Rate

Notes: \* Significant difference at 0.05 level



c) Patients with exenatide or liraglutide

|  |             | Baseline      | Baseline (with 12-month data) | 12-month Follow-Up | Paired difference | P-value for difference = 0 |
|--|-------------|---------------|-------------------------------|--------------------|-------------------|----------------------------|
| Mean BMI (SE), kg/m <sup>2</sup>             | Exenatide   | 35.92 (0.21)  | 36.19 (0.41)                  | 35.57 (0.42)       | -0.62 (0.16)      | <0.001*                    |
|  | Liraglutide | 35.25 (0.13)  | 34.48 (0.16)                  | 34.15 (0.19)       | -0.33 (0.10)      | 0.001*                     |
|  | P-value     | 0.005*        | <0.001*                       | <0.001*            | 0.142             |                            |
| Mean SBP (SE), mmHg                          | Exenatide   | 135.48 (1.09) | 137.12 (1.06)                 | 138.98 (1.28)      | 1.87 (1.19)       | 0.118                      |
|  | Liraglutide | 136.68 (1.83) | 137.96 (0.89)                 | 138.88 (0.85)      | 0.92 (0.69)       | 0.187                      |
|  | P-value     | 0.606         | 0.575                         | 0.949              | 0.454             |                            |
| Mean DBP (SE), mmHg                          | Exenatide   | 78.17 (0.48)  | 76.64 (0.76)                  | 77.01 (0.81)       | 0.37 (0.62)       | 0.556                      |
|  | Liraglutide | 80.00 (0.61)  | 79.57 (0.5)                   | 79.13 (0.52)       | -0.45 (0.42)      | 0.293                      |
|  | P-value     | 0.015*        | 0.001*                        | 0.029*             | 0.276             |                            |
| Mean LDL-C (SE), mmol/L                      | Exenatide   | 2.45 (0.03)   | 2.44 (0.04)                   | 2.32 (0.04)        | -0.12 (0.02)      | <0.001*                    |
|  | Liraglutide | 2.25 (0.02)   | 2.25 (0.02)                   | 2.21 (0.02)        | -0.04 (0.01)      | 0.002*                     |
|  | P-value     | <0.001*       | <0.001*                       | 0.003*             | 0.005*            |                            |
| Mean TC/HDL-C ratio (SE)                     | Exenatide   | 4.54 (0.04)   | 4.54 (0.04)                   | 4.29 (0.04)        | -0.24 (0.03)      | <0.001*                    |
|  | Liraglutide | 4.21 (0.02)   | 4.21 (0.02)                   | 4.14 (0.02)        | -0.07 (0.02)      | <0.001*                    |
|  | P-value     | <0.001*       | <0.001*                       | <0.001*            | <0.001*           |                            |
| Mean triglyceride (SE), mmol/L               | Exenatide   | 2.34 (0.06)   | 2.35 (0.07)                   | 2.05 (0.04)        | -0.31 (0.05)      | <0.001*                    |
|  | Liraglutide | 1.97 (0.03)   | 1.97 (0.03)                   | 1.95 (0.03)        | -0.02 (0.03)      | 0.444                      |
|  | P-value     | <0.001        | <0.001*                       | 0.085              | <0.001*           |                            |
| Mean percentage of total weight loss (SE), % | Exenatide   | 0.00 (0.00)   | 0.00 (0.00)                   | -1.98 (0.46)       | -1.98 (0.46)      | <0.001*                    |
|  | Liraglutide | 0.00 (0.00)   | 0.00 (0.00)                   | -1.51 (0.23)       | -1.51 (0.23)      | <0.001*                    |
|  | P-value     | NA            | NA                            | 0.349              | 0.349             |                            |
| Mean HbA1c (SE), %                           | Exenatide   | 8.97 (0.06)   | 8.97 (0.06)                   | 8.13 (0.06)        | -0.85 (0.06)      | <0.001*                    |
|  | Liraglutide | 8.77 (0.04)   | 8.77 (0.04)                   | 7.94 (0.04)        | -0.83 (0.03)      | <0.001*                    |

|   |             |               |               |               |              |        |
|---|-------------|---------------|---------------|---------------|--------------|--------|
|   | P-value     | 0.008*        | 0.006*        | 0.007*        | 0.797        |        |
| Mean eGFR (SE), mL/min/1.73m <sup>2</sup> | Exenatide   | 107.62 (1.29) | 107.56 (1.29) | 108.86 (1.38) | 1.29 (0.52)  | 0.013* |
|   | Liraglutide | 109.83 (0.88) | 109.6 (0.88)  | 108.67 (0.87) | -0.94 (0.37) | 0.010* |
|   | P-value     | 0.164         | 0.200         | 0.905         | <0.001*      |        |

| Cost items                                   | Mean costs (SE), US\$ |                     |
|--|-----------------------|---------------------|
|  | Exenatide (N=175)     | Liraglutide (N=322) |
| <b>Healthcare services</b>                   | 2610.37 (154.38)      | 2504.18 (265.42)    |
| <b>Hospitalization</b>                       | 1339.22 (137.23)      | 1395.87 (260.66)    |
| General wards                                | 1205.79 (128.25)      | 1248.63 (244.82)    |
| Intensive care units                         | 45.13 (14.05)         | 41.8 (14.56)        |
| Coronary care units                          | 82.83 (27.42)         | 105.44 (60)         |
| High dependency units                        | 5.46 (3.69)           | 0 (0)               |
| <b>Accident and Emergency</b>                | 118.89 (13.33)        | 63.49 (3.75)        |
| <b>General outpatient clinic services</b>    | 83.93 (10.24)         | 46.37 (4.1)         |
| <b>Specialist outpatient clinic services</b> | 1009.11 (21.65)       | 961.11 (14.37)      |
| <b>Allied health professional services</b>   | 59.24 (4.3)           | 37.34 (2.65)        |
| <b>Drug</b>                                  | 8470.2 (175.12)       | 7950.61 (98.35)     |
| <b>Total direct medical costs</b>            | 11080.58 (236.63)     | 10454.79 (292.13)   |

SGLT2i = Sodium Glucose Co-transporter-2 Inhibitors; GLP-1RA = Glucagon-like Peptide-1 Receptor Agonists; BMI = Body Mass Index; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; LDL-C = Low Density Lipoprotein - Cholesterol; TC = Total Cholesterol; HDL-C = High Density Lipoprotein - Cholesterol; HbA1c = Hemoglobin A1c; eGFR = Estimated Glomerular Filtration Rate

Notes: \* Significant difference at 0.05 level