Diabetes, Obesity and Metabolism

Effects of Sodium Glucose Co-transporter 2 Inhibitors on Serum Alanine Aminotransferase Values in Type 2 Diabetes Patients: A Multi-Institutional Cohort Study

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Conflict of interest: None

Acknowledgments: The authors would like to thank Chang Gung Memorial Hospitals for providing Chang Gung Research Database data.

Funding source: This study was supported in part by grants from the Chang Gung Medical Foundation (CNRPG3H1551), Taoyuan, Taiwan.

Article type: Brief Report

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/dom.13875

ABSTRACT

Clinical trials have indicated a favorable effect on serum alanine aminotransferase (ALT) values in type 2 diabetes (T2D) patients receiving sodium glucose co-transporter 2 (SGLT2) inhibitors, but supporting evidence from real-world studies is lacking. We identified T2D patients who initiated SGLT2 inhibitors during 2016-2017 from Chang Gung Research Database covering 1.3 million individuals from 7 hospitals (6% of Taiwan population). We classified patients by the baseline ALT levels and evaluated the changes of ALT values from the baseline to a year after the initiation of SGLT2 inhibitors. We identified 11,690 new users of SGLT2 inhibitors with a mean age of 59.3 (SD 11.8) years. The mean HbA1c and ALT were 8.9% (SD 1.7) and 34.7 U/l (SD 28.9) at baseline, respectively. The mean value of ALT changes was -5.0 U/l (95% CI: -6.4, -3.5) a year after initiation of SGLT2 inhibitors. In patients with ALT≤1X ULN, the change in ALT levels was 1.6 U/l (95% CI: -0.1, 3.4), while in those with ALT>1X ULN, the change in ALT levels was -26.5 U/l (95% CI: -28.6, -24.3). The higher the baseline ALT level, the greater the decline after the SGLT2 inhibitor treatment. Our findings suggested the initiation of SGLT2 inhibitors for T2D management could improve serum ALT levels in clinical practice, especially in patients with higher ALT levels.

Key words

Empagliflozin, dapagliflozin, type 2 diabetes, alanine aminotransferase, multi-institutional

electronic medical records

INTRODUCTION

Sub-analysis of the EMPA-REG OUTCOME (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes) trial has indicated the changes from baseline alanine aminotransferase (ALT) at week 28 were -3.0 ± 0.2 U/L in type 2 diabetes (T2D) patients receiving empagliflozin[1]. A pooled analysis of clinical trials has indicated canagliflozin improved ALT levels in T2D patients with baseline ALT >30 U/L (mean difference of −16.0 ± 18.8 U/L at week 52)[2]. However, patients with ALT >2.5-3X upper limit of normal (ULN) were excluded from these trials.

Some studies have also found SGLT2 inhibitors to have favorable liver effects on non-alcoholic fatty liver disease (NAFLD)[3,4], but these studies were limited by small sample size. Therefore, we used a large real-world database to evaluate ALT changes associated with SGLT2 inhibitors among T2D patients, especially those with different ALT levels.

MATERIALS AND METHODS

Study Design and Settings

We conducted a retrospective cohort study by analyzing data from the Chang Gung Research database (CGRD) during 2016-2017. CGRD is the largest multi-institutional electronic medical records database in Taiwan, covering 1.3 million individuals from 7 hospitals (6% of Taiwan population). The structure of CGRD has been described elsewhere[5]. Compared to primary data collections, secondary data sources such as CGRD can provide efficient, timely evaluations of treatment outcomes. This study has been approved by the Institutional Review Board (IRB) of Chang Gung Medical Foundation (ID: 201801493B0).

Study Population and Follow-up

We included T2D patients who newly received SGLT2 inhibitors during 2016-2017, whereby we defined the first prescription date as the index date. SGLT2 inhibitors are reimbursed in Taiwan for T2D patients who fail to achieve glycemic targets after the maximum dose of metformin. Because SGLT2 inhibitors were approved and available after 2016 in Taiwan, all patients in this study were incident users. We excluded patients of age younger than 18 years old. To ensure sufficient data to evaluate patients' baseline

information, we excluded patients with no visits before the index date (n=267, 1.8%). We also excluded patients without laboratory results for baseline HbA1c, estimated glomerular filtration rate (eGFR), body weight and ALT values (n=1,065, 7.2%), since most of the excluded patients had not received routine medical care in our study hospitals. ALT measurements are covered under Taiwan's insurance program for diabetes patients, whether on a first visit or after transfer to the hospital, so clinicians usually check or confirm ALT levels of patients to decide the treatment. To avoid incomplete follow-up ALT data, we excluded patients without any ALT data in our hospitals after initiation of SGLT2 inhibitors (n=1,795, 12.1%).

We performed intention-to-treat analysis and followed up patients for a year from the index date regardless of subsequent changes of treatment regimen after the SGLT2 inhibitor initiation to reflect real clinical situations. To address the issue of non-adherence, discontinuation of drug and loss of follow-up, we also performed per-protocol analysis, whereby we included a subgroup of patients who had received the SGLT2 inhibitor treatment with routine follow-up for more than one year and whose prescriptions were refilled without any gap exceeding 90 days.

Outcome Measures

The study hospitals in CGRD used a uniform and standardized system for the laboratory test, and the measurements of ALT were consistent. We used the data nearest to the months 3, 6, 9 and 12 as the ALT follow-up outcomes in this study. We defined 50 U/l and 35 U/l as ULN of ALT for males and females, respectively. To examine heterogeneous effects, we classified all SGLT2 recipients based on their ALT levels at baseline (e.g., ALT≤1X ULN; 1X<ALT≤2X; 2X<ALT≤3X and ALT>3X ULN) in order to compare ALT changes among groups.

Co-variables

We described patients' baseline characteristics such as age, sex, healthcare facilities, co-morbidity and concomitant medications, and used the treatment of chronic hepatitis B and hepatitis C diseases (e.g., interferon-based therapy, nucleos(t)ide analogs, and direct-acting antiviral agents) to identify patients with corresponding liver diseases. Additionally, we included the clinical data, including HbA1c, body weight, ALT and eGFR levels nearest to initiation of SGLT2 inhibitors as the baseline information. The definitions of co-morbidity and concomitant medications are described in **Appendix Table 1 and 2**.

Subgroup Analyses

We categorized patients by individual SGLT2 inhibitor (i.e., dapagliflozin and empagliflozin) to test ALT reduction class effects. To test if improvements of ALT values were independent of renal function, key to the pharmacological actions of SGLT2 inhibitors[6], we stratified patients by baseline renal function (eGFR >90 vs. ≤90 ml/min/1.73m^2). Moreover, we stratified patients by their changes of HbA1c value (≤0.7 vs. >0.7%) and body weights (≤1.7 vs. >1.7 kg) after one-year treatment to examine if the improvements of ALT values were independent of glucose or weight-lowering effects. The cutoffs were based on the average effects of SGLT2 inhibitors on these parameters according to a previous meta-analysis of related randomized control trials[7].

Statistical Analyses

We calculated means with standard deviation (SD) and counts with proportion for continuous and categorized variables, respectively. Changes in serum ALT values are described by the differences of means with 95% confidence interval (CI). We used two-tailed paired t-tests to examine the changes of ALT values from index date to one year. We considered statistical significance at a *P*-value <0.05.

RESULTS

Study Population

We included 11,690 T2D adult patients who were treated with SGLT2 inhibitors (empagliflozin, 55.0%; dapagliflozin, 45.0%) during 2016-2017 (**Appendix Figure 1**), 98.9% of whom received SGLT2 inhibitors as adjunct treatment beyond their original anti-hyperglycemic regimens. The patients had a mean age of 59.3 (SD 11.8) years, and baseline HbA1c and ALT were 8.9% (SD 1.7) and 34.7 U/l (SD 28.9), respectively. We found 77.8% of patients had baseline ALT≤1X ULN, and patients with abnormal ALT levels were generally younger and had poorer glycemic controls (**Table 1**).

Primary Outcomes

During the follow-up period, 97 patients (0.8%) died. Overall, the mean ALT values for patients newly receiving SGLT2 inhibitors at baseline, and at months 3, 6, 9 and 12 were 34.7 U/l (SD 28.9), 33.9 U/l (SD 54.2), 30.0 U/l (SD 29.4) and 30.7 U/l (SD 60.1), respectively. The mean change of ALT values was -5.0 U/l (95% CI: -6.4, -3.5) after one year of SGLT2 inhibitor treatment. This improvement of ALT values could appear as early as 6 months after the SGLT2 inhibitor treatment and last for over one year; however, the

magnitude of its changes depended on the baseline ALT level (**Figure2**). For those with ALT≤1X ULN, the change in ALT values was 1.6 U/l (95% CI: -0.1, 3.4). For those with ALT >1X ULN, the change in ALT values was -26.5 U/l (95% CI: -28.6, -24.3) with a trend following the baseline ALT level. Per-protocol analyses (n=5,586) of the subgroup of patients who received continuous SGLT2 inhibitor treatment with routine follow-up over one year showed results consistent with the main analyses.

Subgroup Analyses

The trends within the stratified subgroup analyses were consistent with the main analysis (**Appendix Figure 2-5).** The use of empagliflozin and dapagliflozin could reduce the ALT values by -3.9 U/l (95% CI: -6.3, -1.6) and -6.3 U/l (95% CI: -7.7, -4.9), respectively, after the 1-year treatment. We found improvements of ALT values were independent of baseline renal functions. In addition, compared to patients with adequate glucose or weight-lowering effects, those who did not improve HbA1c or body weight after SGLT2 inhibitor treatment still showed reduced ALT values.

DISCUSSION

Consistent with previous clinical trials[1,4], we found the beneficial effects of SGLT2 inhibitors on ALT values started as early as 6 months after the treatment was initiated and lasted for one year. This improvement in ALT values may, in turn, slow the progression of liver disease[8]. A recent meta-analysis of randomized controlled trials found that serum ALT levels fell by 0.2 U/L (95% CI: 0.3, 0.1) after treatment with SGLT2 inhibitors[9]; however, our data showed greater reduction of ALT values (5.0 U/L, 95% CI: 3.5, 6.4) after SGLT2 inhibitor treatment because we included patients with higher ALT levels (e.g., ALT>2-3X ULN) who had greater improvement of ALT than those with normal ALT levels.

The mechanisms underlying the improvement of liver function with SGLT2 inhibitors remain unknown. SGLT2 inhibitors significantly lower blood glucose levels and body weight[10], which could also improve liver function in T2D patients with NAFLD[11,12]. However, previous studies have produced conflicting results about glucose or weight-lowering effects of SGLT2 inhibitors on liver function improvements in T2D patients[1,13-15]. Our data reveals a reduction in ALT values even in patients with suboptimal

glucose or weight-lowering effects, implying that mechanisms of ALT reduction could be independent of changes in weight or HbA1c levels. In addition, the pharmacological actions of SGLT2 inhibitors depend on glucose filtration capacity as represented by renal function. However, we found patients with different renal functions at baseline could improve ALT values after SGLT2 inhibitor treatment, which may imply that positive changes in ALT values are independent of baseline renal function. Hence, we propose another mechanism which may be related to the liver outcome of SGLT2 inhibitor treatment, namely that SGLT2 inhibitors have recently been found to have anti-inflammatory effects with reduction of oxidative stress in animal models, and this has been suggested as a possible reason for ALT improvements[16]. However, further investigations in humans are needed.

Some limitations of this study must be addressed. First, an estimated 70% of T2D patients had NAFLD[17], but we could not obtain information on the etiology of patients with abnormal ALT levels, due to the difficulty of comprehensively surveying probable etiology of liver injury in a retrospective data analysis. Second, because CGRD is collected independently of specific a-priori research questions, some liver parameters may not be completely recorded. We only evaluated changes of ALT values, this being the most frequently measured indicator in our clinical practice. It serves as a useful indicator for

the progression of liver fibrosis in NAFLD patients[2]. Third, we did not examine reductions of waist circumference to measure the effect of changes in visceral fat on ALT values. In fact, weight reductions from SGLT2 inhibitors may also be attributed to visceral fat loss[18]. Moreover, CGRD does not include lifestyle information (e.g., alcohol consumption, exercise and dietary habits), and prior lifestyle modifications may have caused ALT improvements. We conducted post-hoc analysis to compare the trends of ALT changes 3 years prior to and 1 year post SGLT2 inhibitor initiation. Since we found no obvious ALT changes before initiation of SGLT2 inhibitors in our study patients (**Appendix Figure 6**), any effects from lifestyle modifications on our findings are likely minor.

In conclusion, we confirm the beneficial ALT effects of SGLT2 inhibitors used as intensification therapy for type 2 diabetes patients who failed to achieve their glycemic target, especially in patients with higher ALT levels, whereby the mechanism may be independent of glucose or weight-lowering effects of SGLT2 inhibitors. Further prospective studies based on relevant liver parameters are recommended to confirm our findings.

Acknowledgments

The authors would like to thank Chang Gung Memorial Hospitals for providing Chang Gung Research Database data.

Conflicts of interests

The authors declare that they have no conflict of interest.

Funding Information

This study was supported in part by grants from Chang Gung Medical Foundation (CNRPG3H1551), Taoyuan, Taiwan. The funder had no role in the design, conduct, or data interpretation of the study. The researchers were independent from the funders.

Authors' contributions

Study concept and design: SCS and ECCL; Acquisition of subjects and/or data: YYC; Analysis and interpretation of data: SCS, KCC and ECCL; Preparation of manuscript: All authors.

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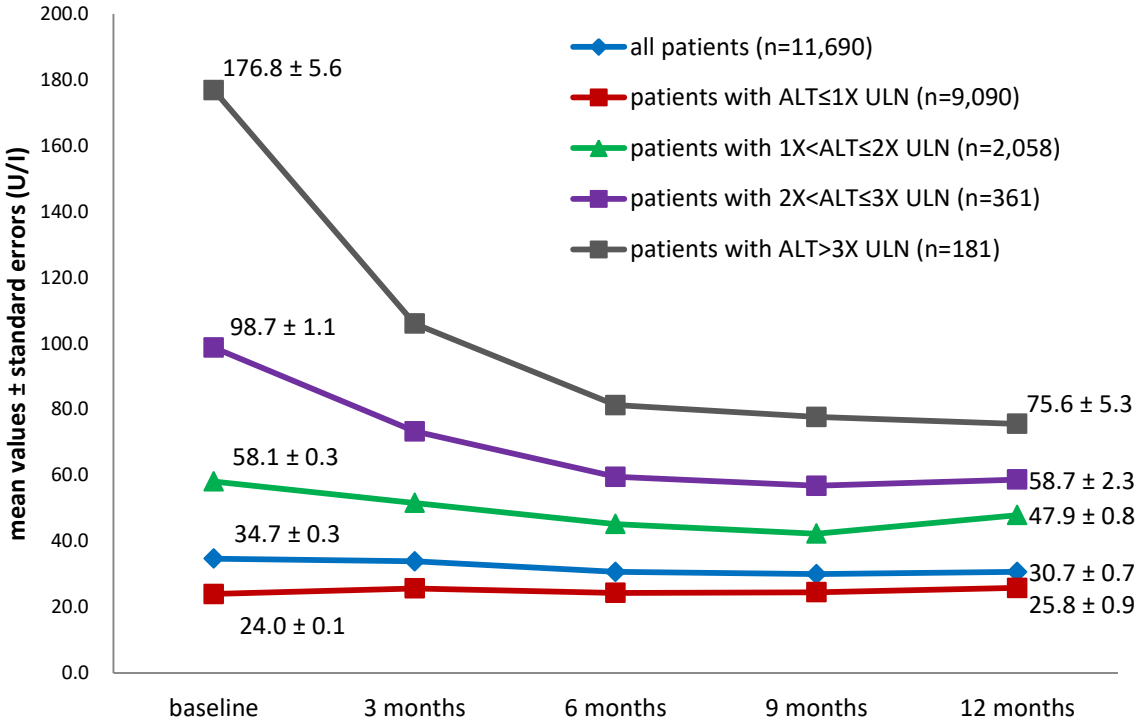
a. Intention-to-treat analysis



b. Per-protocol analysis

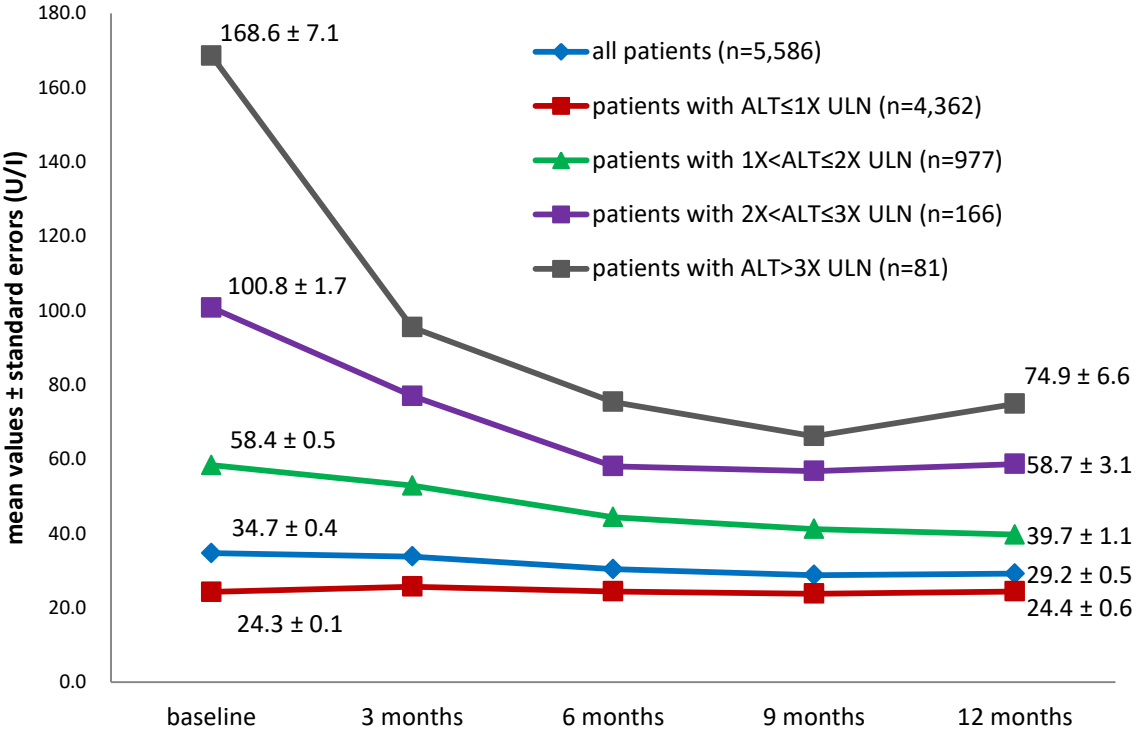


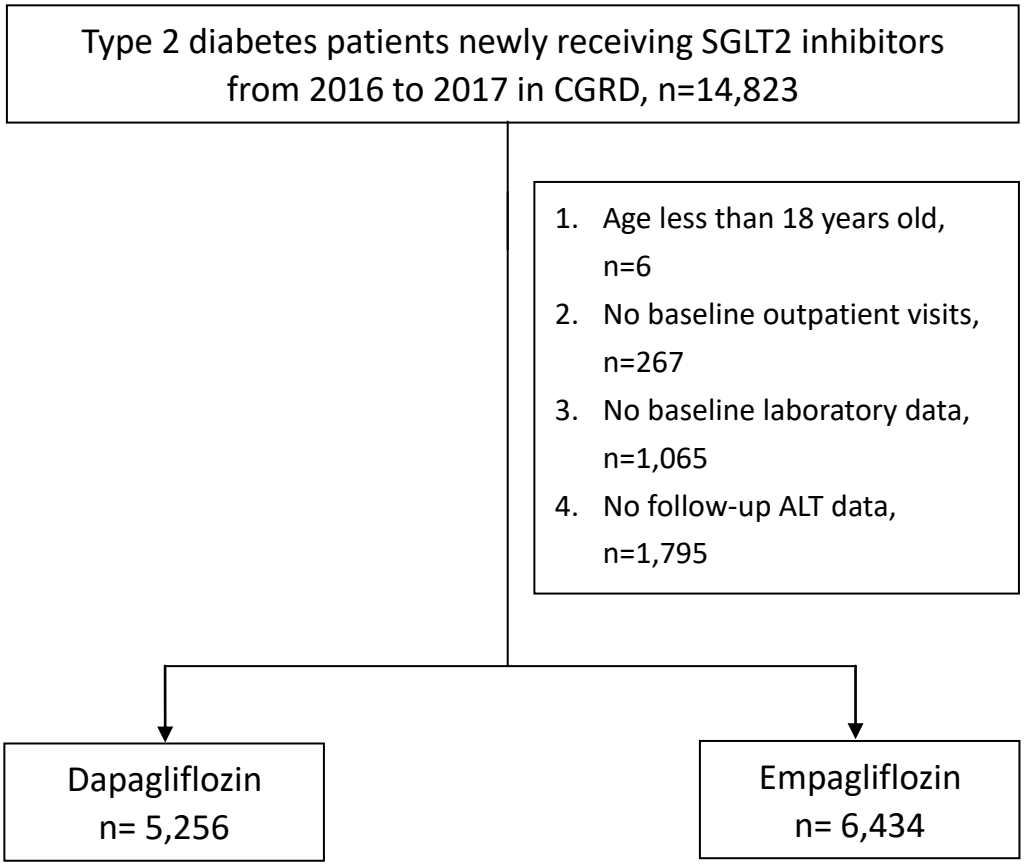
Figure 1. Changes in ALT after the SGLT2 inhibitor treatment over time

ALT, alanine aminotransferase; ULN, upper limit of normal (male: 50 U/l; female: 35 U/l)

Table 1. Baseline characteristics

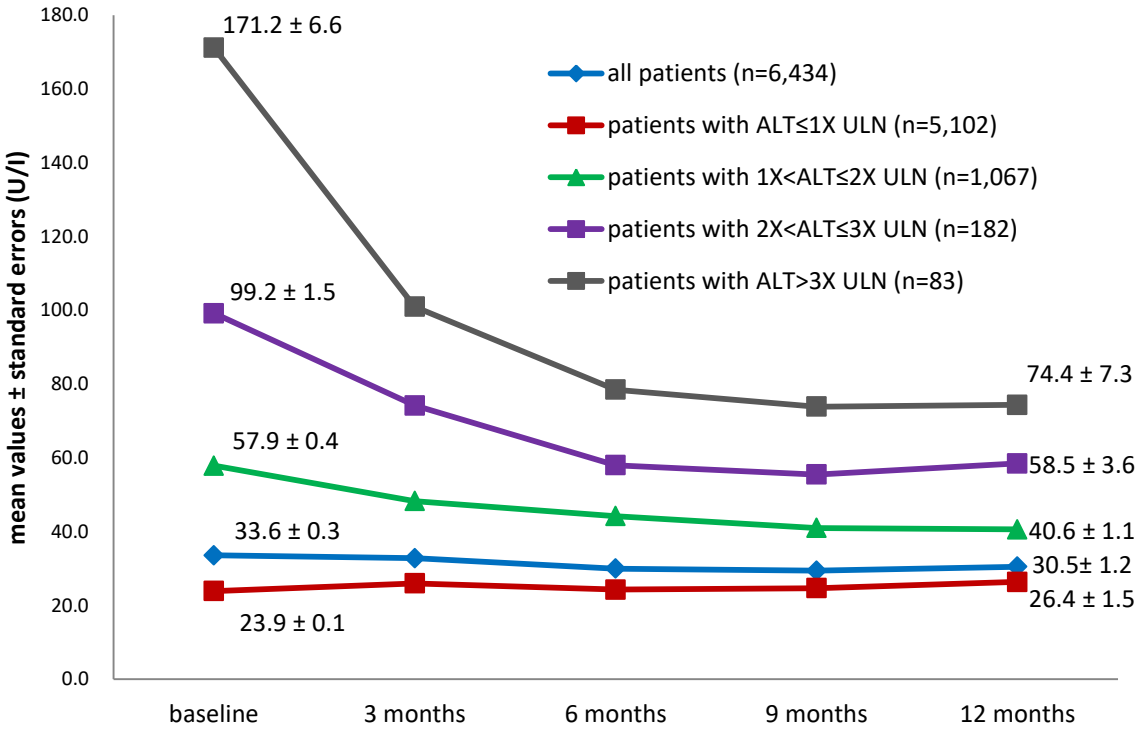
	All	ALT≤1X ULN	1X<ALT≤2X ULN	2X<ALT≤3X ULN	ALT>3X ULN
Patients, n (%)	11,690 (100)	9,090 (77.8)	2,058 (17.6)	361 (3.1)	181 (1.6)
Age, mean years (SD)	59.3 (11.8)	60.5 (11.4)	55.5 (11.7)	52.9 (12.9)	53.6 (14.6)
Female, n (%)	4,927 (42.2)	3,593 (39.5)	1,026 (49.9)	204 (56.5)	104 (57.5)
SGLT2 inhibitors, n (%)					
Empagliflozin	6,434 (55.0)	5,102 (56.1)	1,067 (51.9)	182 (50.4)	83 (45.9)
Dapagliflozin	5,256 (45.0)	3,988 (43.9)	991 (48.2)	179 (49.6)	98 (54.1)
ALT, mean U/l (SD)	34.7 (28.9)	24.0 (9.5)	58.1 (15.2)	98.7 (20.0)	176.8 (75.8)
Body weights, mean kg (SD)	74.5 (16.0)	73.3 (15.2)	78.6 (17.5)	80.9 (19.1)	76.2 (16.3)
HbA1c, n (%)					
>8.5%	5,995 (51.3)	4,598 (50.6)	1,093 (53.1)	189 (52.4)	115 (63.5)
≤8.5%	5,695 (48.7)	4,492 (49.4)	965 (46.9)	172 (47.7)	66 (36.5)
eGFR, n (%)					
>90 ml/min/1.73m^2	6,037 (51.6)	4,444 (48.9)	1,248 (60.6)	230 (63.7)	115 (63.5)
≤90 ml/min/1.73m^2	5,653 (48.4)	4,646 (51.1)	810 (39.4)	131 (36.3)	66 (36.5)
Hospital level, n (%)					
Medical centers	6,426 (55.0)	5,057 (55.6)	1,095 (53.2)	180 (49.9)	94 (51.9)
Regional hospitals	2,950 (25.2)	2,273 (25.0)	523 (25.4)	109 (30.2)	45 (24.9)
District hospitals	2,314 (19.8)	1,760 (19.4)	440 (21.4)	72 (19.9)	42 (23.2)
Department, n (%)					
Metabolism & Endocrinology	7,602 (65.0)	5,893 (64.8)	1,356 (65.9)	241 (66.8)	112 (61.9)
Cardiology	2,784 (23.8)	2,186 (24.1)	468 (22.7)	82 (22.7)	48 (26.5)
Others	1,304 (11.2)	1,011 (11.1)	234 (11.4)	38 (10.5)	21 (11.6)
Comorbidity, n (%)					
Chronic hepatitis B or C diseases	100 (0.9)	67 (0.7)	27 (1.3)	3 (0.8)	3 (1.7)
Cardiovascular diseases					
Hypertension	7,829 (67.0)	6,098 (67.1)	1,392 (67.6)	235 (65.1)	104 (57.5)
Hyperlipidemia	8,688 (74.3)	6,779 (74.6)	1,550 (75.3)	255 (70.6)	104 (57.5)
Coronary heart disease	2,300 (19.7)	1,909 (21.0)	320 (15.6)	46 (12.7)	25 (13.8)
Atrial fibrillation	356 (3.1)	310 (3.4)	38 (1.9)	7 (1.9)	1 (0.6)
Peripheral artery disease	183 (1.6)	162 (1.8)	17 (0.8)	1 (0.3)	3 (1.7)
Heart failure	663 (5.7)	554 (6.1)	81 (3.9)	17 (4.7)	11 (6.1)
Ischemic stroke	502 (4.3)	414 (4.6)	77 (3.7)	7 (1.9)	4 (2.2)
Micro-vascular complications					
Diabetic retinopathy	1,034 (8.9)	878 (9.7)	129 (6.3)	16 (4.4)	11 (6.1)
Diabetic neuropathy	1,205 (10.3)	1,004 (11.1)	167 (8.1)	23 (6.4)	11 (6.1)
Diabetic nephropathy	3,260 (27.9)	2,621 (28.8)	531 (25.8)	74 (20.5)	34 (18.8)
Chronic obstructive pulmonary disease	355 (3.0)	307 (3.4)	37 (1.8)	8 (2.2)	3 (1.7)

Cancer	777 (6.7)	591 (6.5)	146 (7.1)	25 (6.9)	15 (8.3)
Previous hospitalization, n (%)	1,644 (14.1)	1,350 (14.9)	225 (10.9)	41 (11.4)	28 (15.5)
Background anti-diabetes medications, n (%)					
Metformin	10,637 (91.0)	8,194 (90.1)	1,929 (93.7)	345 (95.6)	169 (93.4)
Sulfonylurea	6,904 (59.1)	5,337 (58.7)	1,239 (60.2)	214 (59.3)	114 (63.0)
Dipeptidyl peptidase-4 inhibitors	7,575 (64.8)	5,896 (64.9)	1,344 (65.3)	218 (60.4)	117 (64.6)
Thiazolidinediones	2,802 (24.0)	2351 (25.9)	375 (18.2)	45 (12.5)	31 (17.1)
Acarbose	2,183 (18.7)	1,760 (19.4)	340 (16.5)	52 (14.4)	31 (17.1)
Glinides	240 (2.1)	195 (2.2)	34 (1.7)	7 (1.9)	4 (2.2)
Glucagon-like peptide-1 receptors antagonist	220 (1.9)	154 (1.7)	59 (2.9)	5 (1.4)	2 (1.1)
Insulin	2,517 (21.5)	2,060 (22.7)	371 (18.0)	55 (15.2)	31 (17.1)
Concomitant cardiovascular medications, n (%)					
Beta blockers	2,999 (25.7)	2,362 (26.0)	521 (25.3)	76 (21.1)	40 (22.1)
Angiotensin-converting enzyme inhibitors / angiotensin receptor blockers	7,057 (60.4)	5,513 (60.7)	1,258 (61.1)	197 (54.6)	89 (49.2)
Calcium channel blockers	4,547 (38.9)	3,545 (39.0)	802 (39.0)	136 (37.7)	64 (35.4)
Diuretics	1,275 (10.9)	1,029 (11.3)	196 (9.5)	29 (8.0)	21 (11.6)
Statin	7,829 (67.0)	6,240 (68.7)	1,330 (64.6)	188 (52.1)	71 (39.2)
Fibrate	1,209 (10.3)	954 (10.5)	198 (9.6)	42 (11.6)	15 (8.3)
Ezetimibe	1,413 (12.1)	1,061 (11.7)	269 (13.1)	62 (17.2)	21 (11.6)

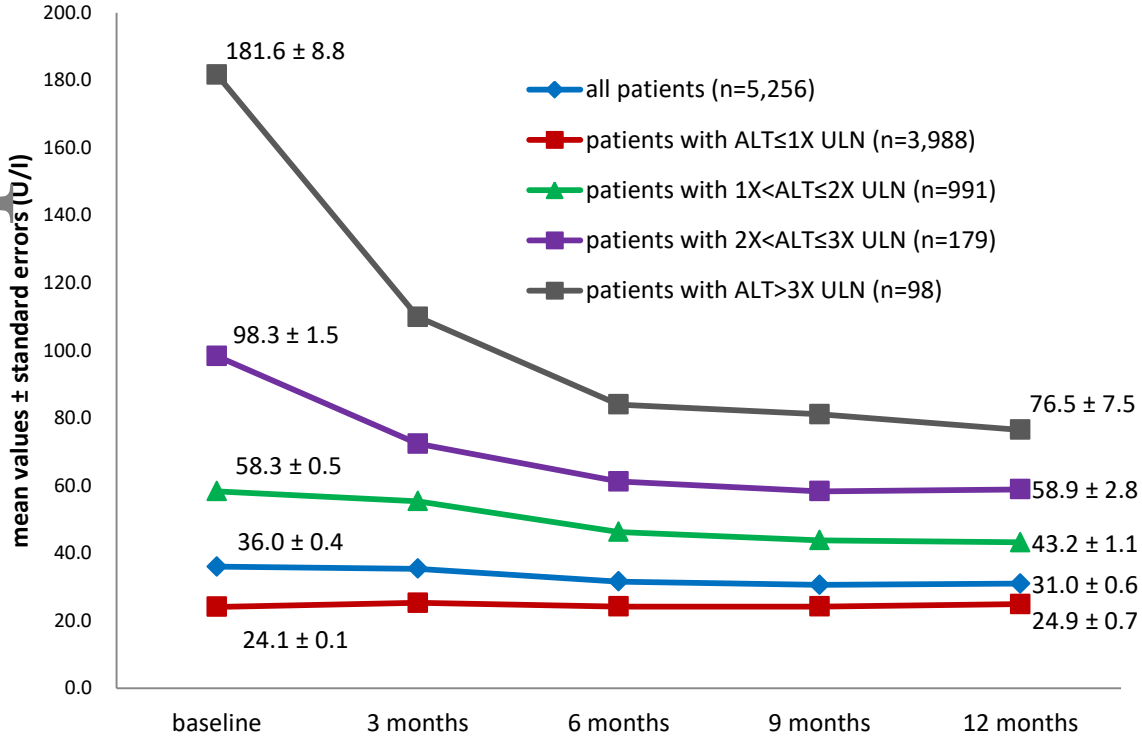


Appendix Figure 1. Patient selection flow chart.
CGRD, Chang Gung Research Database

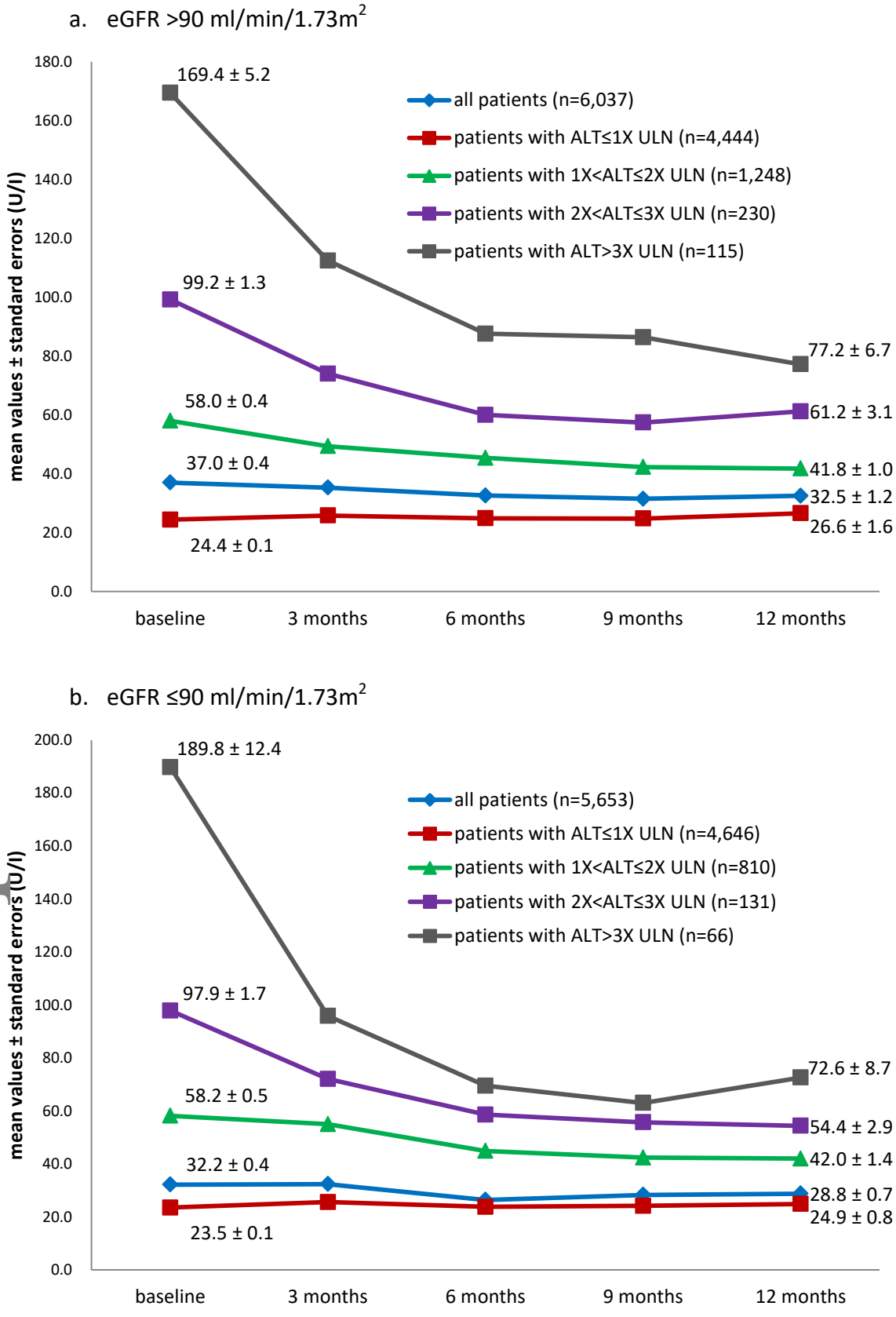
a. Empagliflozin



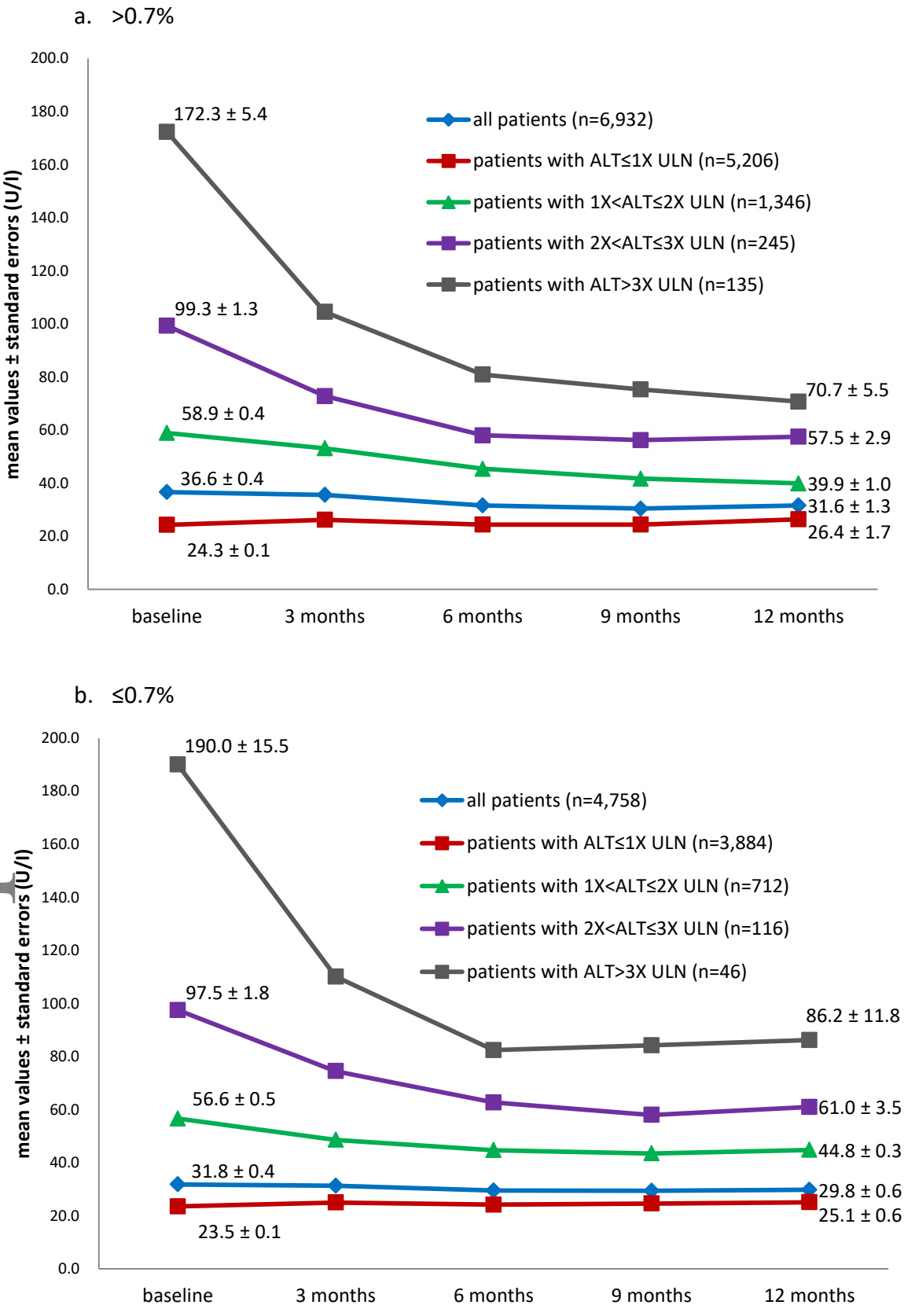
b. Dapagliflozin



Appendix Figure 2. Subgroup analyses: SGLT2 inhibitors

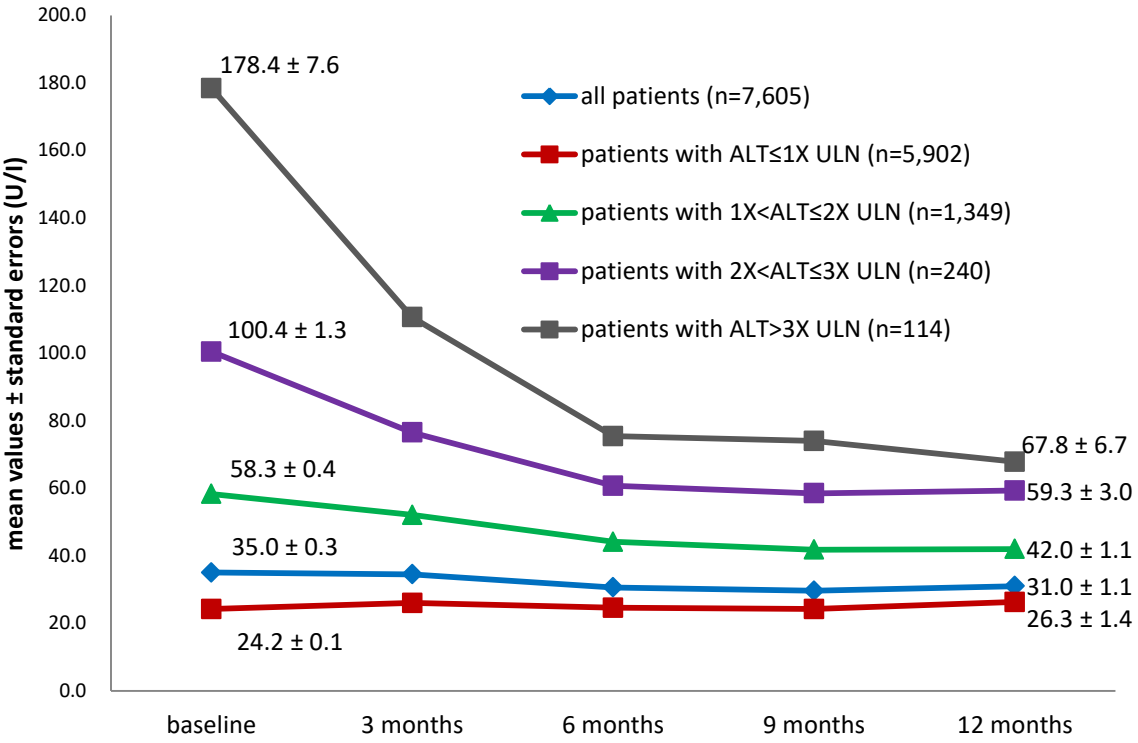


Appendix Figure 3. Subgroup analyses: the initial renal functions

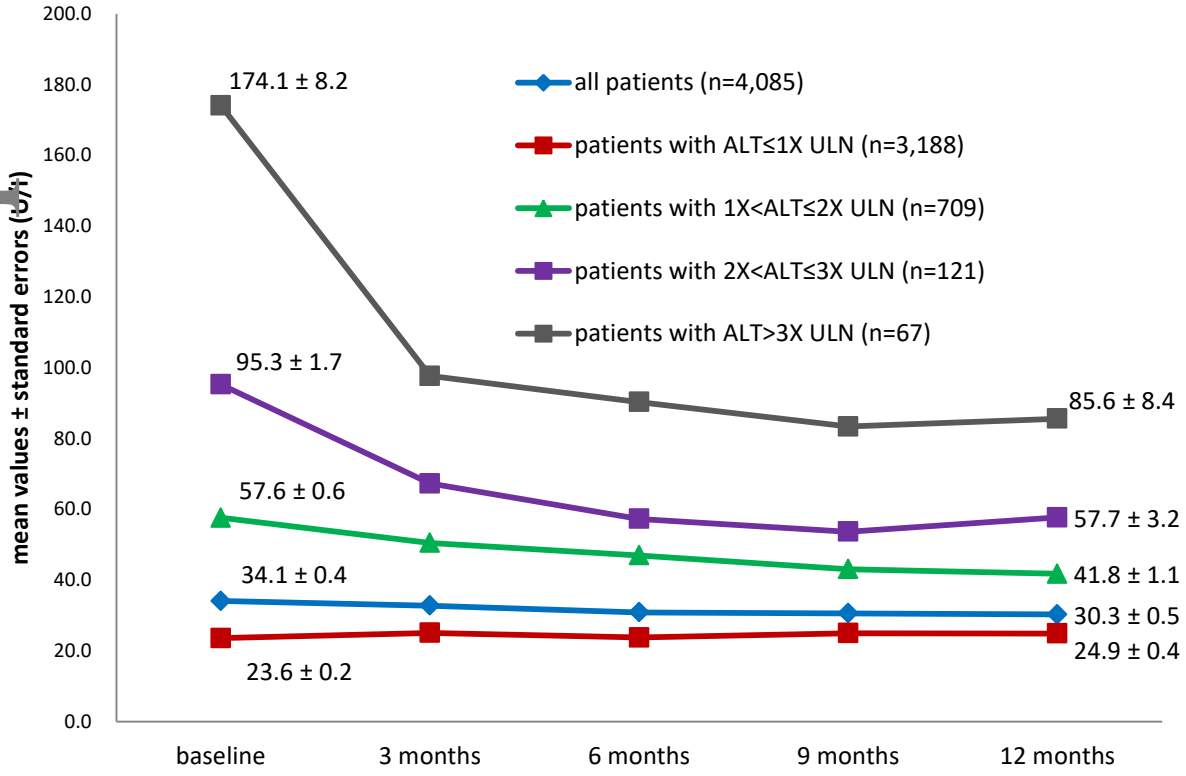


Appendix Figure 4. Subgroup analyses: the changes of HbA1c value after treatment

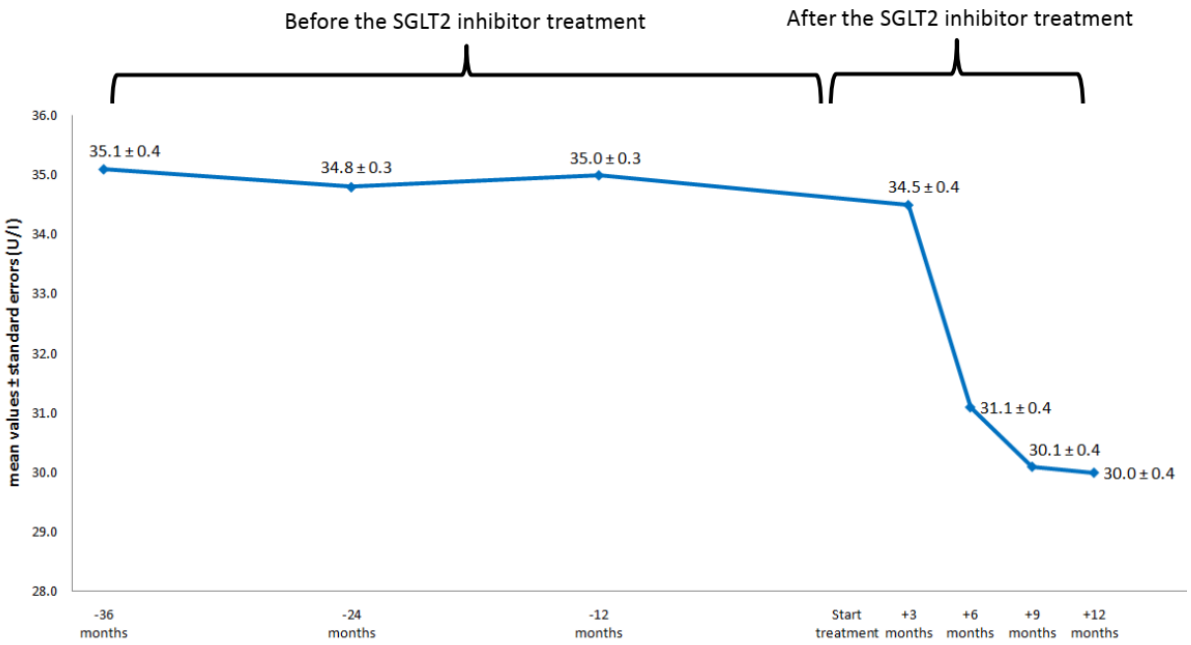
a. >1.7 kg



b. ≤1.7kg



Appendix Figure 5. Subgroup analyses: the changes of body weight after treatment



Appendix Figure 6. Changes in ALT before and after the SGLT2 inhibitor treatment over time (n=8,077)

Appendix Table 1. ICD of Diagnoses for study co-morbidity

Diseases	ICD-9 codes	ICD-10 codes
Hypertension	401, 402, 403, 404, 405	I10, I11, I12, I13, I15, I16
Hyperlipidemia	272	E78
Coronary heart disease	410, 411, 412, 413, 414	I20, I21, I22, I23, I24, I25
Atrial fibrillation	42731	I48
Peripheral artery disease	440	I70, I73
Heart failure	428	I50
Ischemic stroke	433,434	I63
Diabetic retinopathy	2505	E083, E113
Diabetic neuropathy	2506	E084, E114
Diabetic nephropathy	2504	E082, E112
Chronic obstructive pulmonary disease	491, 492, 496	J44
Cancer	140-239	C0-D4

Appendix Table 2. List of co-medications

Drug class	Drug name
Beta blocker	Atenolol, bisoprolol, carvedilol, metoprolol, propranolol,
Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers	Azilsartan, candestartan, captopril, enalapril, fosinopril, irbesartan, losartan, olmesartan, ramipril telmisartan, valsartan
Calcium channel blockers	Amlodipine, diltiazem, felodipine, lercanidipine, nifedipine, verapamil
Diuretics	Acetazolamide, Amiloride, Benzyl hydrochlorothiazide, Bumetanide, Furosemide, Hydrochlorothiazide, Indapamide, Spironolactone
Statin	Atorvastatin, fluvastatin, pitavastatin, rosuvastatin, simvastatin
Fibrate	Fenofibrate, gemfibrozil
Sulfonylurea	Glipizide, gliclazide, glimepiride, glyburide
Dipeptidyl peptidase-4 inhibitors	Alogliptin, linagliptin, saxagliptin, sitagliptin, vidagliptin
Thiazolidinediones	Pioglitzone
Glinides	Mitiglinide, nateglinide, repaglinide
Glucagon-like peptide-1 receptor antagonist	Dulaglutide, exenatide, liraglutide
Insulin	Rapid, short, intermediate and long-acting insulins