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

Authors: Tingting Wu[a*], Carlos KH Wong[a,b,c*], Eric HM Tang[a], Kenneth KC Man[b,d], Simon KH Wong[e,f], Ivan Chi Ho Au[b], Emily TY Tse[a,g], Esther WY Chan[b,c], Eleanor Grieve[i], Olivia Wu[i], Enders KW Ng[e,h], Ian CK Wong[b,c,d]

a. Department of Family Medicine and Primary Care, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China

b. Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China

c. Laboratory of Data Discovery for Health Limited ($D^2$4H), Hong Kong Science Park, New Territories, Hong Kong SAR, China

d. Research Department of Policy and Practice, University College London School of Pharmacy, London, UK

e. Division of Surgery, Chinese University of Hong Kong Medical Centre, Hong Kong SAR, China

f. Department of Surgery, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, China

g. Department of Family Medicine and Primary Care, The University of Hong Kong-Shenzhen Hospital, Shenzhen, China

h. Department of Surgery, Prince of Wales Hospital, Hong Kong SAR, China

i. Health Economics and Health Technology Assessment, Institute of Health & Well-being, University of Glasgow, UK

* contributed equally as first author

Short title: Compare metabolic surgery, SGLT2i, and GLP1RA

Corresponding Author: Carlos KH Wong, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China. Address: Rm 1-01, 1/F, Jockey Club Building for Interdisciplinary Research, 5 Sassoon Road, Pokfulam, Hong Kong. Tel: (+852) 2831-5055 Fax: (+852) 2814-7475 Email: carlosho@hku.hk

Funding

This study was funded by the Health and Medical Research Fund Research Fellowship Scheme, Food and Health Bureau, Hong Kong SAR (Ref No. #02160087). Dr. Carlos K.H. Wong is the grantor. The funder did not have any role in design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Word count: 2757

Highlights

1. Beneficial weight loss and metabolic outcomes at 12-month were observed in metabolic surgery, GLP-1RA, and SGLT2i groups.
2. 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.
3. 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^2, 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^2, 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 [1-5]. Several well-designed placebo-controlled randomized trials have demonstrated that patients on SGLT2i and GLP-1RA had significant and sustainable improvement in glucose levels [1, 3]. 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 [6]. In addition, both SGLT2i and GLP1-RA had robust and consistent reno- and cardio- protective effects [3-5, 7-9].

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 [10]. Despite increased expenditures [11, 12], higher risks of suicide and non-fatal self-harm (even though the absolute risks were low) [13], and re-operations due to complications or weight regain [14], the effects of metabolic surgery on weight reduction, diabetes remission, and renal protection have been widely confirmed [15-17]. 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 [18-21].

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[22], the effectiveness and costs among metabolic surgery, SGLT2i and GLP-1RA in patients with obesity and type 2 diabetes has rarely been compared [23]. 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[24-26]. 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]≥30kg/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^2, 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[27]. Costs of new antidiabetic agents were estimated

from the reference price list by drug classes[28]. 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 [29].

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)[30] was performed to address missing data. The missing values at the baseline were imputed by random chained equation using other known baseline covariates [31] for five iterations [32] 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 [30].

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 [33]. 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 t3 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 and12-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 (-5.39kg/m^2, -0.56kg/m^2, -0.40kg/m^2, $p<0.001$), TC/HDL-C ratio (-0.20, -0.08, -0.12, $p<0.001$),

triglycerides (-0.64mmol/L, -0.11mmol/L, -0.09mmol/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 mL/min/1.73m^2, p<0.001), but decreased significantly in the SGLT2i (-1.37 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 [22], head-to-head comparisons between metabolic surgery and new antidiabetic medications have rarely been made [23]. 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 [22]. Furthermore, systematic reviews focused on patients with type 2 diabetes

on different dosages of SGLT2i[34] and GLP-1RA[35] 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 HbAlc fell within the within the ranges produced by meta-analyses [36, 37]. 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 [38].

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 (≥5 years) compared with the willingness-to-pay threshold of the jurisdiction [39].

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

Acknowledgements

The authors wish to acknowledge the Central Panel on Administrative Assessment of External Data Requests, Hong Kong Hospital Authority Head Office, for the provision of Hospital Authority data.

Competing Interests

Dr CKH Wong reports receipt of research funding from the EuroQoL Group Research Foundation, the Hong Kong Research Grants Council, and the Hong Kong Health and Medical Research Fund. Dr KKC Man reports receipt of CW Maplethorpe Fellowship. Dr EWY Chan reports honorarium from Hospital Authority; and grants from Research Grants Council (RGC, Hong Kong), Research Fund Secretariat of the Food and Health Bureau, National Natural Science Fund of China, Wellcome Trust, Bayer, Bristol-Myers Squibb, Pfizer, Janssen, Amgen, Takeda, and Narcotics Division of the Security Bureau of the Hong Kong Special Administrative Region, outside the submitted work. Prof ICK Wong reports research funding outside the submitted work from Amgen, Bristol-Myers Squibb, Pfizer, Janssen, Bayer, GSK, Novartis, the Hong Kong Research Grants Council, the Food and Health Bureau of the Government of the Hong Kong Special Administrative Region, National Institute for Health Research in England, European Commission, and the National Health and Medical Research Council in Australia; has received speaker fees from Janssen and Medice in the previous 3 years; and is an independent non-executive director of Jacobson Medical in Hong Kong. No other disclosures were reported.

Funding

This study was funded by the Health and Medical Research Fund Research Fellowship Scheme, Food and Health Bureau, Hong Kong SAR (Ref No. #02160087). Dr. Carlos K.H. Wong is the grantor. The funder did not have any role in design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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. Dara 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.

References

1. Rosenstock J, Vico M, Wei L, Salsali A, List JF. Effects of dapagliflozin, an SGLT2 inhibitor, on HbA(1c), body weight, and hypoglycemia risk in patients with type 2 diabetes inadequately controlled on pioglitazone monotherapy. Diabetes Care. 2012;35(7):1473-8.

2. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med. 2017;377(7):644-57.

3. Zinman B, Nauck MA, Bosch-Traberg H, Frimer-Larsen H, Orsted DD, Buse JB, et al. Liraglutide and Glycaemic Outcomes in the LEADER Trial. Diabetes Ther. 2018;9(6):2383-92.

4. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015;373(22):2117-28.

5. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N Engl J Med. 2019;380(24):2295-306.

6. Cai X, Ji L, Chen Y, Yang W, Zhou L, Han X, et al. Comparisons of weight changes between sodium-glucose cotransporter 2 inhibitors treatment and glucagon-like peptide-1 analogs treatment in type 2 diabetes patients: A meta-analysis. J Diabetes Investig. 2017;8(4):510-7.

7. Mosenzon O, Wiviott SD, Cahn A, Rozenberg A, Yanuv I, Goodrich EL, et al. Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes: an analysis from the DECLARE–TIMI 58 randomised trial. The Lancet Diabetes & Endocrinology. 2019;7(8):606-17.

8. Wanner C, Heerspink HJL, Zinman B, Inzucchi SE, Koitka-Weber A, Mattheus M, et al. Empagliflozin and Kidney Function Decline in Patients with Type 2 Diabetes: A Slope Analysis from the EMPA-REG OUTCOME Trial. Journal of the American Society of Nephrology. 2018;29(11):2755-69.

9. Kristensen SL, Rorth R, Jhund PS, Docherty KF, Sattar N, Preiss D, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet Diabetes Endocrinol. 2019;7(10):776-85.

10. Rubino F, Nathan DM, Eckel RH, Schauer PR, Alberti KG, Zimmet PZ, et al. Metabolic Surgery in the Treatment Algorithm for Type 2 Diabetes: A Joint Statement by International Diabetes Organizations. Diabetes Care. 2016;39(6):861-77.

11. Weiner JP, Goodwin SM, Chang HY, Bolen SD, Richards TM, Johns RA, et al. Impact of bariatric surgery on health care costs of obese persons: a 6-year follow-up of surgical and comparison cohorts using health plan data. JAMA Surg. 2013;148(6):555-62.

12. Wu T, Wong SKH, Law BTT, Grieve E, Wu O, Tong DKH, et al. Bariatric surgery is expensive but improves co-morbidity: 5-year assessment of patients with obesity and type 2 diabetes. Br J Surg. 2020.

13. Neovius M, Bruze G, Jacobson P, Sjöholm K, Johansson K, Granath F, et al. Risk of suicide and non-fatal self-harm after bariatric surgery: results from two matched cohort studies. The Lancet Diabetes & Endocrinology. 2018;6(3):197-207.

14. Hjorth S, Näslund I, Andersson-Assarsson JC, Svensson P-A, Jacobson P, Peltonen M, et al. Reoperations After Bariatric Surgery in 26 Years of Follow-up of the Swedish Obese Subjects Study. JAMA Surgery. 2019;154(4):319-26.

15. Chang SH, Stoll CR, Song J, Varela JE, Eagon CJ, Colditz GA. The effectiveness and risks of bariatric surgery: an updated systematic review and meta-analysis, 2003-2012. JAMA Surg. 2014;149(3):275-87.

16. Aminian A, Zajichek A, Arterburn DE, Wolski KE, Brethauer SA, Schauer PR, et al. Association of Metabolic Surgery With Major Adverse Cardiovascular Outcomes in Patients With Type 2 Diabetes and Obesity. JAMA. 2019;332(13):1271-82.

17. Chang AR, Chen Y, Still C, Wood GC, Kirchner HL, Lewis M, et al. Bariatric surgery is associated with improvement in kidney outcomes. Kidney Int. 2016;90(1):164-71.

18. Halperin F, Ding SA, Simonson DC, Panosian J, Goebel-Fabbri A, Wewalka M, et al. Roux-en-Y gastric bypass surgery or lifestyle with intensive medical management in patients with type 2 diabetes: feasibility and 1-year results of a randomized clinical trial. JAMA surgery. 2014;149(7):716-26.

19. Schauer PR, Bhatt DL, Kirwan JP, Wolski K, Aminian A, Brethauer SA, et al. Bariatric Surgery versus Intensive Medical Therapy for Diabetes - 5-Year Outcomes. New England journal of medicine. 2017;376(7):641-51.

20. Schauer PR, Bhatt DL, Kirwan JP, Wolski K, Brethauer SA, Navaneethan SD, et al. Bariatric surgery versus intensive medical therapy for diabetes--3-year outcomes. New England journal of medicine. 2014;370(21):2002-13.

21. Schauer PR, Kashyap SR, Wolski K, Brethauer SA, Kirwan JP, Pothier CE, et al. Bariatric surgery versus intensive medical therapy in obese patients with diabetes. N Engl J Med. 2012;366(17):1567-76.

22. Guo X, Liu X, Wang M, Wei F, Zhang Y, Zhang Y. The effects of bariatric procedures versus medical therapy for obese patients with type 2 diabetes: meta-analysis of randomized controlled trials. Biomed Res Int. 2013;2013:410609.

23. Cohen RV, Pereira TV, Aboud CM, Petry TBZ, Lopes Correa JL, Schiavon CA, et al. Effect of Gastric Bypass vs Best Medical Treatment on Early-Stage Chronic Kidney Disease in Patients With Type 2 Diabetes and Obesity: A Randomized Clinical Trial. JAMA Surg. 2020;155(8):e200420.

24. Lau WC, Chan EW, Cheung CL, Sing CW, Man KK, Lip GY, et al. Association Between Dabigatran vs Warfarin and Risk of Osteoporotic Fractures Among Patients With Nonvalvular Atrial Fibrillation. JAMA. 2017;317(11):1151-8.

25. Wong CKH, Man KKC, Shi M, Chan EW, Ho CW, Tse ETY, et al. Intensification with dipeptidyl peptidase-4 inhibitor, insulin, or thiazolidinediones and risks of all-cause mortality, cardiovascular diseases, and severe hypoglycemia in patients on metformin-sulfonylurea dual therapy: A retrospective cohort study. PLOS Medicine. 2019;16(12):e1002999.

26. Ke C, Lau E, Shah BR, Stukel TA, Ma RC, So W-Y, et al. Excess Burden of Mental Illness and Hospitalization in Young-Onset Type 2 Diabetes: A Population-Based Cohort Study. Annals of Internal Medicine. 2019;170(3):145-54.

27. The Government of the Hong Kong Special Administrative Region. Hospital Authority Ordinance (chapter 113): Revision of List of charges. 2017.

28. Tran KL, Park YI, Pandya S, Muliyil NJ, Jensen BD, Huynh K, 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):178-88.

29. Riddle MC, Cefalu WT, Evans PH, Gerstein HC, Nauck MA, Oh WK, et al. Consensus Report: Definition and Interpretation of Remission in Type 2 Diabetes. Diabetes Care. 2021.

30. Royston P, White IR. Multiple Imputation by Chained Equations (MICE): Implementation in Stata. Journal of Statistical Software. 2011;45(4).

31. Moons KG, Donders RA, Stijnen T, Harrell FE, Jr. Using the outcome for imputation of missing predictor values was preferred. J Clin Epidemiol. 2006;59(10):1092-101.

32. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivariate Behavioral Research. 2011;46(3):399-424.

33. Suissa S. Lower Risk of Death With SGLT2 Inhibitors in Observational Studies: Real or Bias? Diabetes Care. 2018;41(1):6-10.

34. Cai X, Yang W, Gao X, Chen Y, Zhou L, Zhang S, et al. The Association Between the Dosage of SGLT2 Inhibitor and Weight Reduction in Type 2 Diabetes Patients: A Meta-Analysis. Obesity (Silver Spring). 2018;26(1):70-80.

35. Vilsbøll T, Christensen M, Junker AE, Knop FK, Gluud LL. Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analyses of randomised controlled trials. BMJ. 2012;344:d7771.

36. Liakos A, Karagiannis T, Athanasiadou E, Sarigianni M, Mainou M, Papatheodorou K, et al. Efficacy and safety of empagliflozin for type 2 diabetes: a systematic review and meta-analysis. Diabetes Obes Metab. 2014;16(10):984-93.

37. Kayaniyil S, Lozano-Ortega G, Bennett HA, Johnsson K, Shaunik A, Grandy S, et al. A Network Meta-analysis Comparing Exenatide Once Weekly with Other GLP-1 Receptor Agonists for the Treatment of Type 2 Diabetes Mellitus. Diabetes Ther. 2016;7(1):27-43.

38. Liang Z, Wu Q, Chen B, Yu P, Zhao H, Ouyang X. Effect of laparoscopic Roux-en-Y gastric bypass surgery on type 2 diabetes mellitus with hypertension: a randomized controlled trial. Diabetes Res Clin Pract. 2013;101(1):50-6.

39. Xia Q, Campbell JA, Ahmad H, Si L, de Graaff B, Palmer AJ. Bariatric surgery is a cost-saving treatment for obesity-A comprehensive meta-analysis and updated systematic review of health economic evaluations of bariatric surgery. Obes Rev. 2020;21(1):e12932.

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 (N = 2,616)	SGLT2i (N = 1,810)	GLP-1RA (N = 528)	Metabolic Surgery (N = 278)	Maximum pairwise ASMD
Socio-Demographics					
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%	
Clinical Characteristics					
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^2	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^2	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^2)	72.0%	76.1%	71.3%	68.3%	
Stage 2 - 5 (<90 mL/min/1.73m^2)	28.0%	23.9%	28.7%	31.7%	
Mean Charlson Comorbidity Index (SE)[†]	4.3 (0.0)	4.4 (0.0)	4.3 (0.0)	4.2 (0.1)	0.09
Charlson Comorbidity Index[†], (%)					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%	
Treatment morbidity (%)					
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
Disease status (%)					
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).

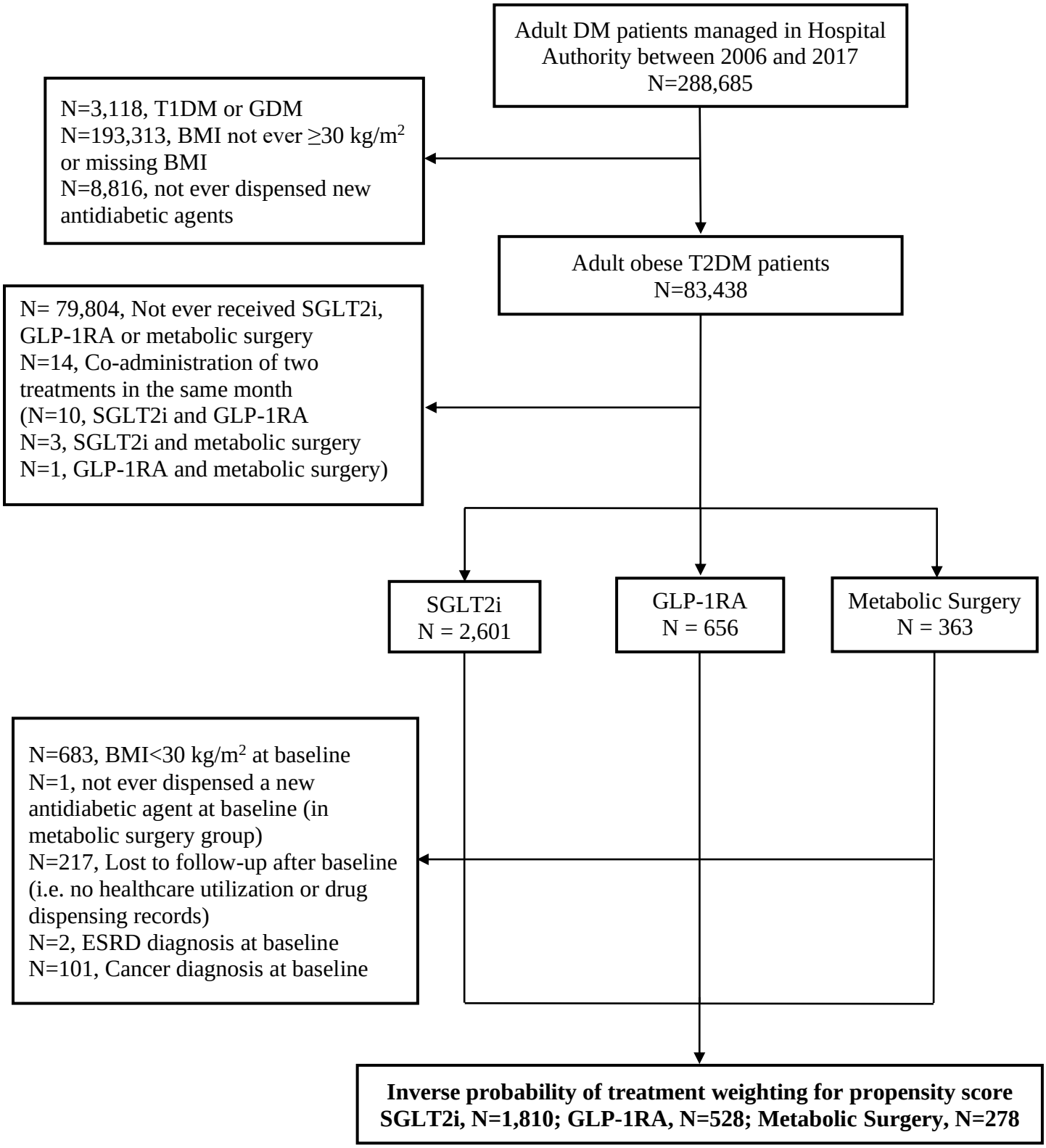
Table 2. 12-month cumulative costs associated with health service and glucose-lowering drugs for each treatment group

	SGLT2i (N = 1,810)	GLP-1RA (N = 528)	Metabolic Surgery (N = 278)	P-value
Mean Health Service Cost (SE), US$				
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*
Mean Drug Cost (SE), US$				
Glucose-lowering medication cost	8,580.43 (81.18)	8,184.08 (87.45)	3,338.99 (107.20)	<0.001*
Mean Total Direct Medical Cost (SE), US$	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

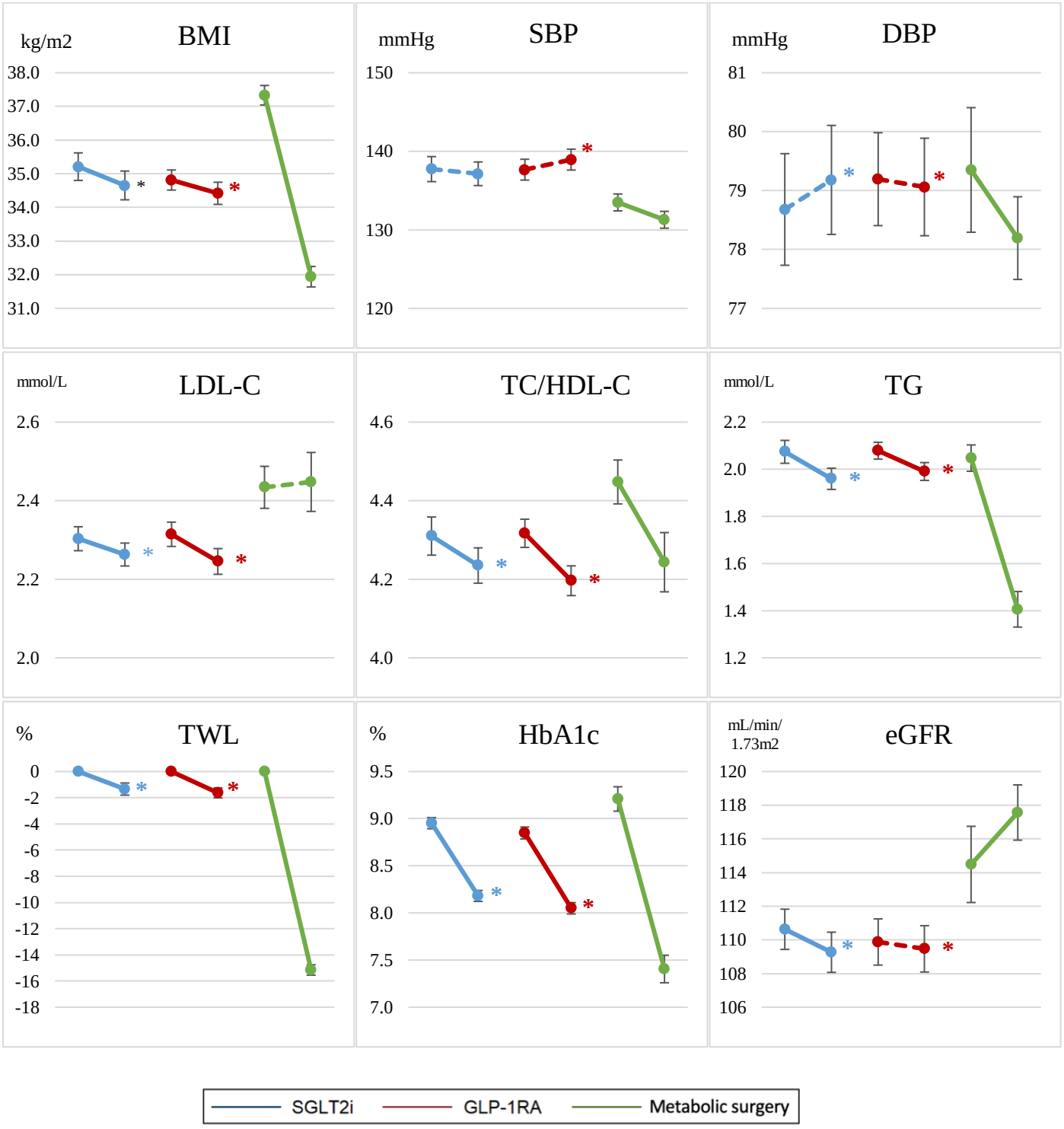
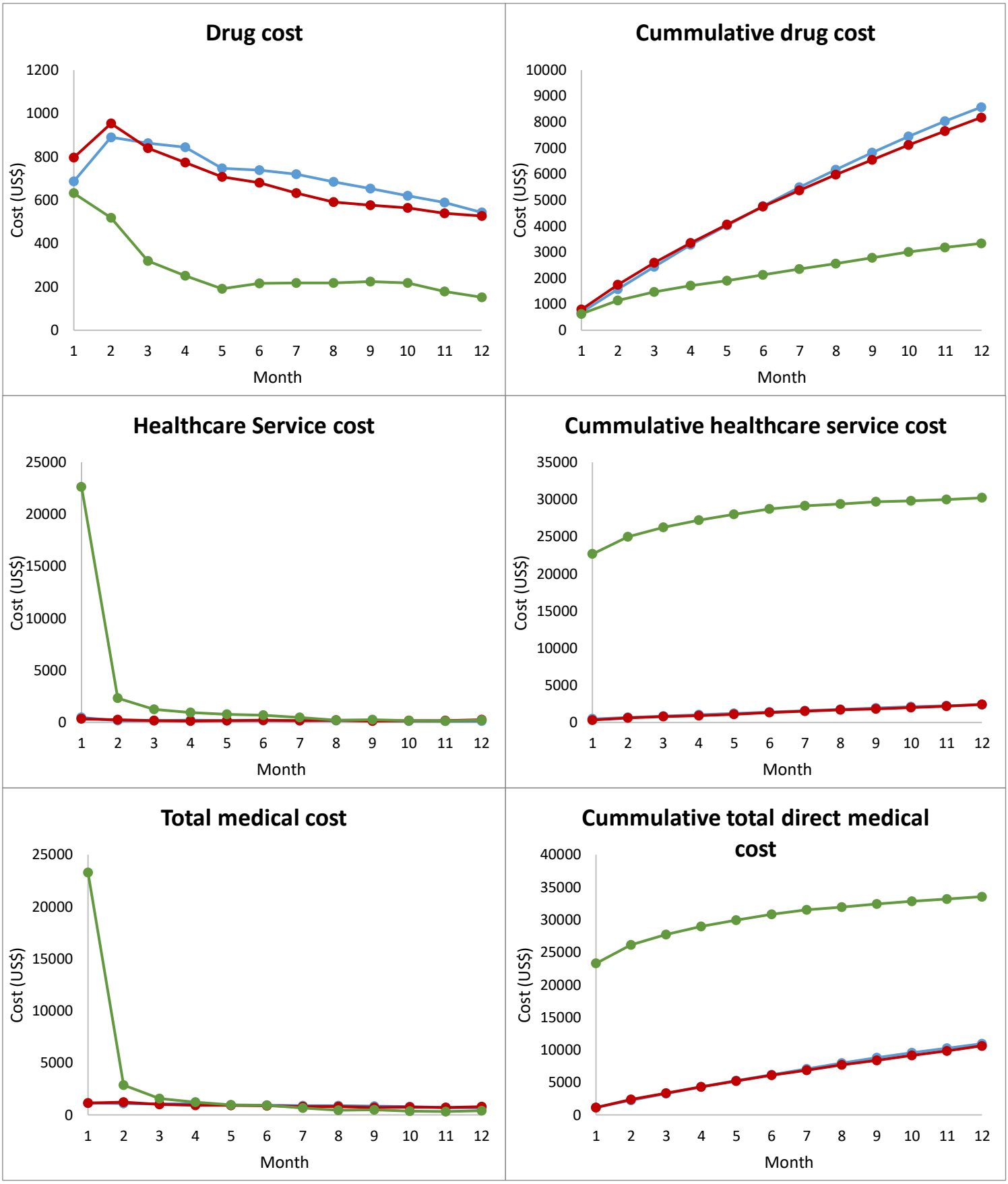


Figure 3. Mean monthly and cumulative costs associated with glucose-lowering drugs, healthcare service and total direct healthcare costs for each month and each group over a 12-month period



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$)[§]	Cost (US$)
Healthcare services[†]		
Clinic visit		
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
Allied health professionals		
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
Hospitalization		
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
Metabolic surgery and revision surgery[‡]		
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-jejunostromy	67,735	8,684
Glucose-lowering medication[¶]		
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:

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

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

[§] At a fixed exchange rate of 1 US= 7.80HK.

[¶] 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 (N = 2,616)	SGLT2i (N = 1,810)	GLP-1RA (N = 528)	Metabolic Surgery (N = 278)	Total (N = 2,616)	SGLT2i (N = 1,810)	GLP-1RA (N = 528)	Metabolic Surgery (N = 278)
Socio-Demographic (%, n)								
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)
Clinical Characteristics (%, n)								
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†	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)
Treatment morbidity, (%)								
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:
† 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 (N = 2,616)	SGLT2i (N = 1,810)	GLP-1RA (N = 528)	Metabolic Surgery (N = 278)	Maximum pairwise ASMD
Socio-Demographics					
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%	
Clinical Characteristics					
Mean BMI (SE), kg/m^2	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^2	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^2)	74.2%	73.4%	74.8%	78.8%	
Stage 2 - 5 (<90 mL/min/1.73m^2)	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)[†]	4.5 (0.0)	4.7 (0.1)	3.9 (0.1)	3.8 (0.1)	0.43
Charlson Comorbidity Index[†], (%)					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
Treatment morbidity (%)					
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
Disease status (%)					
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

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^2	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^2	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

Groups	3 months	6 months	9 months	12 months
SGLT2i (N=1810)	4 (0.22%)	32 (1.77%)	74 (4.09%)	42 (2.32%)
GLP1RA (N=528)	0 (0.00%)	26 (4.92%)	22 (4.17%)	21 (3.98%)
Metabolic surgery (N=278)	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)
Hospitalization							
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
Frequency after baseline - 1 year	Mean	95% CI	Median	Range	Total number of events	Total person-years	Event rate (cases/100 person-years)
Hospitalization							
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	Mean	95% CI	Median	Range	Total number of events	Total person-years	Event rate (cases/100 person-years)
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

Frequency after baseline	Metabolic surgery						
	Mean	95% CI	Median	Range	Total number of events	Total person-years	Event rate (cases/100 person-years)
Hospitalization							
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

Frequency after baseline - 1 year	Mean	95% CI	Median	Range	Total number of events	Total person-years	Event rate (cases/100 person-years)
Hospitalization							
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^2	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^2	110.14 (0.98)	110.14 (0.98)	113.94 (0.83)	3.80 (0.77)	<0.001*

	Mean cost (SE), US$
Cost items	**Sleeve gastrectomy (N=239)**
Healthcare services	29120.20 (682.92)
Hospitalization	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)
Accident and Emergency	71.88 (3.32)
General outpatient clinic services	52.47 (2.29)
Specialist outpatient clinic services	1469.59 (30.94)
Allied health professional services	223.35 (3.89)
Drug	3338.33 (82.57)
Total direct medical costs	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 (N = 1859)	SGLIT2i (N=1237)	GLP1RA (N=449)	Metabolic surgery (N=173)	Maximum pairwise ASMD
Socio-Demographics					
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%	
Clinical Characteristics					
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^2	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), $mL/min/1.73m^2$	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 $mL/min/1.73m^2$)	68.0%	73.9%	66.2%	63.9%	
Stage 2 - 5 (<90 $mL/min/1.73m^2$)	32.0%	26.1%	33.8%	36.1%	
Mean Charlson Comorbidity Index (SE)†	4.5 (0)	4.6 (0.1)	4.6 (0.1)	4.4 (0.1)	0.07
Charlson Comorbidity Index†, (%)					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%	
Treatment morbidity (%)					
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
Disease status (%)					
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^2	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^2	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*	

	Mean cost (SE), US$		
Cost items	**SGLIT2i (N=1237)**	**GLP1RA (N=449)**	**Metabolic surgery (N=173)**
Healthcare services	2823.76 (175.78)	2886.40 (247.04)	
Hospitalization	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)
Accident and Emergency	103.11 (8.13)	80.12 (5.95)	74.09 (3.68)
General outpatient clinic services	43.41 (3.87)	55.37 (4.42)	52.39 (2.57)
Specialist outpatient clinic services	865.79 (14.02)	973.90 (13.94)	1519.09 (31.40)
Allied health professional services	41.07 (2.45)	50.04 (2.82)	198.19 (3.91)
Drug	9775.46 (94.77)	9603.07 (94.92)	4180.09 (81.72)
Total direct medical costs	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^2	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^2	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*	

	Mean costs (SE), US$	
Cost items	**Exenatide (N=175)**	**Liraglutide (N=322)**
Healthcare services	2610.37 (154.38)	2504.18 (265.42)
Hospitalization	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)
Accident and Emergency	118.89 (13.33)	63.49 (3.75)
General outpatient clinic services	83.93 (10.24)	46.37 (4.1)
Specialist outpatient clinic services	1009.11 (21.65)	961.11 (14.37)
Allied health professional services	59.24 (4.3)	37.34 (2.65)
Drug	8470.2 (175.12)	7950.61 (98.35)
Total direct medical costs	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