

# Predictors of weight reduction effectiveness of SGLT2 inhibitors in diabetes mellitus type 2 patients

FRONTIERS IN ENDOCRINOLOGY

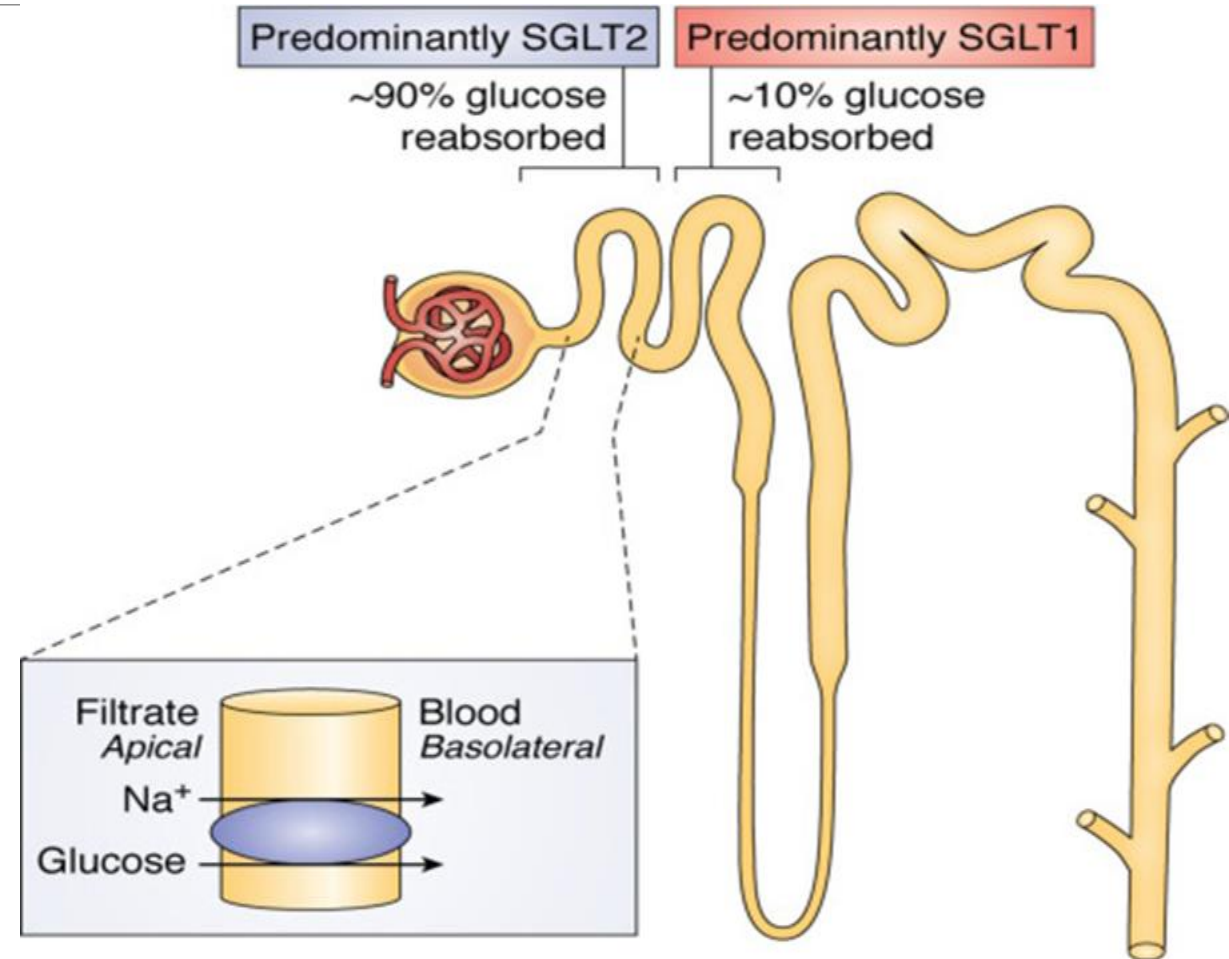
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# SGLT2i Mechanism of action

These agents lower the blood glucose by selectively **inhibiting this co-transporter**, which is expressed almost exclusively in the proximal, convoluted tubule in the kidney.



# Harrison 2022

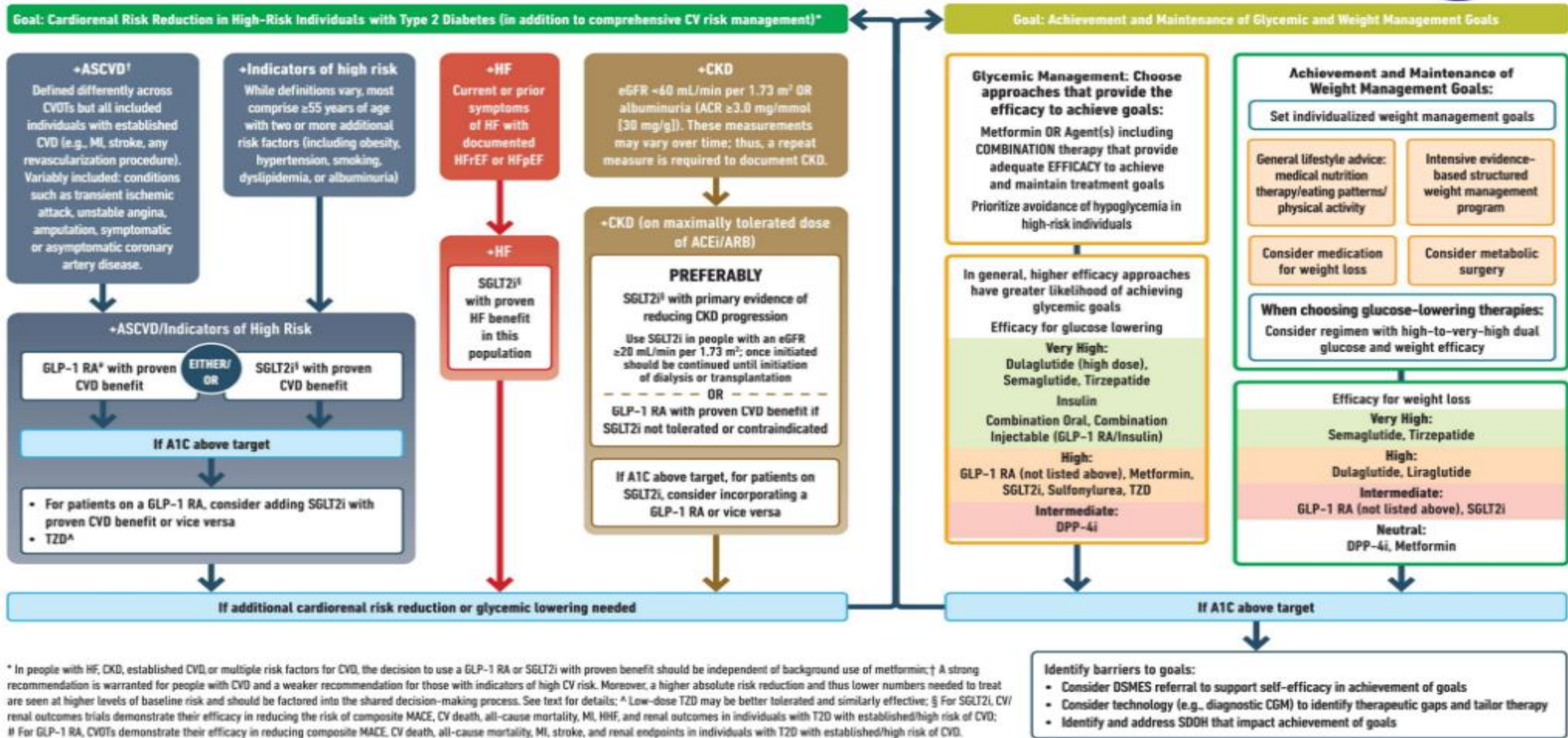
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- the glucose-lowering effect is **insulin independent**
- The loss of urinary glucose may promote **modest weight reduction**
- **3–6 mmHg reduction** in systolic blood pressure
- **urinary and genital mycotic infections** are more common in both men and women
- **Euglycemic DKA** may occur during illness
- All SGLT2 inhibitors may reduce **hospitalization for CHF**
- have all been shown to reduce **progression of diabetic kidney disease**

# USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES



HEALTHY LIFESTYLE BEHAVIORS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)



\* In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin; † A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ‡ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HFrEF, and renal outcomes in individuals with T2D with established/high risk of CVD; ¶ For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and renal endpoints in individuals with T2D with established/high risk of CVD.

# اشکال رایج دارویی در ایران



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# Introduction

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- **Diabesity:** The two most essential components of metabolic syndrome are diabetes mellitus type 2 (T2DM) and obesity
- weight reduction in **GLP-1 receptor agonist** and **SGLT2i**
- SGLT2i has been shown to result in a **slight reduction** in body weight compared to placebo. A meta-analysis of 43 randomized controlled trials comparing SGLT2i with placebo has reported that a mean reduction of **1.88 kg** of body weight was observed in SGLT2i users compared to placebo
- potential mechanisms of weight reduction: **urinary glucose excretion, initially, fluid loss may play a role, caloric loss, activation of lipolysis.**



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- Patients taking SGLT2i have shown **highly variable** weight loss ranging from **2-4%** of initial body weight
  - weight-lowering effect could result from intricate interactions between **non-biological and biological factors**
  - A previous study demonstrated that multiple factors can predict meaningful weight reduction in T2DM patients using SGLT2i, including: **regular exercise, normal renal function, and concurrent use of metformin**
  - That study included only one type of SGLT2i, **dapagliflozin**

# Materials and methods

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retrospective cohort

**Inclusion criteria:** adults aged 18 years and older with T2DM who were first prescribed SGLT2i either as monotherapy or add-on therapy at the Internal Medicine Department, Faculty of Medicine, Chiang Mai University, between 1 January 2018 and 31 December 2022.



INCLUSION  
CRITERIA

# Exclusion criteria

- type 1 diabetes mellitus
- history of GLP1-RA use
- history of herb use
- history of steroid treatment
- duration of follow-up <1 year
- Pregnancy
- chronic kidney disease (CKD)
- Dialysis (peritoneal or hemodialysis)
- bariatric surgery
- other weight-reduction agents
- Uncomplete physical examination and laboratory investigation data



EXCLUSION  
CRITERIA

Follow-up time was defined as the interval from the **starting date of SGLT2i** treatment to the points of interest at **6 and 12** months. **Significant** weight reduction was defined as **>3% weight loss in 12 months.**

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Data obtained from medical records included:

- demographic information(**age and gender**)
- medical history including comorbidities(**HTN, ASCVD, CKD, NAFLD, etc**)
- History of alcohol consumption and tobacco use
- current medication usage(**diabetes drugs, lipid-lowering agents, and anti-hypertensive agents**)
- Anthropometric measurements(**weight, height, and body mass index (BMI)**)
- systolic and diastolic blood pressure
- Biochemical parameters (**HbA1c, FBS, total cholesterol, LDL, HDL, Cr, eGFR**)

**Anthropometric** measurements  
and **biochemical** parameters  
were determined at **baseline** and  
**6 and 12 months**

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# Statistical analysis

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- for **normally** distributed continuous variables( **means & SD**)
- For **non-normally** distributed continuous variables(**medians & IQR**)
- univariable analysis for **normally** distributed variables: **independent t-test**
- univariable analysis for **non-normally** distributed variables: **Wilcoxon rank-sum test**
- analyses of the **predictive factors** for >3% weight loss at one year: **multivariable logistic regression**(reported as OR with 95% CI)
- sample size: at least 250 patients needed to be included to identify the predictors

# Results

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A total of **289** T2DM patients were included in the study categorized into two groups(**significant & no significant weight loss**)

The majority of the cohort were males (n=166, 57.6%)

The median age was **65** years (IQR 59-71)

The median BMI was **25.8** kg/m<sup>2</sup> (IQR 23.4-29)

The median HbA1c was **7.5%** (IQR 6.8-8.5)

The median weight reduction at 1 year was **-2** (IQR -4,0) kg

Of the participants, 45.6% (n=132) achieved a significant weight loss, while 54.4% (n=157) had no significant weight loss



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Median weight reduction at one year in the significant weight loss group was **-4** kg (IQR -6,-3)

in the non-significant weight loss group, the weight reduction was **0** kg (IQR -1, 1.2)

The difference in weight loss between the two groups **was statistically significant**

**Except for body weight change at 12 months, there were no statistically significant differences between the two groups.**

Body weight at 6 months (IQR, kg)	64 (57-74)	67 (60-78)	0.193
Body weight at 12 months (IQR, kg)	66.8 (58.5-74.8)	68 (44.7-79.7)	0.242
Body weight changes at 12 months (IQR, kg)	-4 (-6,-3)	0 (-1, 1.2)	<u>&lt;0.001</u>
Systolic blood pressure (IQR, mmHg)	135 (122-144)	133 (124-142)	0.906
Diastolic blood pressure (IQR, mmHg)	74 (67-83)	75 (68-81)	0.416

# In multivariable analysis:

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**age over 70 years** was found to be associated with a significantly higher likelihood of weight loss (OR 3.26, 95% CI 1.39-7.6, p=0.006)

**Baseline BMI >25 kg/m<sup>2</sup>** also showed a small but statistically significant association with weight loss (OR 1.02, 95% CI 1.01-1.05, p=0.049)

**The use of sulfonylureas** was statistically significantly associated with increased weight loss (OR 2.41, 95% CI 1.15-5.09, p=0.020)

**hydrochlorothiazide (HCTZ) use** was associated with **decreased odds** of weight loss (OR 0.35, 95% CI **0.13-0.96**, p=0.043)

Predictor	OR (95% CI)	p-value			
			Metformin use	1.41 (0.53-3.71)	0.480
			Sulfonylureas use	2.41 (1.15-5.09)	0.020
			Pioglitazone use	0.66 (0.26-1.67)	0.391
Age >70 years	3.26 (1.39-7.6)	0.006	DPP-4 inhibitor use	0.65 (0.31-1.36)	0.262
Male	0.81 (0.35-1.90)	0.642	Insulin use	0.99 (0.40-2.42)	0.988
Baseline BMI >25 kg/m <sup>2</sup>	1.02 (1.01-1.05)	0.049	HCTZ use	0.35 (0.13-0.96)	0.043
Baseline systolic blood pressure	0.99 (0.96-1.01)	0.429	Calcium channel blocker use	0.78 (0.40-1.54)	0.479
Baseline diastolic blood pressure	0.98 (0.95-1.01)	0.632	Baseline HbA1c	1.03 (0.74-1.42)	0.855
NAFLD	0.55 (0.11-2.63)	0.463	HbA1c changes	0.94 (0.71-1.25)	0.700
ASCVD	1.22 (0.50-2.95)	0.650	eGFR	0.44 (0.16-1.22)	0.116
			Patients with creatinine rising >30% after SGLT2i	1.08 (0.51-2.29)	0.827

# Discussion

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there are multiple clinical and biochemical indicators that could potentially assist in predicting significant weight loss in patients with T2DM following treatment with SGLT2i:

**age over 70 years,**

**baseline BMI >25 kg/m<sup>2</sup>,**

**sulfonylureas users,**

**and HCTZ non-users**

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In congruence with previous studies, approximately **half (45.6%)** the T2DM patients in the present study versus **61% in a previous study** had **significant weight** loss after using SGLT2i.

**Unlike** in this present study, having normal renal function and using metformin **had no significant association** with weight reduction.

**The previous** study also reported **no significant association** between significant weight reduction and older age, baseline BMI >25 kg/m<sup>2</sup>, sulfonylureas use, or non-use of HCTZ.

## age over 70 years

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Physiologically, adults aged over 70 years old had a loss of fat-free mass, especially skeletal muscle, and an **increase in fat mass**. As mentioned earlier, the **late phase** of weight loss from SGLT2i can be explained by **fat loss**.

elderly patients tended to have **higher adherence** to diabetes medications than younger patients.(cannot be confirmed, as data regarding medication adherence **was not reported** in this cohort)

## baseline BMI >25 kg/m<sup>2</sup>

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Based on WHO criteria for Asian individuals, a BMI over 25 kg/m<sup>2</sup> was defined as **obesity**.

**more enthusiasm for lifestyle modification**

The p-value of this factor showed a **marginally** significant association with meaningful weight loss



# use of sulfonylureas

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weight gain of approximately 2.0-2.3 kg( two mechanisms: 1) **hypoglycemia** ,2) **increased insulin level** which leads to lipogenesis )

this **excess fat deposition** could be reduced by the effects of SGLT2i, which can promote fat loss in the **latter phase** of the weight reduction mechanism.

## use of HCTZ

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HCTZ has been reported to be associated with **insulin resistance** and an increase in **visceral adipose tissue**. This population tended to have a high incidence of **metabolic syndrome and obesity**, which may have resulted in resistance to SGLT2i-induced weight loss.

# Strengths of study

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it investigated **various types** of SGLT2i, making the results of the present study **more generalizable**.

used multivariable **logistic** regression analysis incorporating **multiple confounders** for adjustment, which made the results more interpretable and more **accurate**.

The results highlight the potential role of **individual characteristics** and **concurrent medication used** in determining weight loss outcomes with SGLT2i therapy.

# limitations

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**retrospective** study design and the reliance on patient records.

not be applicable to all patient populations due to the **specific inclusion criteria** of the study and the fact that the study population was primarily comprised of **Asians**.

**Body composition** was not measured in this cohort, so the underpinning mechanism of weight reduction could not be fully elucidated.

# Conclusion

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This study identified multiple potential predictors of significant weight loss following SGLT2i therapy in T2DM patients, including **advanced age, higher BMI, sulfonylureas use**, and **HCTZ non-use**. These findings could help **optimize** the use of SGLT2i and provide an **efficient** treatment strategy for using SGLT2i for patients with T2DM. Further studies are needed to confirm these findings and elucidate the underlying mechanisms.