Hanmi 한미약품

SGLT2i :

Beyond Glucose Lowering Effects

제2형 당뇨병 치료제
다파론® 정 5mg 10mg
(다파글리플로진비스실산염)

제2형 당뇨병 치료제
다파론듀오® 서방정 5/500mg 5/1000mg 10/500mg 10/1000mg
(다파글리플로진비스실산염/메트포르민염산염)

제2형 당뇨병 치료제
다파론® 정 5mg 10mg
(다파글리플로진비스L-프롤린)

제2형 당뇨병 치료제
다파론듀오® 서방정
(다파글리플로진비스L-프롤린/메트포르민염산염)

Contents

제2형 당뇨병 치료제
다파론® 정 5mg 10mg
(다파글리플로진비스L-프롤린)

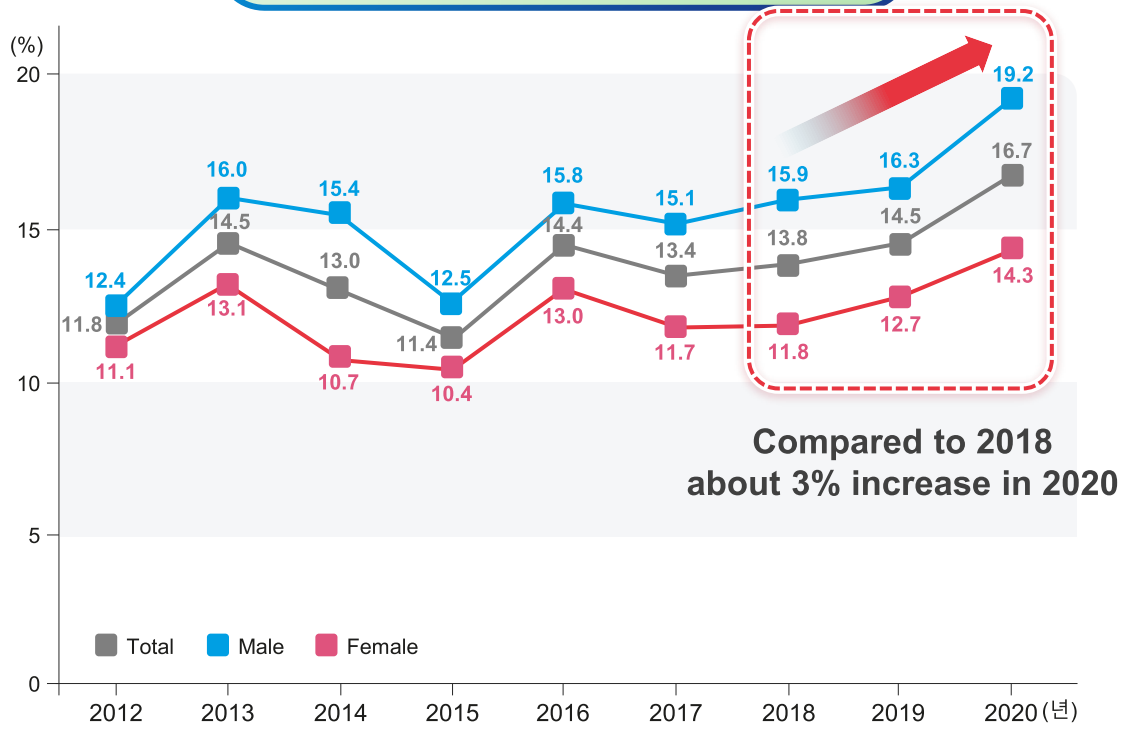
제2형 당뇨병 치료제
다파론듀오® 서방정
(다파글리플로진비스L-프롤린/메트포르민염산염)

Current Status of Diabetes & Diabetes Treatment Guidelines

Diabetes prevalence and Control rate

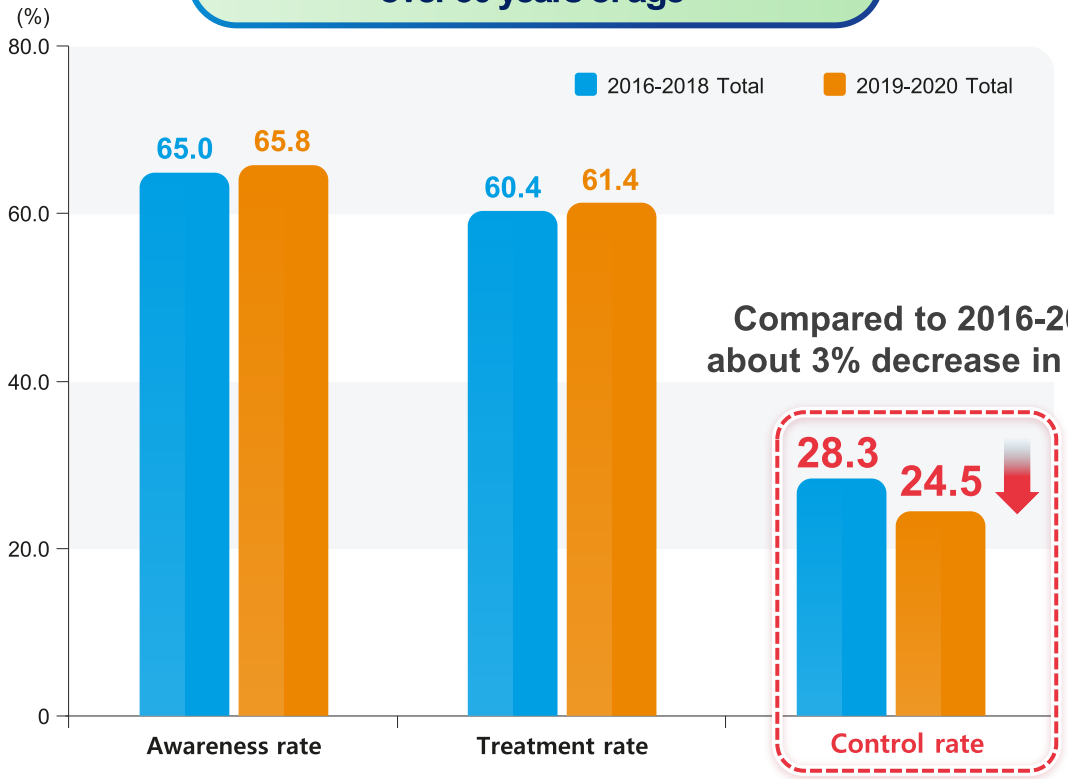
The prevalence of diabetes in Korea is continuously increasing, and the drug treatment rate for diabetic patients has increased, but the control rate of achieving glycated hemoglobin less than 6.5% has actually decreased.

Diabetes prevalence and population changes over the past 9 years



Compared to 2018
about 3% increase in 2020

Diabetes management level for adults over 30 years of age



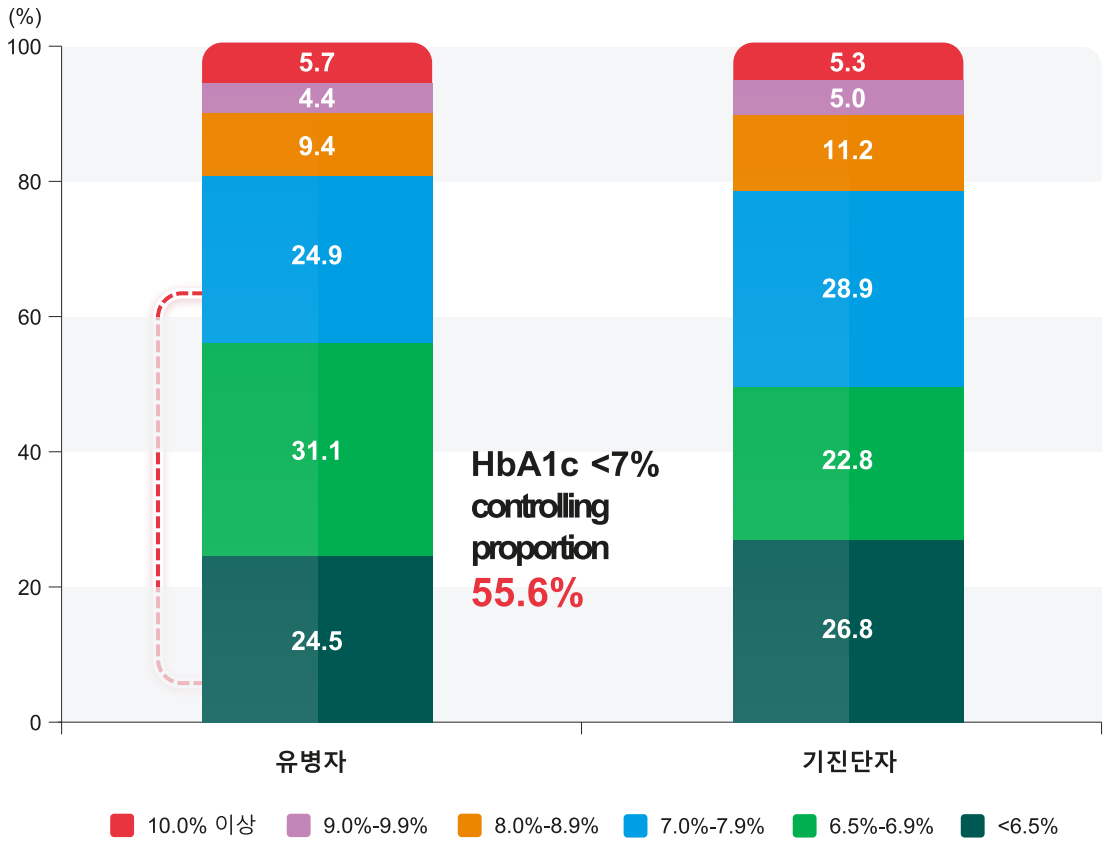
Compared to 2016-2018
about 3% decrease in 2020

- **당뇨병 유병자**: 공복혈당이 126 mg/dL 이상이거나 의사진단을 받았거나 당뇨병약제로 치료 중이거나, 당화혈색소가 6.5% 이상인 경우
- **당뇨병 인지율**: 당뇨병 유병자(당화혈색소 기준) 중 의사로부터 당뇨병 진단을 받은 분율
- **당뇨병 치료율**: 당뇨병 유병자(당화혈색소 기준) 중 현재 당뇨병약제로 치료 중인 분율
- **당뇨병 조절률**: 당뇨병 유병자(당화혈색소 기준) 중 당화혈색소가 6.5% 미만인 분율

References 1. 대한당뇨병학회. Diabetes fact sheet in Korea 2022. 2. 대한당뇨병학회. Diabetes fact sheet in Korea 2020.

Diabetes management level and Glucose control status

In the case of diabetes treatment, the control rate is 24.5%, with about 75% of patients not reaching the control target, and the control rate below 7.0% of glycated hemoglobin is only half, requiring additional glucose control.



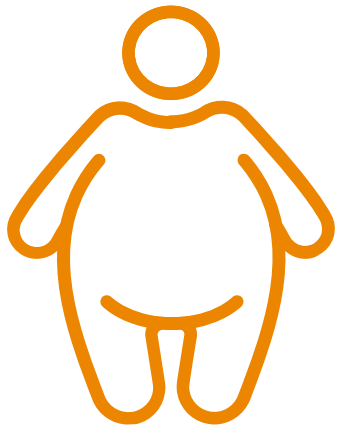
- **당뇨병 유병자**: 공복혈당이 126 mg/dL 이상이거나 의사진단을 받았거나 당뇨병약제로 치료 중이거나, 당화혈색소가 6.5% 이상인 경우
- **당뇨병 인지율**: 당뇨병 유병자(당화혈색소 기준) 중 의사로부터 당뇨병 진단을 받은 분율
- **당뇨병 치료율**: 당뇨병 유병자(당화혈색소 기준) 중 현재 당뇨병약제로 치료 중인 분율
- **당뇨병 조절률**: 당뇨병 유병자(당화혈색소 기준) 중 당화혈색소가 6.5% 미만인 분율

Reference 1. 대한당뇨병학회. Diabetes fact sheet in Korea 2022.

Diabetes and Comorbidites

Because the proportion of diabetes patients with obesity, high blood pressure, and hypercholesterolemia is high, integrated management is required, including not only glucose control, but also weight, blood pressure, and LDL-C control.

+ Obesity
54.4%



+ Hypertension
58.6%

+ Hypercholesterolemia
76.1%

- **당뇨병 유병자**: 공복혈당이 126 mg/dL 이상이거나 의사진단을 받았거나 당뇨병약제로 치료 중이거나, 당화혈색소가 65% 이상인 경우
- **비만(체질량지수 기준)(Kg/m²)** : ① <18.5 저체중 ② 18.5-22.9 정상체중 ③ 23.0-24.9 비만전단계 ④ 25.0-29.9 1단계 비만 ⑤ 30.0-34.9 2단계 비만 ⑥ 35.0 이상 3단계 비만
- **고혈압 유병률**: 수축기 혈압이 140 mmHg 이상이거나 이완기혈압이 90 mmHg 이상 또는 고혈압약제를 복용한 분율.
- **고혈압 조절률**: 수축기 혈압이 140mmHg 미만이고 이완기혈압이 85mmHg 미만인 분율
- **고콜레스테롤혈증 유병률**: 혈중 LDL-C이 100 mg/dL 이상이거나 콜레스테롤강하제를 복용한 분율(%)
- **고콜레스테롤혈증 조절률**: 혈중 LDL-C이 100 mg/dL 미만인 분율(%)

Ref) 대한당뇨병학회. Diabetes fact sheet in Korea 2022.

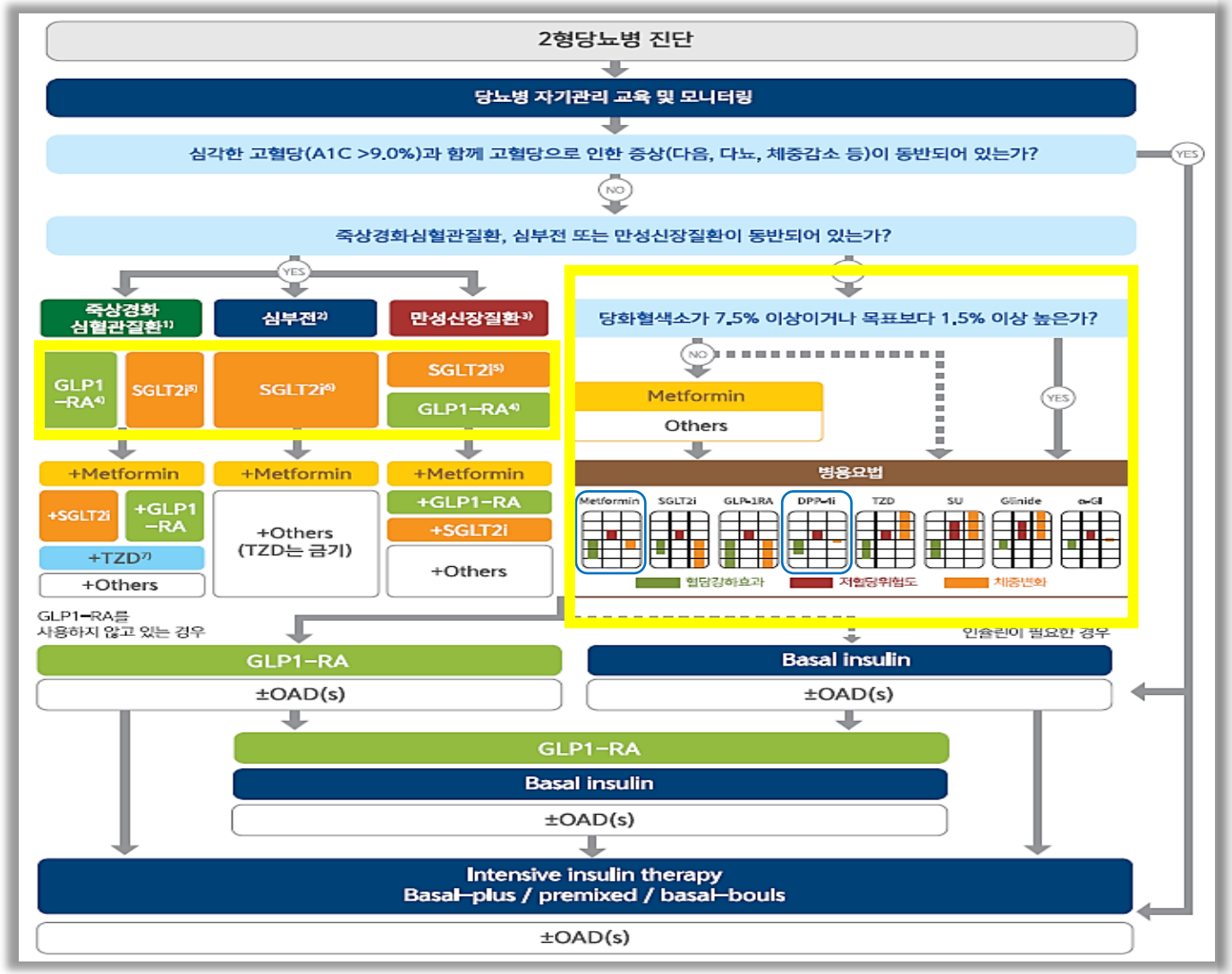
Type 2 Diabetes Medication Treatment Algorithm (2023)

Korean Diabetes Association guideline

Start diabetes treatment → Recommend appropriate drug treatment considering glucose lowering effect, risk of hypoglycemia, side effects, comorbidities etc.

Combination therapy → If the target Hb1Ac is not reached, an increase in the existing drug dose or combination therapy with other drugs (two or more drugs) should be implemented as soon as possible.

Comorbidities → In cases with atherosclerotic cardiovascular disease, heart failure, and chronic kidney disease, GLP1 RA and SGLT2 inhibitors are considered first.



α-GI, alpha-glucosidase inhibitors; ACS, acute coronary syndrome; CHD, coronary heart disease; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; MI, myocardial infarction; SGLT2i, sodium-glucose cotransporter 2 inhibitors; OAD, oral antidiabetic drug; SU, sulfonylurea; TZD, thiazolidinedione

Ref. 당뇨병 진료지침 요약. 2023. 제8판. 대한당뇨병학회

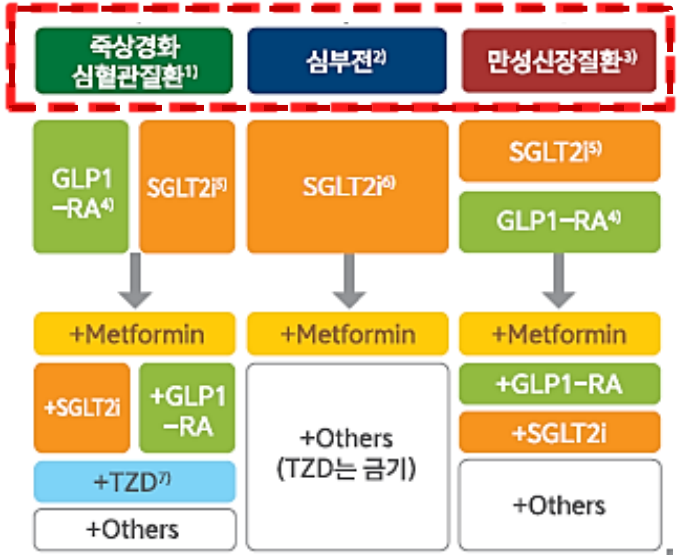
Recommendations for Type 2 Diabetes treatment(2023)

According to the Korean Diabetes Association guidelines,
it is recommended to select SGLT2i drugs
in cases with heart failure, chronic kidney disease, or atherosclerotic cardiovascular disease.

권고 10. 심부전을 동반한 경우 심부전이익이 입증된 SGLT2억제제를 당화혈색소 수치와 무관하게 우선 사용하고 금기나 부작용이 없는 한 유지 [무작위대조연구, 일반적권고]

권고 11. 알부민뇨가 있거나 추정사구체여과율이 감소한 경우 신장이익이 입증된 SGLT2억제제를 당화혈색소 수치와 무관하게 우선 사용하고 금기나 부작용이 없는한 유지[무작위대조연구, 일반적권고]

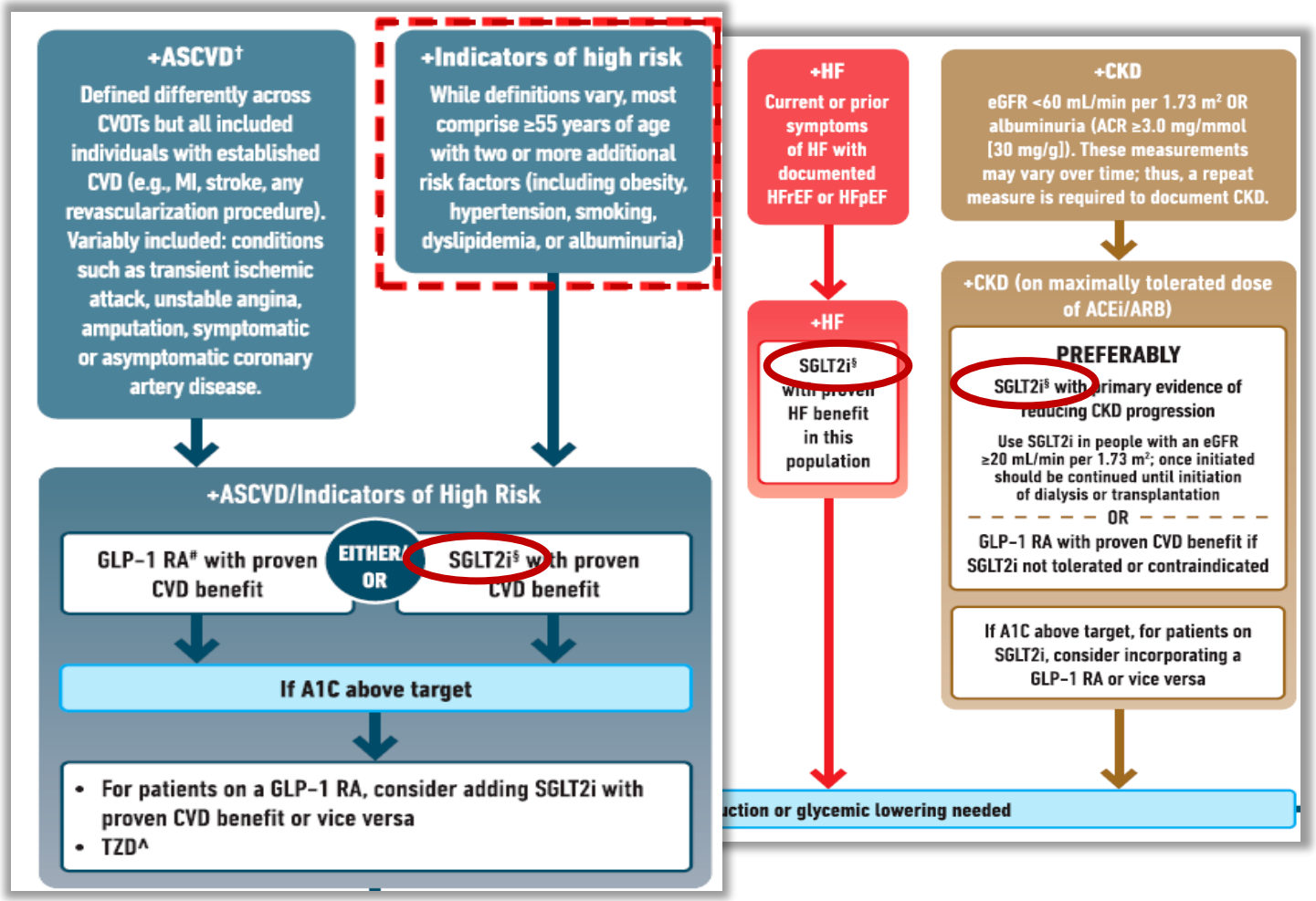
권고 12. 죽상경화심혈관질환을 동반한 경우 심혈관이익이 입증된 GLP-1수용체작용제 혹은 SGLT2억제제를 포함한 치료를 우선[무작위대조연구, 일반적권고]



Ref.> 당뇨병 진료지침 전문. 2023. 제8판. 대한당뇨병학회

2023 American Diabetes Association(ADA) Guideline

The 2023 ADA guidelines recommended SGLT2i first for type 2 diabetes patients with ASCVD, HF, and CKD, as well as type 2 diabetes patients at high cardiovascular risk.



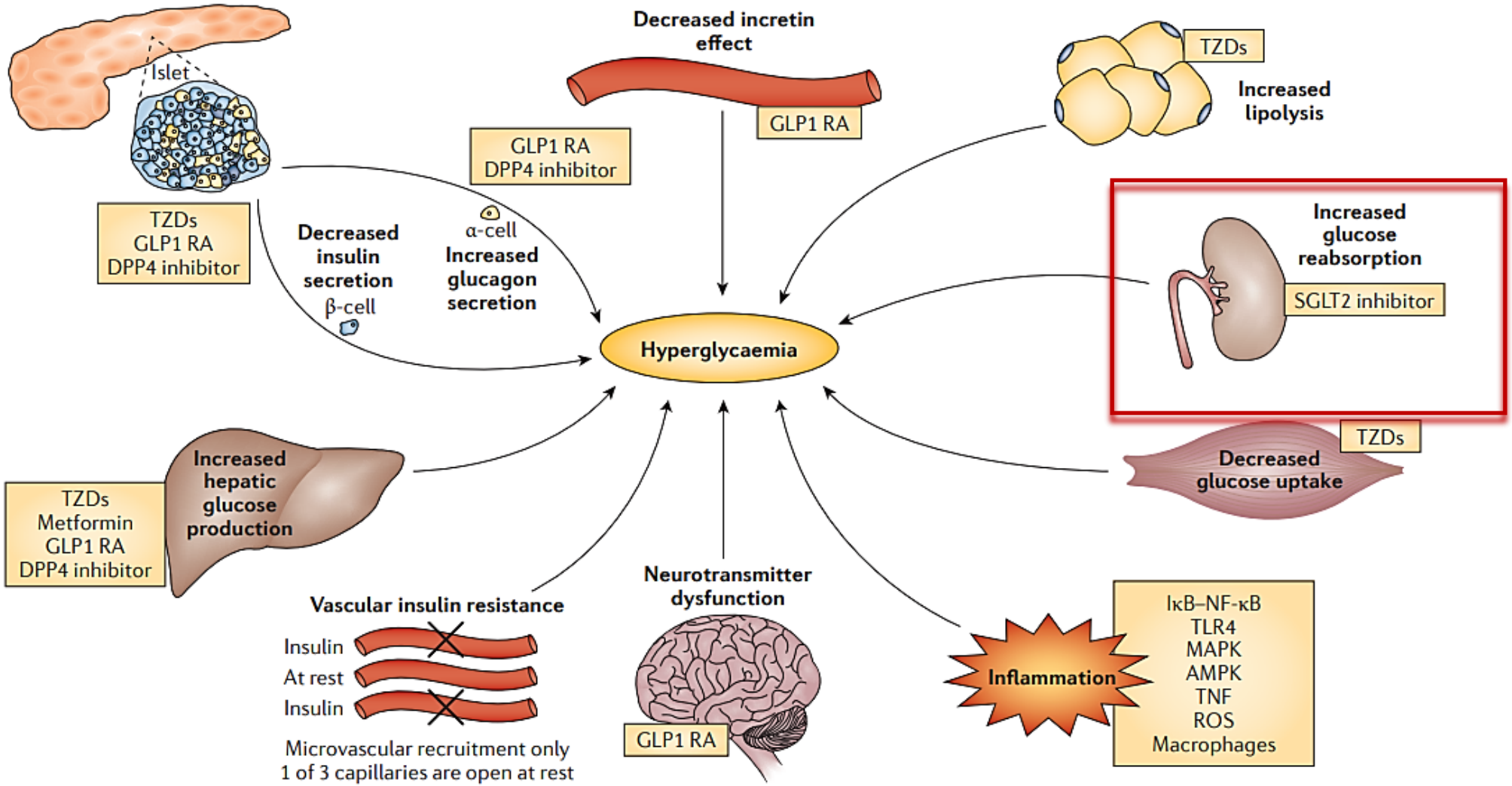
ACEi, angiotensin-converting enzyme inhibitor; ACR, albumin-to-creatinine ratio; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; CGM, continuous glucose monitoring; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; DPP-4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalization for heart failure; MACE, major adverse cardiovascular events; MI, myocardial infarction; SDOH, social determinants of health; SGLT2i, sodium-glucose cotransporter 2 inhibitor; T2D, type 2 diabetes; TZD, thiazolidinedione.

Ref.> ElSayed NA, Aleppo G, Aroda VR, et al. *Diabetes Care*. 2023;46(Suppl 1):S140-S157.

Glucose Lowering Effect

Type 2 Diabetes Pathogenesis : "The Ominous Octet"

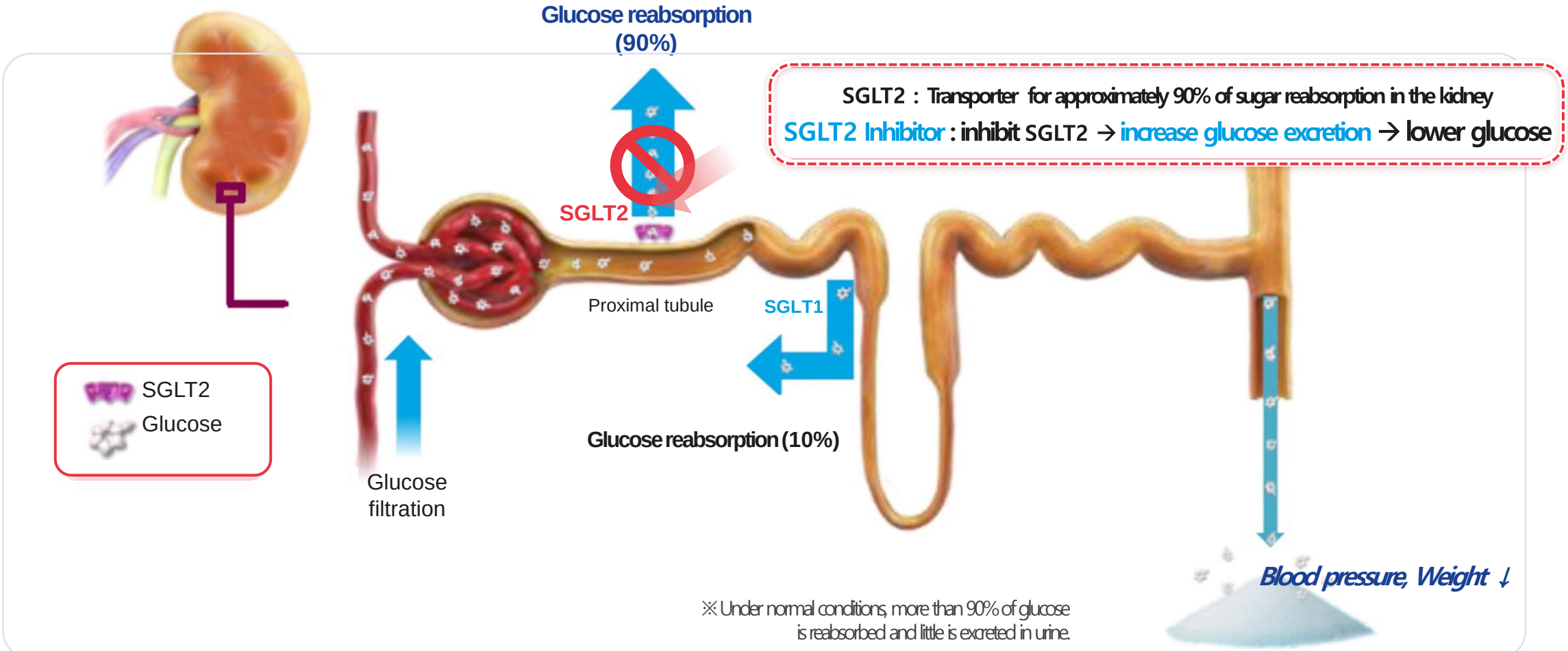
Increased glucose reabsorption by SGLT2 in the kidney worsens hyperglycemia.



SGLT2, sodium glucose cotransporter 2; DPP-4, dipeptidyl peptidase-4; GLP-1 RA, glucagon-like peptide 1 receptor agonist; TZD, thiazolidinedione

Ref) DeFronzo RA, Ferrannini E, Groop L, et al. Type 2 diabetes mellitus. Nat Rev Dis Primers. 2015 Jul 23;1:15019.

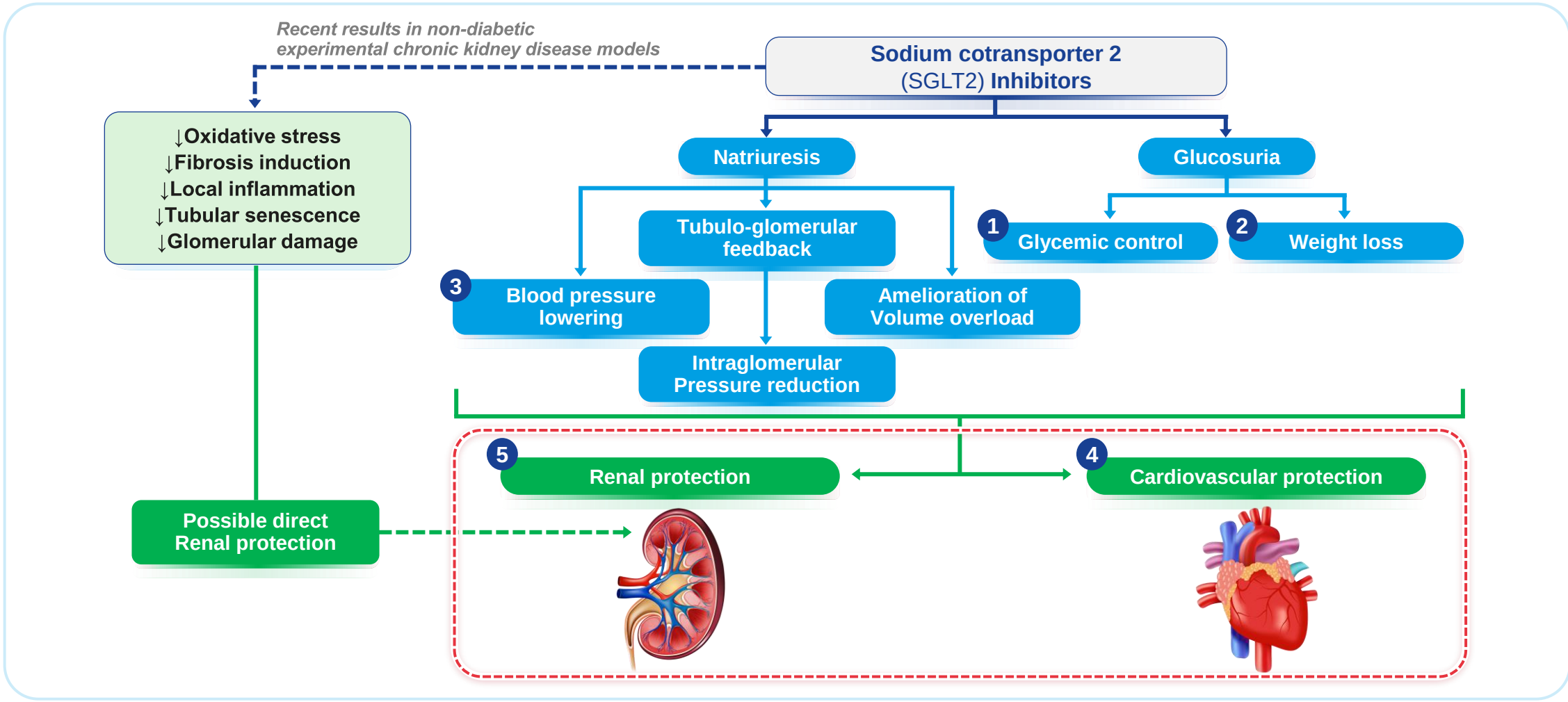
SGLT2 (Sodium GLucose coTransporter 2) Inhibitor's Mechanism of Action



SGLT2i, sodium glucose cotransporter 2 inhibitor.

Ref) Jung CH, Jang JE, Park JY. A Novel Therapeutic Agent for Type 2 Diabetes Mellitus: SGLT2 Inhibitor. Diabetes Metab J. 2014 Aug;38(4):261-73.

5 Characteristics of SGLT2-I



Ref) Zelniker, T.A. et al. J Am Coll Cardiol. 2020;75(4):422-34.

Comparison of Glucose lowering effects of Diabetes Medications (Harrison's Principles 21th edition)

SGLT2-I vs. DPP4-I → equal or higher glucose lowering effect

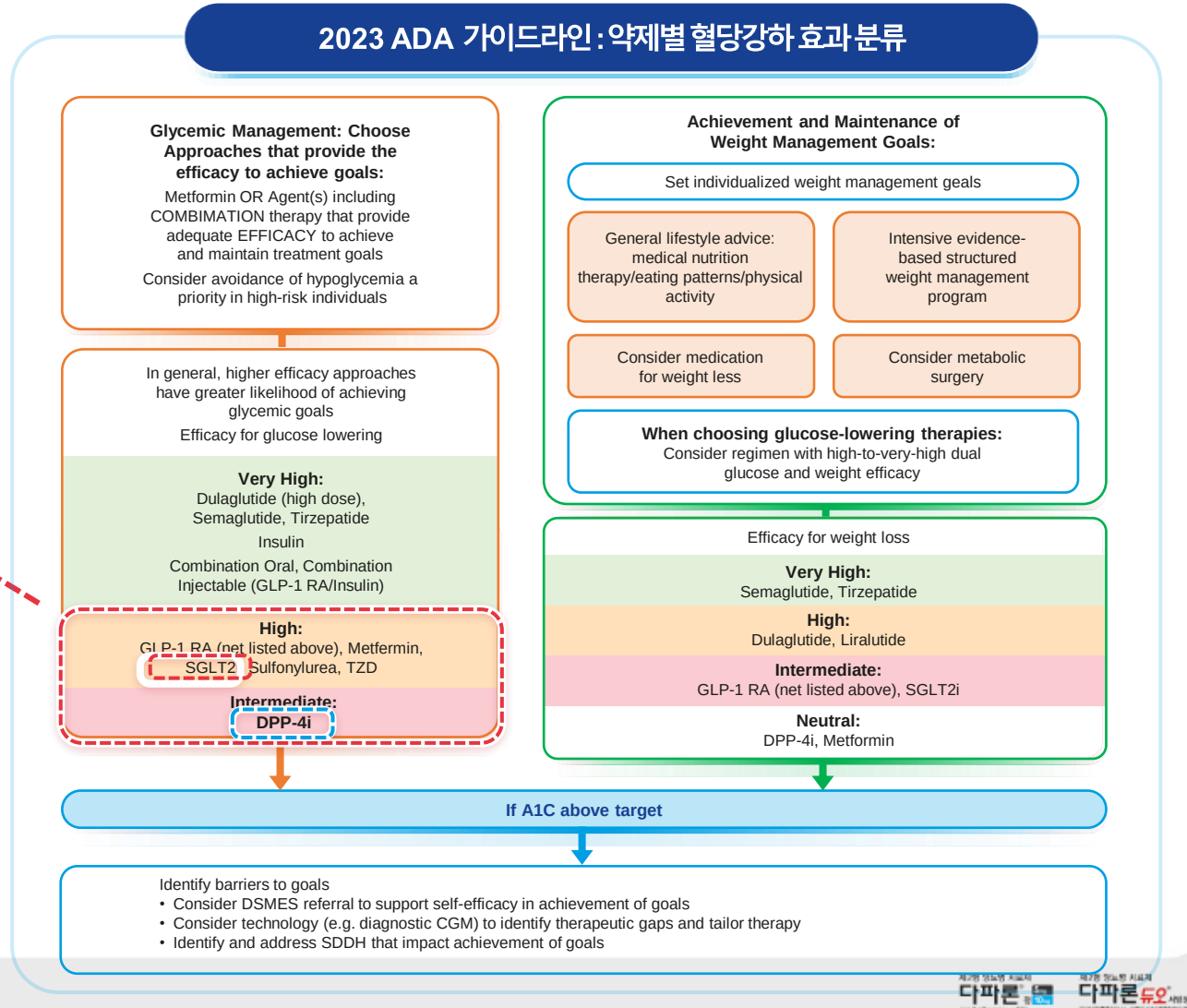
	Mechanism of Action	Examples[a]	HbA_{1c} Reduction (%) [b]
Biguanides[c*]	↓ Hepatic glucose production	Metformin	1-2
α-Glucosidase inhibitors[c]**	↓ GI glucose absorption	Acarbose, miglitol, voglibose	0.5-0.8
DPP4 inhibitors[c*]**	Prolong endogenous GLP-1 action	Alogliptin, anagliptin, gemigliptin, linagliptin, saxagliptin, sitagliptin, teneligliptin, vildagliptin	**0.5-0.8**
Insulin secre-tagogues: sulfonylureas[c*]	↑ Insulin secretion	Glibornuride, gliclazide, glimepiride, glipizide, gliquidone, glyburide, glyclopyramide	1-2
Insulin secre-tagogues: nonsulfonylureas[c*]**	↑ Insulin secretion	Nateglinide, repaglinide, mitiglinide	0.5-1.0
SGLT-2 inhibitors[***]	↑ Urinary glucose excretion	Canagliflozin, dapagliflozin, empagliflozin	**0.5-1.0**
Thiazolidinediones[c*]**	↓ Insulin resistance, ↑ glucose utilization	Rosiglitazone, pioglitazone	0.5-1.4

[a]Examples are approved for use in the United States; others are available in other countries. Examples may not include all agents in the class. [b]HbA_{1c} reduction (absolute) depends partly on starting HbA_{1c}. [c]Used for treatment of type 2 diabetes. [d]Used in conjunction with insulin for treatment of type 1 diabetes. Cost of agent in the United States. *low, **moderate, ***high, ****variable.
CHF, congestive heart failure; CV, cardiovascular; DM, diabetes mellitus; GI, gastrointestinal; DKA, diabetic ketoacidosis; GLP-1, glucagon-like peptide-1; DPP4i, dipeptidyl peptidase-4 inhibitor; SGLT2i, sodium-glucose cotransporter 2 inhibitors

SGLT2 inhibitors vs. DPP4 inhibitors : Glucose Lowering Effect

SGLT2i is evaluated as a drug with a higher weight loss effect compared to other classes in the KDA guidelines, and is classified as a drug with a stronger glucose lowering effect than DPP4i in the ADA guidelines.

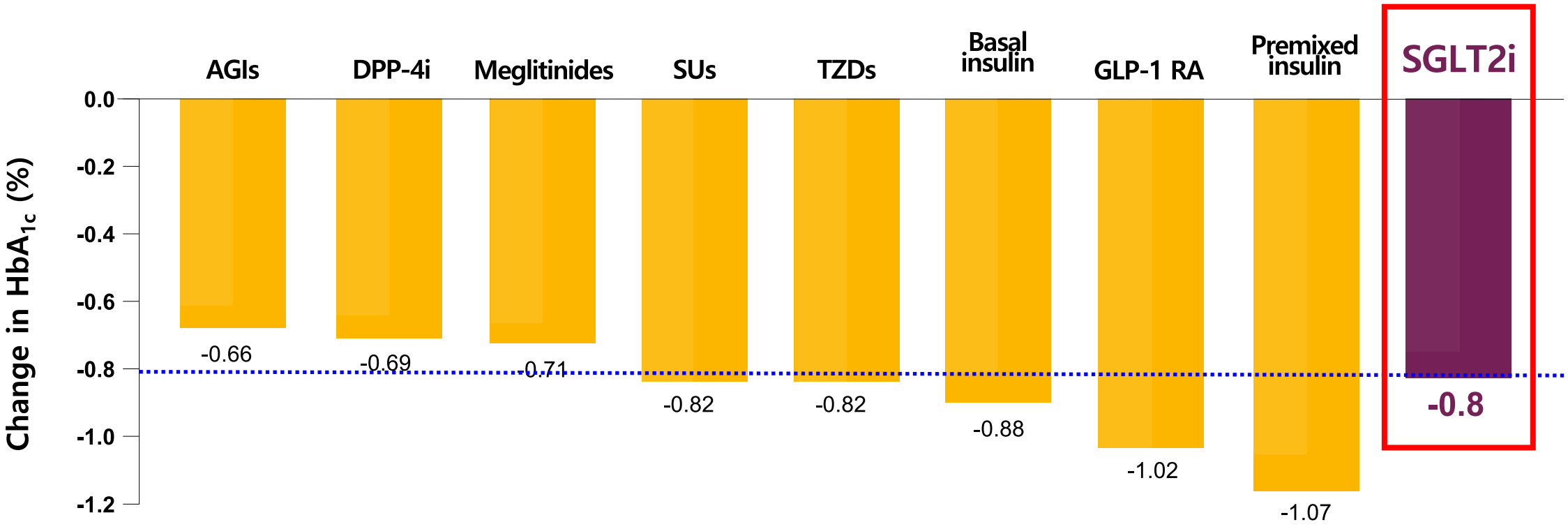
[Efficacy for Glucose Lowering]
- **High : SGLT2i**
- **Intermediate : DPP4i**



Ref. 1) ElSayed NA, et al. Diabetes Care. 2023 Jan 1;46(Suppl 1):S140-S157.

SGLT2-I Add-on to Metformin : Glucose Lowering Effect

In a meta-analysis comparing other diabetes treatments,
when SGLT2-I was used in combination with Metformin,
additional 0.8% reduction in glycated hemoglobin (HbA1c).



AGI, α glucosidase inhibitor; SGLT2i, sodium glucose sotransporter-2 inhibitor.

*All antihype3rglycemic classes were significantly different vs placebo.+An estimate of HbA1c reduction; SGLT2 inhibitors were not included in the network meta analysis[2]

Ref) 1. Liu SC, et al. Diabetes Obes Metab. 2012;14:810-820 2. Fujita Y, et al. J Diabetes Investig. 2014;5:2650275.

Dapagliflozin Mono & Combination & Initial Combination : Glucose Lowering Effect

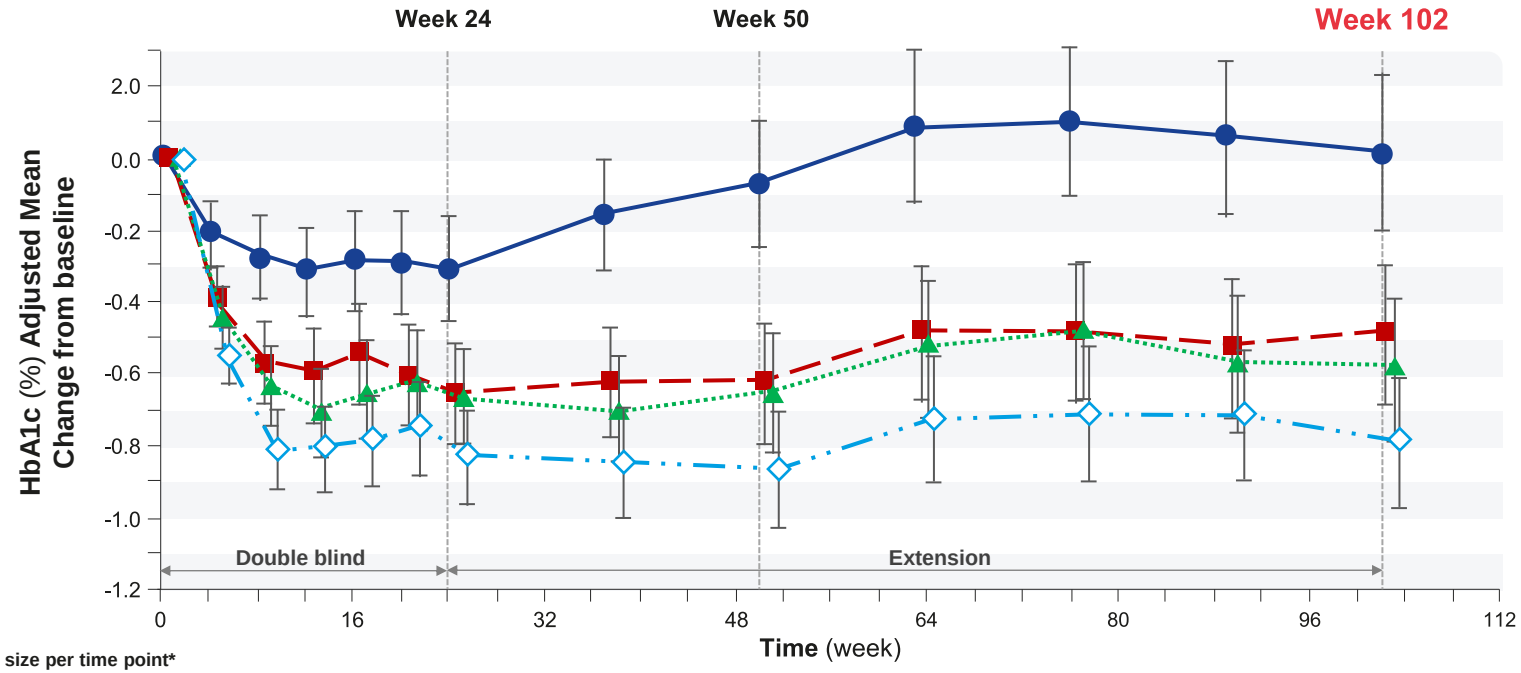
Dapagliflozin has shown excellent hypoglycemic effects in diabetic patients as monotherapy and in combination with various drugs.

MET, metformin; **SU**, sulfonylurea; **DPP-4**, dipeptidyl peptidase-4; **OAD**, oral antidiabetic drug.

References **1.** Ji L, et al. Clin Ther. 2014 Jan 1;36(1):84-100.e9. **2.** Henry RR, et al. Int J Clin Pract. 2012 May;66(5):446-56. **3.** Bailey CJ, et al. Lancet. 2010 Jun 26;375(9733):2223-33. **4.** Matthaei S, et al. Diabetes Care. 2015 Mar;38(3):365-72. **5.** Mathieu C, et al. Diabetes Care. 2015 Nov;38(11):2009-17. **6.** Wilding JP, et al. Ann Intern Med. 2012 Mar 20;156(6):405-15.

Dapagliflozin Add-on to Metformin (Long-term therapy) : Glucose Lowering Effect

Additional combination of Dapagliflozin with Metformin showed a continuous hypoglycemic effect when administered for a long period (102 weeks).



Sample size per time point*

PBO+MET n=	133	128	127	120	115	102	100	96	74	60	46	38	28
DAPA 2.5mg+MET n=	135	133	133	128	127	118	117	115	96	82	65	57	36
DAPA 5mg+MET n=	133	131	131	128	127	122	118	116	94	84	64	59	47
DAPA 10mg+MET n=	132	130	130	126	128	114	117	113	102	96	80	75	57

Adjusted Mean Change from Baseline at week 102 (95% CI)

+0.02 % (-0.20, 0.23)
PBO + MET

-0.48 %(-0.68, -0.29),
p=0.0008
DAPA 2.5 mg + MET

-0.58 % (-0.77, -0.39),
p<0.0001
DAPA 5 mg + MET

-0.78 % (-0.97, -0.60),
p<0.0001
DAPA 10 mg + MET

p value: *vs.* PBO + MET

-0.80%
Difference
(-1.08, -0.52)

Study Design

Metformin 단독요법으로혈당이조절되지않는T2DM 환자(HbA1C 7-10%)를대상으로dapagliflozin군(2.5 mg, n=137; 5 mg, n=137; or 10 mg, n=135) 또는위약군(n=137)으로무작위배정하여오픈라벨의metformin (≥1500 mg) 과 함께102주간(24주+78주 extension) 투여후혈당강화효과를비교한다기관,평행군,이중맹검,3상 임상시험

DAPA, dapagliflozin; **MET,** metformin; **PBO,** placebo; **CI,** confidence interval.

Ref) Bailey CJ, Gross JL, Hennicken D, et al. Dapagliflozin add-on to metformin in type 2 diabetes inadequately controlled with metformin: a randomized, double-blind, placebo-controlled 102-week trial. BMC Med. 2013 Feb 20;11:43.

제2형 당뇨병 치료제
다파론® 정 5mg 10mg
(다파글리플로진비스L-프롤린)

제2형 당뇨병 치료제
다파론듀오® 서방정
(다파글리플로진비스L-프롤린/메트포르민염산염)

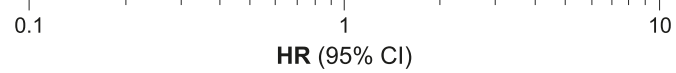
Safety & Medication Guidance

No Increased Risk of CV Events

A meta-analysis of cardiovascular events in 21 phase 2b/3 clinical trials using Dapagliflozin found no increased risk of major cardiovascular events (cardiovascular death, stroke, myocardial infarction, and hospitalization for unstable angina).

MACE + UA and MACE

Subgroup	DAPA		Control		Favours DAPA ← → CTRL	HR (95% CI)
	n/N	Event rate/ 100 p-y	n/N	Event rate/ 100 p-y		
MACE+UA						
Overall	95/5699	1.46	81/3240	2.15		0.787 (0.579, 1.070)
CVD History	67/1826	2.94	61/1333	3.76		0.806 (0.562, 1.156)
Elderly patients with CVD risk	33/653	4.19	32/535	5.06		0.824 (0.497, 1.365)
MACE						
Overall	72/5418	1.15	62/3101	1.69		0.772 (0.543, 1.097)
CVD History	50/1799	2.21	45/1325	2.76		0.802 (0.527, 1.221)
Elderly patients with CVD risk	26/653	3.28	23/535	3.61		0.916 (0.512, 1.640)



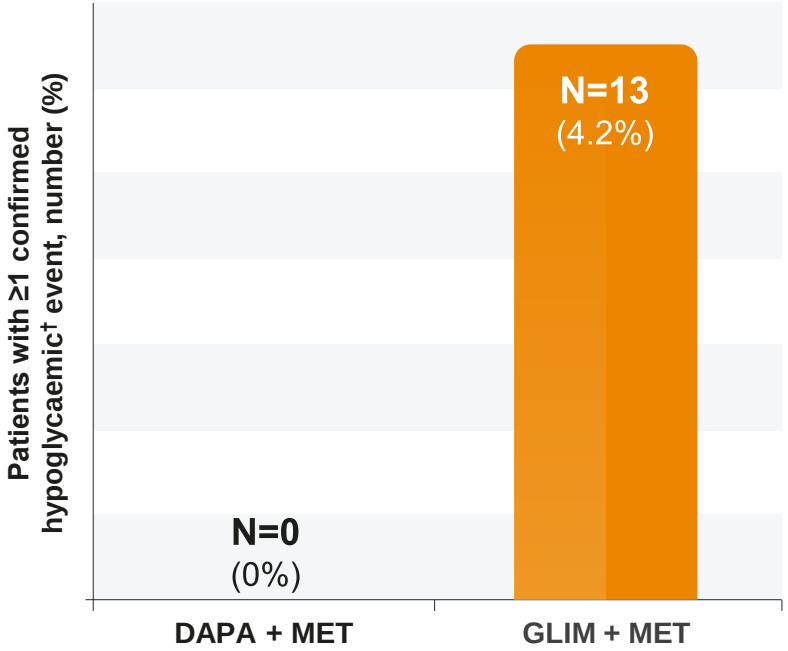
Data presented for the overall population, the subgroup of patients with a history of CVD (CVD history) and the subgroup of elderly patients aged ≥65 years with a history of CVD and hypertension (Elderly patients with CVD risk).
n is the number of patients with an event; N is the number of patients in treatment group.
CI confidence interval, CTRL control, CVD cardiovascular disease, DAPA dapagliflozin, HR hazard ratio, MACE major adverse cardiovascular events (cardiovascular death, myocardial infarction and stroke), MACE + UA MACE plus unstable angina, p–y = patient years.

Ref) Sonesson C, Johansson PA, Johnsson E, Gause-Nilsson I. Cardiovascular effects of dapagliflozin in patients with type 2 diabetes and different risk categories: a meta-analysis. Cardiovasc Diabetol. 2016 Feb 19;15:37.

Dapagliflozin vs. Sulfonylurea : Low incidence of Hypoglycemia

With Metformin, Dapagliflozin showed a significantly lower incidence of hypoglycemia compared to SU (glimepiride).

Incidence of Hypoglycaemia



†**Confirmed hypoglycaemia**: typical symptoms with glucose ≤2.8 mmol/L (≤50 mg/dL)

Adverse event category	Number (%) of patients	
	DATA + MET (n = 313)	GLIM + MET (n = 312)
Hypoglycaemia, number of events (proportion of total events in each category, %)[a] prior to rescue		
Overall events (N = 358)	10 (2.8)	329 (91.9)
Major hypoglycaemia[b] (N = 0)	0	0
Episode of hypoglycaemia[c] (N = 224)	1 (0.4)	216 (96.4)
Other episode of hypoglycaemia[d] (N = 65)	7 (10.8)	48 (73.8)
Confirmed hypoglycaemia[e] (N = 26)	0	25 (96.2)
Asymptomatic hypoglycaemia[f] (N = 69)	2 (2.9)	65 (94.2)

[a] Percentages reflect total number of each type of event across all treatment groups.
[b] Major hypoglycaemic episode: symptomatic episode requiring external assistance with glucose <3.0 mmol/L (<54 mg/dL).
[c] Hypoglycaemia: symptomatic episode with glucose ≤3.9 mmol/L (≤70 mg/dL).
[d] Other episode of hypoglycaemia: symptomatic episode, with or without glucose >3.9 mmol/L (>70 mg/dL).
[e] Confirmed hypoglycaemia: typical symptoms with glucose ≤2.8 mmol/L (≤50 mg/dL).
[f] Asymptomatic hypoglycaemia: event with absence of symptoms but with glucose ≤3.9 mmol/L (≤70 mg/dL).

Study Design

Among 939 T2DM patients (HbA1C 7.5-10.5%) who had taken metformin (≥1500 mg/day) for more than 8 weeks, dapagliflozin 10 mg (n=314), dapagliflozin 10 mg + saxagliptin 5 mg (n=312) , 52-week, multicenter, parallel group, double-blind, active control group, phase 4 clinical trial comparing efficacy and safety by randomly assigning to glimepiride 1-6 mg (n=313) treatment group.

CI, confidence interval; **DAPA,** dapagliflozin; **GLIM,** glimepiride; **HbA1c,** glycated haemoglobin; **MET,** metformin; **SBP,** systolic blood pressure; **SU;** sulfonylurea.

Ref) Müller-Wieland D, Kellerer M, Cypryk K,, et al. Efficacy and safety of dapagliflozin or dapagliflozin plus saxagliptin versus glimepiride as add-on to metformin in patients with type 2 diabetes. Diabetes Obes Metab. 2018 Nov;20(11):2598-2607.

Urinary Tract and Genital Infections

Dapagliflozin has been reported to cause urinary tract infections and genital infections due to its mechanism of action, which involves eliminating excess glucose through the kidneys.

A comparable safety profile was also seen in real-world observational studies[2-5]

Events (%)	Placebo-controlled pool (short-term)[1]	
	Dapagliflozin 10 mg	Placebo (N=2295)
UTIs	**110** (4.7%)	**81** (3.5%)
Genital infections	**130** (5.5%)	**14** (0.6%)

- Most urinary tract infections (UTIs) and genital infections* were mild to moderate in severity;
- Rarely, it has resulted in discontinuation of dapagliflozin and can usually resolve with a single dose of standard treatment[1].
- Pyelonephritis was uncommon and occurred at a similar frequency to controls[1].

*Genital infection includes the preferred terms: Vulvovaginal mycotic infection, vaginal infection, balanitis, genital infection fungal, vulvovaginal candidiasis, vulvovaginitis, balanitis candida, genital candidiasis, genital infection, genital infection male, penile infection, vulvitis, vaginitis bacterial and vulval abscess.

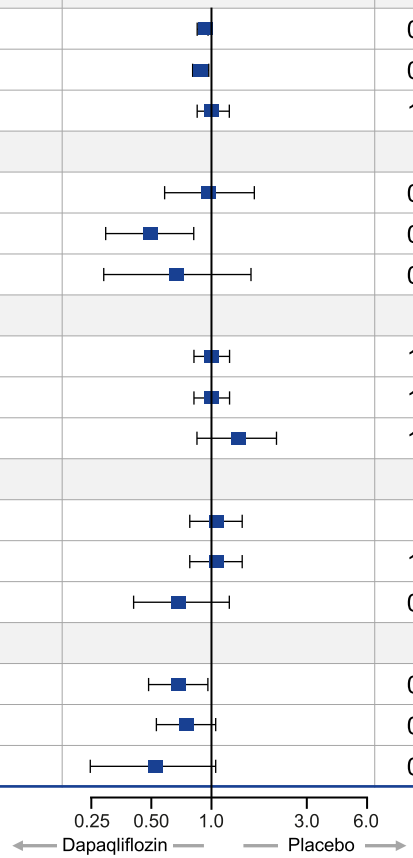
UTI, urinary tract infection.

Ref. 1) 식품의약품안전처. 다파론정/다파론듀오서방정 허가사항. 2) Scheen AJ. Nat Rev Endocrinol 2020;16:556-77. 3) McGovern AP, et al. Br J Diabetes Vasc Dis 2014;14:138–43. 4) Hitke ZZ, et al. Diabetes Medicine 2015;32(Suppl. 1):29 (Abstract P471). 5) Bellan Kannan RB. et al. Diabetic Medicine 2015;32(Suppl. 1):29 (Abstract P470). 6) Down S, et al. Diabetes Medicine 2015;32(Suppl. 1):29 (Abstract P246).

Safety for Elderly Patients

Dapagliflozin can be used **safely in elderly patients** without increasing the risk of side effects.

	Dapaqliflozin		Placebo				
	n/N(%)	Rates per 1000 person-years	n/N(%)	Rates per 1000 person-years	Hazard ratio (95%, CI)	p value	p Interaction
Serious adverse event							
<65 years	1450/4626 (31.3%)	103.4	1503/4619 (32.5%)	111.3	0.93 (0.86, 1.00)	0.0395	0.2667
65 · <75 years	1215/3411(35.6%)	122	1333/3395 (39.3%)	141	0.88 (0.81, 0.95)	0.0012	
≥75 years	260/537 (48.4%)	191.7	264/555 (47.6%)	190.5	1.02 (0.85, 1.21)	0.8648	
Major hypoglycemic event							
<65 years	28/4626 (0.6%)	1.7	28/4619 (0.6%)	1.7	0.97 (0.58, 1.64)	0.9149	0.2107
65 · <75 years	21/3411 (0.6%)	1.7	41/3395 (1.2%)	3.5	0.50 (0.29, 0.84)	0.0095	
≥75 years	9/537 (1.7%)	5.2	14/555 (2.5%)	7.9	0.68 (0.29, 1.57)	0.3611	
Fracture							
<65 years	205/4626 (4.4%)	11.3	200/4619 (4.3%)	11.1	1.02 (0.84, 1.24)	0.8642	0.5245
65 · <75 years	212/3411 (6.2%)	15.9	208/3395 (6.1%)	15.7	1.02 (0.84, 1.23)	0.8728	
≥75 years	40/537 (7.4%)	19.9	32/555 (5.8%)	15.1	1.36 (0.85, 2.17)	0.1994	
Symptoms of volume depletion							
<65 years	96/4626 (2.1%)	5.8	86/4619 (1.9%)	5.4	1.07 (0.8, 1.44)	0.6316	0.4046
65 · 75 years	96/3411 (2.8%)	8.0	90/3395 (6.1%)	7.7	1.06 (0.79, 1.41)	0.7076	
≥75 years	21/537 (3.9%)	12.1	31/555 (5.6%)	17.6	0.70 (0.40, 1.23)	0.2169	
Acute kidney injury							
<65 years	58/4626 (1.3%)	3.5	80/4619 (1.7%)	5.0	0.69 (0.49, 0.97)	0.0319	0.6922
65 · <75 years	56/3411 (1.6%)	4.6	73/3395 (2.2%)	6.2	0.75 (0.53, 1.07)	0.1135	
≥75 years	11/537 (2%)	6.3	22/555 (4%)	12.3	0.52 (0.25, 1.08)	0.0778	



Ref) Cahn A, Mosenzon O, Wiviott SD, et al. Efficacy and Safety of Dapagliflozin in the Elderly: Analysis From the DECLARE-TIMI 58 Study. Diabetes Care. 2020 Feb;43(2):468-475.

Medication Guidance : Urinary Tract and Genital Infections

1. **Drink 1-2 more glasses of water[2,3)]**

2. **Stay clean by considering the mechanism of action[3)]**
   - After urinating, wipe from front to back with a clean toilet paper[4)]
   - Using a mild bidet helps with cleanliness[5)]

3. **Please maintain a healthy lifestyle[1)]**
   - Avoid excessive alcohol consumption and eat a balanced diet

4. **If you experience itching or pain, consult your doctor**
   - Genital itching or pain can be improved through topical ointment treatment[4)]
   - The sitting bath in lukewarm water helps improve symptoms[4)]

Ref. 1. The Journal of Korean Diabetes 2014;15(3):158-162. 2. Foxiga package leaflet : Information for the patient. EMA. 2016 3. American pharmacists Association. SGLT-2 inhibitors for type 2 diabetes : clinical consideration. Available at http://www.pharmacists.com/ accessed on Aug 2016 4. Joishy M, et al. Do we need to treat vulvovaginitis in prepubertal girls? BMJ 2005;330:186-188 5. Ryoo SB, et al. effect of electronic toilet system (Bidet) on anorectal pressure in normal healthy volunteer : influence of Different type of water stream and temperature 6. http://dx.doi.org/10.1136/bmjdrc-2020-001238

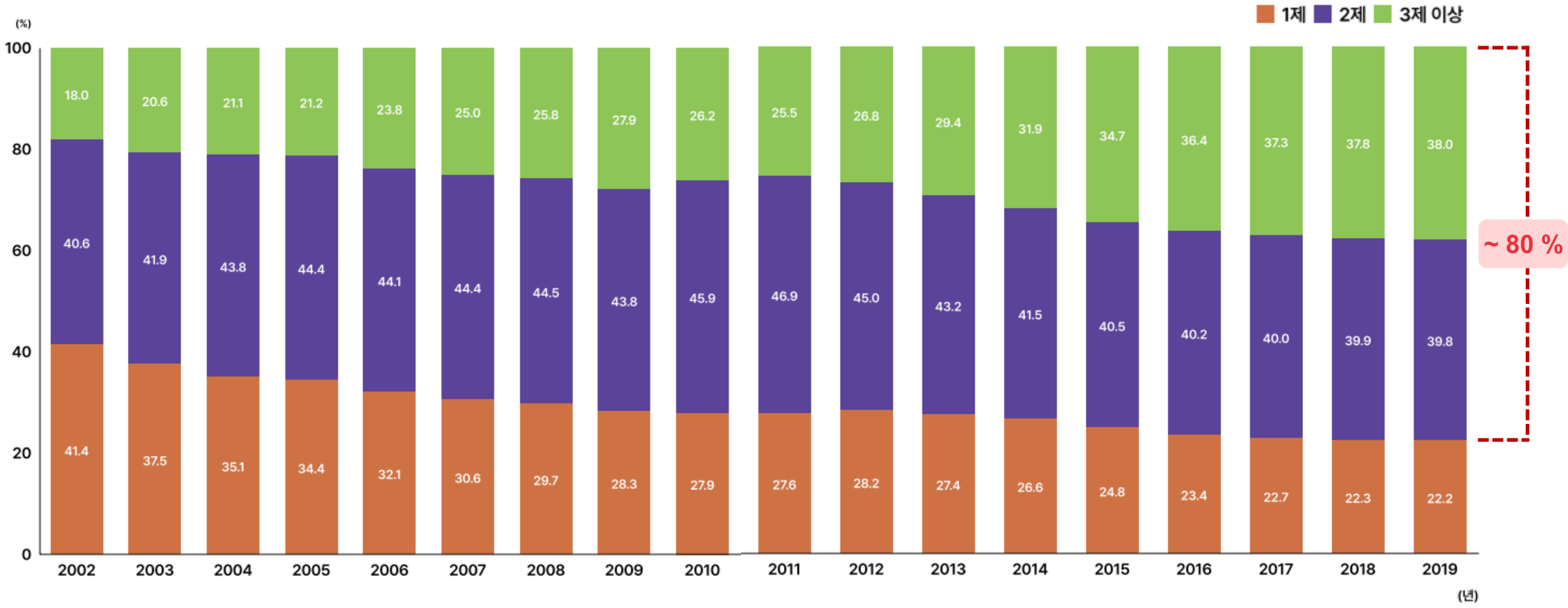
제2형 당뇨병 치료제
다파론® 5mg 정 10mg
(다파글리플로진비스L-프롤린)

제2형 당뇨병 치료제
다파론듀오® 서방정
(다파글리플로진비스L-프롤린/메트포르민염산염)

IDEAL Combination Therapy – DPP4i

Current status of combination therapy with diabetes medications

Combination therapy with oral hypoglycemic agents has steadily increased every year, and as of 2019, approximately 80% of patients are taking two or three or more drugs in combination.



Ref) 대한당뇨병학회. Diabetes fact sheet in Korea 2022.

Diabetes medication reimbursable combination therapy
– SGLT2i combination newly established

From April 2023, Met + SGLT2i + DPP4i triple therapy becomes reimbursable.

(3) 인정 가능 2제 요법

구 분		Metformin	Sulfonylurea	Meglitinide	α-glucosedase inhibitor	Thiazoli-dinedione	DPP-IV inhibitor	SGLT-2 inhibitor			
								dapagli flozin	ipragli flozin	Empagli flozin	ertugli flozin
Metformin			인정	인정	인정	인정	인정	인정	인정	인정	인정
Sulfonylurea		인정			인정	인정	인정	인정	인정	인정	인정
Meglitinide		인정			인정	인정					
α-glucosidase inhibitor		인정	인정	인정							
Thiazoli-dinedione		인정	인정	인정			인정				
DPP-IV inhibitor		인정	인정			인정					
SGLT-2 inhibitor	Dapagli Flozin	인정	인정								
	Ipragli Flozin	인정	인정								
	Empagli Flozin	인정	인정								
	Ertugli Flozin	인정	인정								

(4) 2제요법 투여대상으로 2제요법 인정 가능 성분 중 1종만 투여한 경우도 인정함.

나) 3제요법

○ 2제요법을 2-4개월 이상 투여해도 HbA1C가 7% 이상인 경우에는 다른 기전의 당뇨병 치료제 1종을 추가한 병용요법을 인정함. 단, 2제 요법(다음의 3제 요법은 인정함 (2제 요법 후 HbA1C≥7.0%) <삭 제> ~~나, Metformin+Sulfonylurea+Empagliflozin은 인정함.~~

~~다음의 3제요법은 인정함~~

- 다 음 -

(1) metformin + SGLT-2 inhibitor + DPP-IV inhibitor

(2) metformin + SGLT-2 inhibitor(ertugliflozin 제외) + Thiazolidinedione

나. Insulin 요법

1) 단독요법: (현행과 같음)

2) 경구제와 병용요법

Insulin 단독요법 또는 경구용 당뇨병치료제 투여에도 HbA1C가 7% 이상인 경우 Insulin과 경구용 당뇨병 치료제의 병용요법을 인정함.

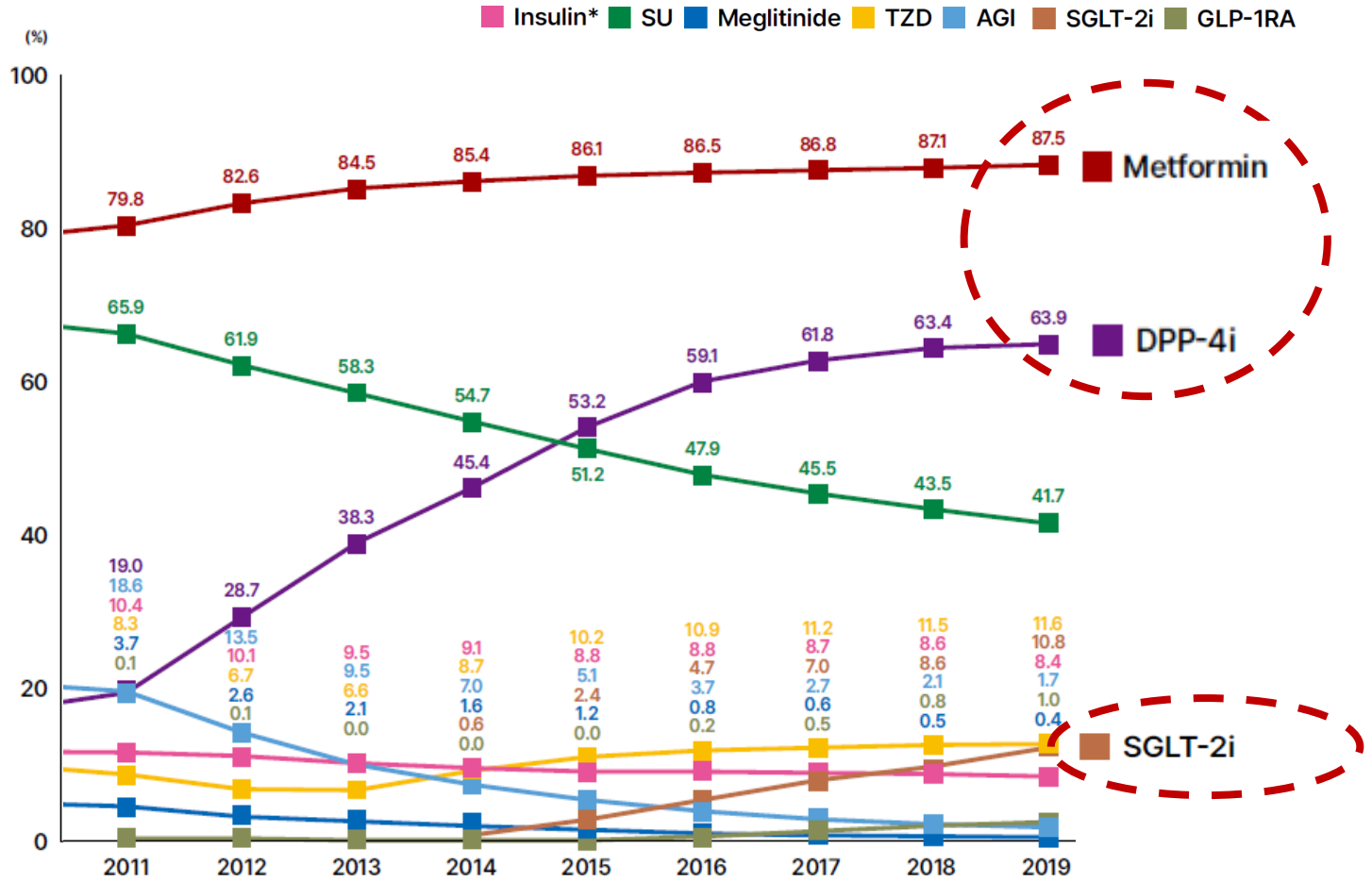
가) Insulin과 경구용 당뇨병치료제 2종까지 병용요법을 인정함. 단, 경구용 당뇨병 치료제 2제 요법에서 인정되지 않는 약제의 조합이 포함 되어서는 아니 됨. <삭 제> ~~나) Ertugliflozin, Ipragliflozin은 Insulin 주사제와 병용사 인정하지 아니함.~~

<이하 현행과 같음>

다파론 다파론듀오

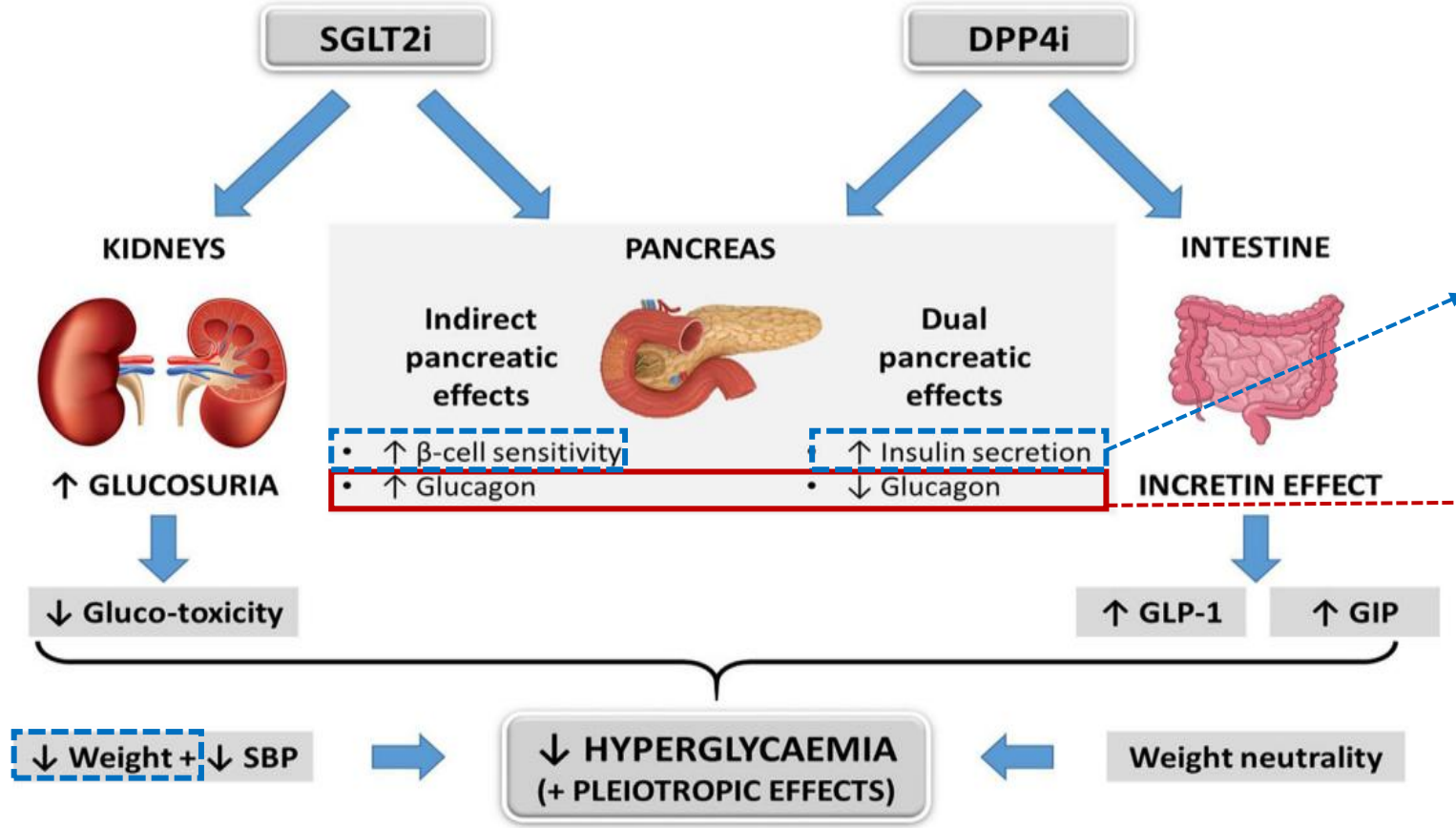
Analysis of prescription patterns by diabetes medication ingredient

Metformin, DPP-4i, and SGLT-2i have been steadily increasing until recently, and in particular, the two drugs Metformin and DPP-4i are showing **a high prescription rate of over 60%.**



Ref) 대한당뇨병학회. Diabetes fact sheet in Korea 2022.

Clinical effect of Combination with SGLT2 inhibitor and DPP4 inhibitor by Mechanism



<Glucose Lowering properties>

SGLT2i: Lowering glucose before meals + Lowering 24-hour average glucose
DPP4i: Lower glucose level before/after meal + Lower average glucose level for 24 hours + Reduce glucose fluctuation range

SGLT2i: Weight loss effect (energy loss through urinary glucose excretion), insulin resistance improvement effect
DPP4i: Glucose-dependent insulin secretion promoting action

Increased glucagon secretion by SGLT2i
→ Causes glucose fluctuations
Together with DPP4i, glucagon secretion is suppressed
→ Reduces blood sugar volatility

SGLT2i & DPP4i inhibit sympathetic nerve activity
→ Positive impact on cardiovascular disease

Positive Synergic Effect

T2DM, type 2 diabetes mellitus; **DPP-4,** dipeptidyl peptidase-4; **SGLT-2,** sodium-glucose cotransporter-2; **GLP,** glucagon-like peptide.

Ref.> Larsson H et al. Acta Physiol Scand. 1997;160:413-422; Drucker DJ. Diabetes. 1998;47:159-169

Considerations when selecting the optimal combination of diabetes medications

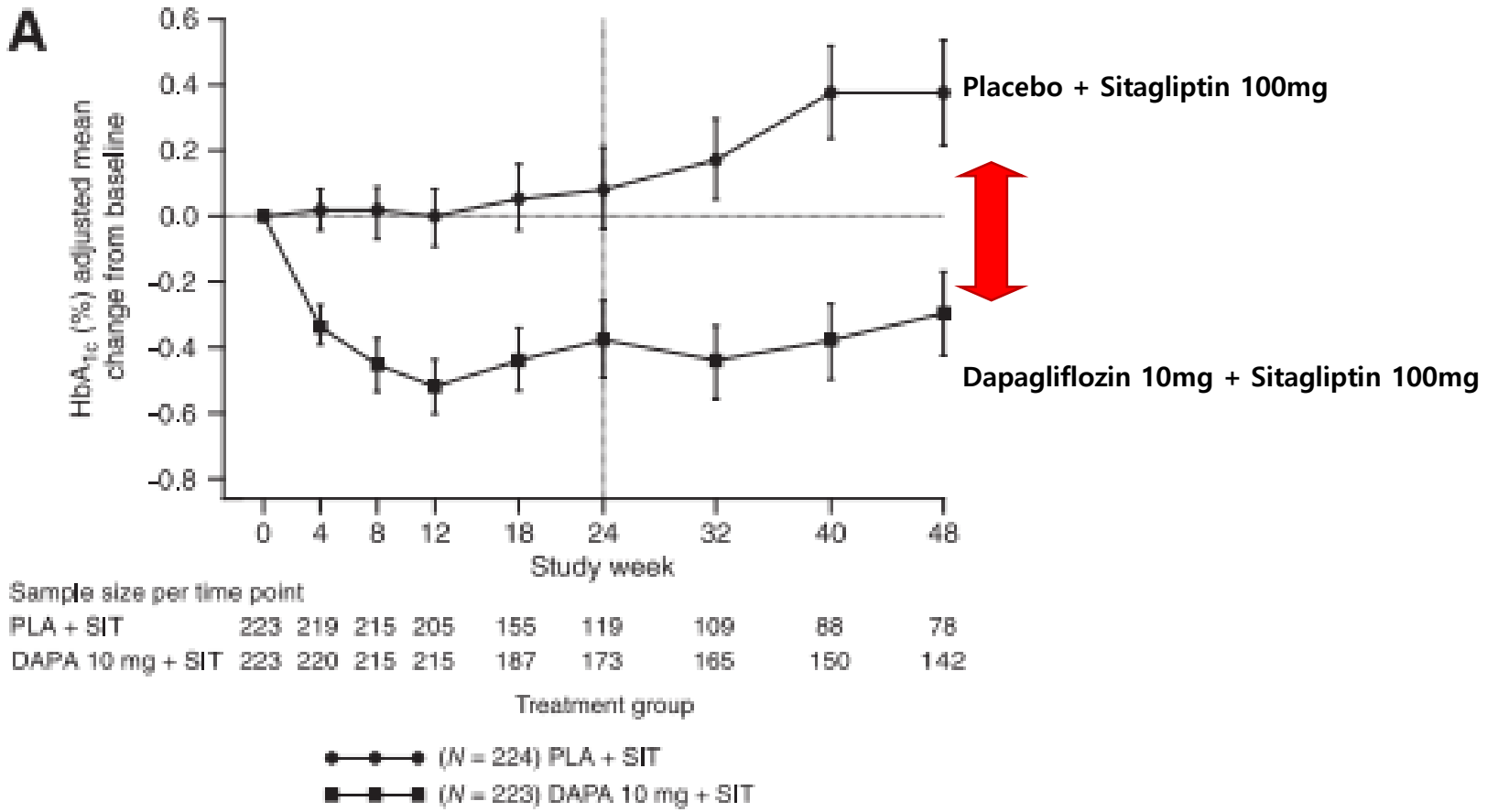
Physiologic Effects	
Pathophysiology	Insulin secretion
	Glucagon secretion
	Hepatic Glucose Production
	Insulin sensitivity
Pleiotropic	Body weight
	Food intake
	Blood pressure
	Lipid profile
Cardio-renal	CV benefit
	HF benefit
	Renal benefit

CV, Caridovascular; **HF**, Heart Failure

Dapagliflozin + Sitagliptin Phase 3 clinical result

Phase 3 clinical result showed a clear HbA1c reduction effect when Sitagliptin Add on treatment with dapagliflozin in type 2 diabetes patients.

Fig. I. Adjusted mean change from baseline in HbA1c over time



[Study] This study is phase 3, randomized, 24 weeks, double-blinded, placebo controlled, parallel group, open label, study included adult patients with glycated hemoglobin (HbA1c) ≥ 7% and ≤ 10% to compare efficacy and safety of Dapagliflozin + Sitagliptin vs Sitagliptin. All patients received sitagliptin 100mg/day. Dapagliflozin 10mg or placebo was adiministered orally once daily.

Ref. Dapagliflozin Is Effective as Add-on Therapy to Sitagliptin With or Without Metformin: A 24-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study, Serge A. Jabbour,1 Elise Hardy,2 Jennifer Sugg,2 and Shamik Parikh,2 for the Study 10 Group*, Diabetes Care Volume 37, March 2014

FDC (DAPA + SITA +MET) ER vs (SITA + MET) SR vs (DAPA + MET) ER

The DAPA + SITA + MET three-drug regimen was well tolerated, and the adverse event rate was similar to the two-drug regimen.

	DAPA + SITA + MET ER (*N* = 137)		SITA + MET SR (*N* = 139)		DAPA + MET (*N* = 139)	
	n (%)	*E*	*n* (%)	E	*n* (%) *E*	*E*
Any TEAEs	14 (10.2%)	24	11 (7.9%)	17	13 (9.4%)	17
Serious TEAEs	0	0	0	0	0	0
TEAEs leading to study drug discontinuation	0	0	0	0	0	0
Hypoglycemia	0	0	1 (0.7%)	1	0	0
TEAEs by PT with ≥ 1% overall incidence in any of the arms						
Diarrhea	1 (0.7%)	1	3 (2.2%)	3	0	0
Gastritis	3 (2.2%)	3	1 (0.7%)	1	0	0
Hyperchlorhydria	2 (1.5%)	2	1 (0.7%)	1	1 (0.7%)	1
Vomiting	3 (2.2%)	3	1 (0.7%)	1	1 (0.7%)	1
Asthenia	0	0	1 (0.7%)	1	2 (1.4%)	2
Pyrexia	1 (0.7%)	1	3 (2.2%)	3	1 (0.7%)	1
Headache	1 (0.7%)	1	0	0	3 (2.2%)	3

*1 case of hypoglycemia (level 1) occurred in the SITA+MET SR group

DAPA, dapagliflozin; ER, extended release; FDC, fixed-dose combination; SITA, sitagliptin; SR, sustained release; TEAE, treatment-emergent adverse event

[Study] This study is phase 3, randomized, open-label, active-controlled study included adult patients with glycated hemoglobin (HbA1c) ≥ 8% (64 mmol/mol) and ≤ 11% (97 mmol/mol) to compare efficacy and safety of triple drug FDC of DAPA+SITA+MET ER vs. SITA+MET SR vs. DAPA+MET ER. Randomization was in 1:1:1 ratio to receive either FDC of DAPA+SITA+MET ER (10/100/1000 mg) tablets once daily (n = 137) or co-administration of SITA+MET SR (100/1000 mg) tablets once daily (n = 139) or FDC of DAPA+MET ER(10/1000 mg) tablets once daily (n = 139). Primary endpoint was mean change in HbA1c from baseline to week 16.

Sahay RK, Giri R, Shembalkar JV, et al. *Adv Ther*. 2023;10.1007/s12325-023-02523-z.

Considerations when selecting the optimal combination of diabetes medications

Physiologic Effects		SGLT-2i	DPP-4i	Combination
Pathophysiology	Insulin secretion	↔	↑	↑
	Glucagon secretion	↑	↓	↔
	Hepatic Glucose Production	↑	↓	↔
	Insulin sensitivity	↑	↔	↑
Pleiotropic	Body weight	↓	↔	↓
	Food intake	↔ ↑	↔	↑ ↔
	Blood pressure	↓	↔	↓
	Lipid profile	↓	↔	↓
Cardio-renal	CV benefit	↑	↔	↑
	HF benefit	↑	↔ ↓	↔
	Renal benefit	↑	↔ ↑	↑
Side effect	Hypoglycemia	↓	↓	↓ ↓
	Genital infection	↑	↔	↑ or ↔

CV, Caridovascular; **HF**, Heart Failure

제2형 당뇨병 치료제
다파론® 정 5mg 10mg
(다파글리플로진비스L-프롤린)

제2형 당뇨병 치료제
다파론듀오® 서방정
(다파글리플로진비스L-프롤린/메트포르민염산염)

Summary & Product Information

Take Home Message

Diabetes increases the risk of developing cardiovascular disease due to **obesity, high blood pressure, etc.,** so **integrated management** of accompanying disease is **necessary.**

- **Dapagliflozin** is a SGLT2i drug that **reduces glucose levels** by **inhibiting glucose reabsorption in the kidneys** and **increase glucose excretion in urine.**
- **Dapagliflozin** shows glucose effect **regardless of the action of insulin,** so it can be used in **combination with various complementary drugs** with different mechanisms of action.
- **Dapagliflozin** has shown **strong hypoglycemic effects both** as **monotherapy** and **combination with various drugs.**
- **Dapagliflozin** shows **a significantly lower incidence of hypoglycemia** and has **a superior glucose lowering effect compared to SU** or **DPP4i.**
- **Dapagliflozin** due to the mechanism of action, mild to moderate **urinary tract infections** and **genital infections** have been reported, but cases that lead to drug discontinuation are rare and are generally **resolved with standard treatment.**

Product Information

제품명	다파론정		다파론듀오서방정			
성분	Dapagliflozin		Dapagliflozin + Metformin			
함량(mg)	5mg	10mg	5/500mg	5/1000mg	10/500mg	10/1000mg
약가(원)	262원	393원	342원	381원	473원	512원
성상						
효능·효과	단독 or 병용투여가 적합한 성인 제2형 당뇨병 환자의 혈당조절		병용투여가 적합한 성인 제2형 당뇨병 환자의 혈당조절			
용법·용량	1일 1회 5mg 또는 10mg		1일 1회 / 최대 Dapagliflozin 10mg, Metformin 2000mg			

※효능·효과, 용법·용량 및 그 외 자세한 사항은 제품 설명서 참조

제품 특장점

- **5mg** 저함량 출시로 처방 옵션 확대
- 대조약 대비 **정제크기 감소** (다파론듀오 최대 약 46%)
- 대조약 대비 **경제적인 약가**
- 한미약품 기술력을 통한 **자체 개발** 및 **자체 생산**
- 다파론 10mg **분할선 보유**

Product Information

제품명	실다파정	실다파엠서방정		
성분	Dapagliflozin + Sitagliptin	Dapagliflozin + Sitagliptin + Metformin		
함량(mg)	10/100mg	5/50/500mg	5/50/750mg	5/50/1000mg
약가(원)	846원	633원	633원	682원
성상				
효능·효과	단독 or 병용투여가 적합한 성인 제2형 당뇨병 환자의 혈당조절	병용투여가 적합한 성인 제2형 당뇨병 환자의 혈당조절		
용법·용량	1일 1회 최대 100mg	1일 1회 , 2정		

※효능·효과, 용법·용량 및 그 외 자세한 사항은 제품 설명서 참조

제품 특장점

- 한미약품 기술력을 통한 자체 개발 고품질 의약품
- 타 계열 성분을 1알로 복용함으로써 Compliance 개선
- 약제 병용시 대비 최대 21% 경제적 약가 (실다파정)

Thank you