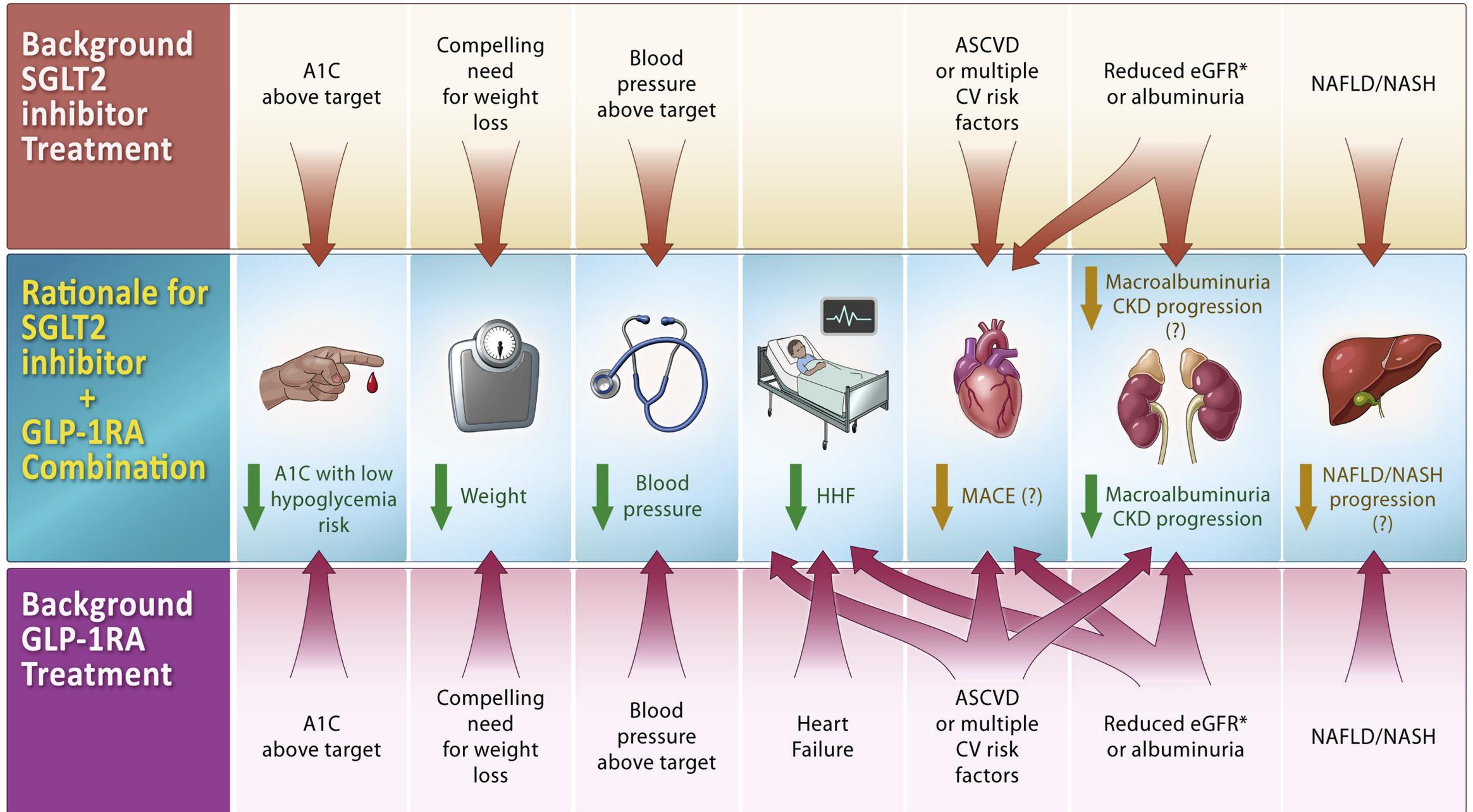


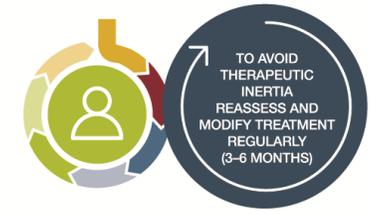
# GLP-1 RA 및 SGLT2 억제제: 당뇨와 비만 사이

# Characteristics of GLP-1RA and SGLT2i-treated individuals and rationale for combining a GLP-1RA with an SGLT2i



# 당뇨병에서 SGLT2i와 GLP-1RA의 사용

**FIRST-LINE THERAPY depends on comorbidities, patient-centered treatment factors, including cost and access considerations, and management needs and generally includes metformin and comprehensive lifestyle modification<sup>^</sup>**



**ASCVD/INDICATORS OF HIGH RISK, HF, CKD†**

**NONE**

**RECOMMEND INDEPENDENTLY OF BASELINE A1C, INDIVIDUALIZED A1C TARGET, OR METFORMIN USE‡**

**+ASCVD/INDICATORS OF HIGH RISK\***

**EITHER/OR**

- GLP-1 RA with proven CVD benefit<sup>1</sup>
- SGLT2i with proven CVD benefit<sup>1</sup>

**IF A1C ABOVE TARGET**

- For patients on a GLP-1 RA, consider incorporating SGLT2i with proven CVD benefit and vice versa<sup>1</sup>
- TZD<sup>2</sup>

**IF A1C remains above target, consider treatment intensification based on comorbidities, patient-centered treatment factors, and management needs**

**+HF\***

SGLT2i with proven benefit in this population<sup>1</sup>

**+CKD\*\***

CKD and albuminuria (e.g., ≥200 mg/g creatinine)	CKD without albuminuria (e.g., eGFR <60 mL/min/1.73 m <sup>2</sup> )
--	--

**PREFERABLY**

SGLT2i with primary evidence of reducing CKD progression

**OR**

SGLT2i with evidence of reducing CKD progression in CVOTs

**OR**

GLP-1 RA with proven CVD benefit<sup>1</sup> if SGLT2i not tolerated or contraindicated

For patients with CKD (e.g., eGFR <60 mL/min/1.73 m<sup>2</sup>) without albuminuria, recommend the following to decrease cardiovascular risk

**EITHER/OR**

- GLP-1 RA with proven CVD benefit<sup>1</sup>
- SGLT2i with proven CVD benefit<sup>1</sup>

**IF A1C above target, for patients on SGLT2i, consider incorporating a GLP-1 RA and vice versa**

**Incorporate agents that provide adequate EFFICACY to achieve and maintain glycemic goals**

**Higher glycemic efficacy therapy: GLP-1 RA; insulin; combination approaches (Table 9.2)**

- Consider additional comorbidities, patient-centered treatment factors, and management needs in choice of therapy, as below:

**MINIMIZE HYPOGLYCEMIA**

No/low inherent risk of hypoglycemia: DPP-4i, GLP-1 RA, SGLT2i, TZD

For SU or basal insulin, consider agents with lower risk of hypoglycemia<sup>3,4</sup>

**IF A1C ABOVE TARGET**

Incorporate additional agents based on comorbidities, patient-centered treatment factors, and management needs

**MINIMIZE WEIGHT GAIN/PROMOTE WEIGHT LOSS**

**PREFERABLY**

GLP-1 RA with good efficacy for weight loss

**OR**

SGLT2i

**IF A1C ABOVE TARGET**

For patients on a GLP-1 RA, consider incorporating SGLT2i and vice versa

- If GLP-1 RA not tolerated or indicated, consider DPP-4i (weight neutral)

Incorporate additional agents based on comorbidities, patient-centered treatment factors, and management needs

**CONSIDER COST AND ACCESS**

Available in generic form at lower cost:

- Certain insulins: consider insulin available at the lowest acquisition cost
- SU
- TZD

**IF A1C ABOVE TARGET**

Incorporate additional agents based on comorbidities, patient-centered treatment factors, and management needs

1. Proven benefit refers to label indication (see Table 9.2)
2. Low dose may be better tolerated though less well studied for CVD effects
3. Choose later generation SU to lower risk of hypoglycemia
4. Risk of hypoglycemia: degludec / glargine U-300 < glargine U-100 / detemir < NPH insulin
5. Consider country- and region-specific cost of drugs

<sup>^</sup>For adults with overweight or obesity, lifestyle modification to achieve and maintain ≥5% weight loss and ≥150 min/week of moderate- to vigorous-intensity physical activity is recommended (See Section 5: Facilitating Behavior Change and Well-being to Improve Health Outcomes).

<sup>†</sup>Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.

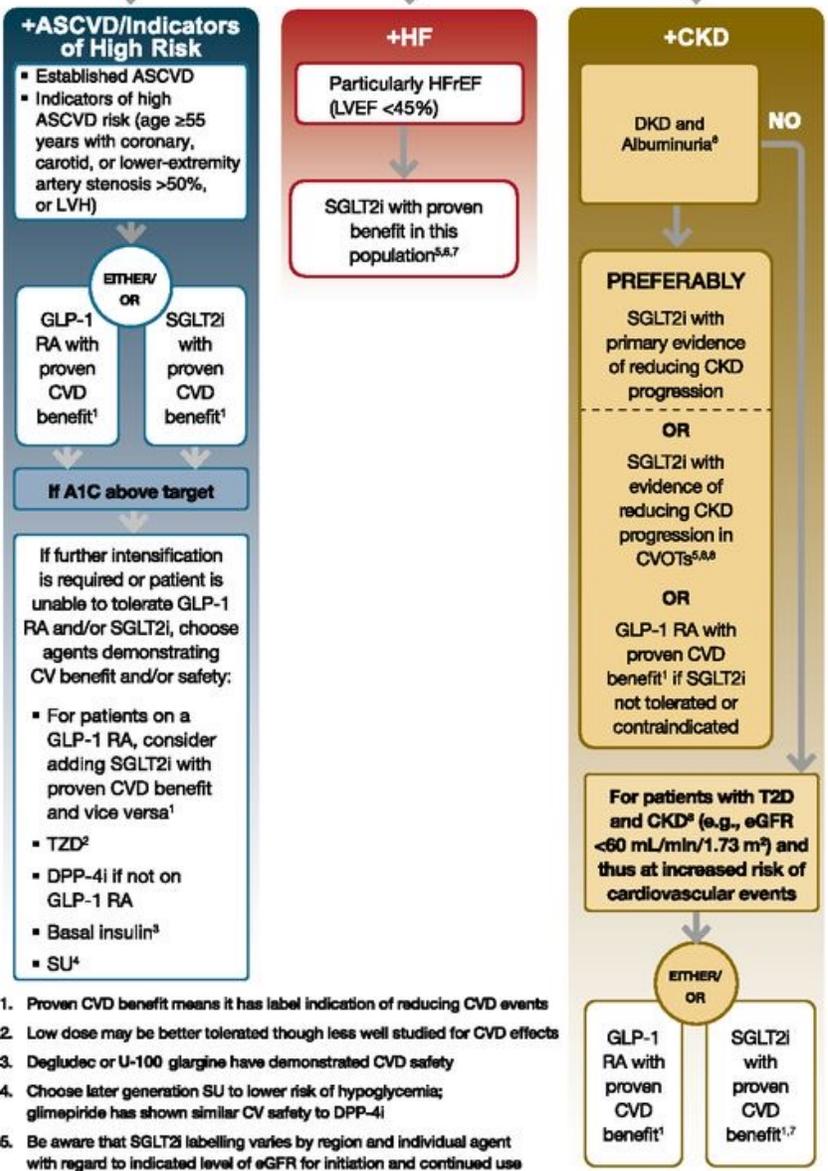
<sup>‡</sup>Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.

<sup>\*</sup>Refer to Section 10: Cardiovascular Disease and Risk Management.

<sup>\*\*</sup>Refer to Section 11: Chronic Kidney Disease and Risk Management and specific medication label for eGFR criteria.

**INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CKD, OR HF<sup>1</sup>**

**CONSIDER INDEPENDENTLY OF BASELINE A1C, INDIVIDUALIZED A1C TARGET, OR METFORMIN USE\***



1. Proven CVD benefit means it has label indication of reducing CVD events
2. Low dose may be better tolerated though less well studied for CVD effects
3. Degludec or U-100 glargine have demonstrated CVD safety
4. Choose later generation SU to lower risk of hypoglycemia; glimepiride has shown similar CV safety to DPP-4i
5. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use

# ADA에서는 어떤 경우에 다른 class의 초치료를 권하나?

- ASCVD or high risk
  - GLP-1 RA with proven CVD benefit
  - SGLT2i with proven CVD benefit
- HF
  - SGLT2i with proven benefit in this population
- CKD
  - SGLT2i with evidence of reducing CKD progression
  - GLP-1 RA with proven CVD benefit

# KDA 2021

- KDA 2021의 T2DM 약물치료 주요 변경점
- 약물 선택 시 환자의 개별화 조건 세분화
- 혈당조절 실패의 위험을 낮추기 위해 진단 초기부터 병용요법을 적극적으로 고려
- 강력한 혈당강하를 위한 주사제 치료 강조
- 혈당조절 중심 약제 선택과 동반질환 유무에 따른 약제선택을 분리해서 권고

2021 제7판

## 당뇨병 진료지침 온라인

당뇨병 진단 및 약제 처방시 참고가 가능한 최신 당뇨병 진료지침을 반영한 웹 기반 임상 의사결정지원시스템

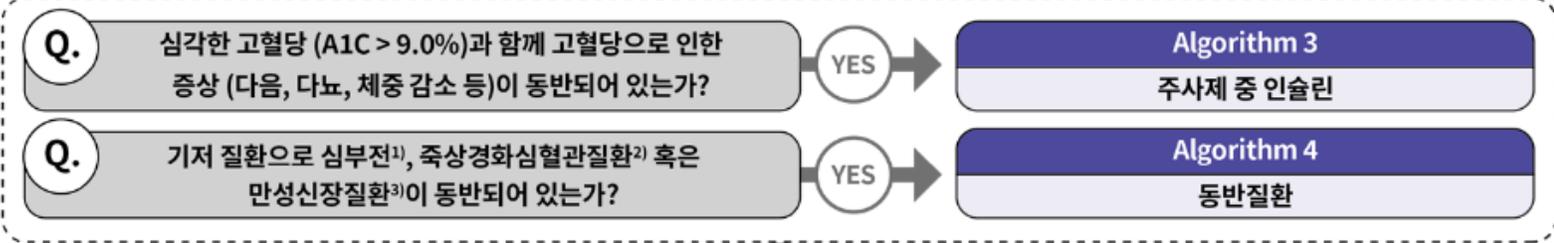
Korean Diabetes Association Support System (KDASS)

<http://kdaguideline.com/>



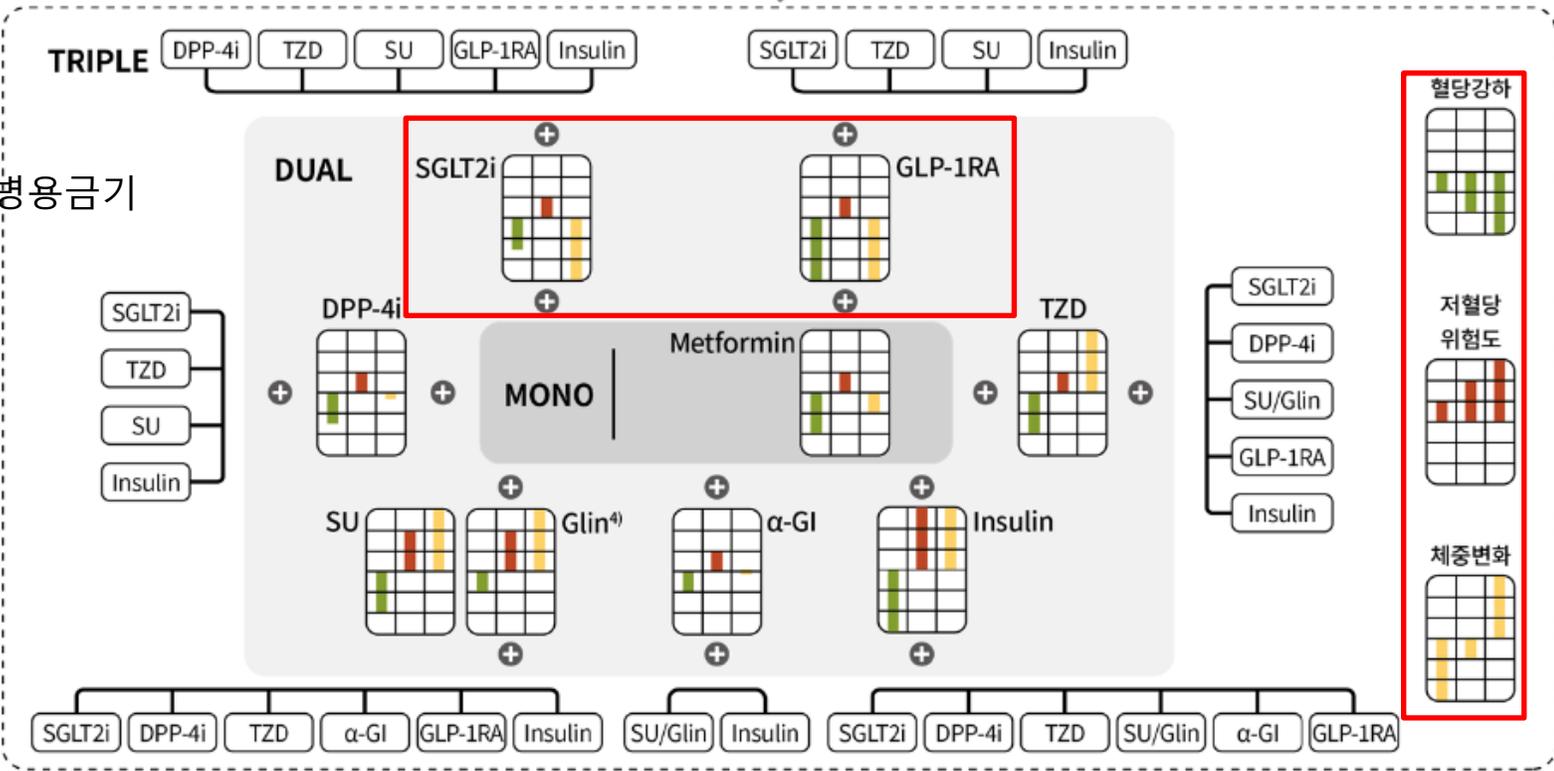
Dr. Frederick Banting  
Who discovered the  
insuline





**NO**

DPP4i와 GLP-1a는 병용금지



**Q.** 목표 A1C에 도달하였는가?

**YES**

**NO**

현재 치료 유지  
저혈당, 부작용, 금기가 있을 경우 약물 조정

기존 약물의 증량 혹은 타계열 약물로 변경 (2제), 타계열 약물 추가 (3제 이상)  
주사제를 포함한 치료 계획 시 Algorithm 3 참조

# 국내 사용 가능한 GLP-1 RA와 SGLT2i

- 고시 제2022-56호(약제) – 2022.3.1.
- SGLT-2 inhibitor계
  - Dapagliflozin, Empagliflozin, Ertugliflozin, Ipragliflozin
  - Dapagliflozin + Metformin HCl, Empagliflozin + Metformin HCl
- GLP-1 수용체 효능제
  - Dulaglutide, Exenatide
  - Insulin glargine + Lixisenatide, Insulin degludec + Liraglutide

# CVD benefit이 인정되는 약물

- GLP-1 RA for ASCVD
  - Benefit: Dulaglutide, liraglutide, semaglutide
  - Neutral: Exenatide once weekly, lixisenatide
- SGLT2i
  - For ASCVD: Empagliflozin, canagliflozin
  - For HF: Empagliflozin, canagliflozin, dapagliflozin
- TZD
  - For ASCVD: Pioglitazone
  - For HF: increased risk

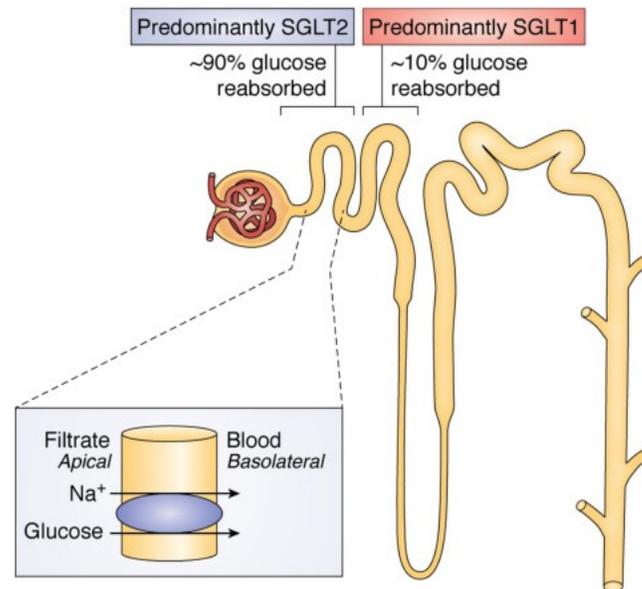
## '포시가' 이어 '자디앙'까지.. 'SGLT-2 억제제' 변신 완료

제2형 당뇨병 치료제에서 이제는 독자적인 심부전과 신장질환에 허가



# SGLT2i

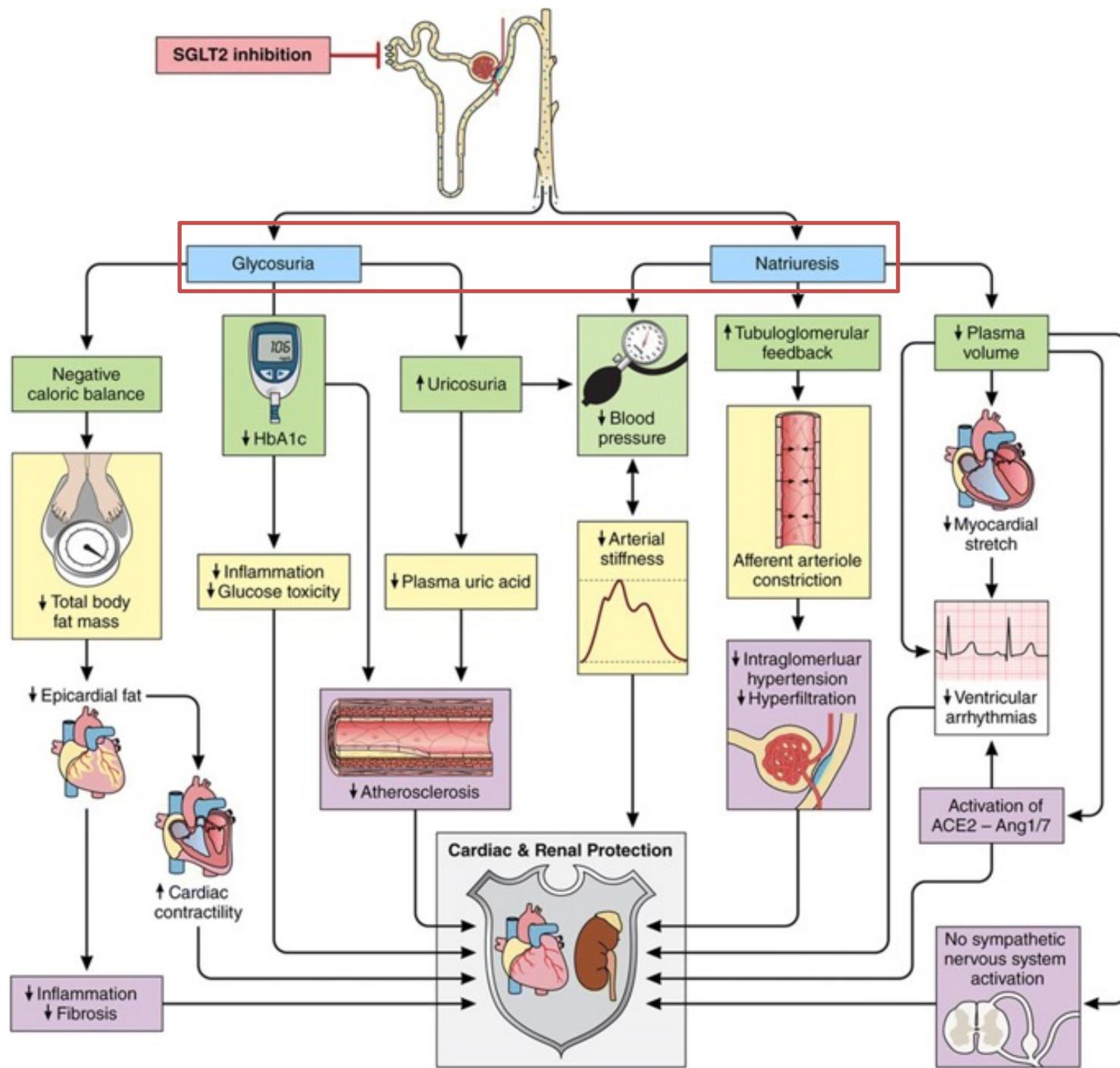
- 신장에서 포도당 재흡수를 억제하여 당뇨를 유발
  - 인슐린 작용과 무관하므로 저혈당 위험성이 적음
- 간접적으로 glucose toxicity를 개선함으로써
  - 베타세포 기능이상과 인슐린 저항성 교정
  - 글루카곤 생산증가



# SGLT2i

- Dapagliflozin, Empagliflozin, Ipragliflozin, Ertugliflozin
- 혈당강하효과: HbA1c 0.5-1.0%
- 부작용: 요로생식기감염, 배뇨증가, 회음부 괴저, 저혈압, GFR감소, 케톤산증
- 금기: 유당불내성(Dapa, Empa), 신부전
- 주의: 고령자(75세 이상), 중증 간장애, 저혈압(Ertu)

eGFR (mL/min/1.73 m <sup>2</sup> )	CKD1-2	CKD3a	CKD3b	CKD4	ESKD
	≥ 60	59-45	44-30	29-15	< 15
<b>SGLT2 inhibitors</b>					
Dapagliflozin	10 mg	제한적 사용			자료 없음
Empagliflozin	10 mg/25 mg	제한적 사용			자료 없음
Ertugliflozin	5 mg			자료 없음	
Ipragliflozin	50 mg			자료 없음	





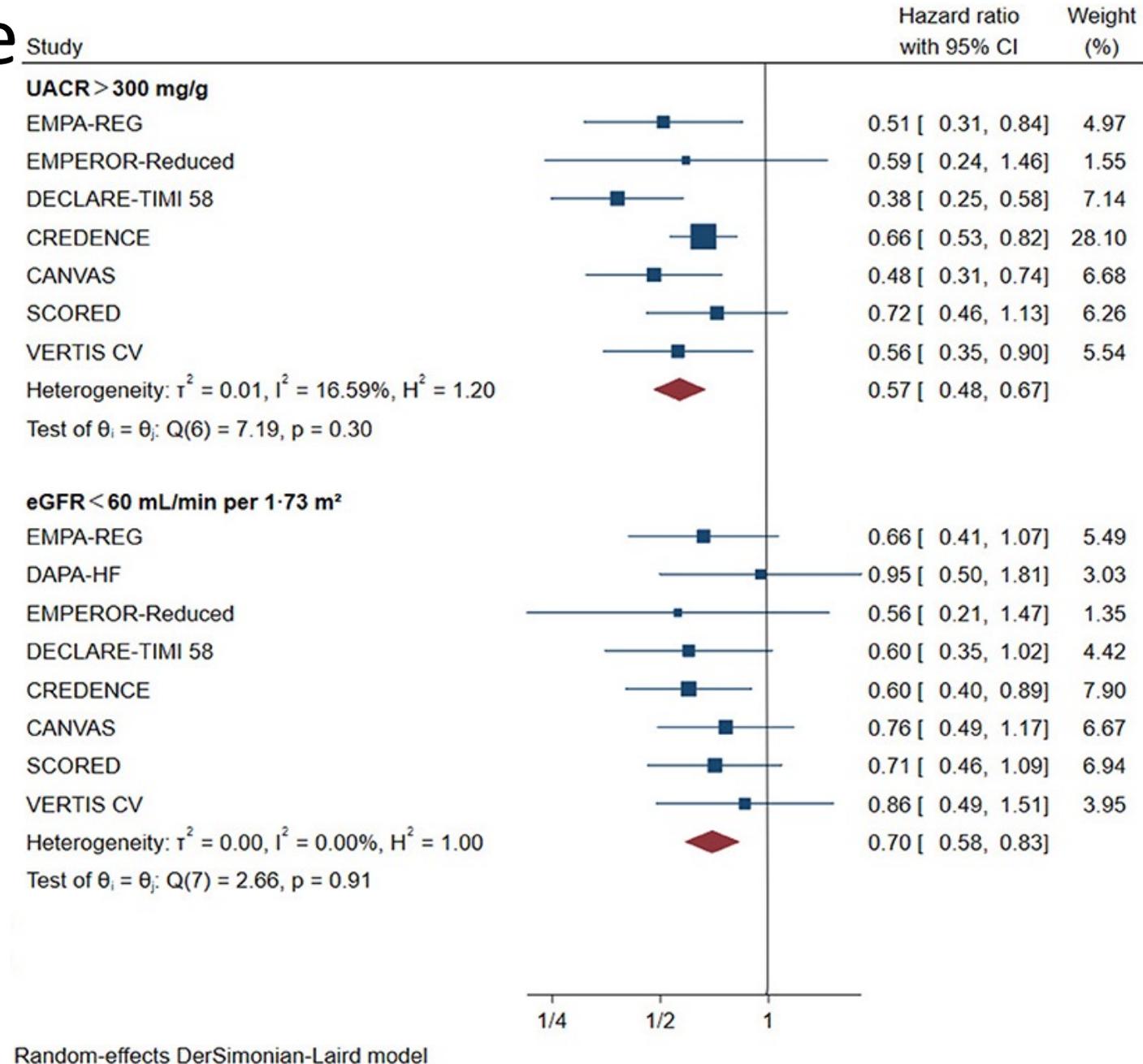
# SGLT2i - CVOT

**Table 1** Pairwise comparison results from network meta-analysis for major adverse cardiovascular events

<b>Canagliflozin</b>	1.11 (0.96, 1.28)	1.03 (0.86, 1.23)	1.16 (0.98, 1.37)	<b>1.19 (1.07, 1.32)</b>	1 (0.83, 1.21)
0.9 (0.78, 1.04)	<b>Dapagliflozin</b>	0.92 (0.77, 1.1)	1.04 (0.88, 1.24)	1.08 (0.97, 1.19)	0.9 (0.75, 1.09)
0.98 (0.81, 1.17)	1.08 (0.91, 1.29)	<b>Empagliflozin</b>	1.13 (0.93, 1.38)	<b>1.16 (1, 1.35)</b>	0.98 (0.79, 1.21)
0.86 (0.73, 1.02)	0.96 (0.81, 1.13)	0.89 (0.73, 1.08)	<b>Ertugliflozin</b>	1.03 (0.9, 1.18)	0.87 (0.7, 1.07)
<b>0.84 (0.76, 0.93)</b>	0.93 (0.84, 1.03)	<b>0.86 (0.74, 1)</b>	0.97 (0.85, 1.11)	<b>Placebo</b>	<b>0.84 (0.72, 0.99)</b>
1 (0.83, 1.21)	1.11 (0.92, 1.34)	1.02 (0.82, 1.27)	1.15 (0.94, 1.42)	<b>1.19 (1.01, 1.39)</b>	<b>Sotagliflozin</b>

# SGLT2i - Renal outcome

- Direct renal effect
  - 혈당조절과 관련 없이 신장에 영향을 미침
- Renal tubular glucose reabsorption 감소
- 체중감소
- 혈압감소
- 사구체내압감소
- 최근에는 신장의 산화 스트레스를 50% 이상 줄인다는 연구

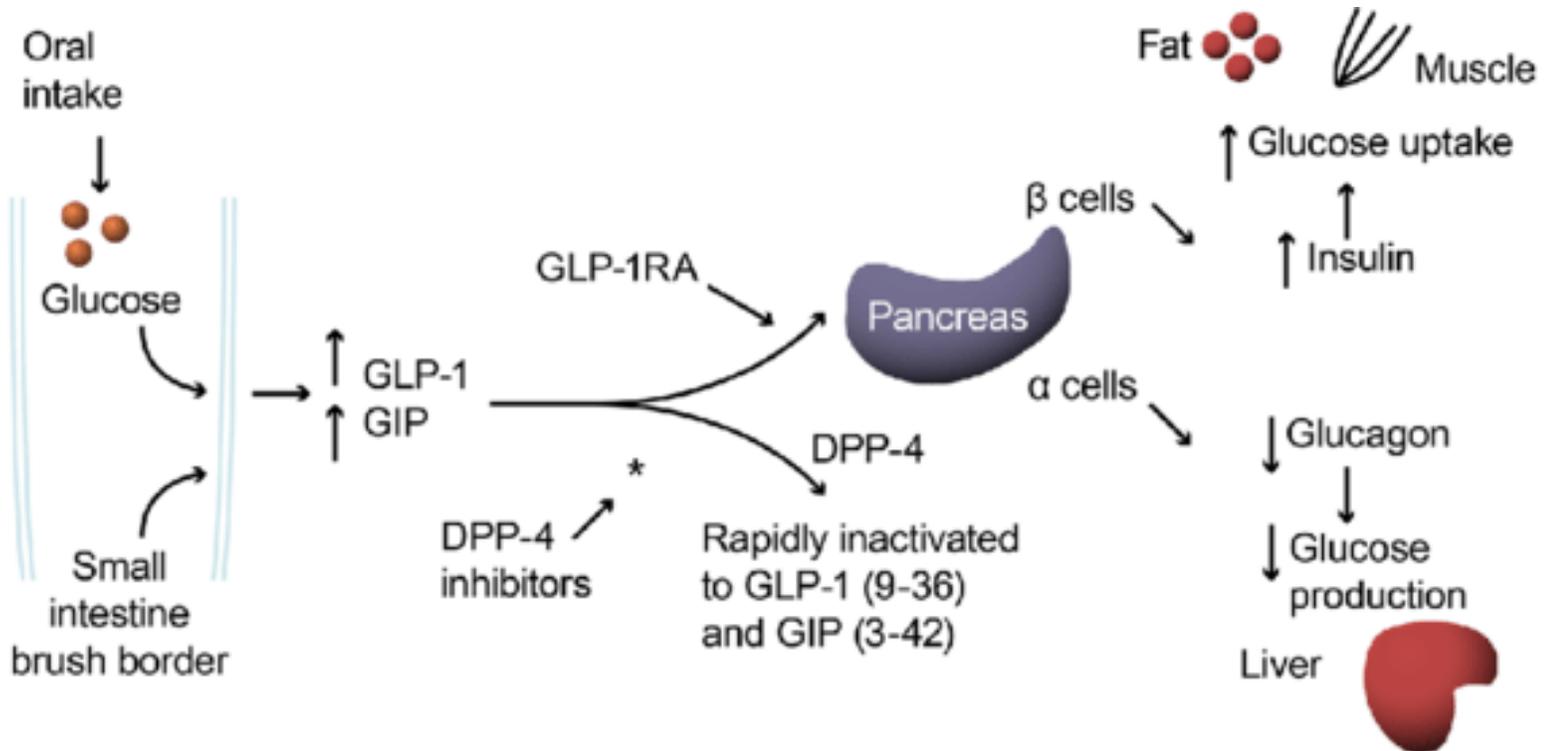


**TABLE 2** Prevention of adverse events with SGLT2 inhibitors

	<b>At risk</b>	<b>Measures to prevent adverse event</b>
Genital mycotic infections	Women, prior candidiasis	Perineal hygiene, changing pads/tampons frequently, avoid tight synthetic underwear. With recurrent infection: consider treating partner
Urinary tract infection	Prior UTI Neurogenic bladder, paraparesis, indwelling urinary catheter	Probably avoid SGLT2i in patients at very high risk
Hypoglycaemia	Currently taking SU and/or insulin with current insulin or SU treatment, higher risk with prior hypoglycaemia, in elderly, or with impaired renal function	A1C <8.0 consider stopping or reducing dose of SU and or reducing insulin dose when initiating an SGLT2i Do not discontinue insulin
Diabetic ketoacidosis	Acute illness, surgery, reduced oral intake, alcohol abuse or inappropriate reduction of insulin dosage	Stop SGLT2i with acute illness/surgery Maintain insulin, if necessary, make only small adjustments to insulin dosage Beware DKA can present with normal or minimally increased blood glucose in patients receiving SGLT2i Do not use SGLT2i in patients with type 1 diabetes or with prior history of DKA
Hypotension	SBP < 100 mm Hg postural hypotension	Assess for volume depletion/hypotension (Figure 1) Consider reducing diuretic
Acute kidney injury	Hypotension volume depletion	Stop SGLT2i with acute illness/surgery. Maintain euvolemia
Fractures	Osteoporosis renal impairment	Avoid SGLT2i in patients at very high risk Use of vitamin D is of unproven benefit
Amputations	Ischemic ulcers, neuropathy Peripheral vascular disease Lower limb ischemia Prior amputation	Avoid SGLT2i in patients with rest ischemia, ischemic ulcers, and prior amputations

# GLP-1RA

- 작용기전
  - 포도당 의존 인슐린 분비증가, 식후 글루카곤 분비감소
  - 위배출 억제
- 혈당강하효과:  
HbA1c 0.8-1.5%

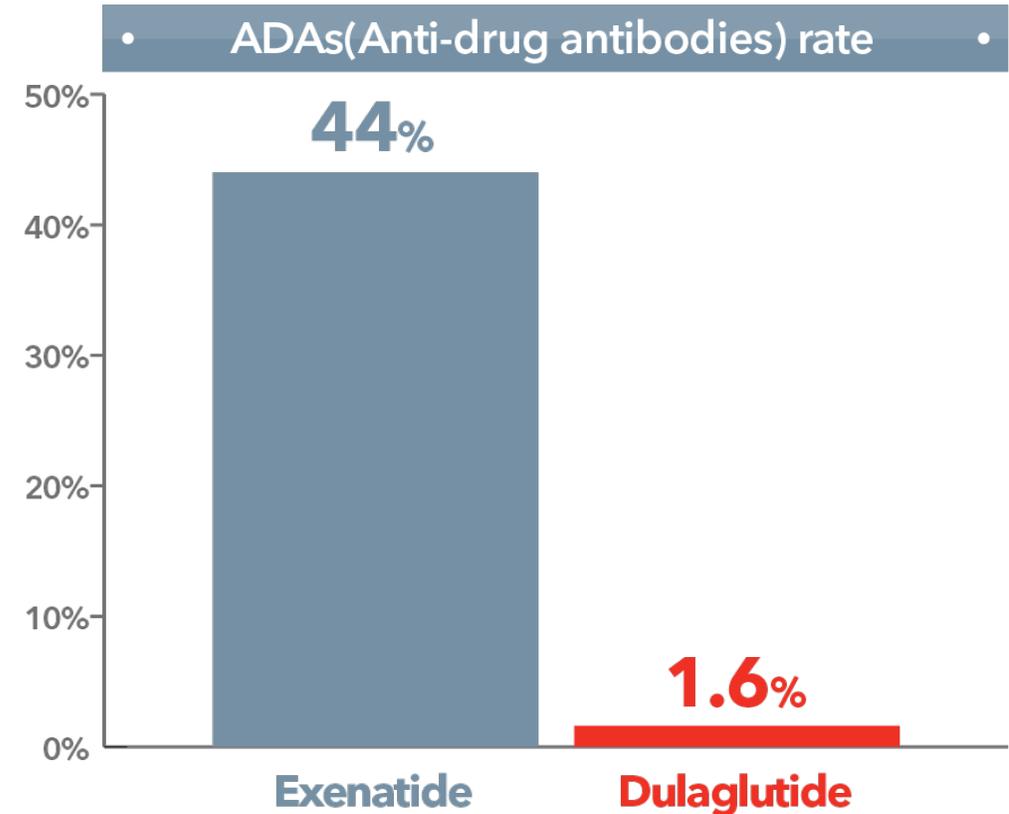
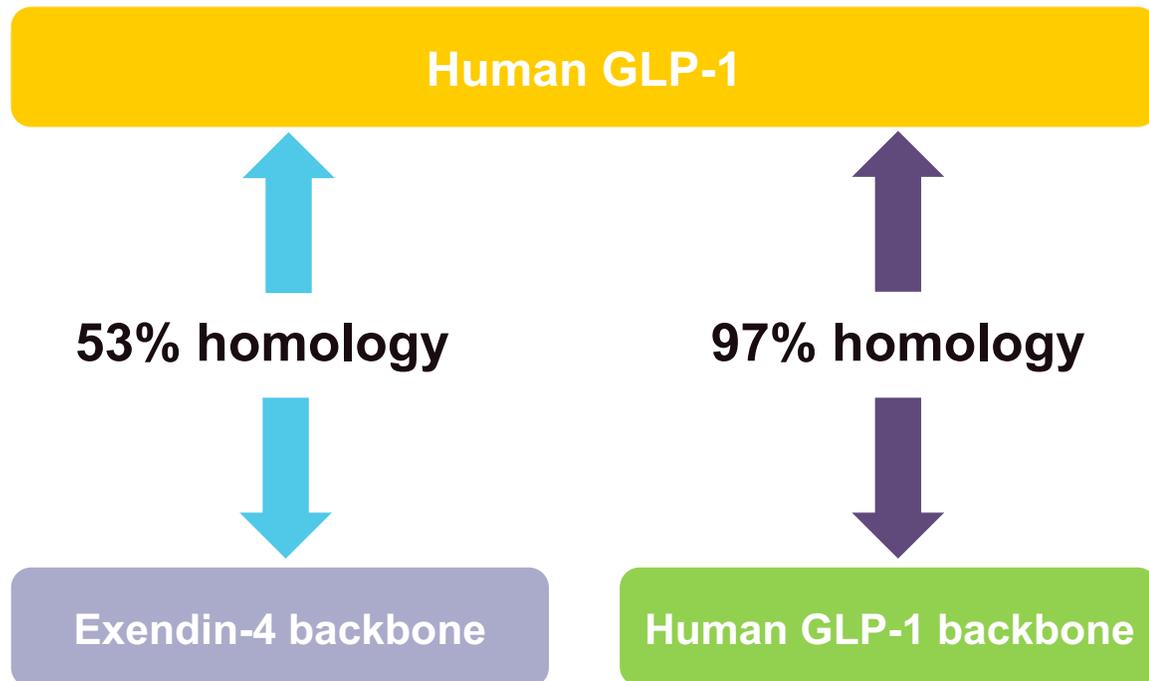


# GLP-1RA

**Table 1 — Characteristics of GLP-1 RAs that have been approved to treat type 2 diabetes as of 2020.**

GLP-1 RA	First approved (date)	Molecular weight (Da) <sup>c</sup>	Reference amino acid sequence	Other important components	Elimination half-life	Administration schedule	Pharmaceutical company	Reference
<b>For subcutaneous injection</b>								
<i>Short-acting compounds</i>								
Exenatide b.i.d.	2005 (USA); 2006 (Europe); Byetta	4186.6	Exendin-4	None	3.3–4.0 h	Twice daily	AstraZeneca <sup>i</sup>	[21]
Lixisenatide	2013 (Europe); Lyxumia; 2016 (USA); Adlyxin	4858.5	Exendin-4	Poly-lysine tail	2.6 h	Once daily	Sanofi	[22]
<i>Long-acting compounds/preparations</i>								
Liraglutide	2009 (Europe); 2010 (USA); Victoza	3751.2	Mammalian GLP-1	Free fatty acid <sup>e</sup>	12.6–14.3 h	Once daily	Novo Nordisk	[23]
Once-weekly exenatide	2012; BYDUREON <sup>®</sup>	4186.6	Exendin-4	Active ingredient encapsulated in microspheres of poly-(D,L-lactide-co-glycolide)	3.3–4.0 h <sup>f</sup>	Once weekly	AstraZeneca <sup>i</sup>	[21]
Dulaglutide	2014; Trulicity	59670.6	Mammalian GLP-1	Immunoglobulin Fc fragment	4.7–5.5 d	Once weekly	Eli Lilly and Company	[24]
Albiglutide	2014 (Europe); Eperzan Tanzeum (USA) <sup>b</sup>	72971.3	Mammalian GLP-1	Albumin	5.7–6.8 d	Once weekly	GlaxoSmithKline	[25]
Semaglutide	2017 (USA); 2019 (Europe); Ozempic	4113.6	Mammalian GLP-1	Free fatty acid <sup>e</sup>	5.7–6.7 d	Once weekly	Novo Nordisk	[26]

# Human GLP-1 vs. Exedine-4 backbone



Fc = fragment crystallisation; IgG = immunoglobulin G.

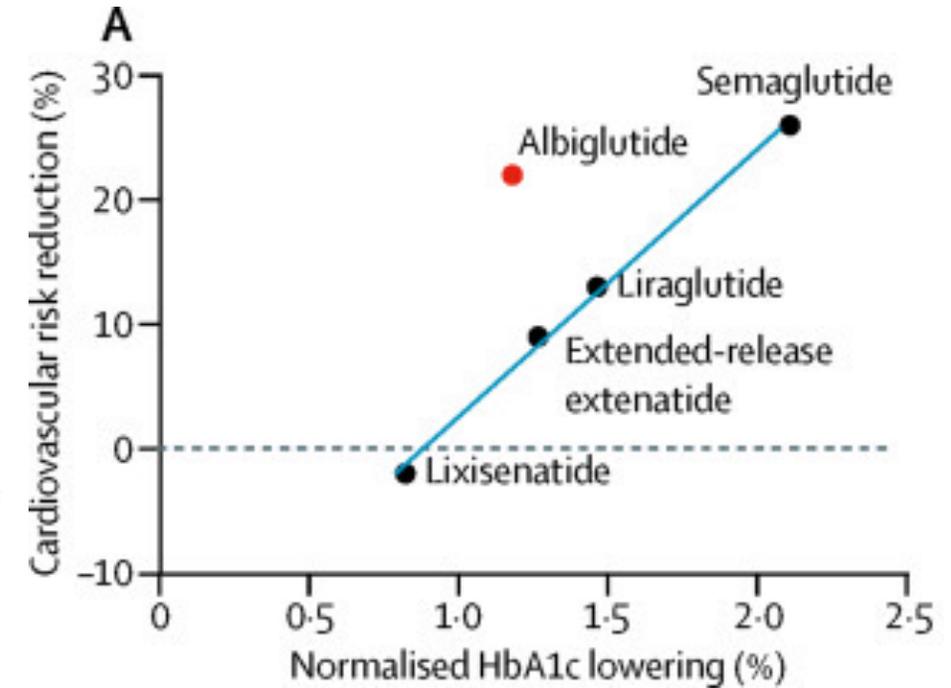
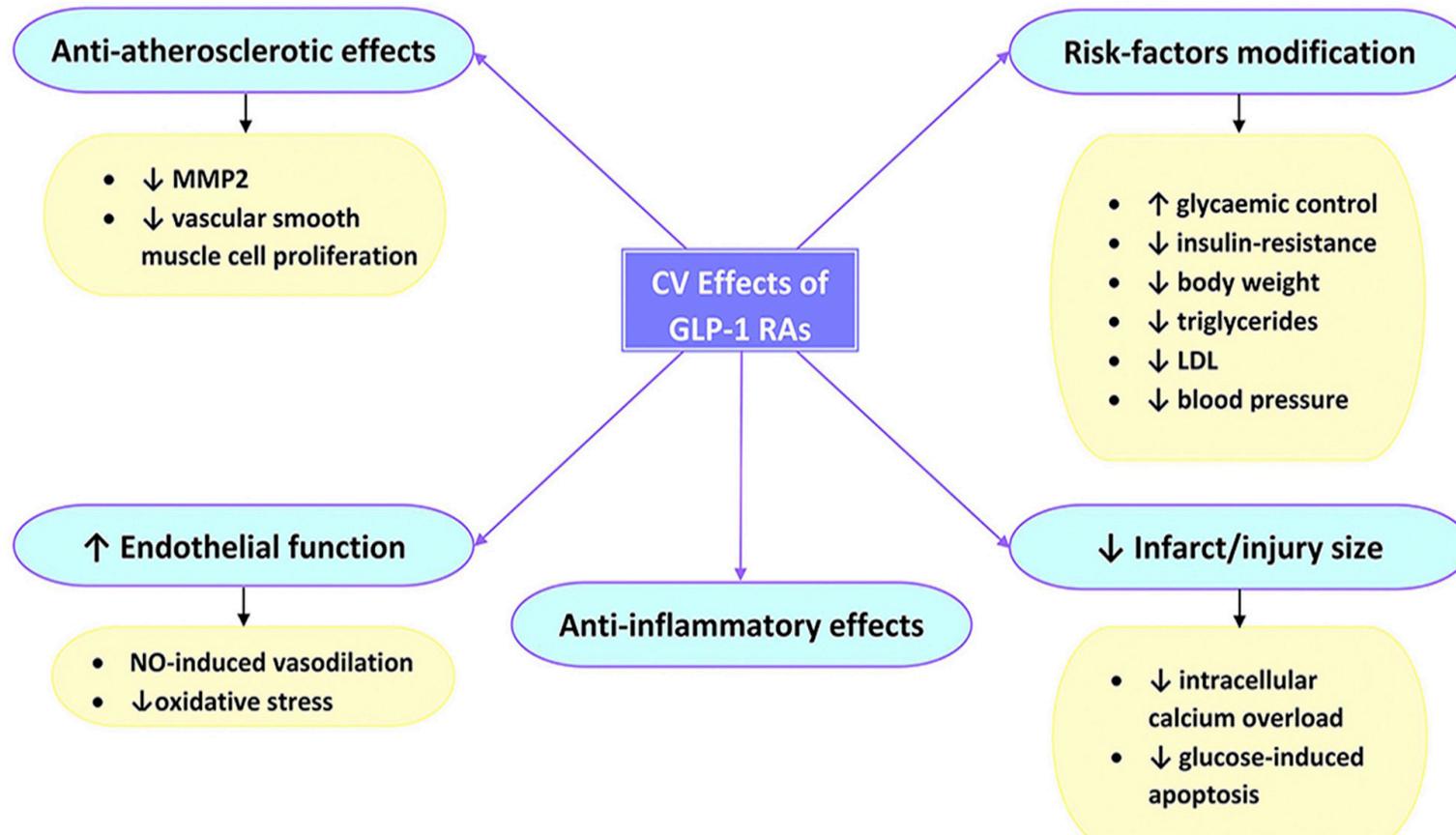
1. Neumiller JJ. *J Am Pharm Assoc* 2009;49(Suppl 1):S16-29
2. Glaesner, et al. 2011, *PepTalk*.
3. Wysham C, et al. *Diabetes Care*. 2014;37(8):2159-2167.

# GLP-1RA

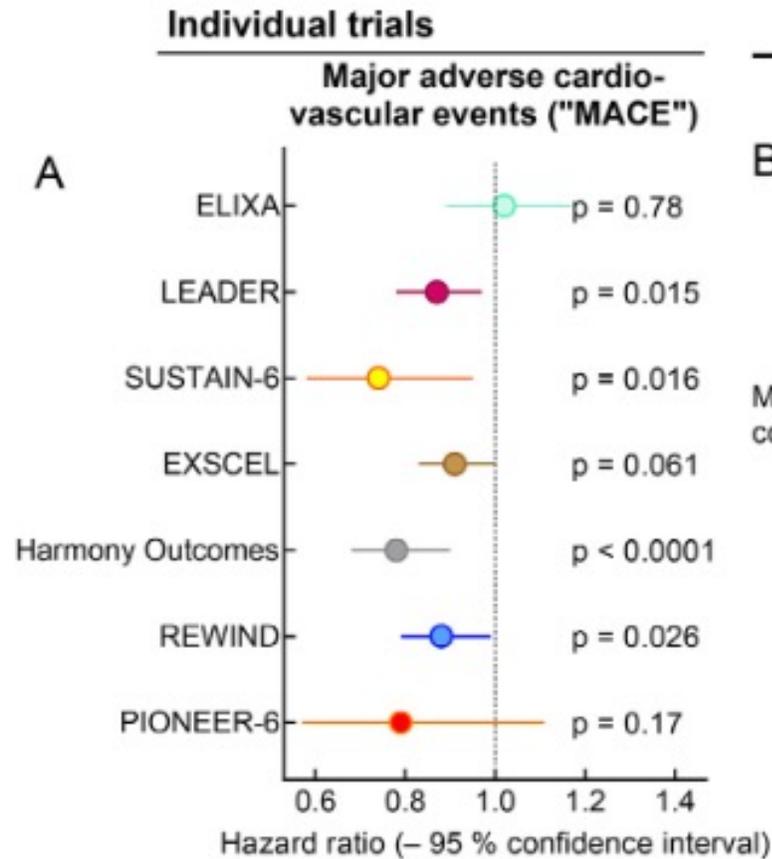
- 부작용: 위장관 장애
- 금기: 갑상선 수질암의 과거력 또는 가족력, MEN2
- 주의: 췌장염, 중증 간, 신장애, 중증 위장관 질환

eGFR (mL/min/1.73 m <sup>2</sup> )	CKD1-2	CKD3a	CKD3b	CKD4	ESKD
	≥ 60	59-45	44-30	29-15	< 15
GLP-1 receptor agonists					
Liraglutide					자료 없음
Dulaglutide					

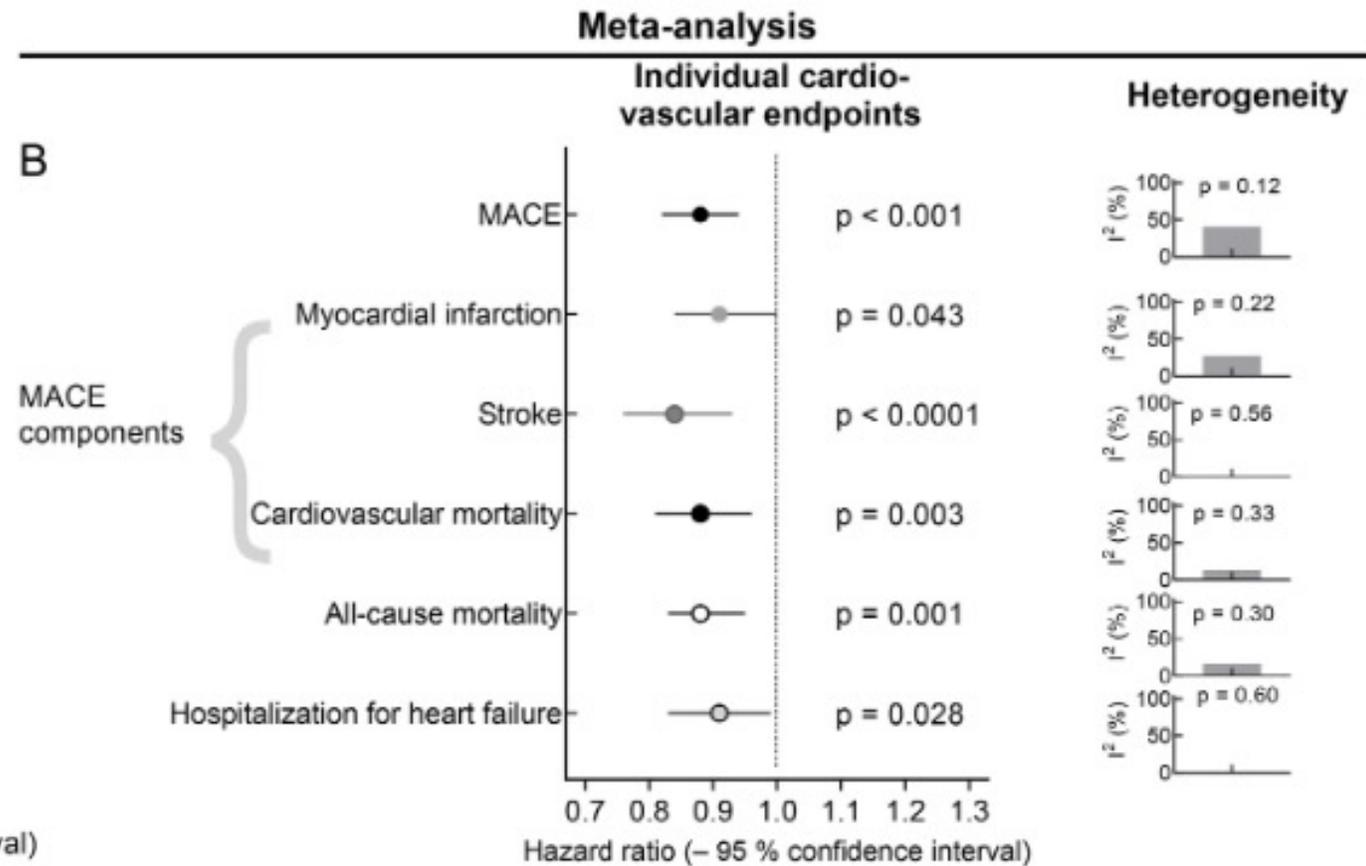
# GLP-1RA - CV benefit



# GLP-1RA - CVOT

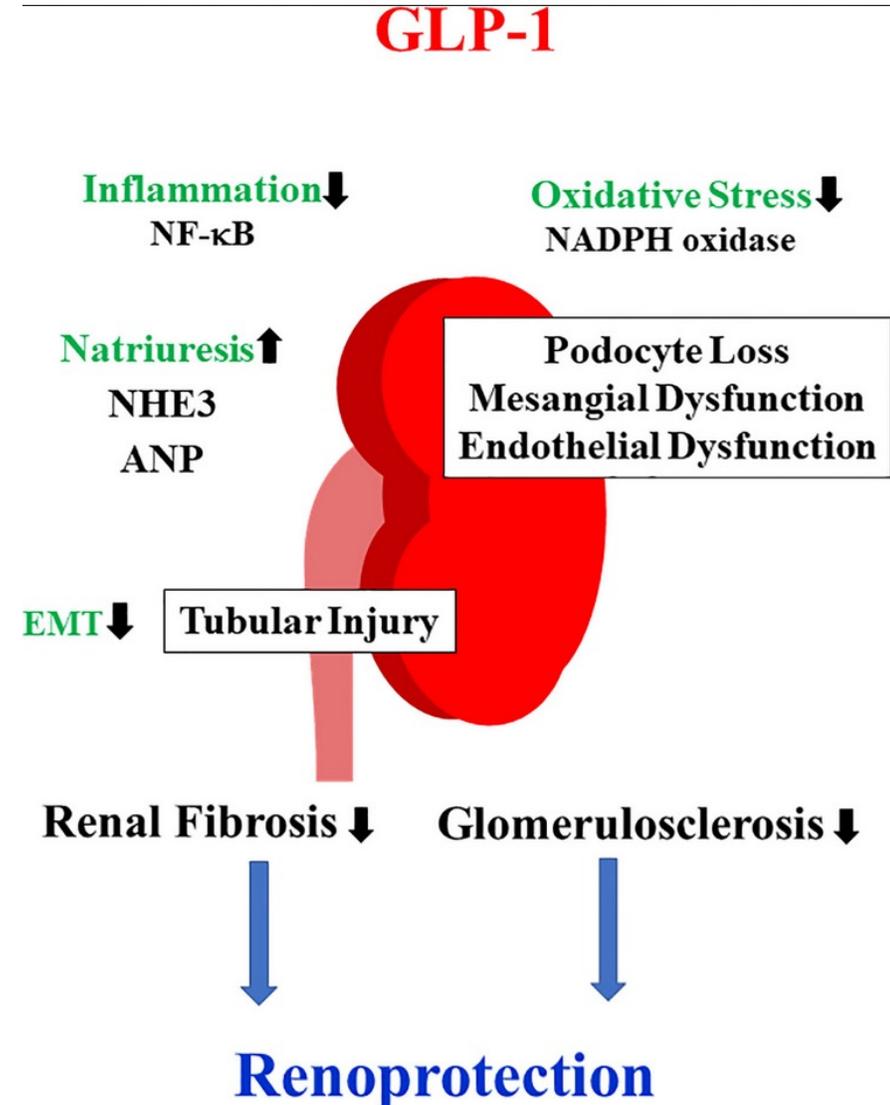


- Lixisenatide
- Liraglutide
- Semaglutide s.c.
- Exenatide q.w.
- Albiglutide
- Dulaglutide
- Oral semaglutide



# GLP-1RA - Renal outcome

- New onset microalbuminuria 를 예방
- Urinary albumin excretion 을 감소
- eGFR을 천천히 감소
- 투석 및 신장이식 필요의 감소
- 하지만 정확한 기전은 밝혀지지 않음



# 급여기준에서 인정 가능 2제 요법

구분	Metformin	Sulfonylurea	Meglitinide	α-glucosidase inhibitor	Thiazolidinedione	DPP-IV inhibitor	SGLT-2 inhibitor			
							dapagliflozin	ipragliflozin	empagliflozin	ertugliflozin
Metformin	인정	인정	인정	인정	인정	인정	인정	인정	인정	인정
Sulfonylurea	인정	인정	×	인정	인정	인정	인정	×	×	×
Meglitinide	인정	×	인정	인정	인정	×	×	×	×	×
α-glucosidase inhibitor	인정	인정	인정	인정	×	×	×	×	×	×
Thiazolidinedione	인정	인정	인정	×	인정	인정	×	×	×	×
DPP-IV inhibitor	인정	인정	×	×	인정	인정	×	×	×	×
SGLT-2 inhibitor	dapagliflozin	인정	인정	×	×	×	×	×	×	×
	ipragliflozin	인정	×	×	×	×	×	×	×	×
	empagliflozin	인정	×	×	×	×	×	×	×	×
	ertugliflozin	인정	×	×	×	×	×	×	×	×

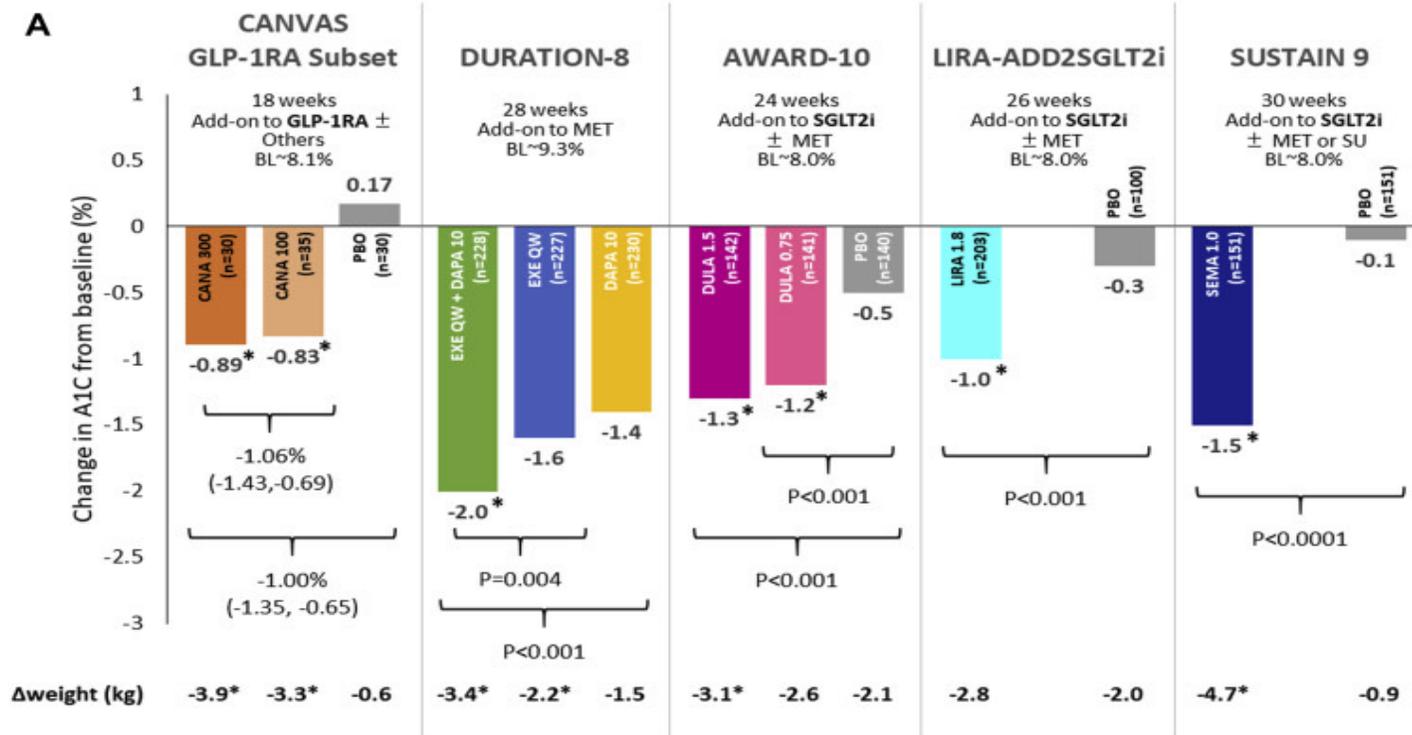
## 나) 3제요법

○ 2제 요법을 2-4개월 이상 투여해도 HbA1C가 7% 이상인 경우에는 다른 기전의 당뇨병 치료제 1종을 추가한 병용요법을 인정함. 단, 2제 요법에서 인정되지 않는 약제의 조합이 포함되어서는 아니되나, Metformin+Sulfonylurea +Empagliflozin은 인정함.

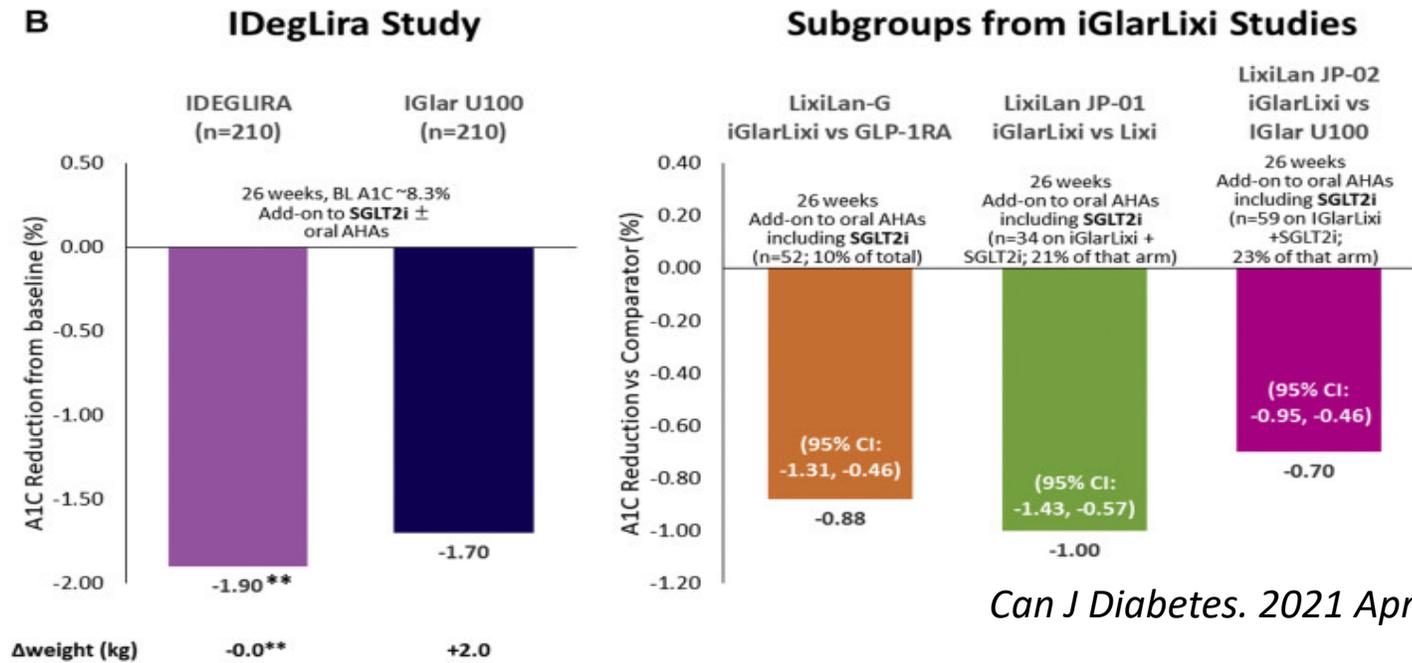
# GLP-1 RA를 사용하려면,

- Metformin+Sulfonylurea계 약제 병용투여로 충분한 혈당조절을 할 수 없는 환자 중 BMI $\geq$ 25 또는 인슐린 사용불가 환자
- 테크트리
  - Met+SU 사용 후 (기간 제한이 없으므로 2개월 안 기다려도)
  - 혈당조절부족 기준 (단기간이라면 FBS 130, PPG 180 기준으로)
  - Met+SU + GLP-1 RA
  - Met+SU 외의 다른 치료를 하고 있다면, Met+SU로 우선 변경!!
- 인슐린 + (Met) 상태에서 A1c 7 이상시 병용 (inj 복합제 사용가능)
  - Glargine + lixi + (Met)
  - Degludec + lira + Met (Met 빼면 인정 안됨)

# Major GLP-1RA plus SGLT2 inhibitor combination studies

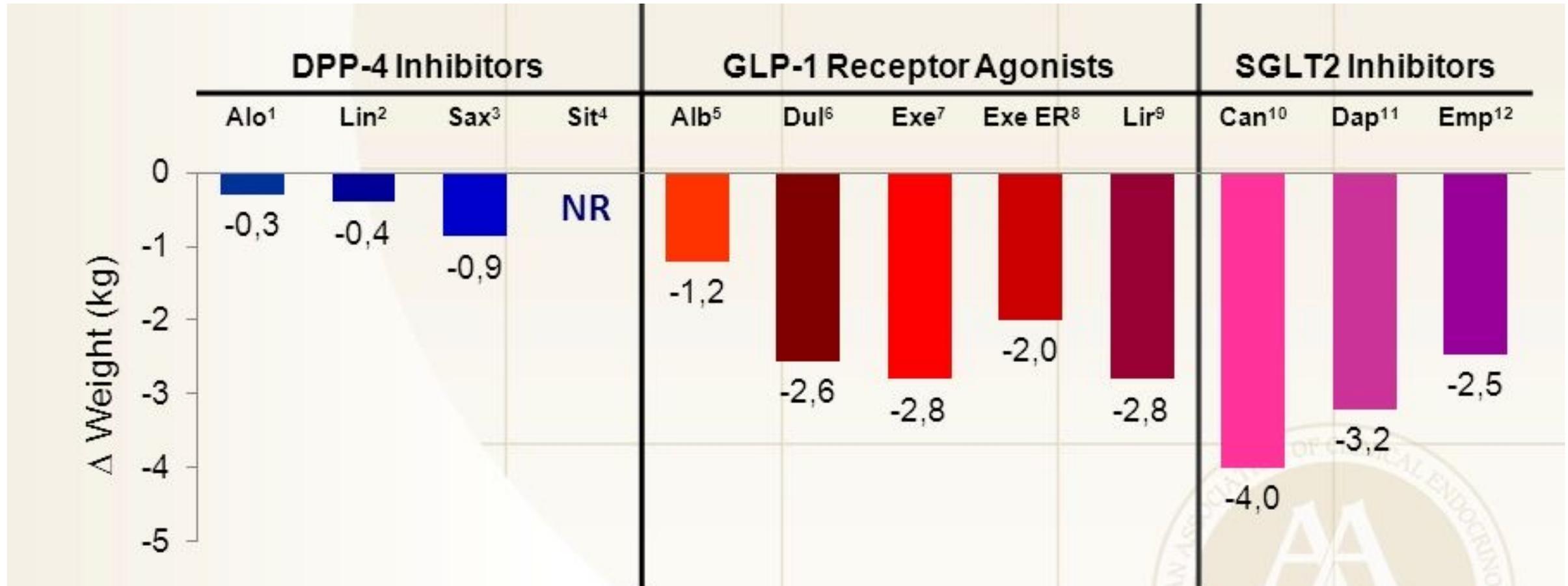


# Studies using fixed-ratio combinations of GLP-1RA plus basal insulin in individuals on an SGLT2 inhibitor



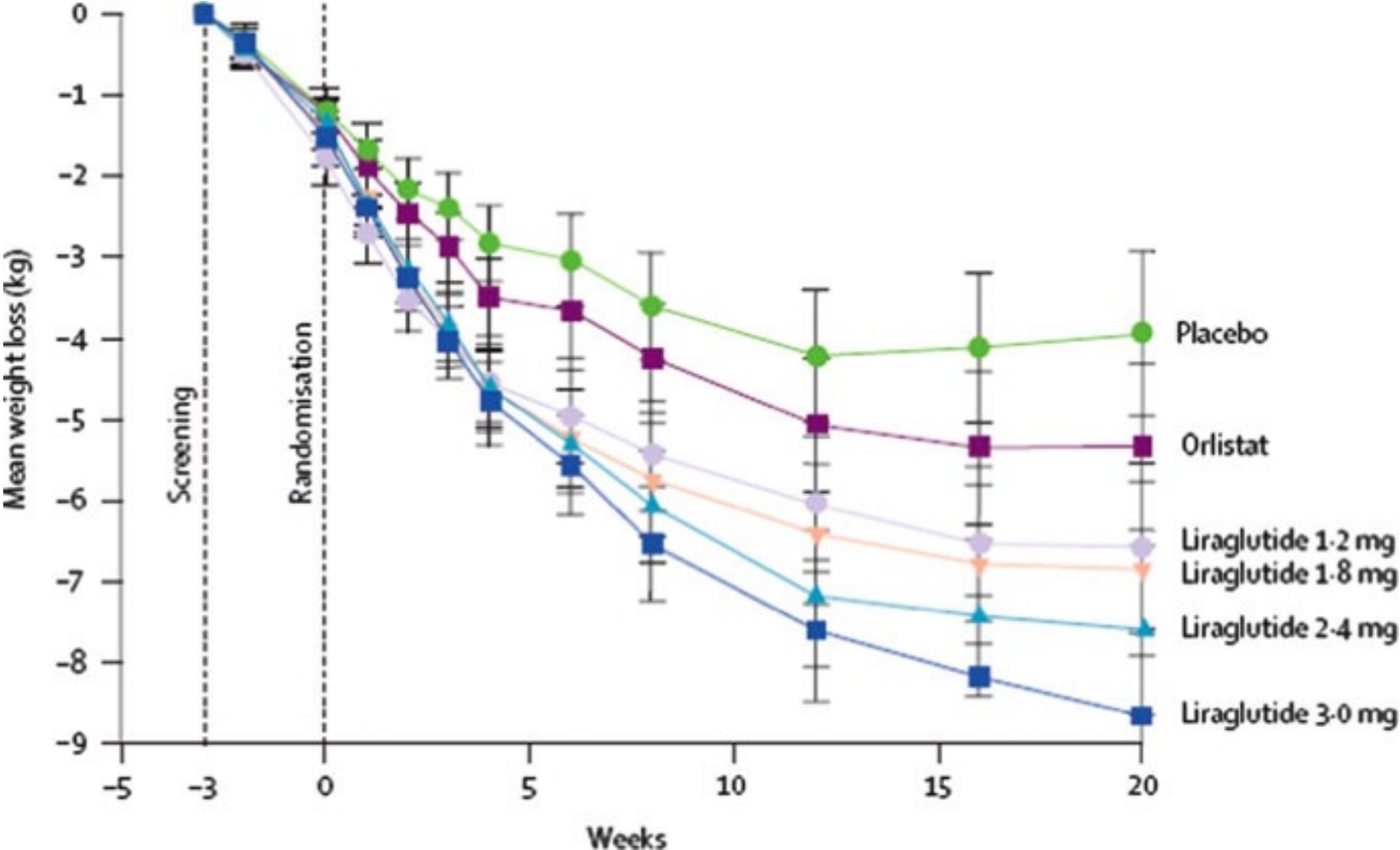
# **SGLT2i, GLP-1RA와 체중 변화**

# Weight Reduction (not head-to-head)

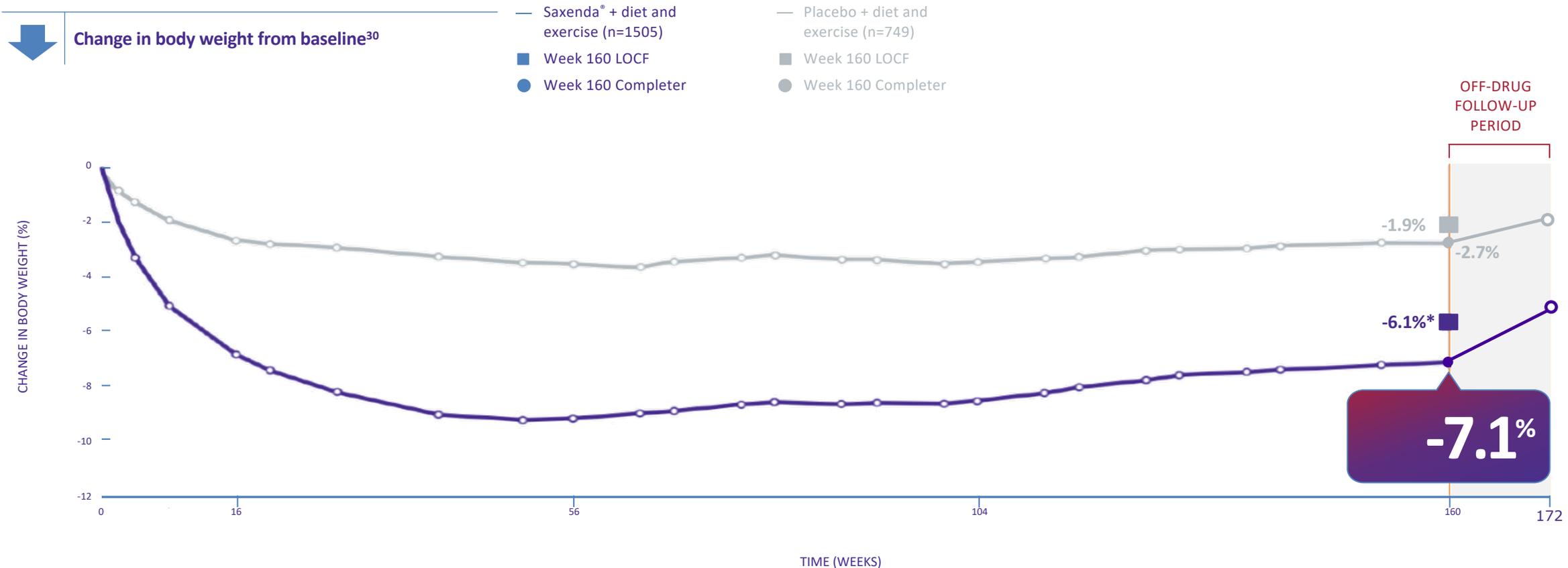


1. Nauck MA, et al. *Int J Clin Pract.* 2009;63:46-55. 2. Taskinen MR, et al. *Diabetes Obes Metab.* 2011;13:65-74. 3. DeFronzo RA, et al. *Diabetes Care.* 2009;32:1649-1655. 4. Charbonnel B, et al. *Diabetes Care.* 2006;29:2638-2643. 5. Ahrén B, et al. *Diabetes Care.* 2014;37:2141-2148. 6. Dungan KM, et al. *Lancet.* 2014;384:1349-1357. 7. DeFronzo RA et al. *Diabetes Care.* 2005;28:1092-1100. 8. Bergenstal RM, et al. *Lancet.* 2010;376:431-439. 9. Pratley RE, et al. *Lancet.* 2010;375:1447-1456. 10. Cefalu WT, et al. *Lancet.* 2013;382:941-950. 11. Nauck MA, et al. *Diabetes Care.* 2011;34:2015-2022. 12. Haring HU, et al. *Diabetes Care.* 2014;37:1650-1659.

# Dose dependent effects of liraglutide on body weight in obese subjects.



# Patients treated with Saxenda<sup>®</sup> lost weight and sustained their weight loss for 3 years<sup>1</sup>



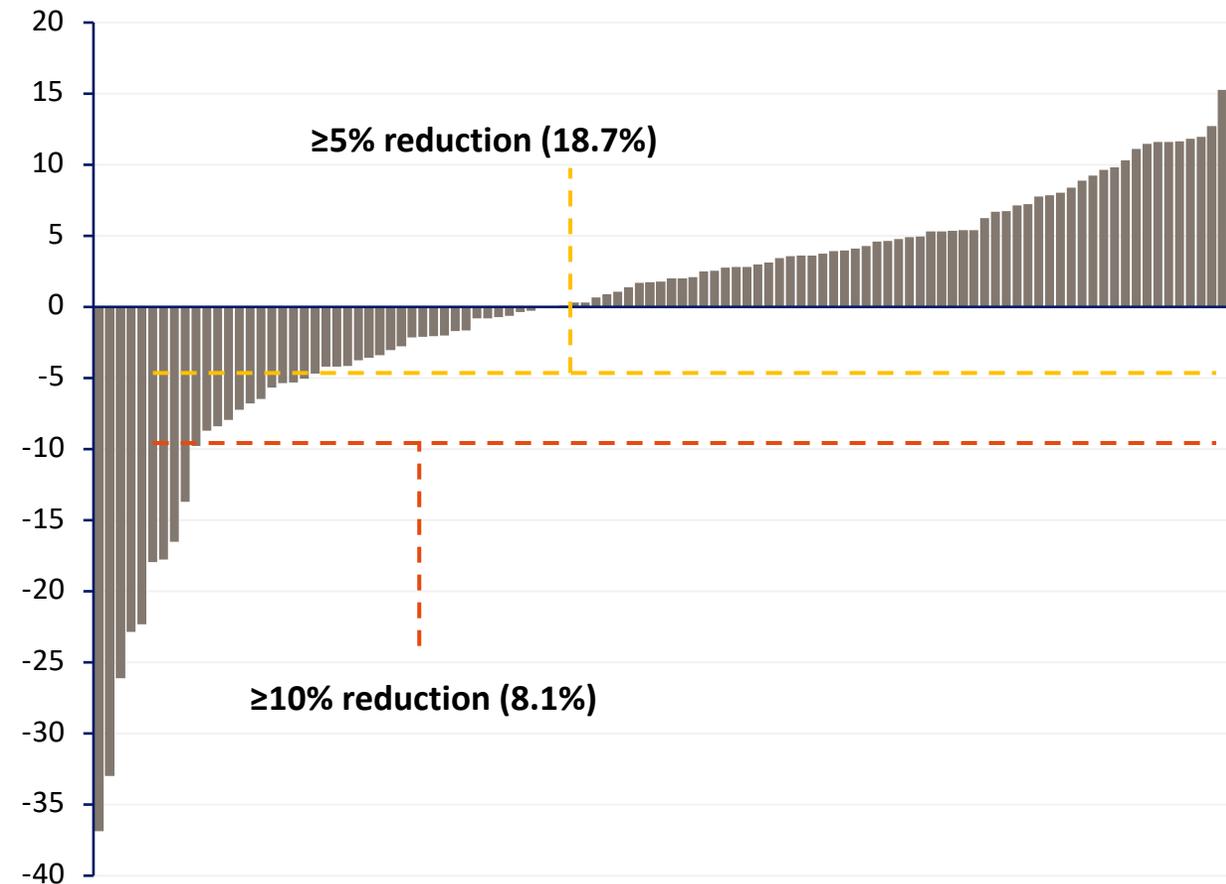
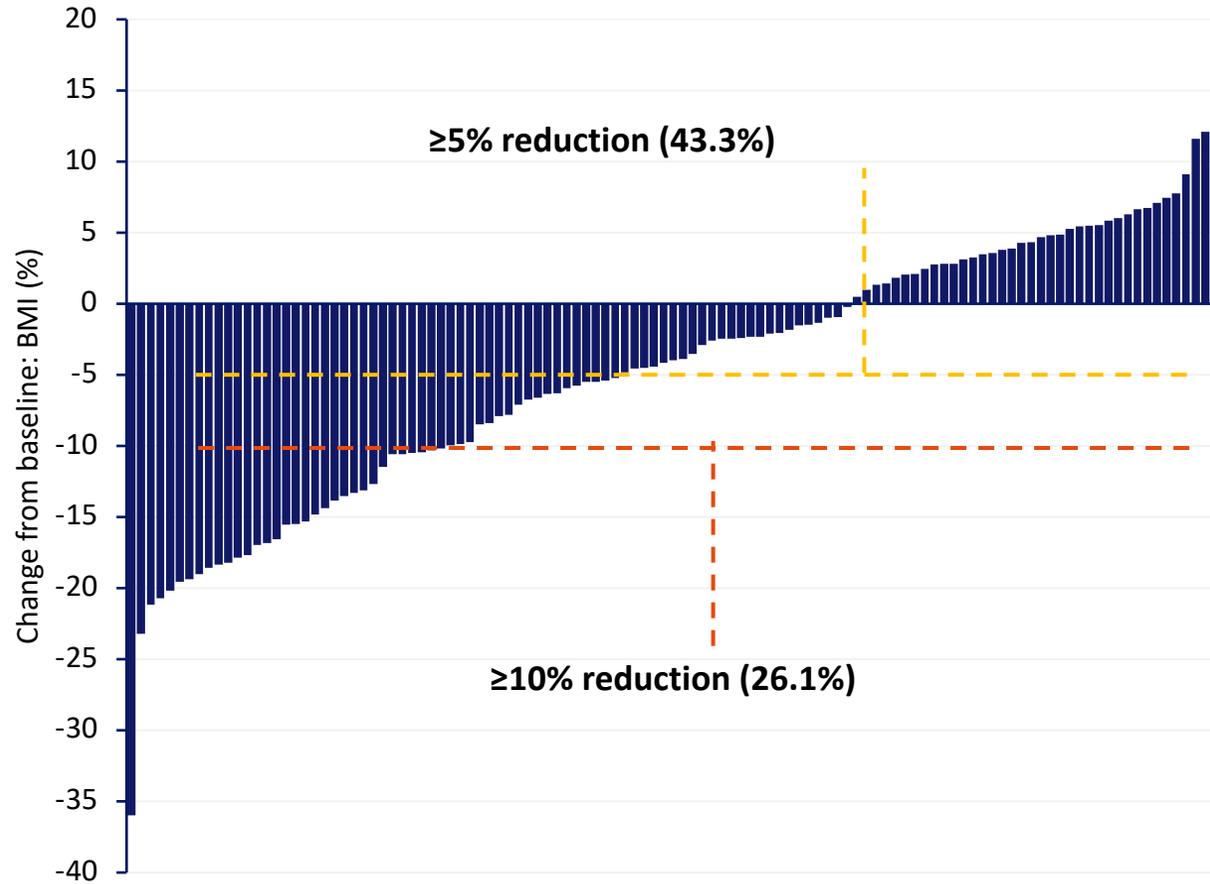
Line graphs are observed means.  
 LOCF=last observation carried forward.  
 \* $P < 0.0001$ .<sup>30</sup>

# SCALE-TEENS: Change in BMI percent

BMI corresponding to  $\geq 30$  kg/m<sup>2</sup> for adults and  $\geq 95^{\text{th}}$  percentile for age and gender

0-56-weeks

■ Liraglutide 3.0 mg    ■ Placebo

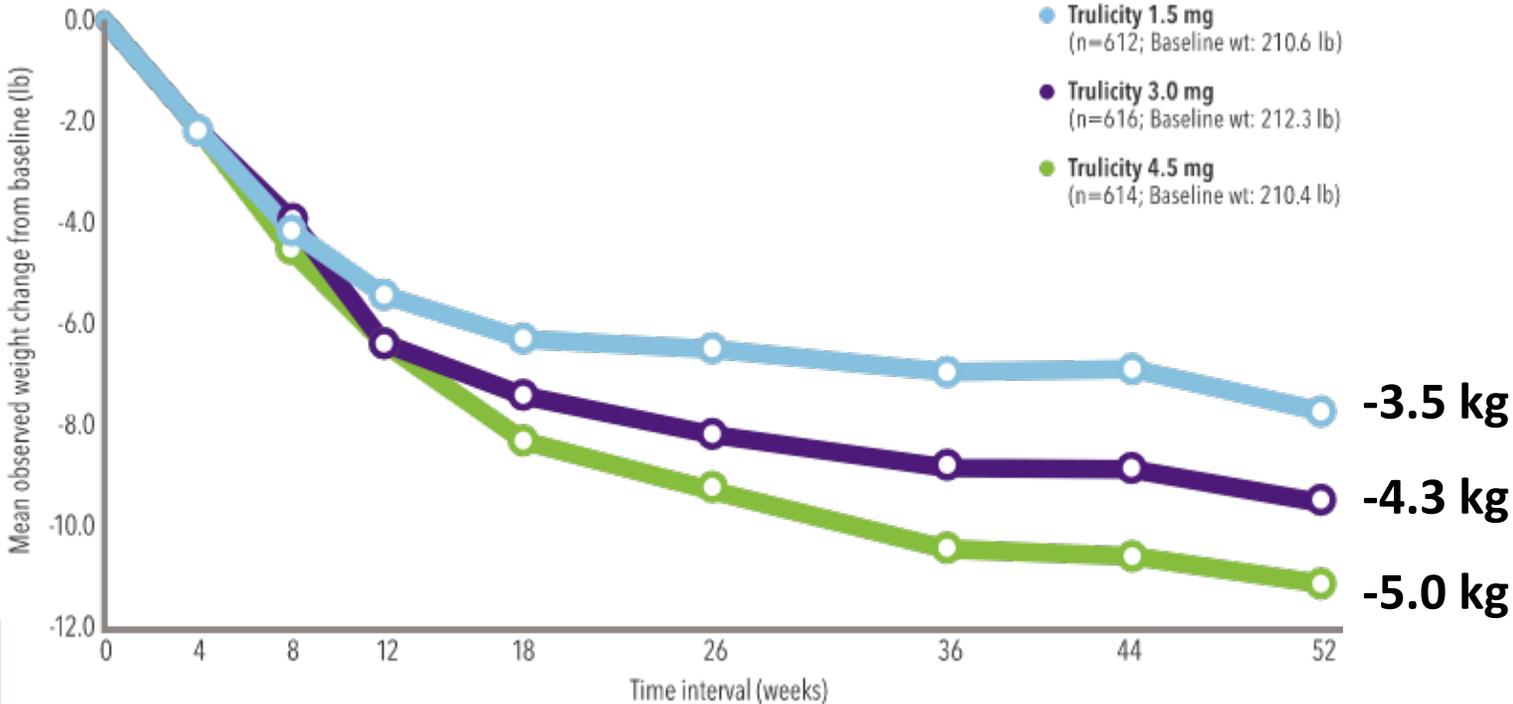


Full analysis set. Statistical analysis is logistic regression with jump-to-reference missing data imputation.  
BMI, body mass index.

# Dulaglutide and weight loss



Available in Korea



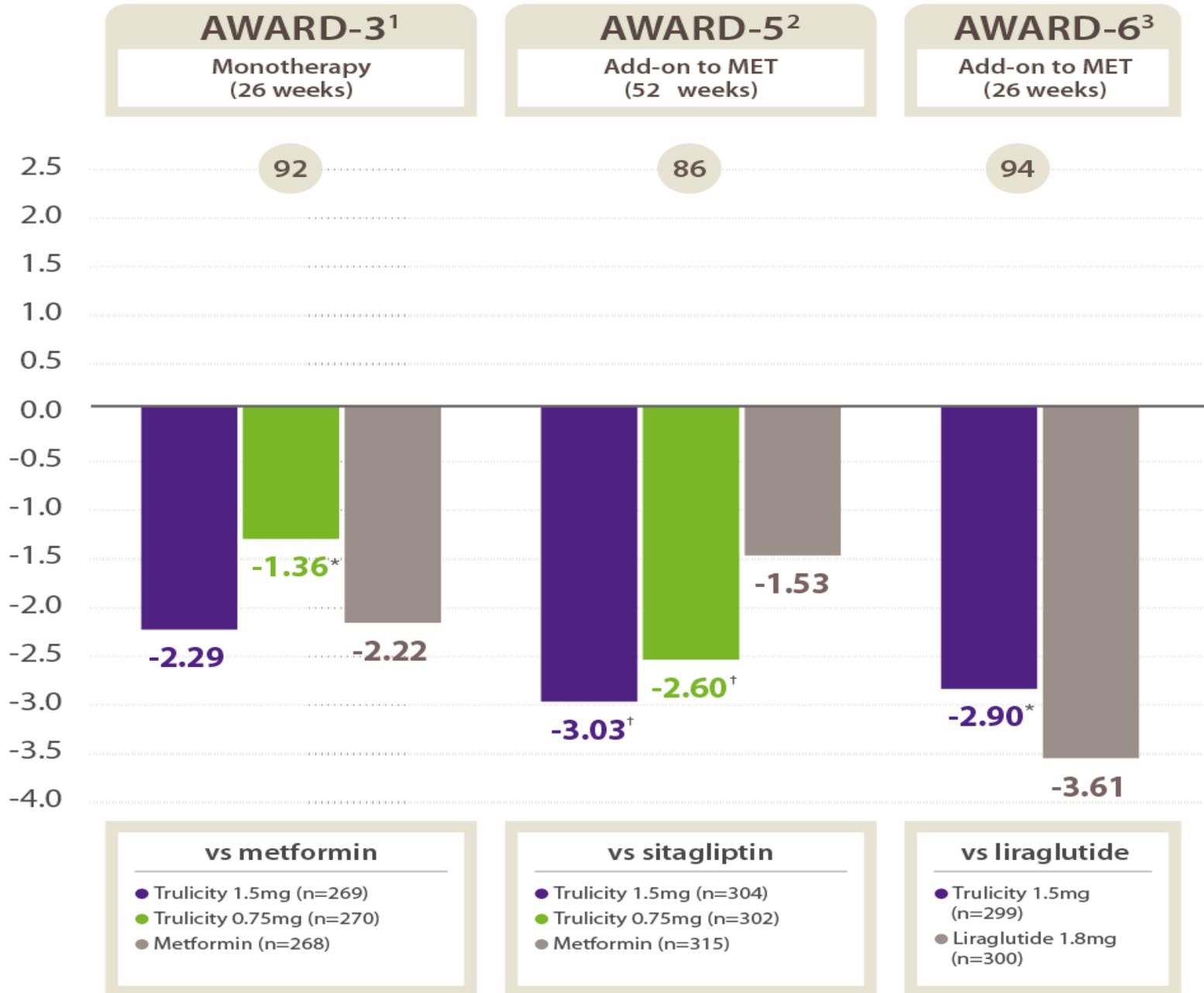
**A1c**

Trulicity 1.5 mg  
**-1.5%**

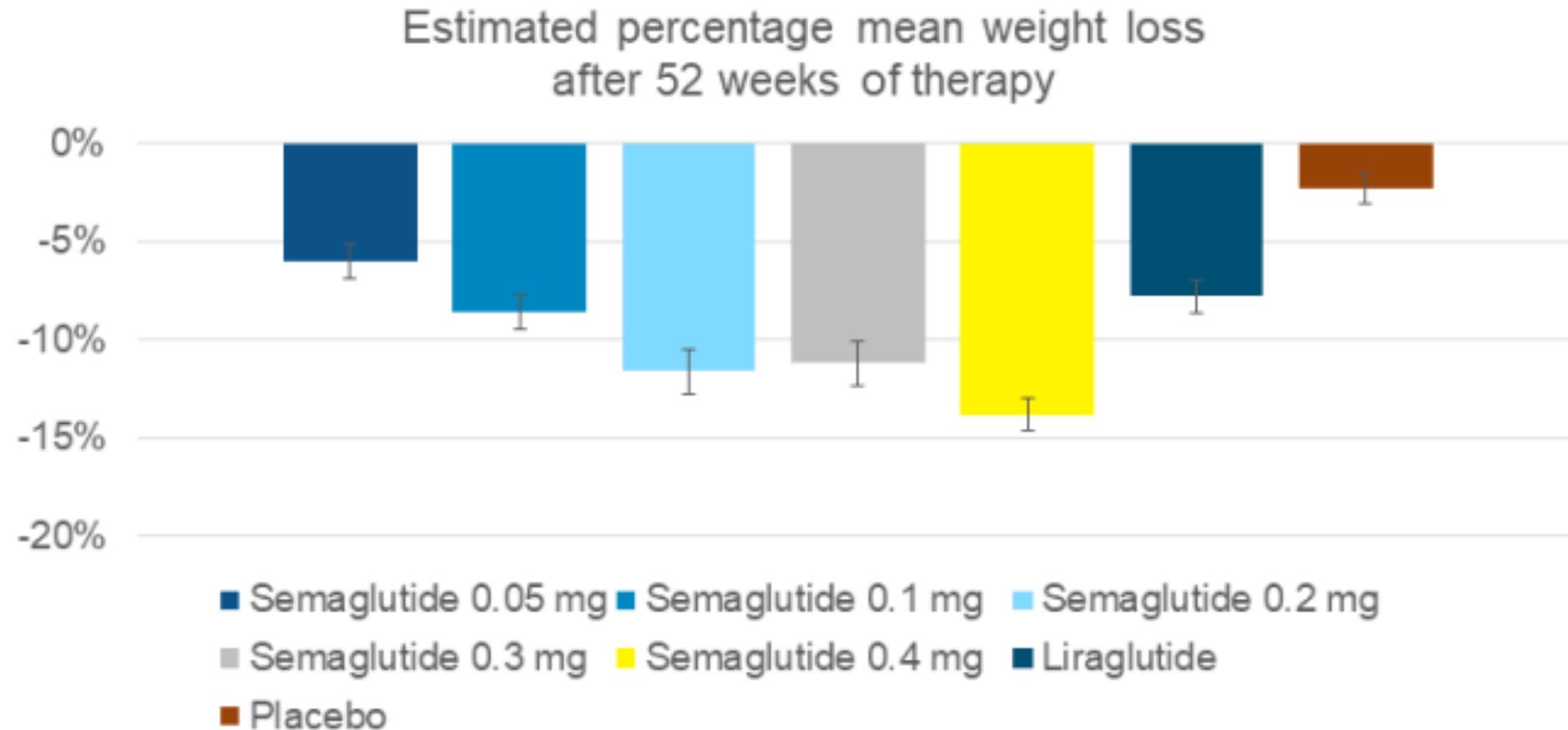
Trulicity 3.0 mg  
**-1.6%\***

Trulicity 4.5 mg  
**-1.8%**

base weight  
Average Reduction in Weight  
(kg, LS mean ± SE)

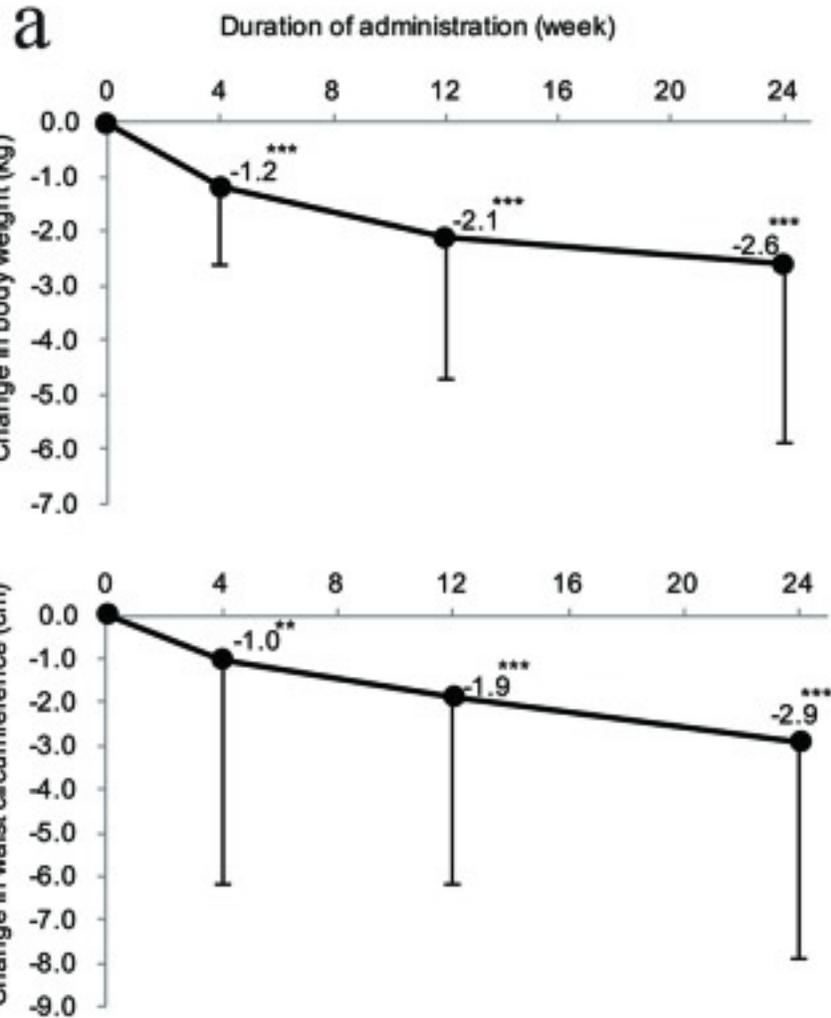


# Semaglutide Phase 2 Trial

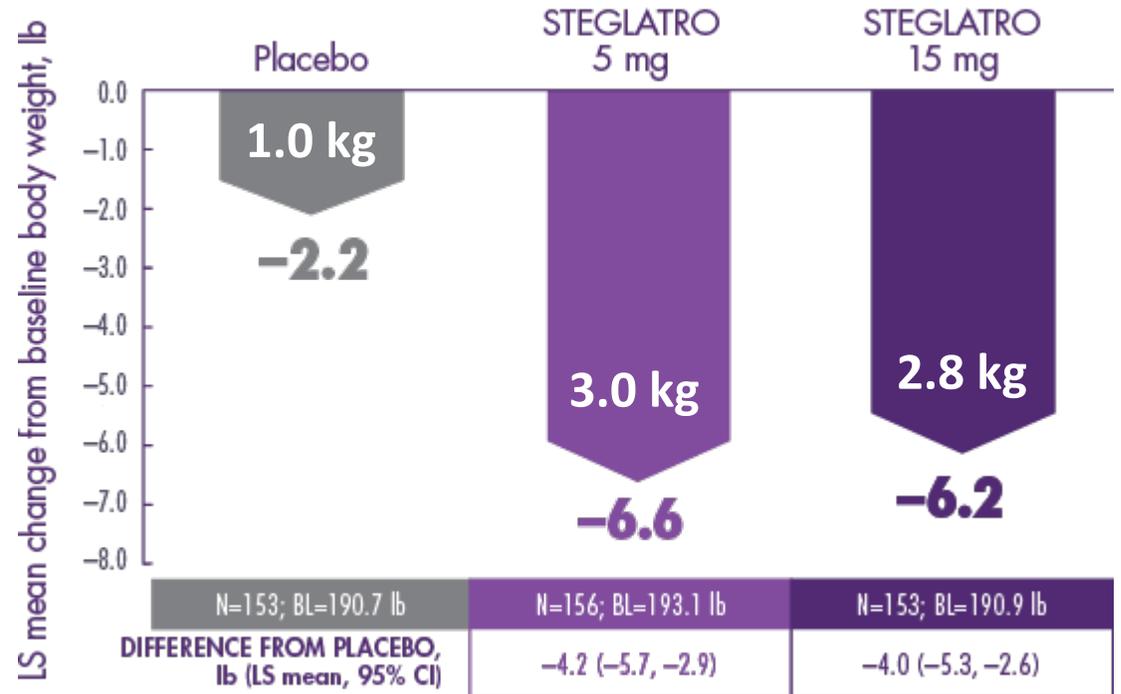


# SGLT2i and weight loss

Ipragliflozin 50mg once daily



Ertugliflozin administration



# Summary in GLP-1RA and SGLT2i

- 두 종류의 약제는 최근 당뇨치료에서 동맥경화성심혈관질환, 심부전, 만성신질환 등의 경우 가정 우선적으로 고려될 필요가 있다.
- 외국에서는 두 종류 약물의 복합치료 임상 자료들도 모이고 있다.
- 두 종류의 약제는 체중 감량 효과가 있다.
  - SGLT2i는 -2.5~-3.0 kg 정도의 감량을 기대할 수 있다.
  - GLP-1RA 가운데 고용량으로 투여시 비만에 적응증을 둘 수 있다.