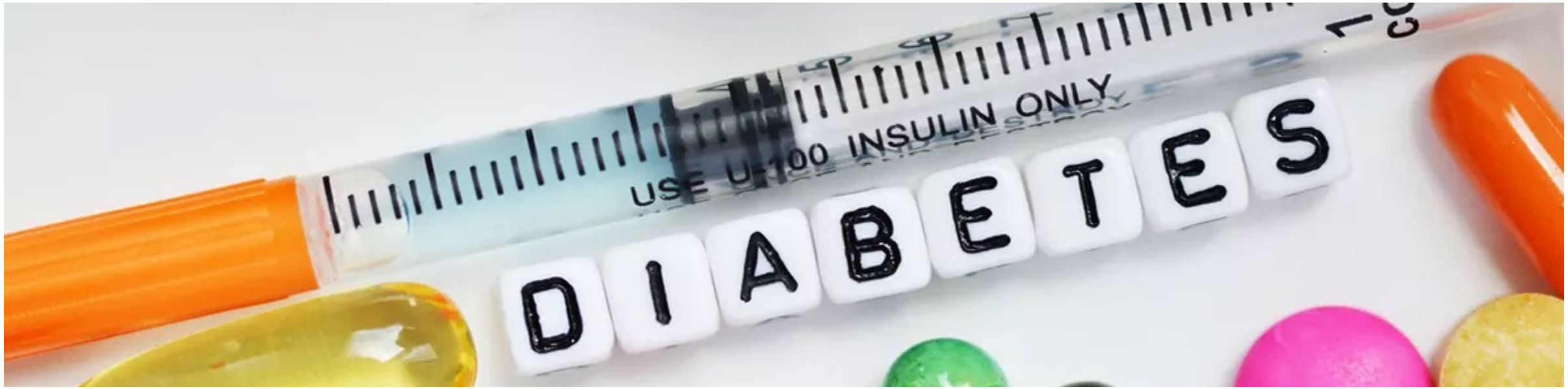
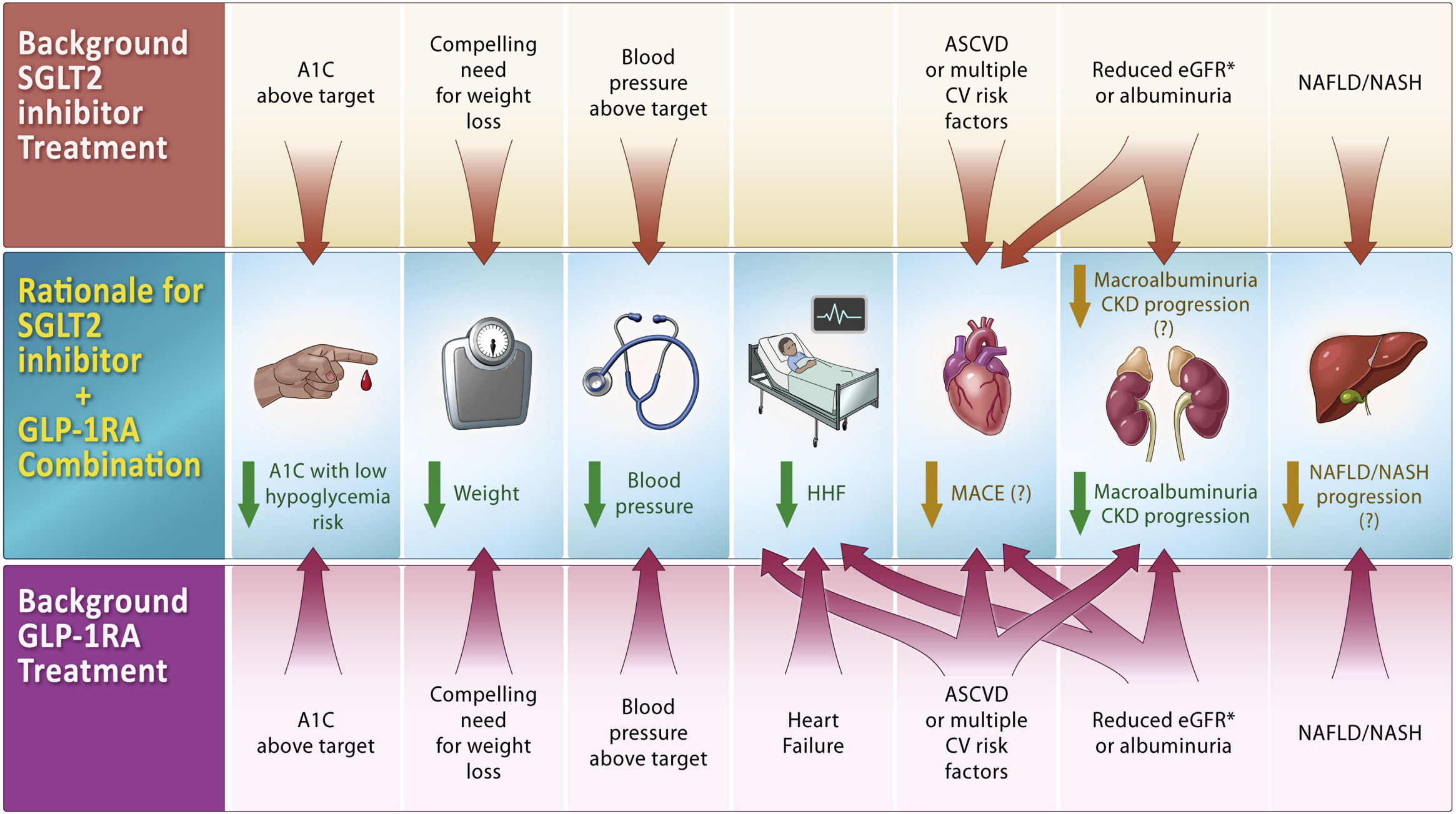


GLP-1 RA 및 SGLT2 억제제: 당뇨와 비만 사이

CHA 의과학대학교
CHA 분당차병원

가정의학과 김 영 상

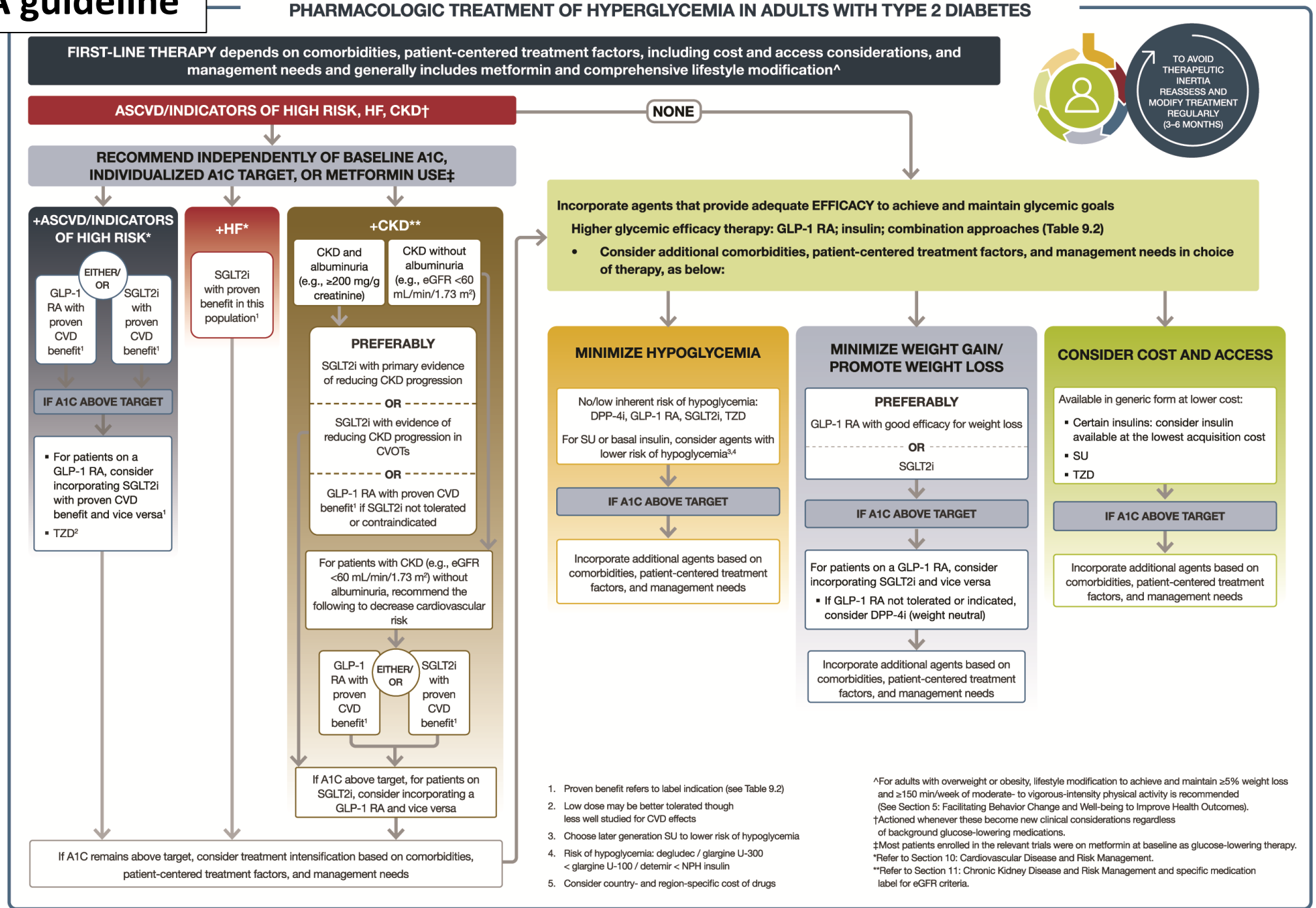
Characteristics of GLP-1RA and SGLT2i-treated individuals and rationale for combining a GLP-1RA with an SGLT2i

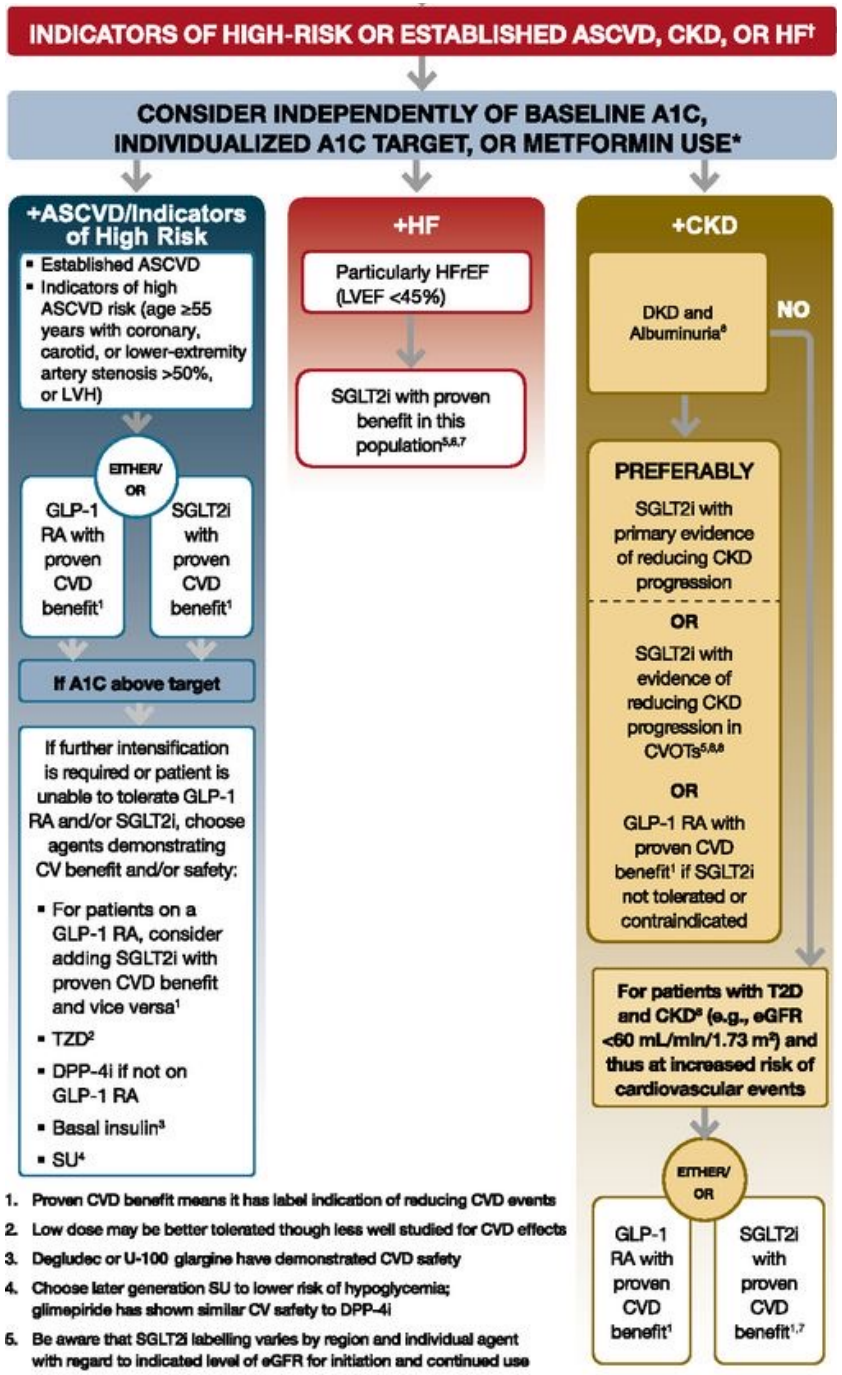


Can J Diabetes. 2021 Apr;45(3):291-302.

당뇨병에서 SGLT2i와 GLP-1RA의 사용

2022 ADA guideline





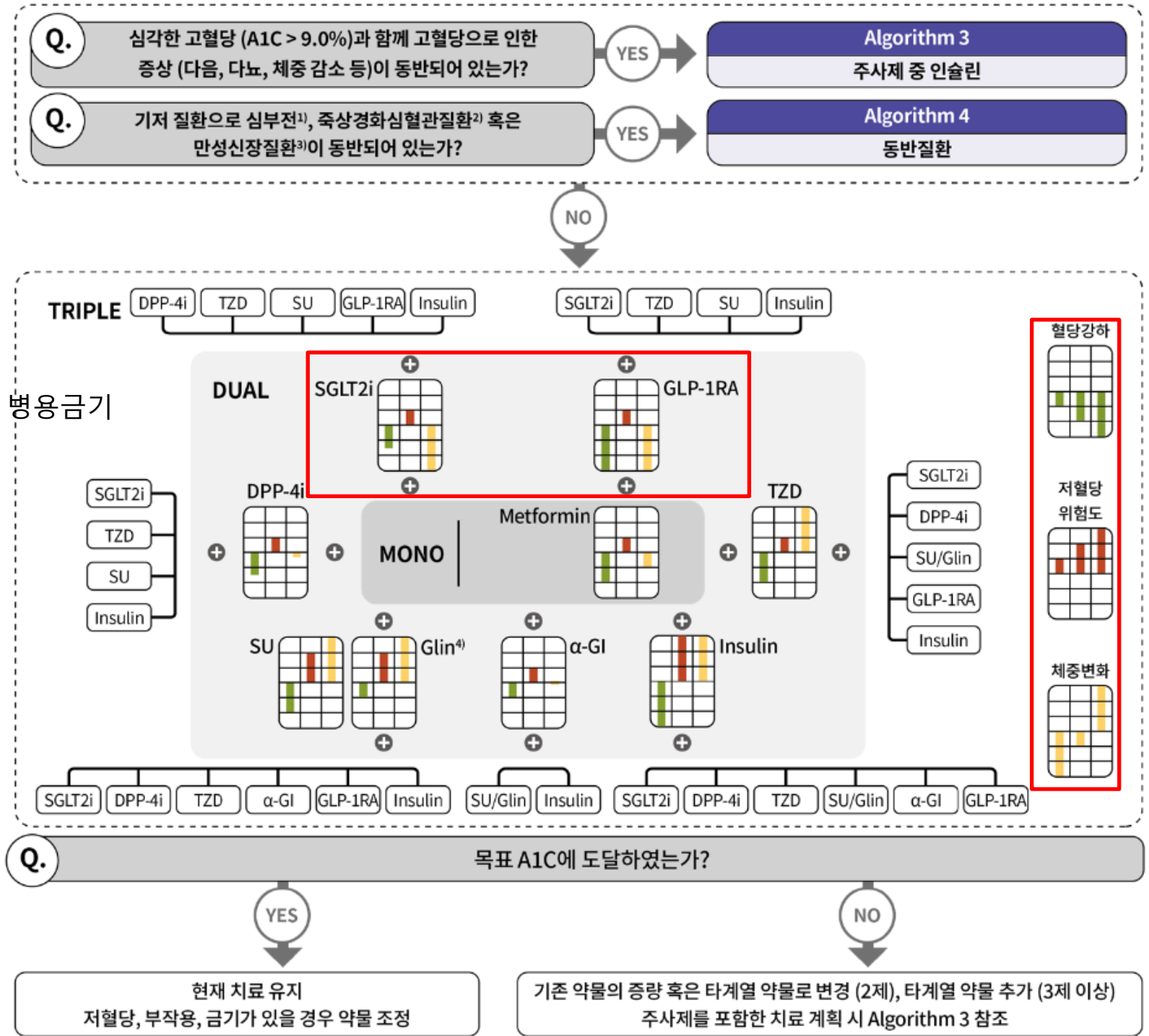
ADA에서는 어떤 경우에 다른 class의 초치료를 권하나?

- 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

DPP4i와 GLP-1a는 병용금기



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

medipana
메디파나뉴스

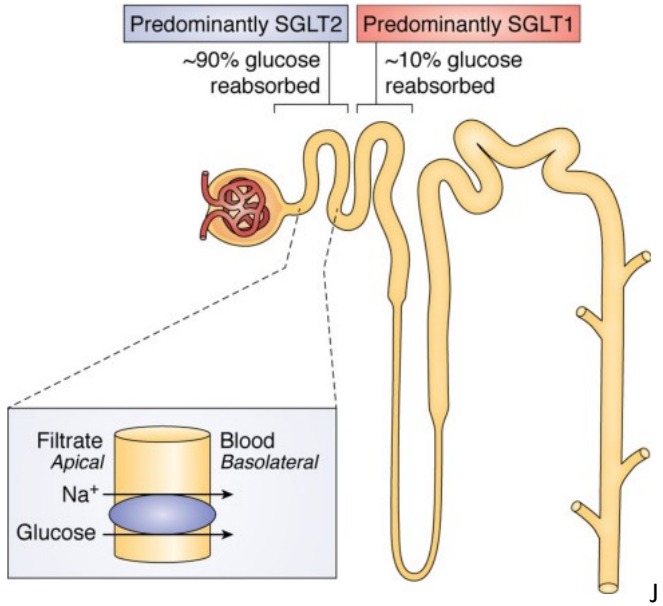
박으뜸기자 acepark@medipana.com 2021-08-23 11:55

'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

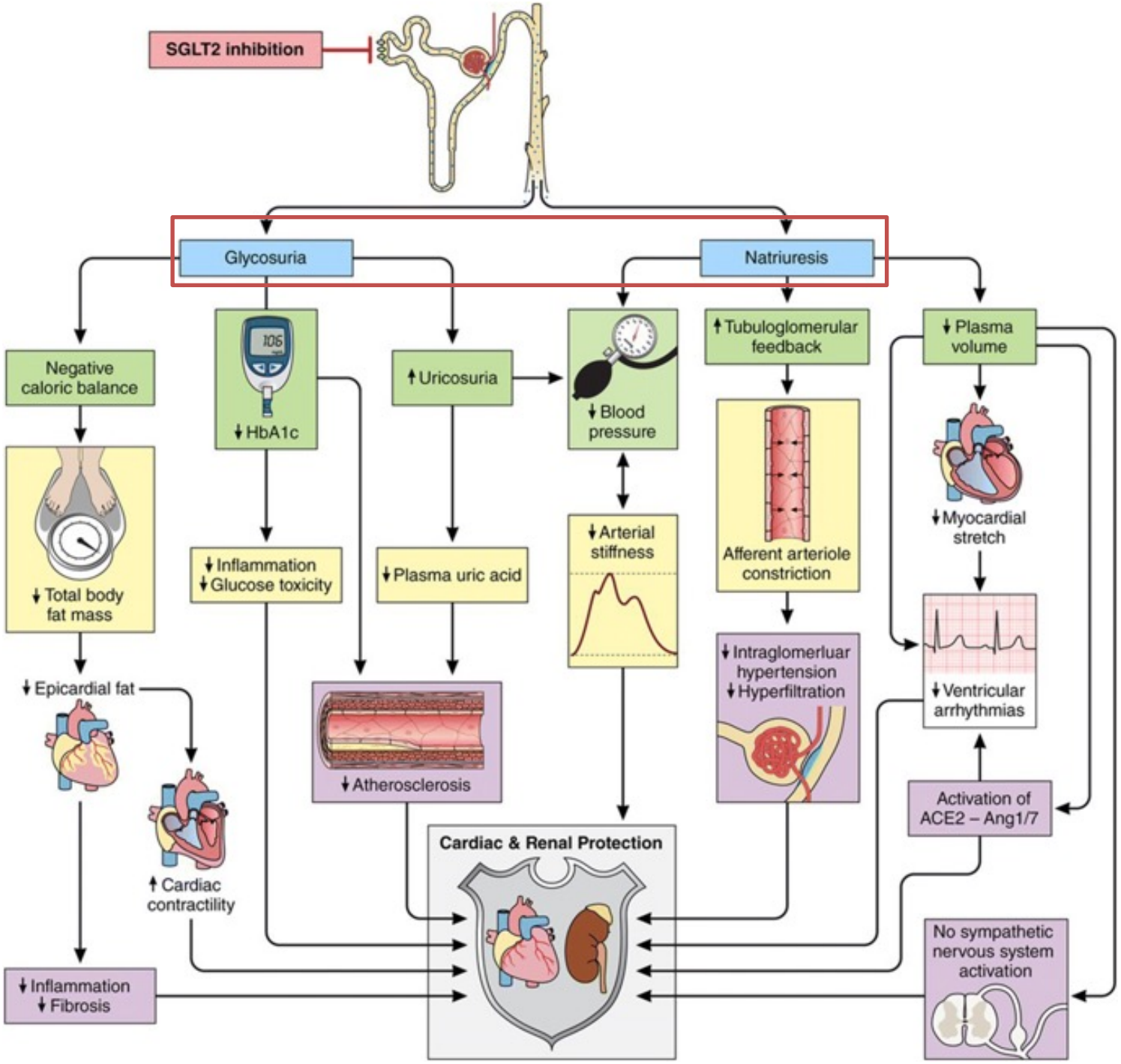


J Biol Chem. 2020 Oct 16;295(42):14379-14390.

SGLT2i

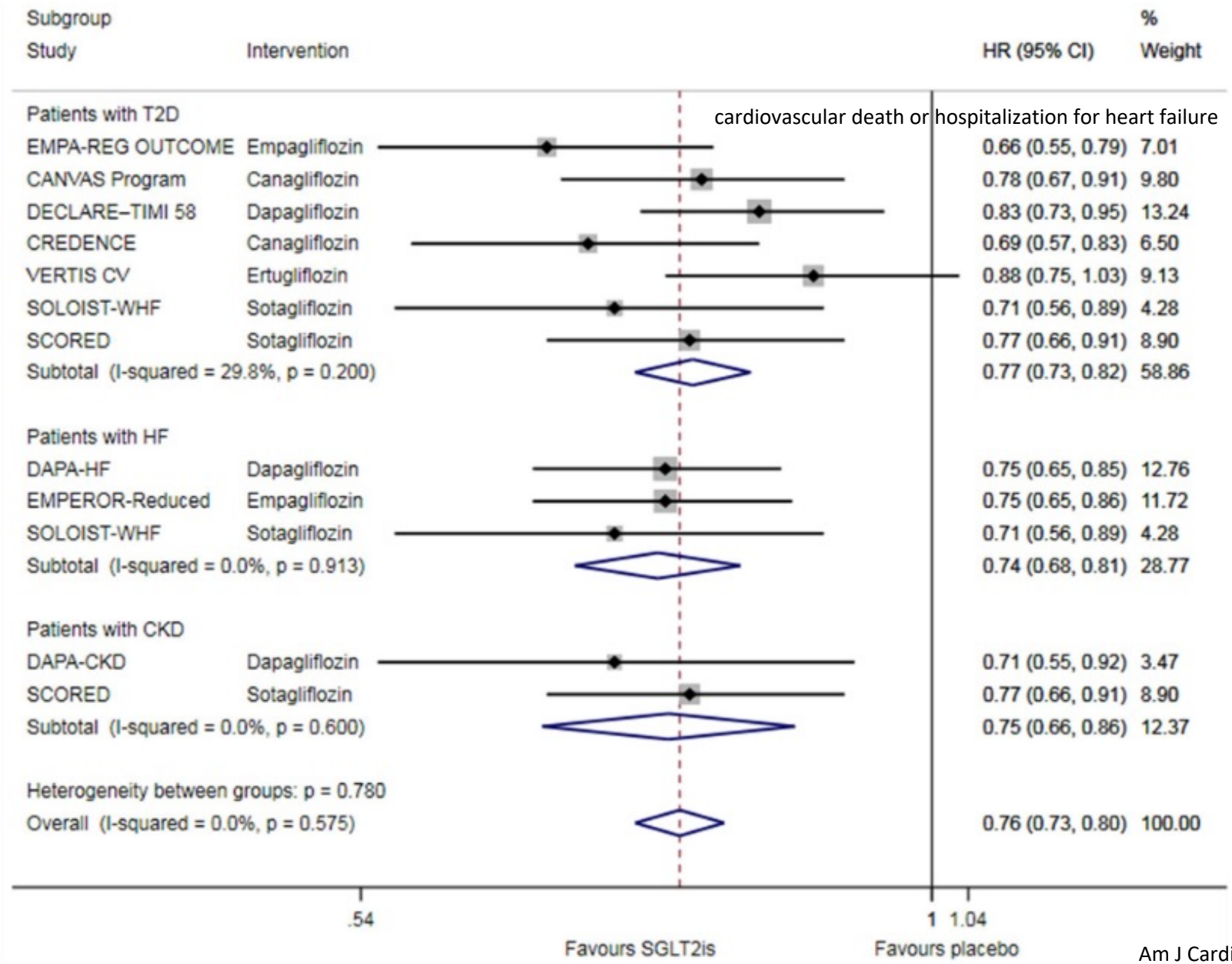
- Dapagliflozin, Empagliflozin, Ipragliflozin, Ertugliflozin
- 혈당강하효과: HbA1c 0.5-1.0%
- 부작용: 요로생식기감염, 배뇨증가, 회음부 괴저, 저혈압, GFR감소, 케톤산증
- 금기: 유당불내성(Dapa, Empa), 신부전
- 주의: 고령자(75세 이상), 중증 간장애, 저혈압(Ertu)

eGFR (mL/min/1.73 m²)	CKD1-2	CKD3a	CKD3b	CKD4	ESKD
	≥ 60	59-45	44-30	29-15	< 15
SGLT2 inhibitors					
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			



Diabetes Therapy volume 10, pages1595–1622(2019)
Diabetes Care 2016 Jul; 39(7): 1115-1122

SGLT2i - CVOT



Am J Cardiovasc Drugs. 2022 Jan;22(1):69-81.

SGLT2i - CVOT

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

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

Am J Cardiovasc Drugs. 2022 Jan;22(1):69-81.

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

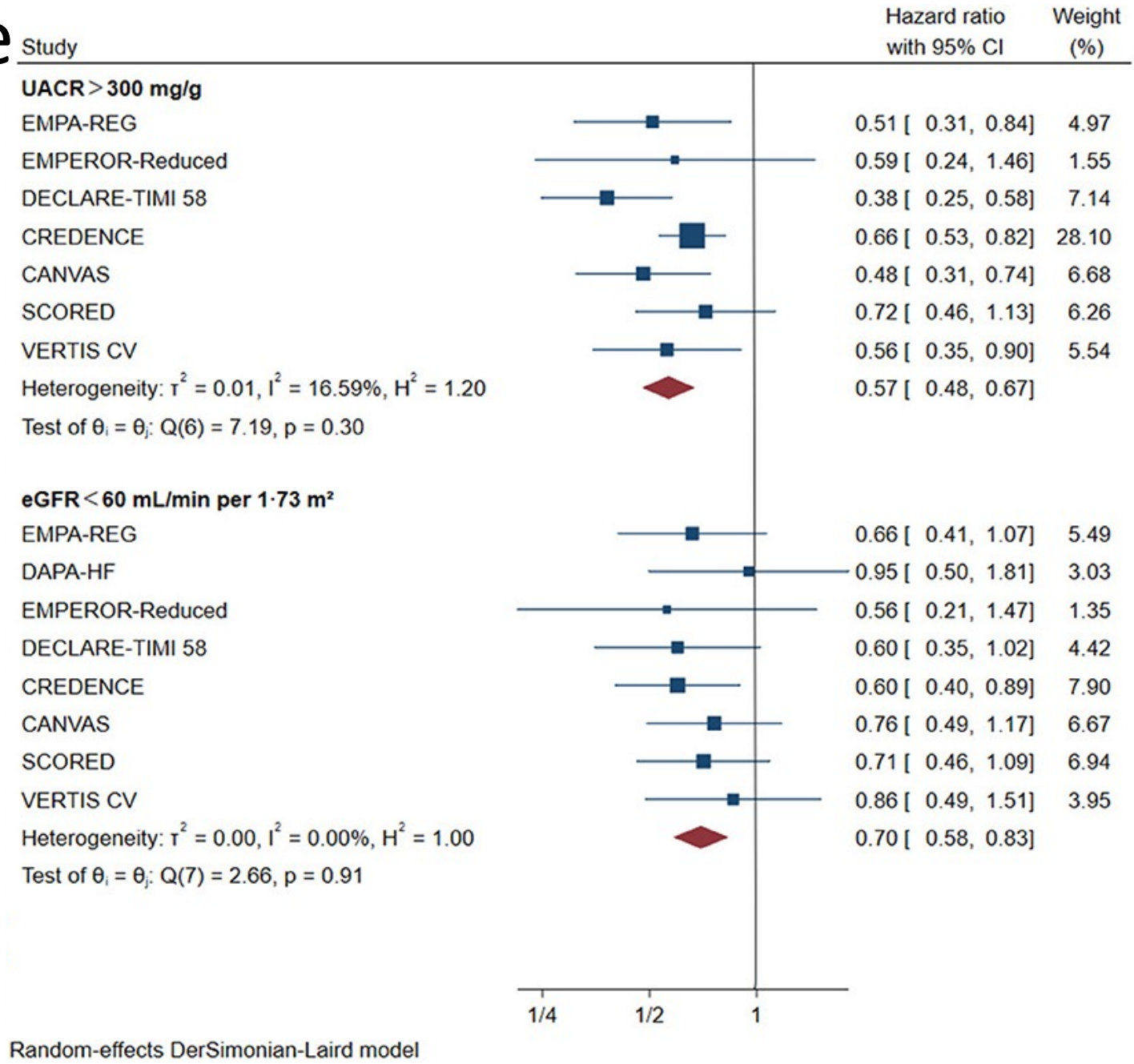


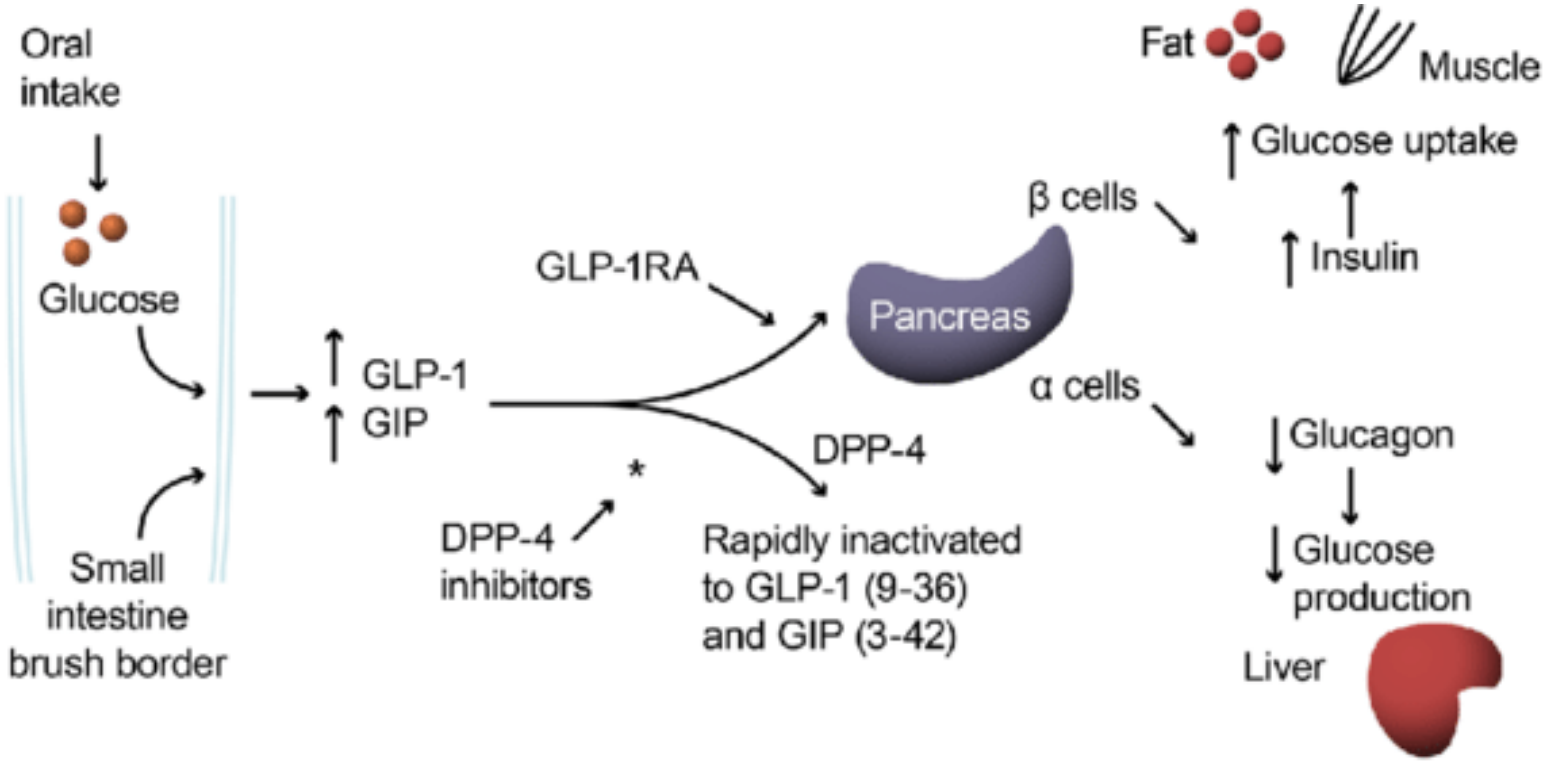
TABLE 2 Prevention of adverse events with SGLT2 inhibitors

	At risk	Measures to prevent adverse event
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

Diabetes Obes Metab. 2019 Apr;21 Suppl 2:34-42

GLP-1RA

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



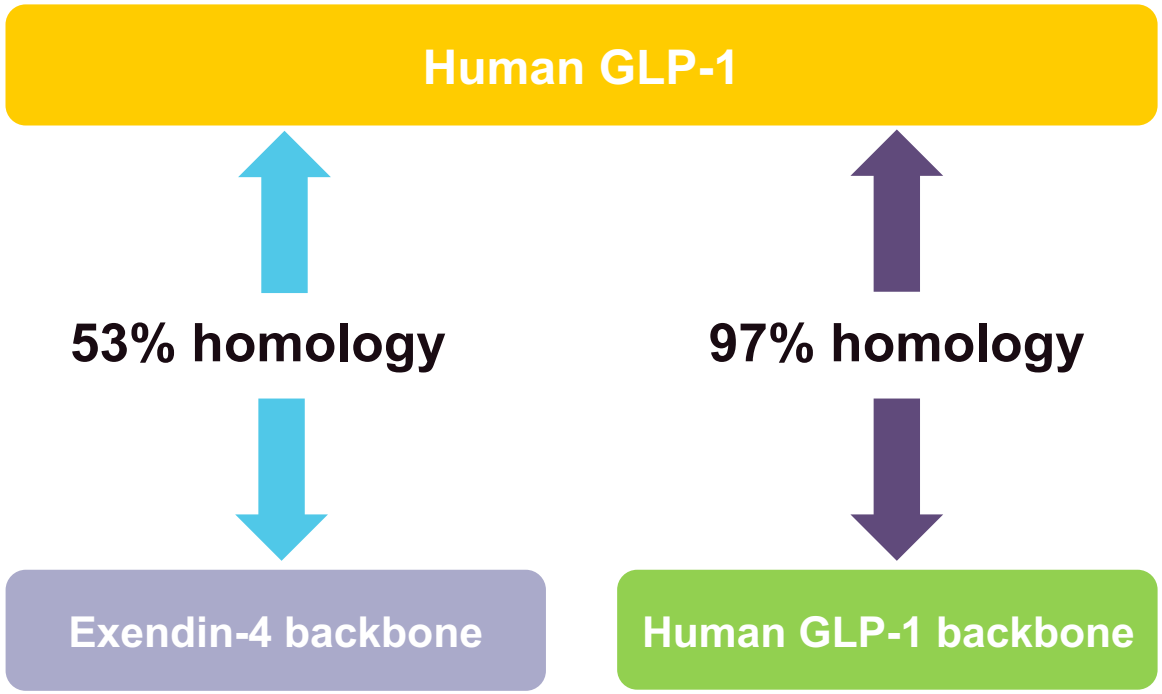
GLP-1RA

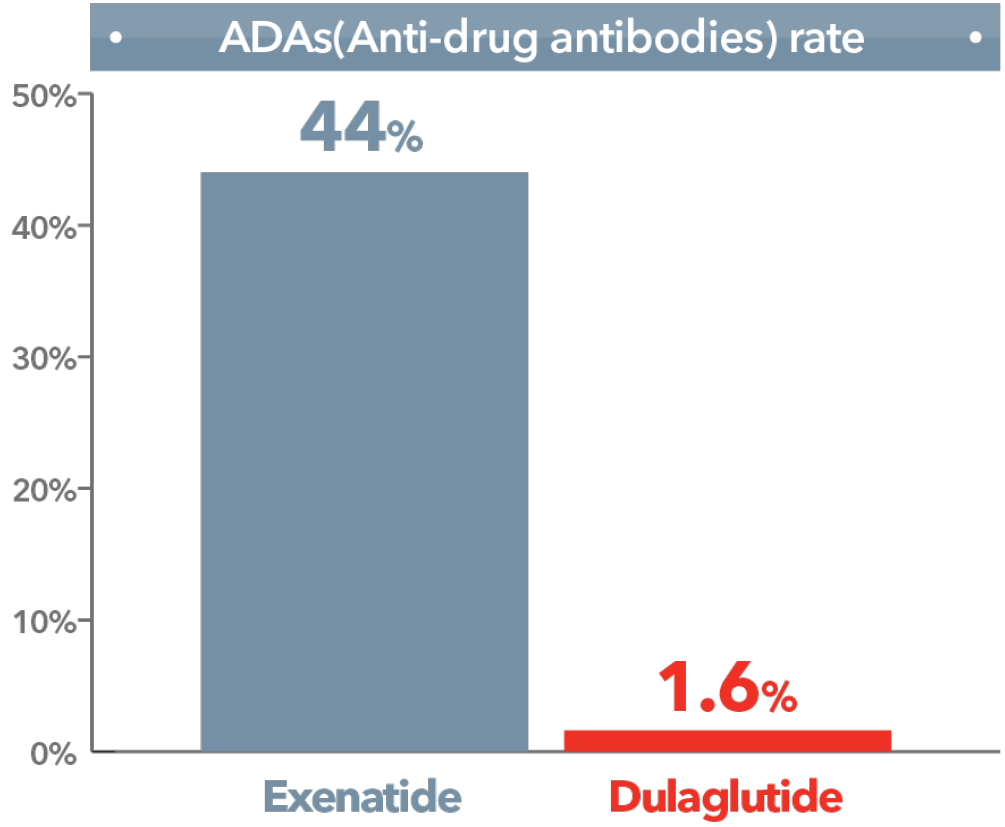
Table 1 — Characteristics of GLP-1 RAs that have been approved to treat type 2 diabetes as of 2020.

GLP-1 RA	First approved (date)	Molecular weight (Da)[c]	Reference amino acid sequence	Other important components	Elimination half-life	Administration schedule	Pharmaceutical company	Reference
For subcutaneous injection								
Short-acting compounds								
Exenatide b.i.d.	2005 (USA); 2006 (Europe); Byetta	4186.6	Exendin-4	None	3.3—4.0 h	Twice daily	AstraZeneca[i]	[21]
Lixisenatide	2013 (Europe); Lyxumia; 2016 (USA); Adlyxin	4858.5	Exendin-4	Poly-lysine tail	2.6 h	Once daily	Sanofi	[22]
Long-acting compounds/preparations								
Liraglutide	2009 (Europe); 2010 (USA); Victoza	3751.2	Mammalian GLP-1	Free fatty acid[e]	12.6—14.3 h	Once daily	Novo Nordisk	[23]
Once-weekly exenatide	2012; BYDUREON[a]	4186.6	Exendin-4	Active ingredient encapsulated in microspheres of poly-(D,L-lactide-co-glycolide)	3.3—4.0 h[f]	Once weekly	AstraZeneca[i]	[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)[b]	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[e]	5.7—6.7 d	Once weekly	Novo Nordisk	[26]

Mol Metab. 2021 Apr;46:101102.

Human GLP-1 vs. Exedine-4 backbone





Fc = fragment crystallisation; IgG = immunoglobulin G.

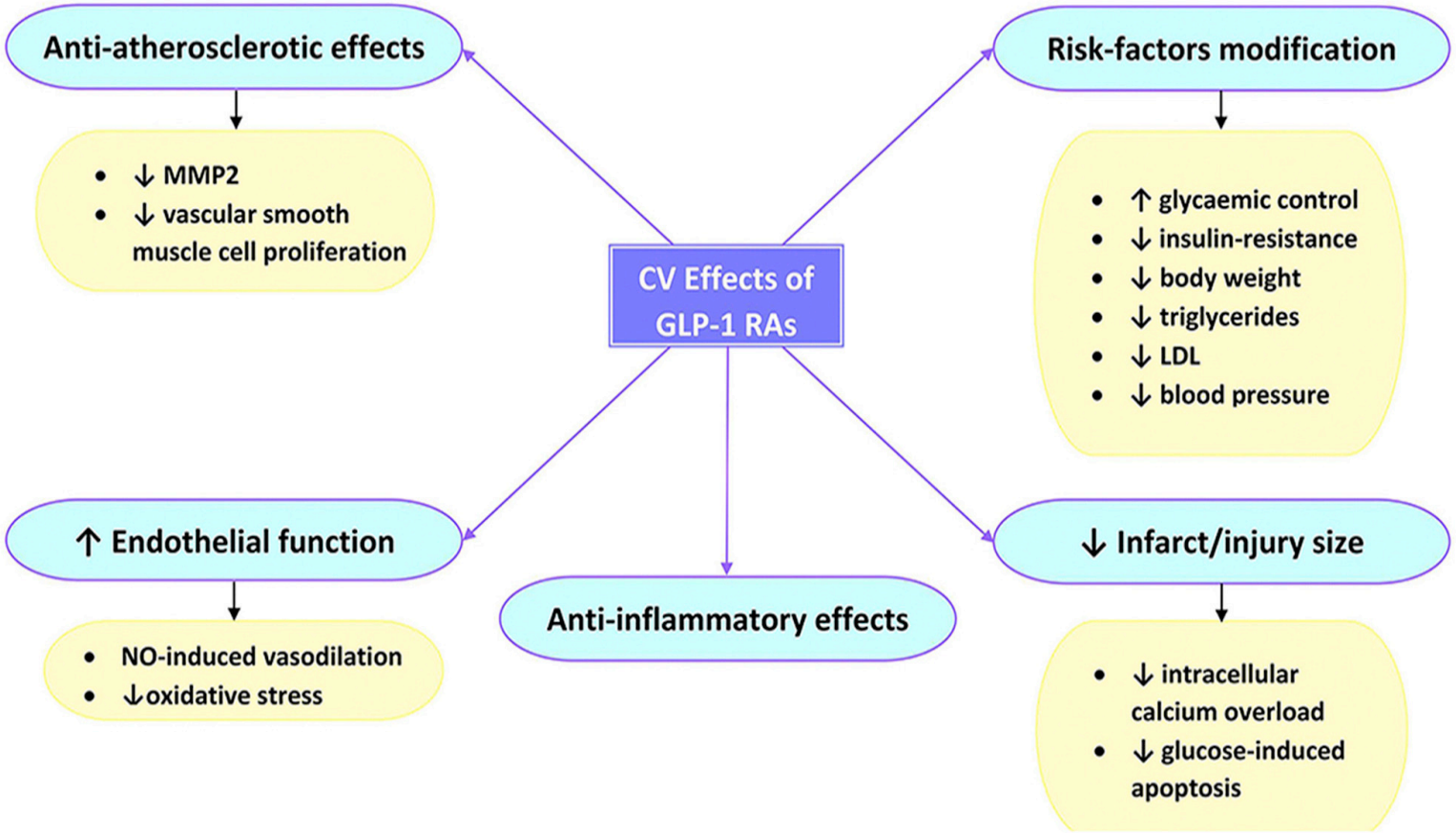
1. Neumiller JJ. J Am Pharm Assoc 2009;49(Suppl 1):S16-29
2. Glaesner, et al. 2011, PepTalk.
3. Wysham C, et al. Diabetes Care. 2014;37(8):2159-2167.

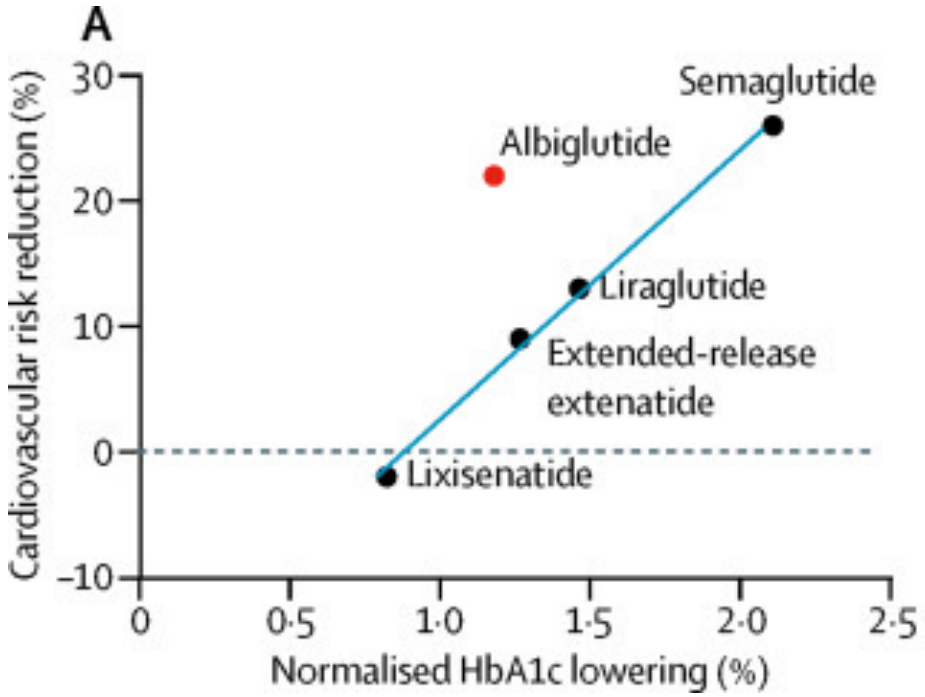
GLP-1RA

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

eGFR (mL/min/1.73 m²)	CKD1-2	CKD3a	CKD3b	CKD4	ESKD
	≥ 60	59-45	44-30	29-15	< 15
GLP-1 receptor agonists					
Liraglutide					자료 없음
Dulaglutide					

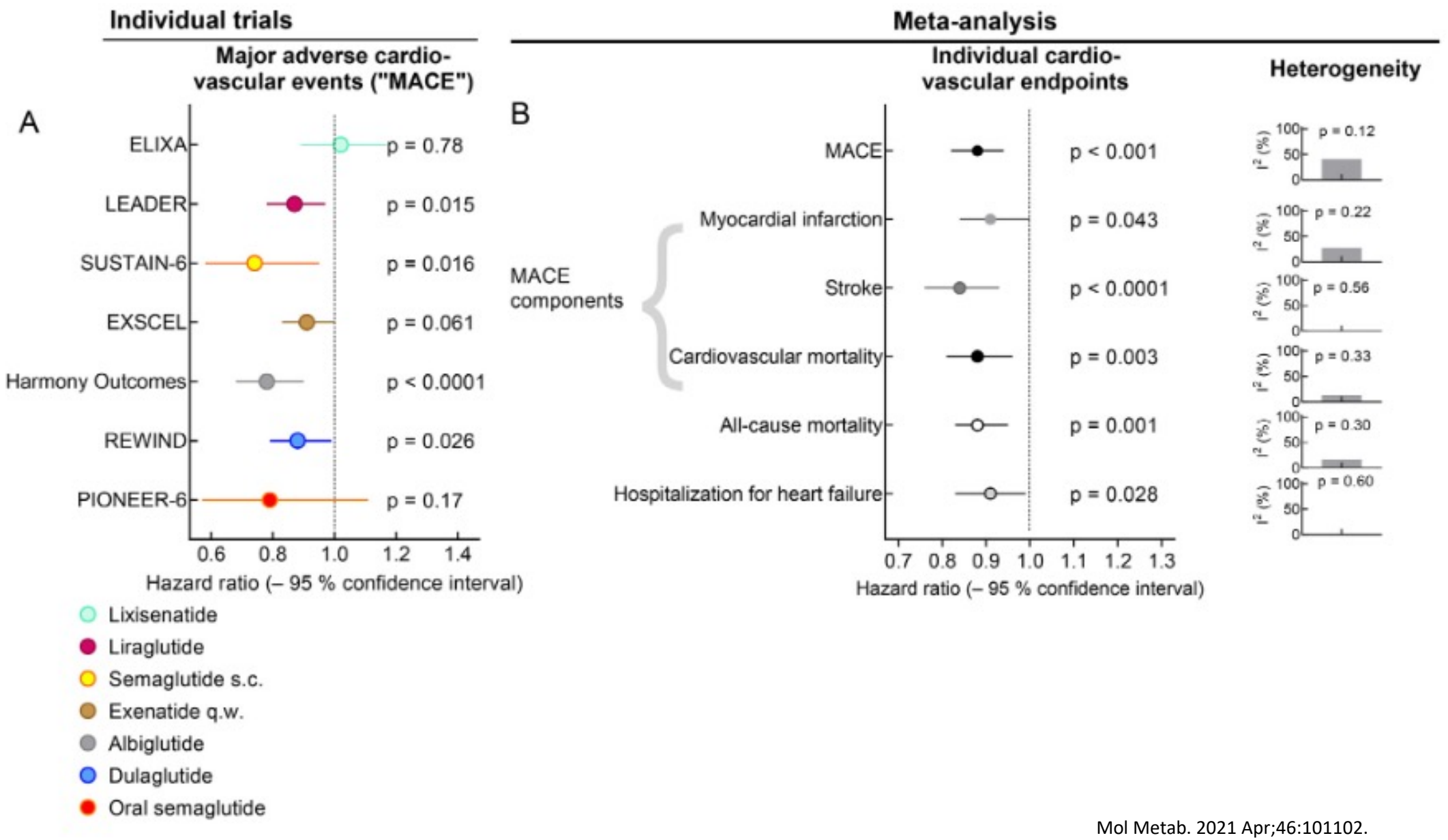
GLP-1RA - CV benefit





Hellenic J Cardiol. 2018 Dec 6. pii: S1109-9666(18)30408-1
Lancet Diabetes Endocrinol. 2019 Feb;7(2):89-90

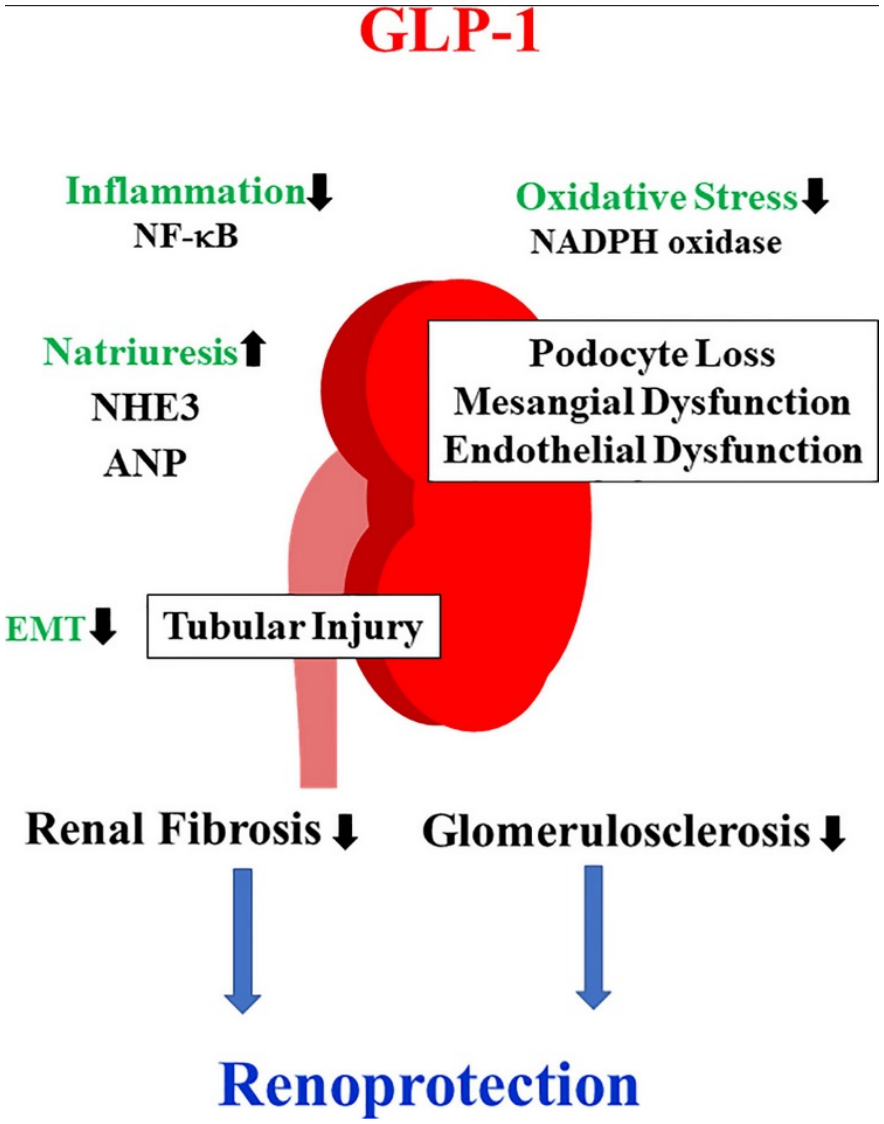
GLP-1RA - CVOT



Mol Metab. 2021 Apr;46:101102.

GLP-1RA - Renal outcome

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



급여기준에서 인정 가능 2제 요법

구 분		Metformin	Sulfonyl urea	Megliti nide	α-glucosid ase inhibitor	Thiazoli-dinedione	DPP-IV inhibitor	SGLT-2 inhibitor			
								dapagli flozin	ipragli flozin	empaglif lozin	ertugli flozin
Metformin			인정	인정	인정	인정	인정	인정	인정	인정	인정
Sulfonylurea		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	dapagliflozin	인정	인정								
	ipragliflozin	인정									
	empagliflozin	인정									
	ertugliflozin	인정									

나) 3제요법

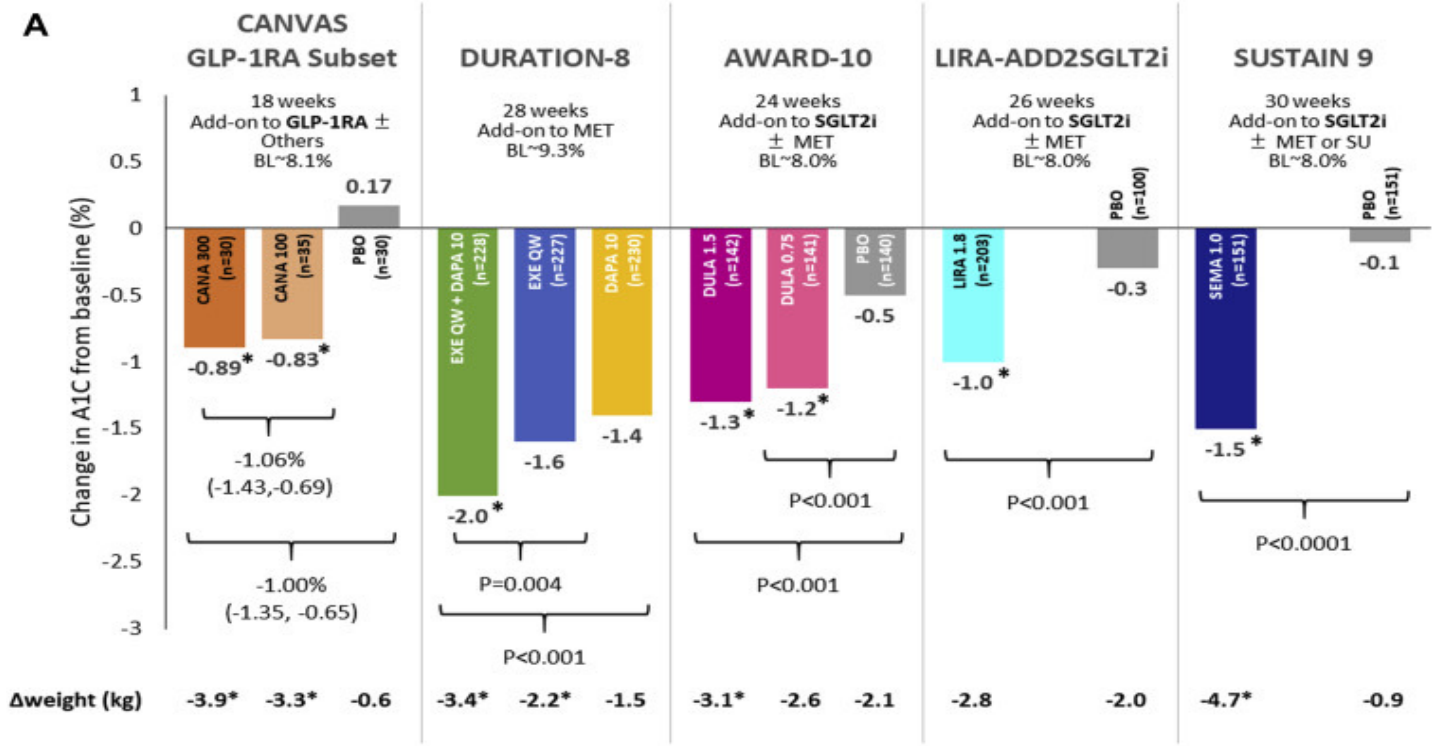
○ 2제 요법을 2-4개월 이상 투여해도 HbA1C가 7% 이상인 경우에는 다른 기전의 당뇨병 치료제 1종을 추가한 병용요법을 인정함. 단, 2제 요법에서 인정되지 않는 약제의 조합이 포함되어서는 아니되나, Metformin+Sulfonylurea +Empagliflozin은 인정함.

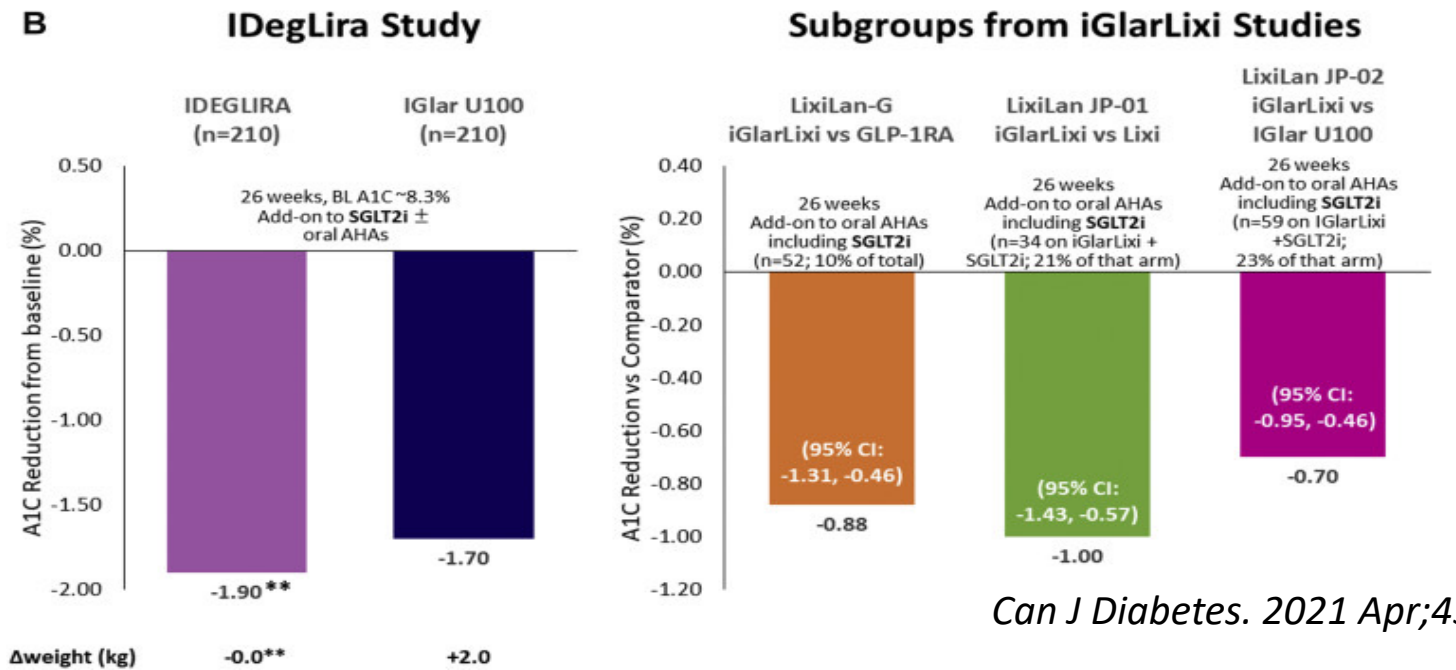
GLP-1 RA를 사용하려면,

- Metformin+Sulfonylurea계 약제 병용투여로 충분한 혈당조절을 할 수 없는 환자 중 BMI≥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

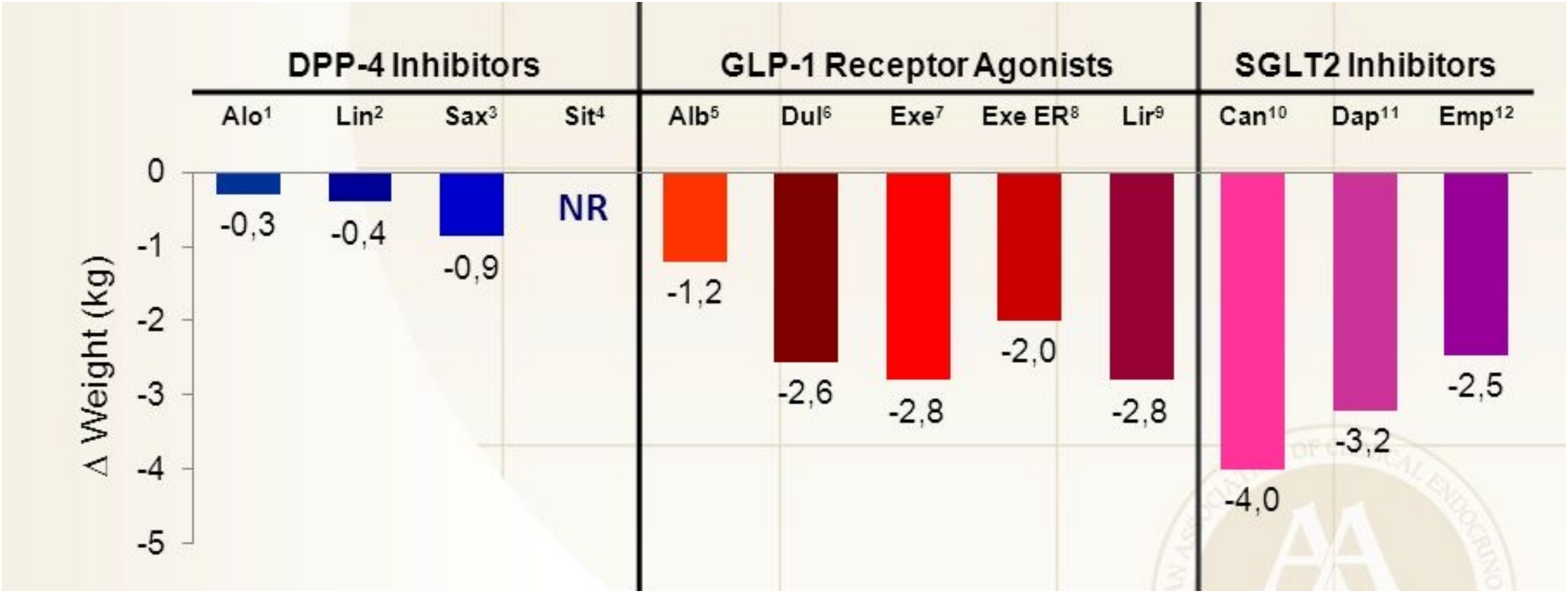




Can J Diabetes. 2021 Apr;45(3):291-302.

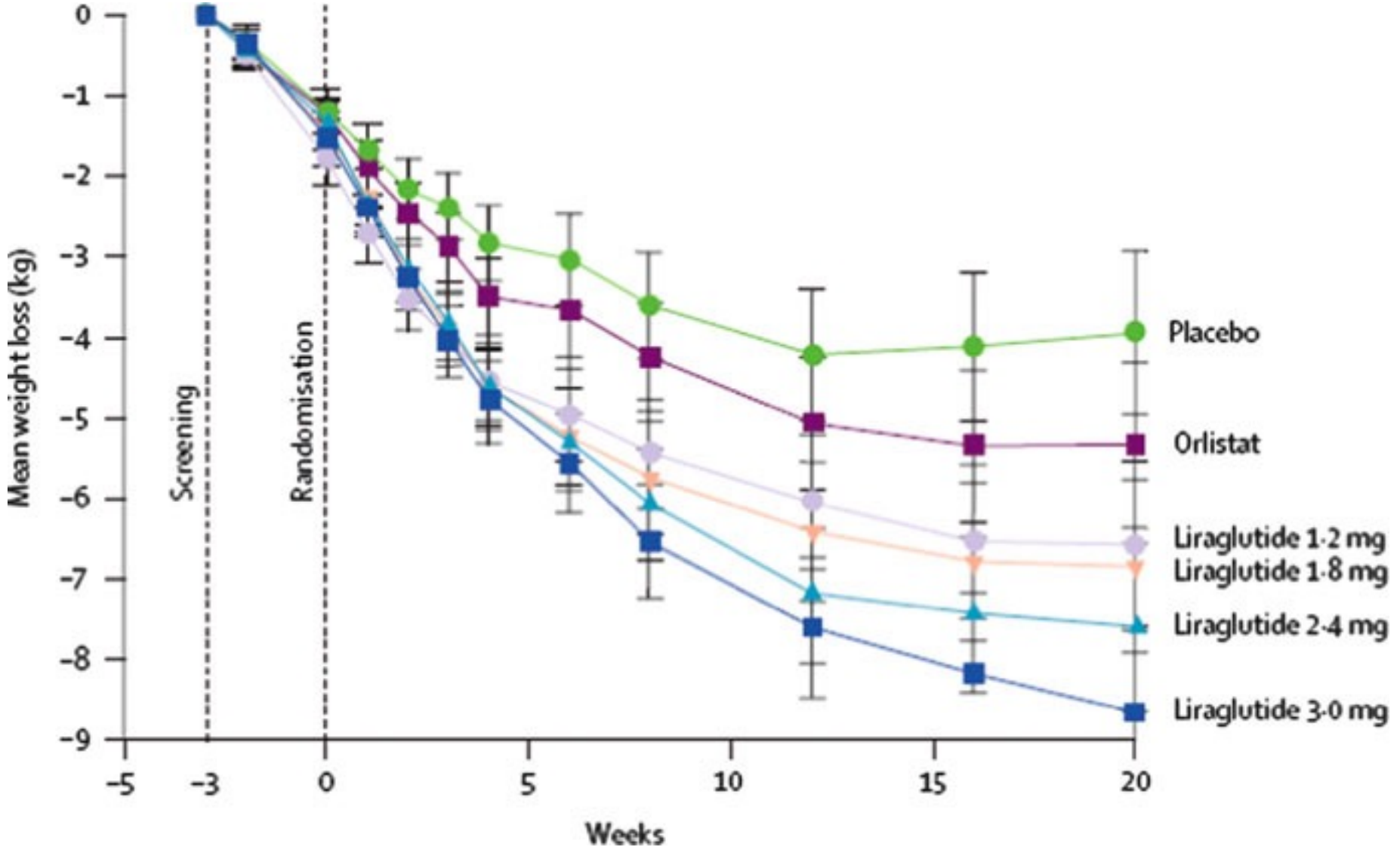
SGLT2i, GLP-1RA와 체중 변화

Weight Reduction (not head-to-head)



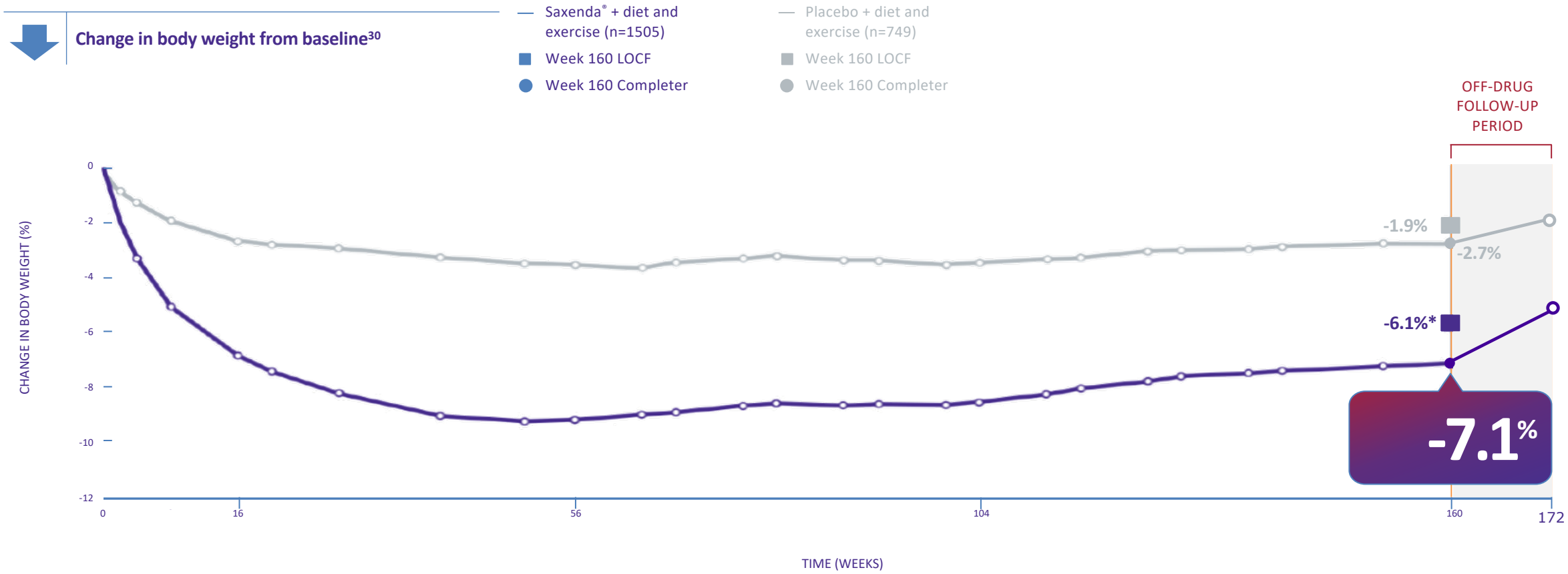
1. Nauck MA, et al. *Int J Clin Pract*. 2009;63:46-55. 2. Taskinen MR, et al. *Diabetes Obes Metab*. 2011;13:65-74. 3. DeFronzo RA, et al. *Diabetes Care*. 2009;32:1649-1655. 4. Charbonnel B, et al. *Diabetes Care*. 2006;29:2638-2643. 5. Ahrén B, et al. *Diabetes Care*. 2014;37:2141-2148. 6. Dungan KM, 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.



Anorexigenic Effects of GLP-1 and Its Analogues, Handbook of Experimental Pharmacology 209(209):185-207

Patients treated with Saxenda® lost weight and sustained their weight loss for 3 years[1]

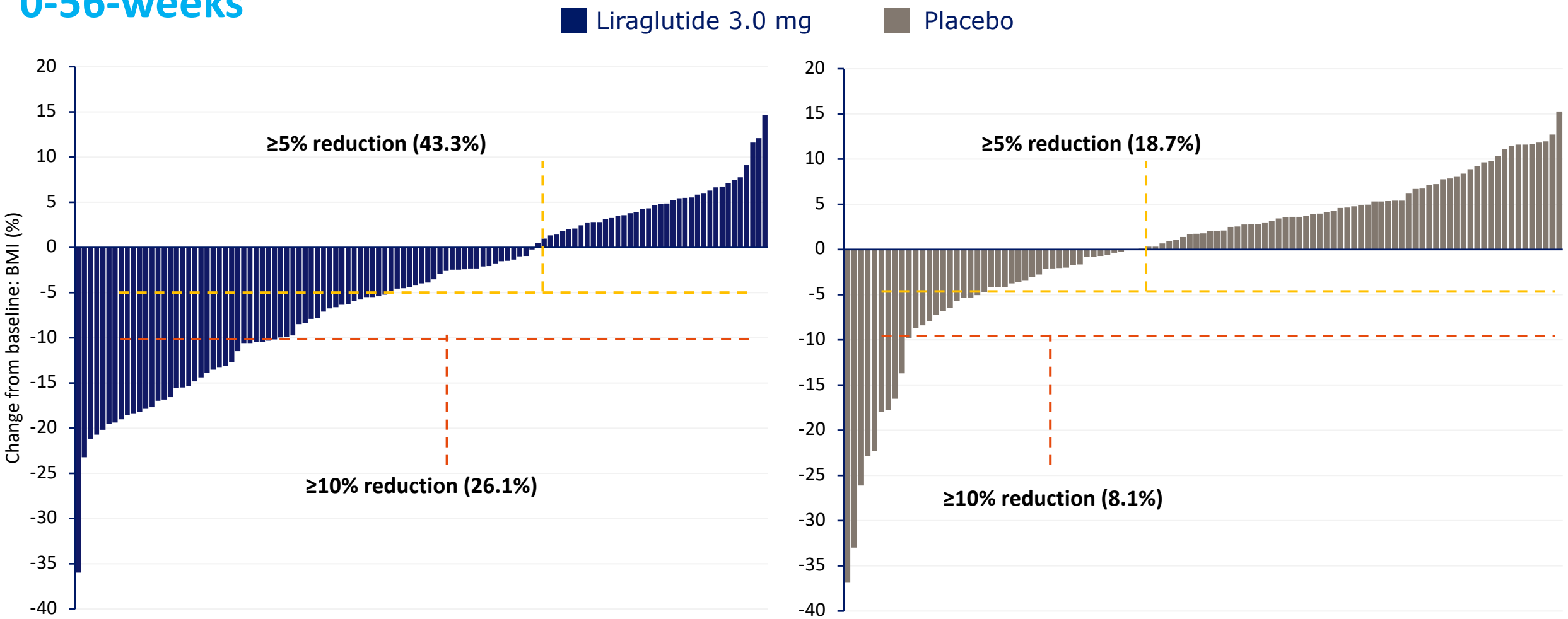


Line graphs are observed means.
LOCF=last observation carried forward.
*P<0.0001.[30]

SCALE-TEENS: Change in BMI percent

BMI corresponding to ≥30 kg/m^2 for adults and ≥95th percentile for age and gender

0-56-weeks



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

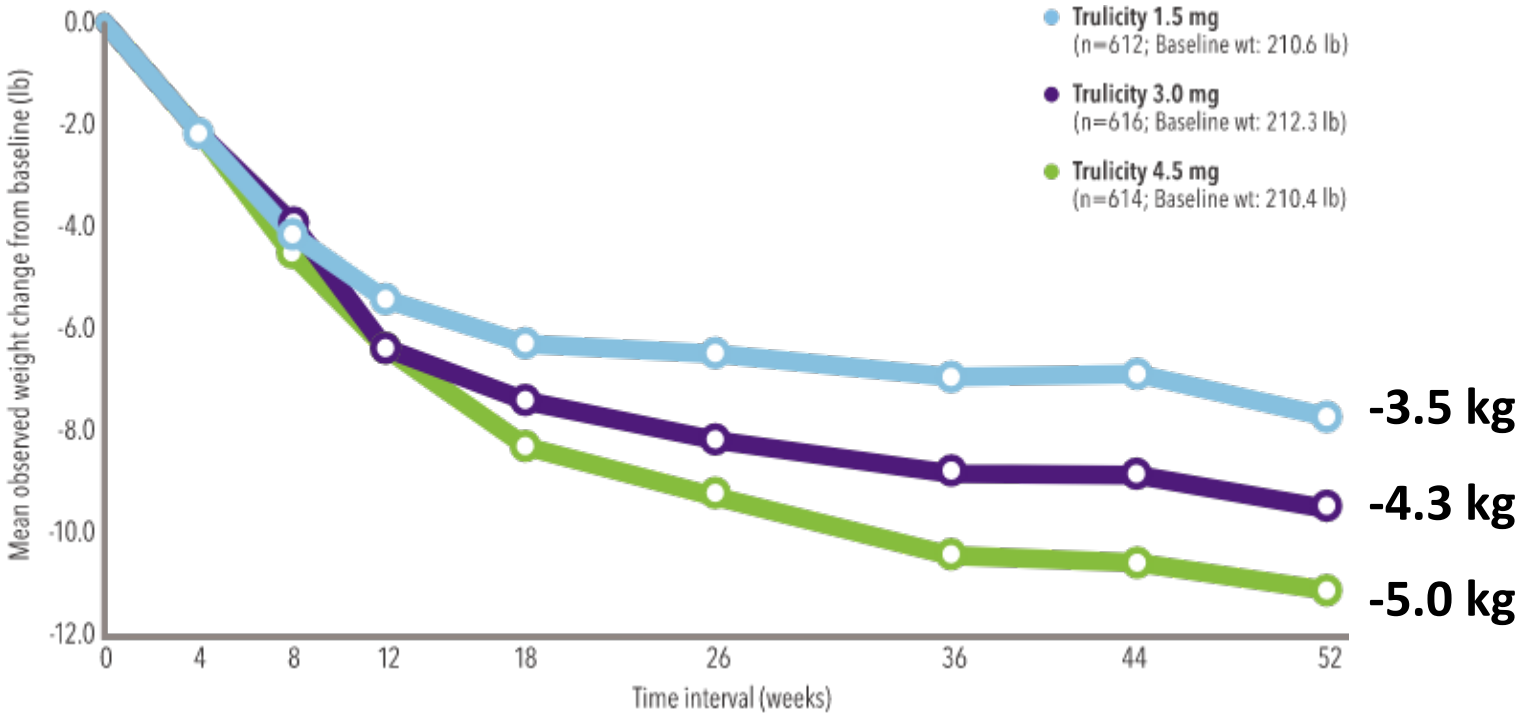
Kelly *et al*. *N Engl J Med.* 2020 Mar 31

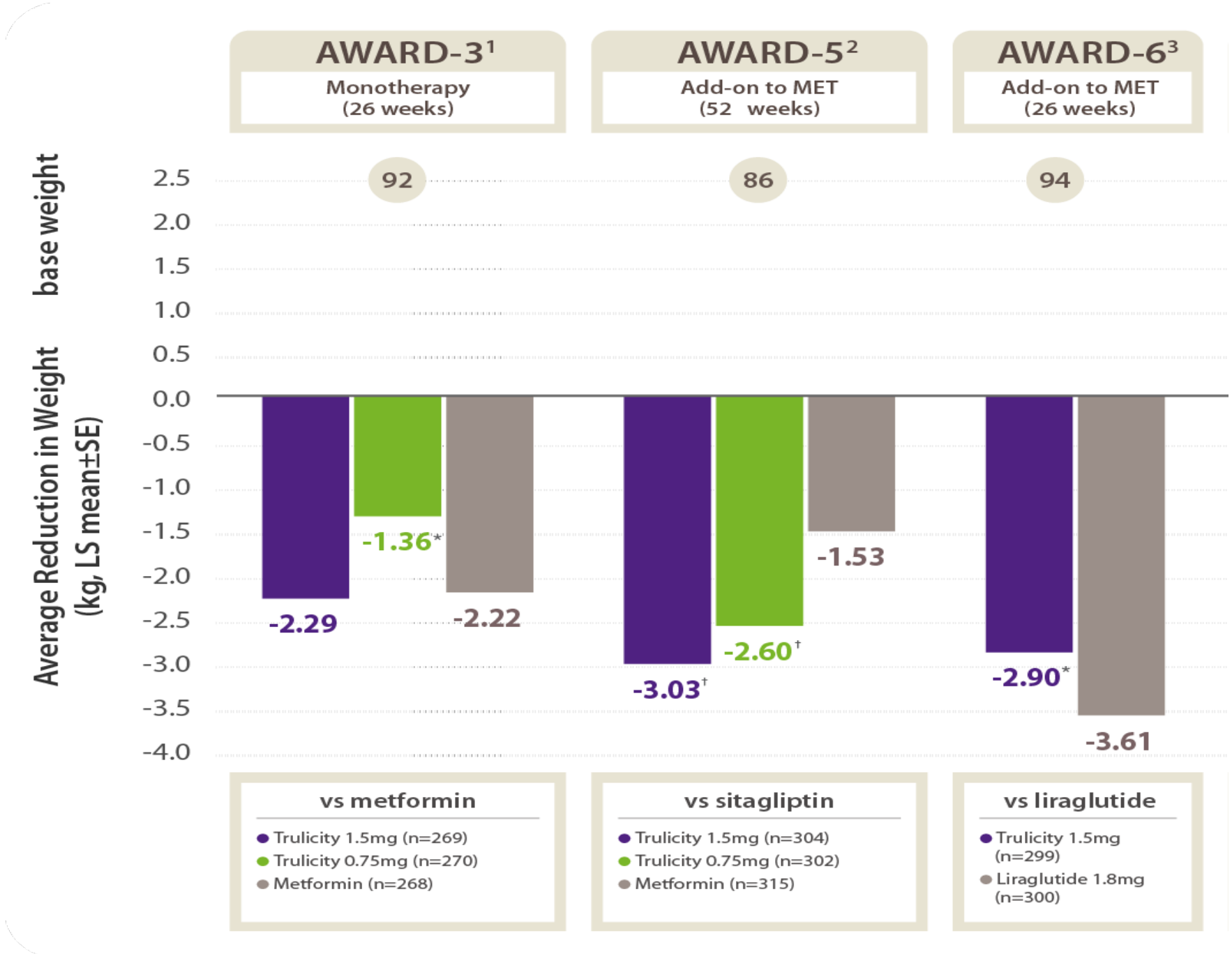
Dulaglutide and weight loss

Available in Korea

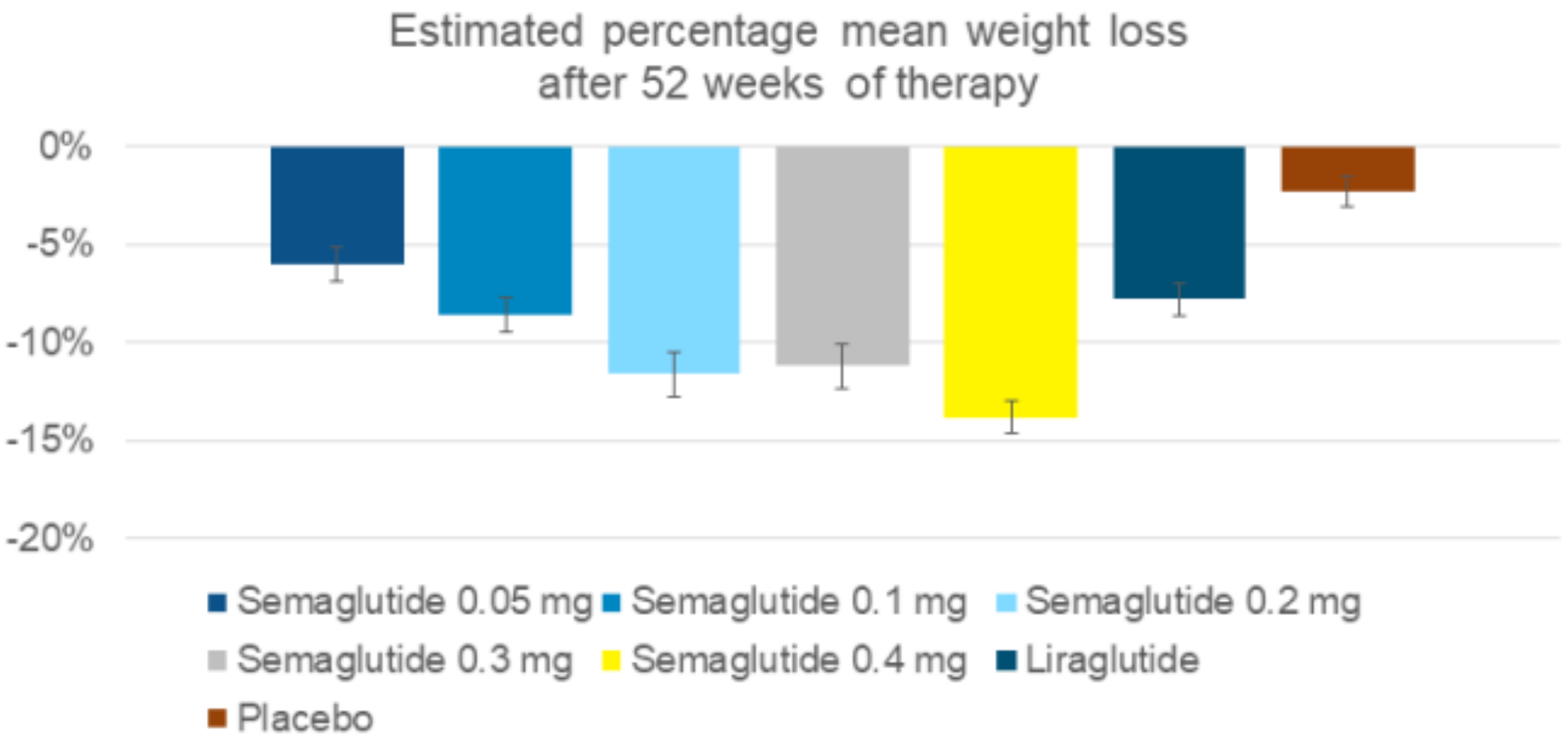
A1c

Trulicity 1.5 mg	Trulicity 3.0 mg	Trulicity 4.5 mg
-1.5%	-1.6%*	-1.8%




AWARD-3[1]
Monotherapy
(26 weeks)
AWARD-5[2]
Add-on to MET
(52 weeks)
AWARD-6[3]
Add-on to MET
(26 weeks)
Average Reduction in Weight (kg, LS mean±SE) base weight
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-3.5
-4.0
92
86
94
-2.29
-1.36*
-2.22
-3.03†
-2.60†
-1.53
-2.90*
-3.61
vs metformin
Trulicity 1.5mg (n=269)
Trulicity 0.75mg (n=270)
Metformin (n=268)
vs sitagliptin
Trulicity 1.5mg (n=304)
Trulicity 0.75mg (n=302)
Metformin (n=315)
vs liraglutide
Trulicity 1.5mg (n=299)
Liraglutide 1.8mg (n=300)

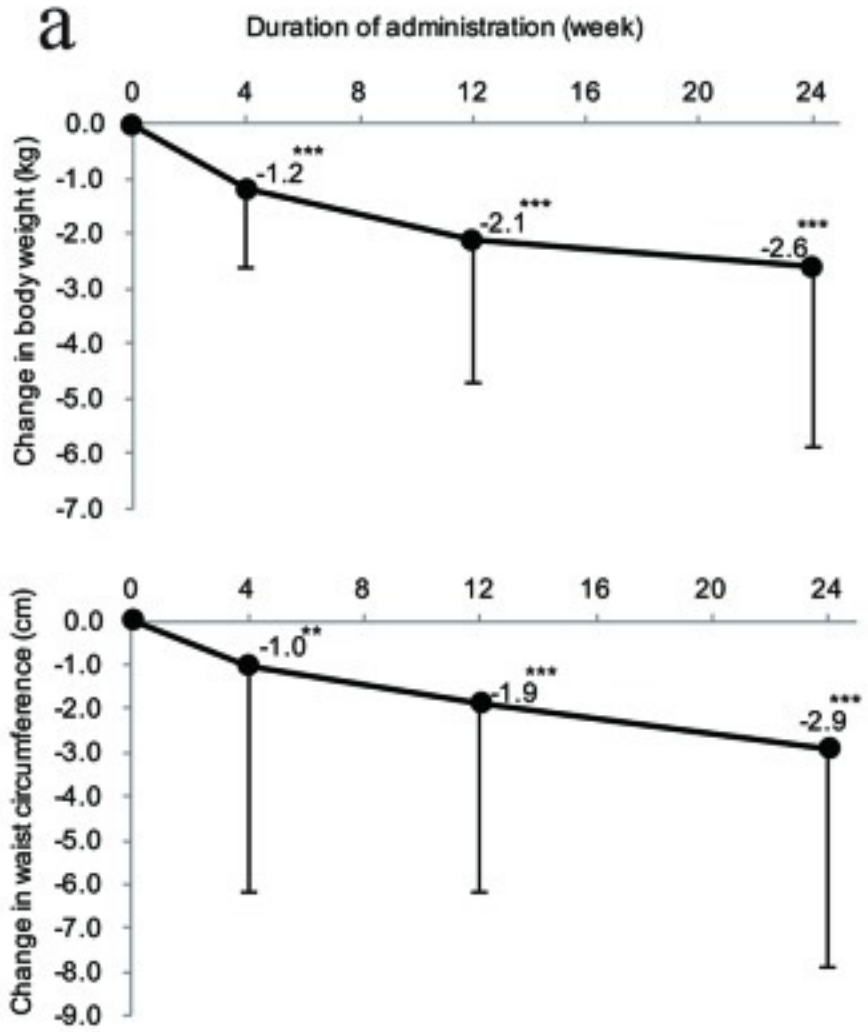
Semaglutide Phase 2 Trial



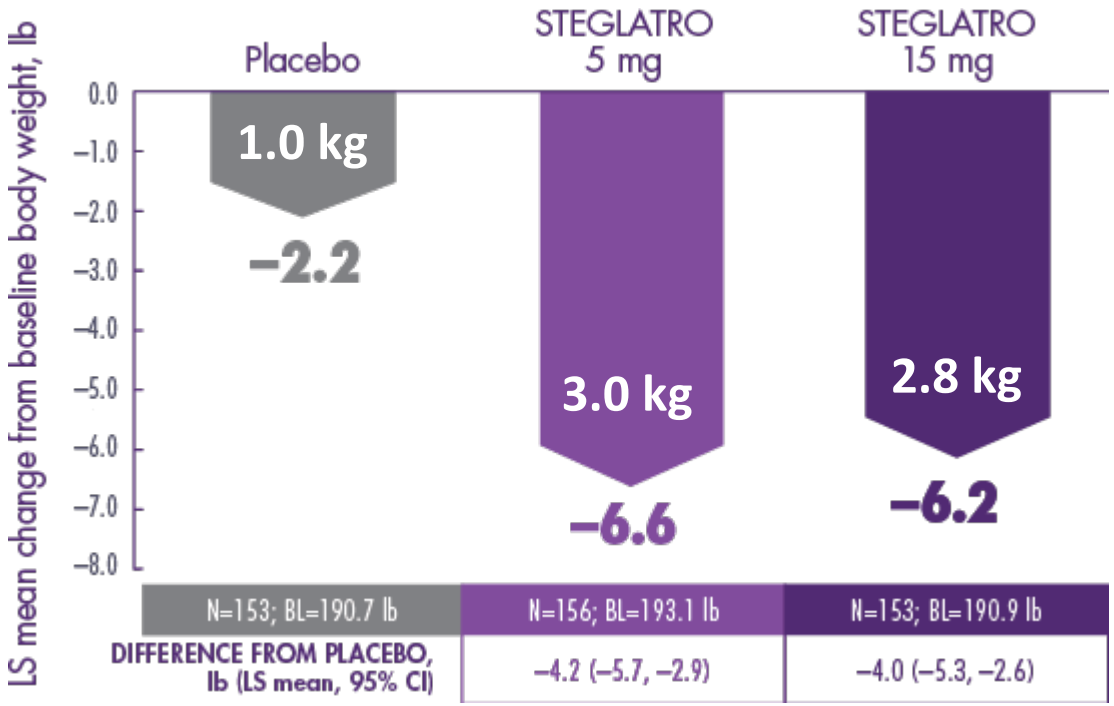
Lancet. 2018 Aug 25;392(10148):637-649.

SGLT2i and weight loss

Ipragliflozin 50mg once daily



Ertugliflozin administration



J Clin Med Res. 2017 Jul; 9(7): 586–595.

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.