28° Congresso Interassociativo AMD-SID Lombardia 2022

la Cura

14-15 ottobre 2022

Auditorium Giorgio Gaber - Grattacielo Pirelli
Piazza Duca d'Aosta, 3 - Milano

SID Società Italiana di Diabetologia
fondata nel 1964

AMD ASSOCIAZIONE MEDICI DIABETOLOGI
1974 ANNO DI FONDAZIONE

28° Congresso Interassociativo AMD-SID Lombardia 2022

Associazione Inibitori del Trasportatore Sodio-Glucosio e Agonisti del Glucagon-like Peptide 1

Cesare C. Berra

IRCCS MultiMedica Sesto San Giovanni

14-15 ottobre 2022

Auditorium Giorgio Gaber - Grattacielo Pirelli
Piazza Duca d'Aosta, 3 - Milano

SID Società Italiana di Diabetologia

AMD Associazione Medici Diabetologi

Conflitti interesse

Tipo di affiliazione o supporto finanziario	*Sponsor*
Partecipazione board scientifici	Eli Lilly, Astra Zenica, Novo Nordisk, Boehringer, Mundipharma, Sanofi
Studi Clinici	Eli Lilly, Novo Nordisk, Sofar
Letture sponsorizzate	Boehringer, Eli Lilly, Novo Nordisk, Sanofi

Fixed-Dose combination agents for T2D

Single-pill oral	Injectable
DPP4i + biguanide[1-3]	GLP-1 RA + basal insulin
Meglitinide + biguanide[1]	FDCs available for patients with T2D
SGLT2i + biguanide[1,4-7]	
SU + biguanide[1]	
TZD + biguanide[1]	
SGLT2i + DPP4i[1]	
DPP4i + TZD	
SU + TZD	

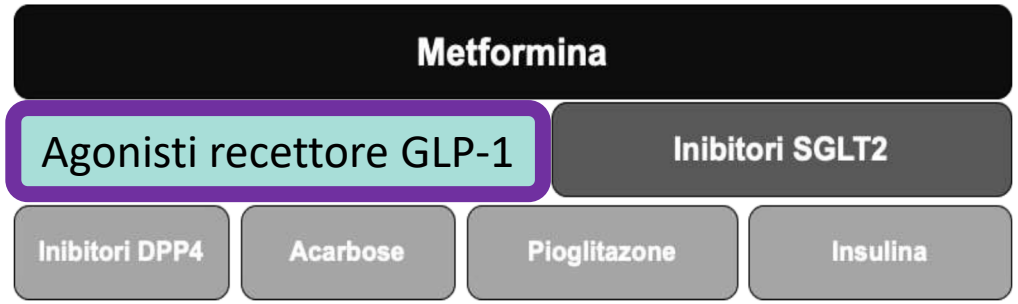
DPP4i, dipeptidyl peptidase-4 inhibitors; FDC, fixed-dose combination; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose cotransporter 2 inhibitor; SU, sulfonylurea; T2D, type 2 diabetes; TZD, thiazolidinediones.

Paul, SK et al.Cardiovasc. Diabetol. 14: 100, 2015

Linea Guida della Società Italiana di Diabetologia (SID) e dell'Associazione dei Medici Diabetologi (AMD)

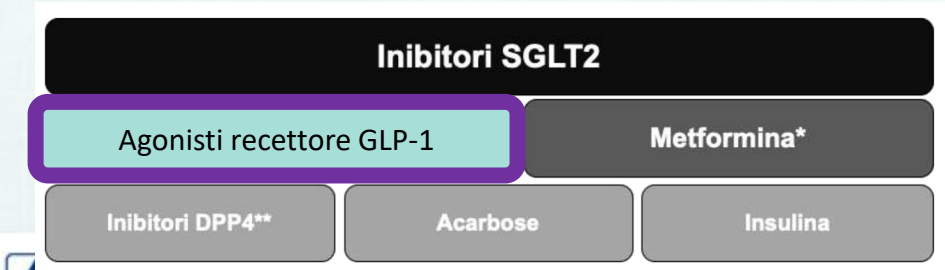
La terapia del diabete mellito di tipo 2

Terapia farmacologica per il trattamento a lungo termine in pazienti con diabete di tipo 2 senza pregressi eventi cardiovascolari



Terapia farmacologica per il trattamento a lungo termine in pazienti con diabete di tipo 2 con pregressi eventi cardiovascolari e senza scompenso cardiaco

Terapia farmacologica per il trattamento a lungo termine in pazienti con diabete di tipo 2 con scompenso cardiaco



Recommendations

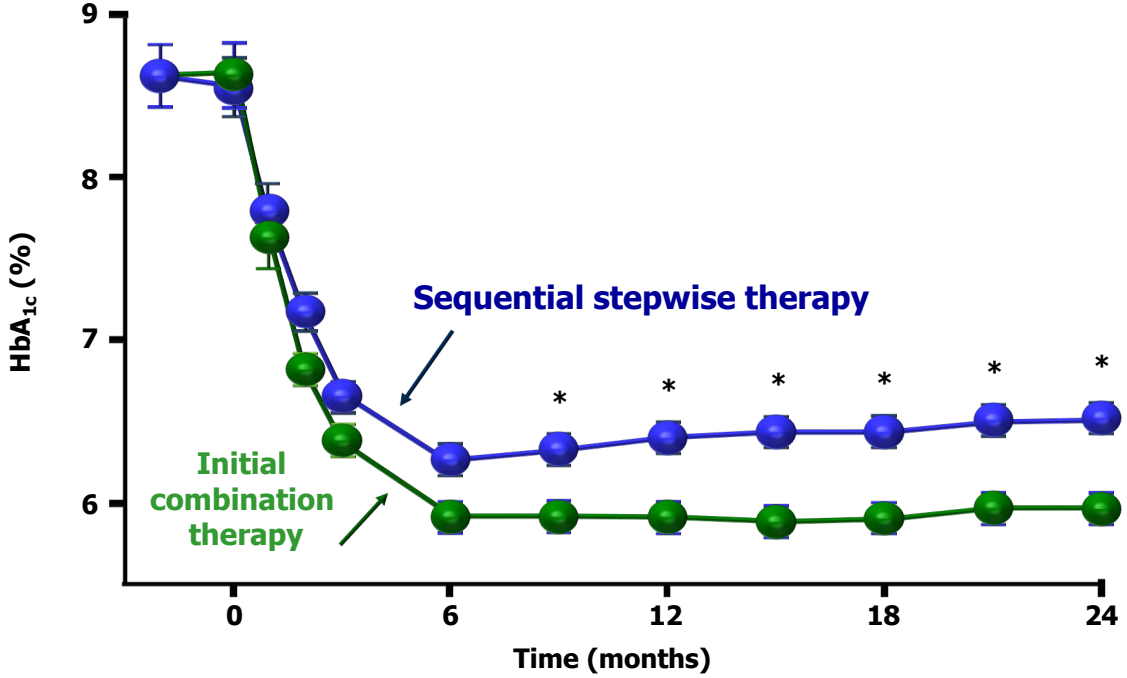
- **Early combination therapy can be considered in some patients at treatment initiation to extend the time to treatment failure.** *A*

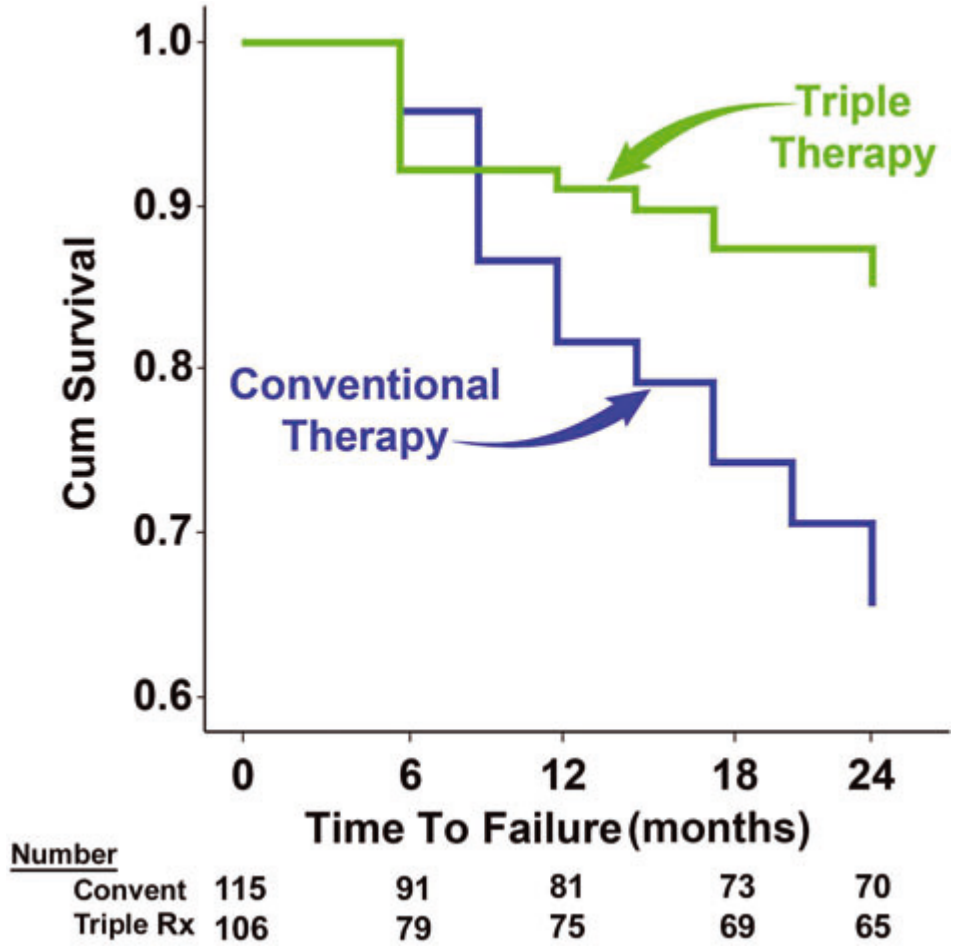
- **Recommendation for treatment intensification for patients not meeting treatment goals should not be delayed.** *A*

- **If insulin is used, combination therapy with a glucagon-like peptide 1 receptor agonist is recommended for greater efficacy and durability of treatment effect.** *A*

Initial combination therapy with metformin, pioglitazone and exenatide is more effective than sequential add-on therapy in subjects with new-onset diabetes

The intensive group was treated with MET/TZD/GLP-1 RA, and the conventional group was treated with metformin with sequential addition of an SU and then glargine insulin.





Abdul-Ghani MA et al. Diabetes Obes Metab.17:268–275, 2015

Recommendations

- Early combination therapy can be considered in some patients at treatment initiation to extend the time to treatment failure. *A*

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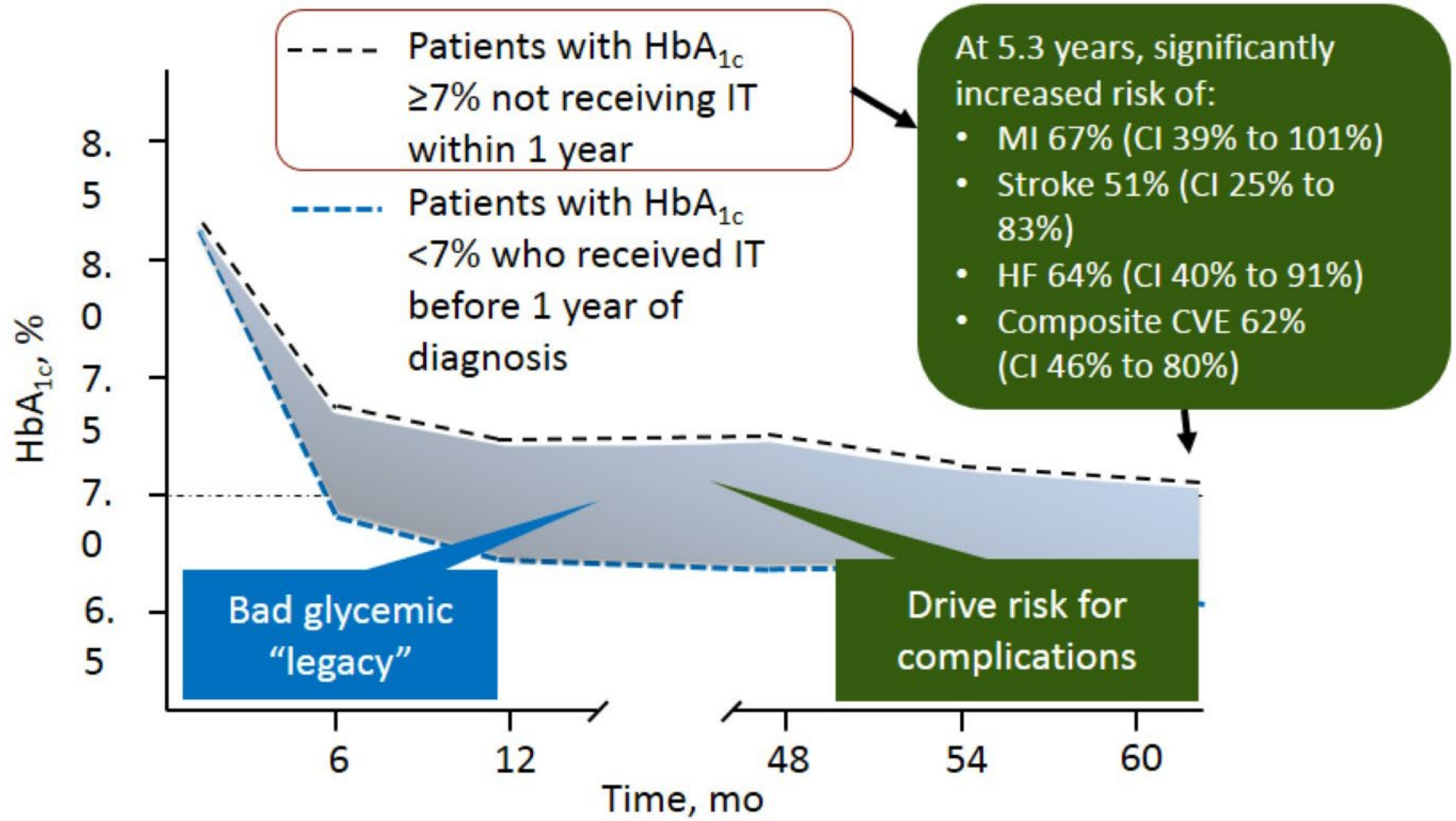
Consequences of delayed intervention in patients with T2DM



Paul, SK et al.Cardiovasc. Diabetol. 14: 100, 2015

Recommendations

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- Recommendation for treatment intensification for patients not meeting treatment goals should not be delayed. *A*
- If insulin is used, combination therapy with a glucagon-like peptide 1 receptor agonist is recommended for greater efficacy and durability of treatment effect. *A*

Diabetes Care 45 (Suppl. 1):S125-S143, 2022

Is the combined use of GLP-1RA and SGLT2 inhibitor an option?

	SGLT2I	GLP-1 RA	Combination
Appetite	− (?)	+	+
Body weight	+	+	++
Ischemic CV events	+	+	++
Heart failure events	+	=	+
Insulin levels	−	+	+
Glucagon secretion	−	+	=
Hepatic glucose output	−	+	=
Ketone body production	−	+	=
Muscle glucose uptake	+	+	++
Diuresis, natriuresis	+	+	+
Urinary glucose secretion	+	=	+
Renoprotection	+	=	+

Nauck MA, et al. *Lancet Diabetes Endocrinol*. 2016;963-964; Frías JP, et al. *Lancet Diabetes Endocrinol*. 2016;4:1004-1016; Lundkvist P, et al. *Diabetes Obes Metab*. 2017;19:49-60.

Razionale fisiopatologico alla base dell'associazione GLP1RA + SGLT2i

Table 2. Effect of SGLT-2is, GLP-1RAs, and their combination on cardiovascular risk factors or pathophysiologic mechanisms [43,57].[a]

	SGLT2is	GLP-1RAs	SGLT-2is + GLP-1RAs
Glycemia (A1c)	↓ ↓	↓ ↓	↓ ↓ ↓
Insulin sensitivity	↑	↑	↑ ↑
β-cell function	↑ ↑	↑ ↑ ↑	↑ ↑ ↑
Hemodynamics	↑ ↑	↑	↑ ↑
Blood pressure	↓	↓	↓ ↓
Lipid profile	–	↑	↑
Body weight	↓	↓ ↓	↓ ↓ ↓
Visceral fat	↓	↓	↓ ↓
Endothelial function	–	↑	↑
Natriuresis	↑ ↑	↑	↑ ↓
Inflammation	–	↓	↓

Adapted from DeFronzo RA. Combination therapy with GLP-1 receptor agonist and SGLT2 inhibitor. *Diabetes Obes Metab*. 2017;19(10):1353–1362, Copyright 2017, with permission from John Wiley & Sons Ltd [57].

[a]Upward arrows indicate improvement or increase; downward arrows indicate reduction; dashes indicate neutral effect. The number of arrows represent the relative potency of the effect where ↓ = moderate, ↓↓ = strong, and ↓↓↓ = very strong.

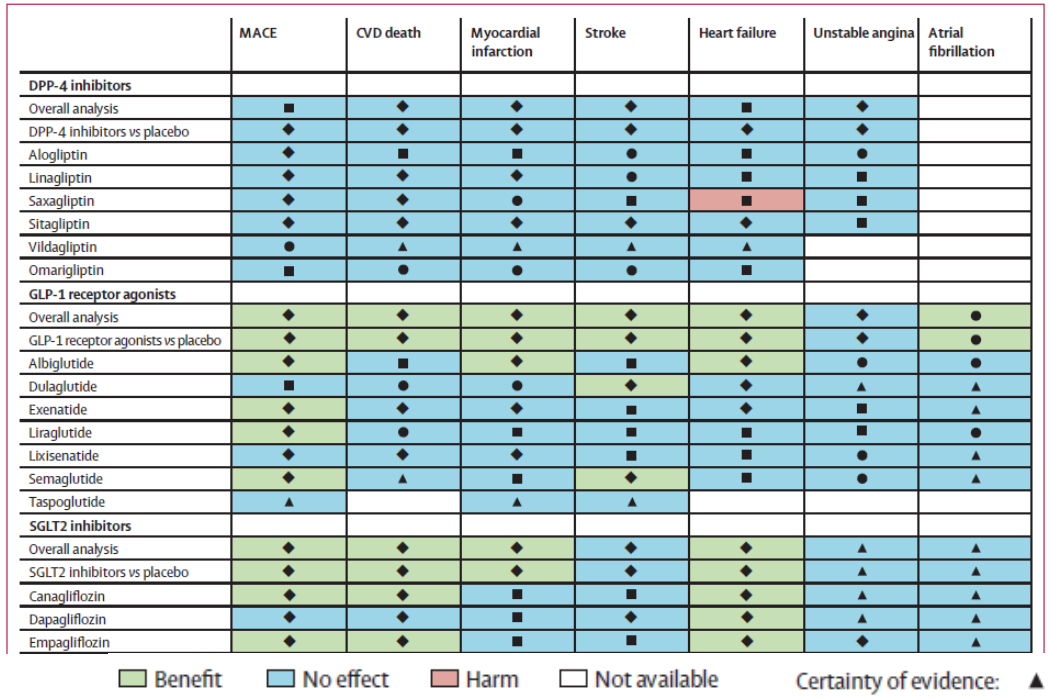
A1c: glycated hemoglobin; GLP-1RA: glucagon-like peptide-1 receptor agonist; SGLT-2i: sodium–glucose cotransporter-2 inhibitor.

Lajara 2019,) Combination therapy with SGLT-2 inhibitors and GLP-1 receptor agonists as complementary agents that address multi-organ defects in type 2 diabetes, Postgraduate Medicine, 131:8, 555-565

Association of glucose-lowering medications with cardiovascular outcomes: an umbrella review and evidence map

Lancet Diabetes Endocrinol
2020; 192–205

Jianhong Zhu, Xiaoxia Yu*, Yayuan Zheng*, Jianfang Li*, Yong Wang*, Yin Lin, Zhichao He, Wenxia Zhao, Chuxiong Chen, Kaifeng Qiu, Junyan Wu*



	MACE	CVD death	Myocardial infarction	Stroke	Heart failure	Unstable angina	Atrial fibrillation
DPP-4 inhibitors							
Overall analysis	■	◆	◆	◆	■	◆	
DPP-4 inhibitors *vs* placebo	◆	◆	◆	◆	◆	◆	
Alogliptin	◆	■	■	●	■	●	
Linagliptin	◆	◆	◆	●	■	■	
Saxagliptin	◆	◆	●	■	■	■	
Sitagliptin	◆	◆	◆	◆	◆	■	
Vildagliptin	●	▲	▲	▲	▲		
Omarigliptin	■	●	●	●	■		
GLP-1 receptor agonists							
Overall analysis	◆	◆	◆	◆	◆	◆	●
GLP-1 receptor agonists *vs* placebo	◆	◆	◆	◆	◆	◆	●
Albiglutide	◆	■	◆	■	◆	●	●
Dulaglutide	■	●	●	◆	◆	▲	▲
Exenatide	◆	◆	◆	■	◆	■	▲
Liraglutide	◆	●	■	■	■	■	●
Lixisenatide	◆	◆	◆	■	■	●	▲
Semaglutide	◆	▲	■	◆	■	●	▲
Taspoglutide	▲		▲	▲			
SGLT2 inhibitors							
Overall analysis	◆	◆	◆	◆	◆	▲	▲
SGLT2 inhibitors *vs* placebo	◆	◆	◆	◆	◆	▲	▲
Canagliflozin	◆	◆	■	■	◆	▲	▲
Dapagliflozin	◆	◆	■	◆	◆	▲	▲
Empagliflozin	◆	◆	■	■	◆	◆	▲

Benefit No effect Harm Not available Certainty of evidence: ▲ Very low ● Low ■ Moderate ◆ High

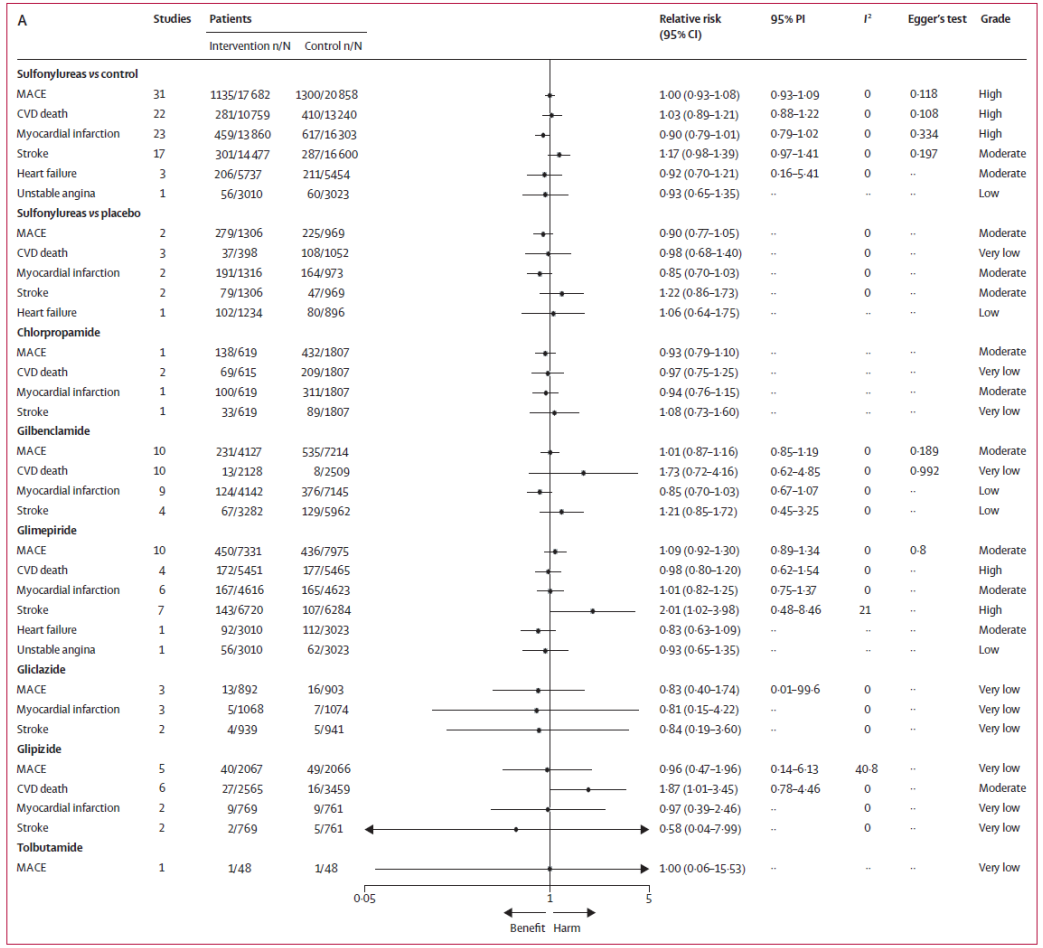
Gli Inib SGLT2 e iGLP1 RA esprimono un profilo di Massima efficacia su outcomes CV

Association of glucose-lowering medications with cardiovascular outcomes: an umbrella review and evidence map

Jianhong Zhu, Xiaoxia Yu*, Yayuan Zheng*, Jianfang Li*, Yong Wang*, Yin Lin, Zhichao He, Wenxia Zhao, Chuxiong Chen, Kaifeng Qiu, Junyan Wu*

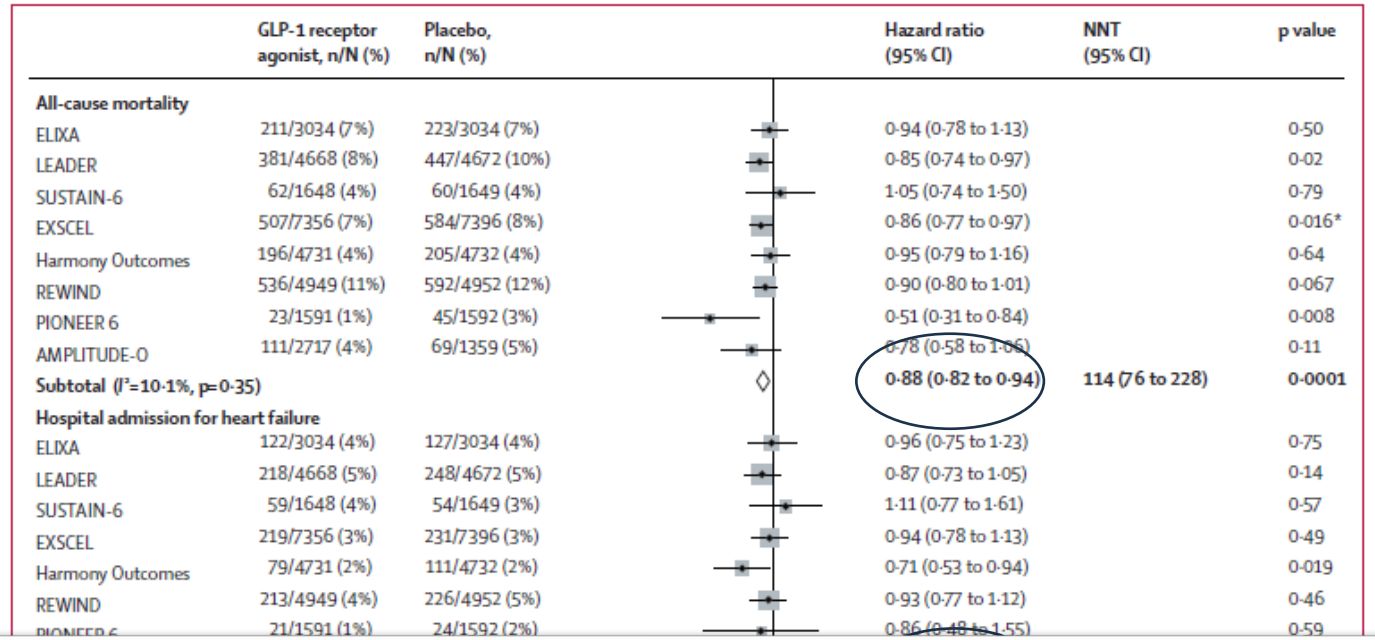
Le SU non esprimono alcuna efficacia su otcomes CV, in particolare Glibenclamide, Glipizide e Glimepiride determinano un aumentato rischio di Morte CV e Stroke

Lancet Diabetes Endocrinol
2020; 192–205



A	Studies	Patients		Relative risk (95% CI)	95% PI	I^2	Egger's test	Grade
		Intervention n/N	Control n/N					
Sulfonylureas vs control								
MACE	31	1135/17 682	1300/20 858	1·00 (0·93–1·08)	0·93–1·09	0	0·118	High
CVD death	22	281/10 759	410/13 240	1·03 (0·89–1·21)	0·88–1·22	0	0·108	High
Myocardial infarction	23	459/13 860	617/16 303	0·90 (0·79–1·01)	0·79–1·02	0	0·334	High
Stroke	17	301/14 477	287/16 600	1·17 (0·98–1·39)	0·97–1·41	0	0·197	Moderate
Heart failure	3	206/5737	211/5454	0·92 (0·70–1·21)	0·16–5·41	0	..	Moderate
Unstable angina	1	56/3010	60/3023	0·93 (0·65–1·35)	..	..	..	Low
Sulfonylureas vs placebo								
MACE	2	279/1306	225/969	0·90 (0·77–1·05)	..	0	..	Moderate
CVD death	3	37/398	108/1052	0·98 (0·68–1·40)	..	0	..	Very low
Myocardial infarction	2	191/1316	164/973	0·85 (0·70–1·03)	..	0	..	Moderate
Stroke	2	79/1306	47/969	1·22 (0·86–1·73)	..	0	..	Moderate
Heart failure	1	102/1234	80/896	1·06 (0·64–1·75)	..	..	..	Low
Chlorpropamide								
MACE	1	138/619	432/1807	0·93 (0·79–1·10)	..	..	..	Moderate
CVD death	2	69/615	209/1807	0·97 (0·75–1·25)	..	..	..	Very low
Myocardial infarction	1	100/619	311/1807	0·94 (0·76–1·15)	..	..	..	Moderate
Stroke	1	33/619	89/1807	1·08 (0·73–1·60)	..	..	..	Very low
Gilbenclamide								
MACE	10	231/4127	535/7214	1·01 (0·87–1·16)	0·85–1·19	0	0·189	Moderate
CVD death	10	13/2128	8/2509	1·73 (0·72–4·16)	0·62–4·85	0	0·992	Very low
Myocardial infarction	9	124/4142	376/7145	0·85 (0·70–1·03)	0·67–1·07	0	..	Low
Stroke	4	67/3282	129/5962	1·21 (0·85–1·72)	0·45–3·25	0	..	Low
Glimepiride								
MACE	10	450/7331	436/7975	1·09 (0·92–1·30)	0·89–1·34	0	0·8	Moderate
CVD death	4	172/5451	177/5465	0·98 (0·80–1·20)	0·62–1·54	0	..	High
Myocardial infarction	6	167/4616	165/4623	1·01 (0·82–1·25)	0·75–1·37	0	..	Moderate
Stroke	7	143/6720	107/6284	2·01 (1·02–3·98)	0·48–8·46	21	..	High
Heart failure	1	92/3010	112/3023	0·83 (0·63–1·09)	..	..	..	Moderate
Unstable angina	1	56/3010	62/3023	0·93 (0·65–1·35)	..	..	..	Low
Gliclazide								
MACE	3	13/892	16/903	0·83 (0·40–1·74)	0·01–99·6	0	..	Very low
Myocardial infarction	3	5/1068	7/1074	0·81 (0·15–4·22)	..	0	..	Very low
Stroke	2	4/939	5/941	0·84 (0·19–3·60)	..	0	..	Very low
Glipizide								
MACE	5	40/2067	49/2066	0·96 (0·47–1·96)	0·14–6·13	40·8	..	Very low
CVD death	6	27/2565	16/3459	1·87 (1·01–3·45)	0·78–4·46	0	..	Moderate
Myocardial infarction	2	9/769	9/761	0·97 (0·39–2·46)	..	0	..	Very low
Stroke	2	2/769	5/761	0·58 (0·04–7·99)	..	0	..	Very low
Tolbutamide								
MACE	1	1/48	1/48	1·00 (0·06–15·53)	..	..	..	Very low

Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials.



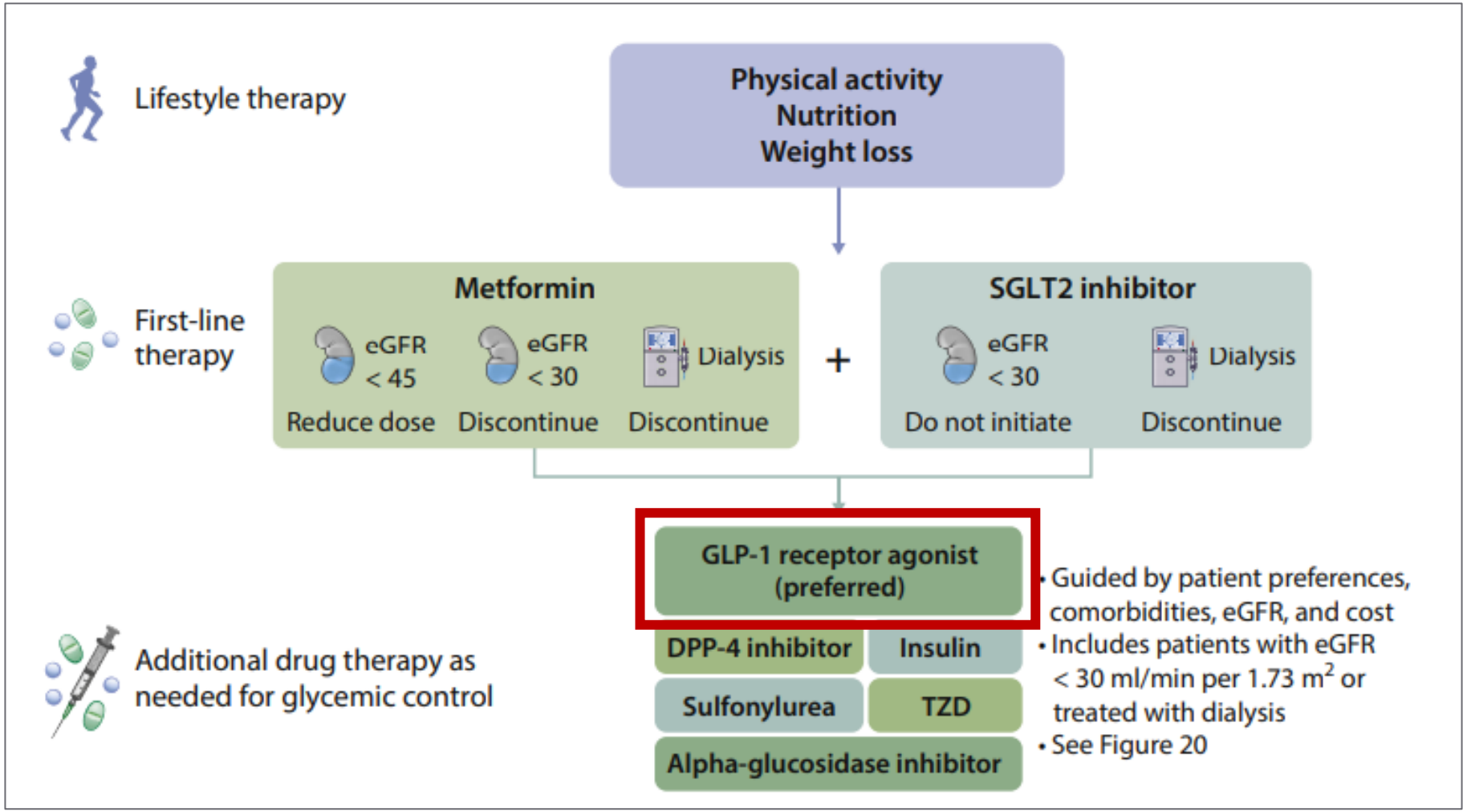
CV protection in 60.080 patients treated with GLP-1 RA

Composite Kidney: RR reduction 21%

e-GFR: RR reduction 14%

Sattar N. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials.

KDIGO 2020
Linee guida per la gestione del diabete nella malattia renale cronica



KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease - VOLUME 98 | ISSUE 4S | OCTOBER 2020

2020 KDIGO guidelines for the treatment of diabetes in the CKD

			Primary outcome		Kidney outcomes		
Drug	**Trial**	**Kidney-related eligibility criteria**	**Primary outcome**	**Effect on primary outcome**	**Effect on albuminuria or albuminuria-containing composite outcome**	**Effect on GFR loss[a]**	**Adverse effects**
SGLT2 inhibitors							
Empagliflozin	EMPA-REG OUTCOME	eGFR ≥30 ml/min per 1.73 m²	MACE	↓	↓↓	↓↓	Genital mycotic infections, DKA
Canagliflozin	CANVAS trials	eGFR ≥30 ml/min per 1.73 m²	MACE	↓	↓↓	↓↓	Genital mycotic infections, DKA, amputation
	CREDENCE	ACR >300 mg/g [30 mg/mmol] and eGFR 30–90 ml/min per 1.73 m²	Progression of CKD[b]	↓↓	↓↓	↓↓	Genital mycotic infections, DKA
Dapagliflozin	DECLARE-TIMI 58	CrCl ≥60 ml/min	Dual primary outcomes: MACE and the composite of hospitalization for heart failure or CV death[c]	↔/↓	↓	↓↓	Genital mycotic infections, DKA
GLP-1 receptor agonists							
Lixisenatide	ELIXA	eGFR ≥30 ml/min per 1.73 m²	MACE	↔	↓	↔	None notable
Liraglutide	LEADER	eGFR ≥15 ml/min per 1.73 m²	MACE	↓	↓	↔	GI
Semaglutide[d]	SUSTAIN-6	Patients treated with dialysis excluded	MACE	↓	↓↓	NA	GI
	PIONEER 6	eGFR ≥30 ml/min per 1.73 m²	MACE	↔	NA	NA	GI
Exenatide	EXSCEL	eGFR ≥30 ml/min per 1.73 m²	MACE	↔	↔	↔	None notable
Albiglutide	HARMONY	eGFR ≥30 ml/min per 1.73 m²	MACE	↓	↔	NA	Injection site reactions
Dulaglutide	REWIND	eGFR ≥15 ml/min per 1.73 m²	MACE	↓	↓	↓	GI

KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease - VOLUME 98 | ISSUE 4S | OCTOBER 2020

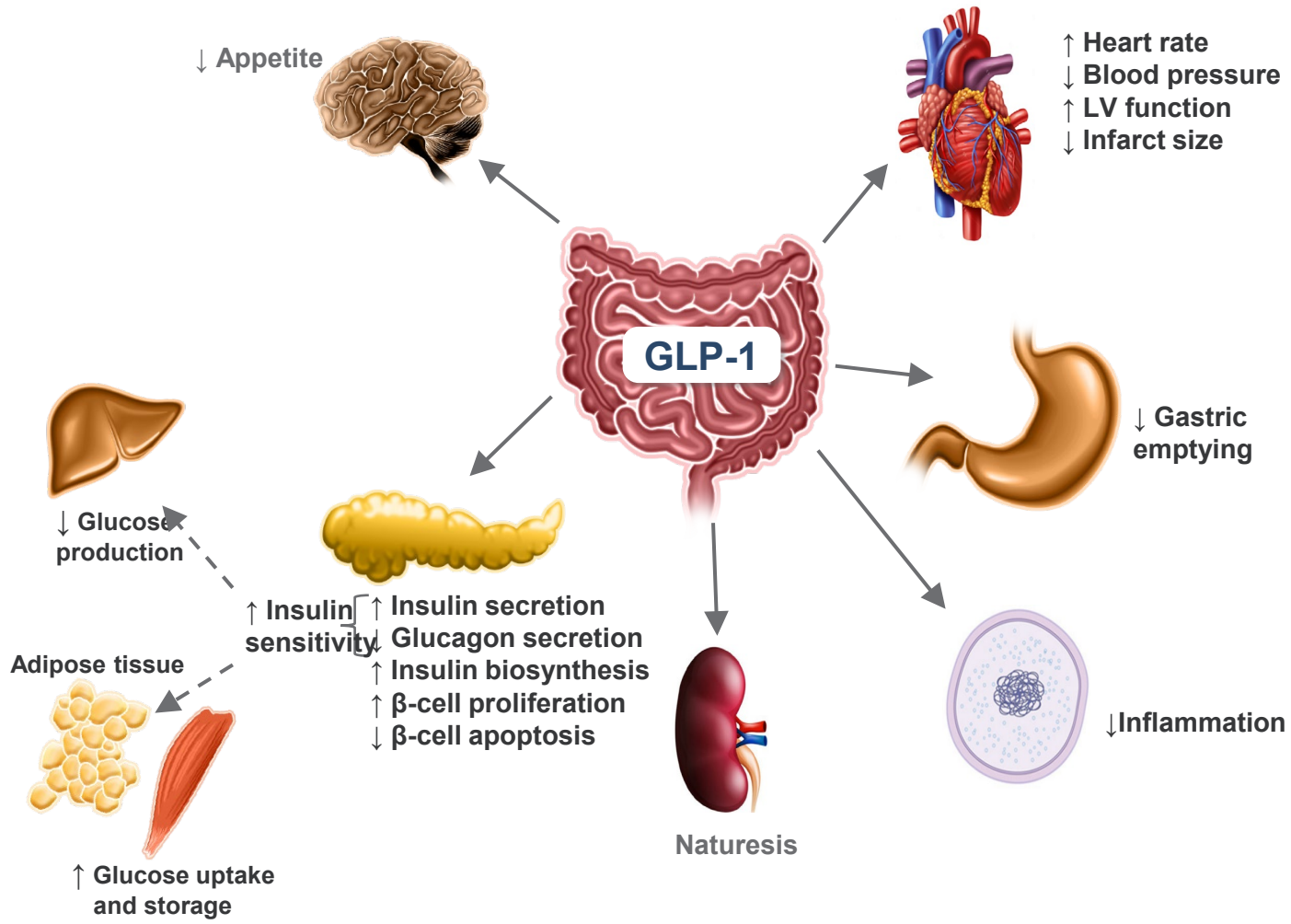
The Role of Glucagon-Like Peptide 1 (GLP-1) Receptor Agonists in the Prevention and Treatment of Diabetic Kidney Disease

Table 1. Postulated mechanisms of cardiorenal protection of glucagon-like peptide 1 receptor agonists

Kidney	Cardiac	Systemic
Oxygenation • Decreased oxygen consumption • Improved ATP availability GFR and urine albumin excretion • Improved GFR • Decreased urine albumin-creatinine ratio Sodium and fluid balance • Decreased sodium retention • Decreased BP	Lipids • Decreased LDL • Decreased triglycerides Metabolic profile • Decreased weight BP • Decreased BP	Blood glucose concentrations • Decreased blood glucose • Improved insulin resistance Inflammatory response • Decreased inflammatory cytokines Coagulation profile • Improved coagulation profile

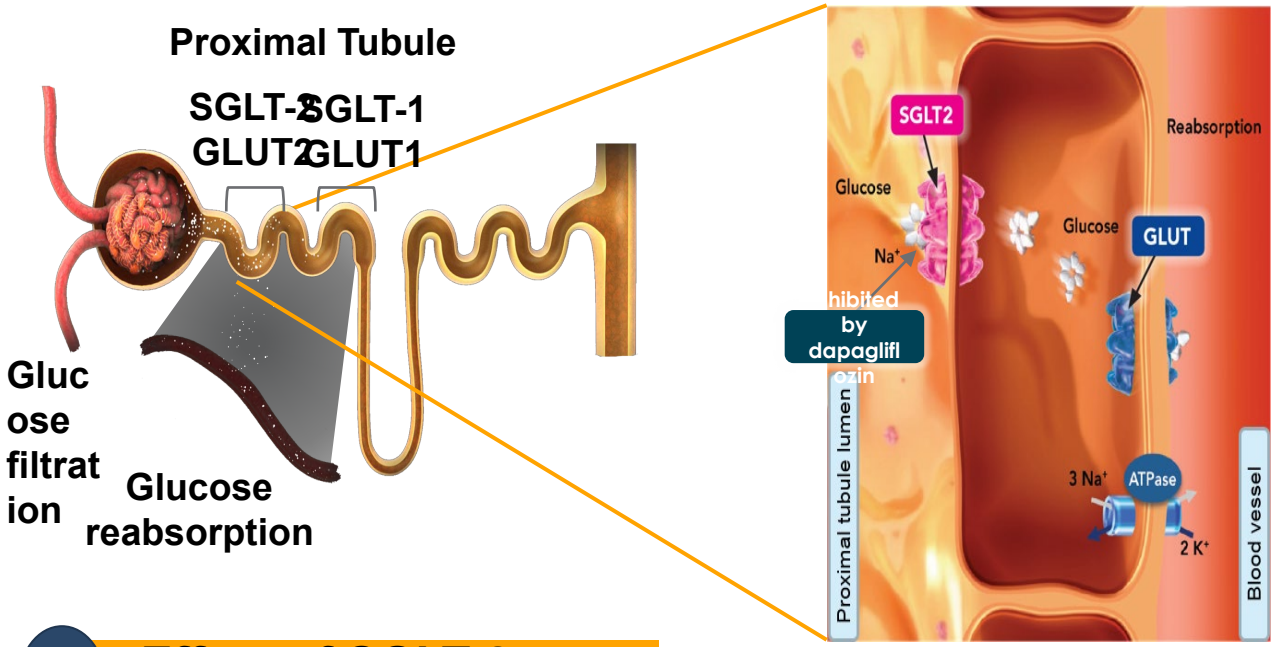
Tommerdahl KL, Kendrick J, and Bjornstad P. CJASN ePress. Published on April 8, 2022 as doi:

Physiologic Actions and Effects of GLP-1 Receptor Agonists



1. Drucker DJ et al. *Diabetes*. 2015;64:317-326. 2. Campbell JE et al. *Cell Metab.* 2013;17:819-837. 3. Baggio LL et al. *Gastroenterology*. 2007;132:2131-2157. 4. Ussher JR et al. *Circ Res.* 2014;114:1788-1803.

Physiologic Actions and Effects of SGLT-2 Inhibitors



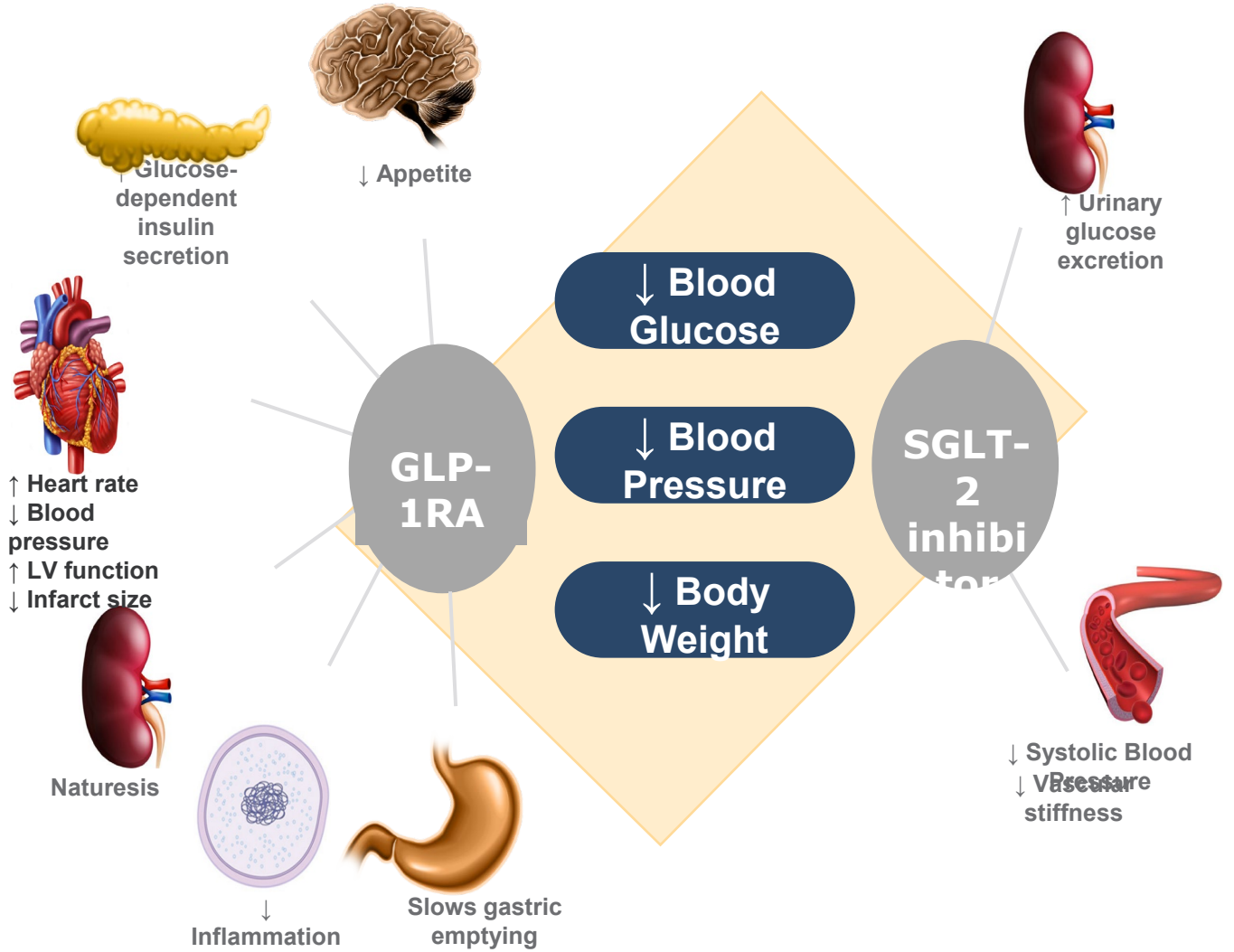
Effect of SGLT-2 inhibitors

- ↑ Urinary glucose excretion
- ↓ HbA1c levels
- ↓ FPG and PPG
- ↓ Body weight
- ↓ Systolic blood pressure
- ↓ Vascular stiffness

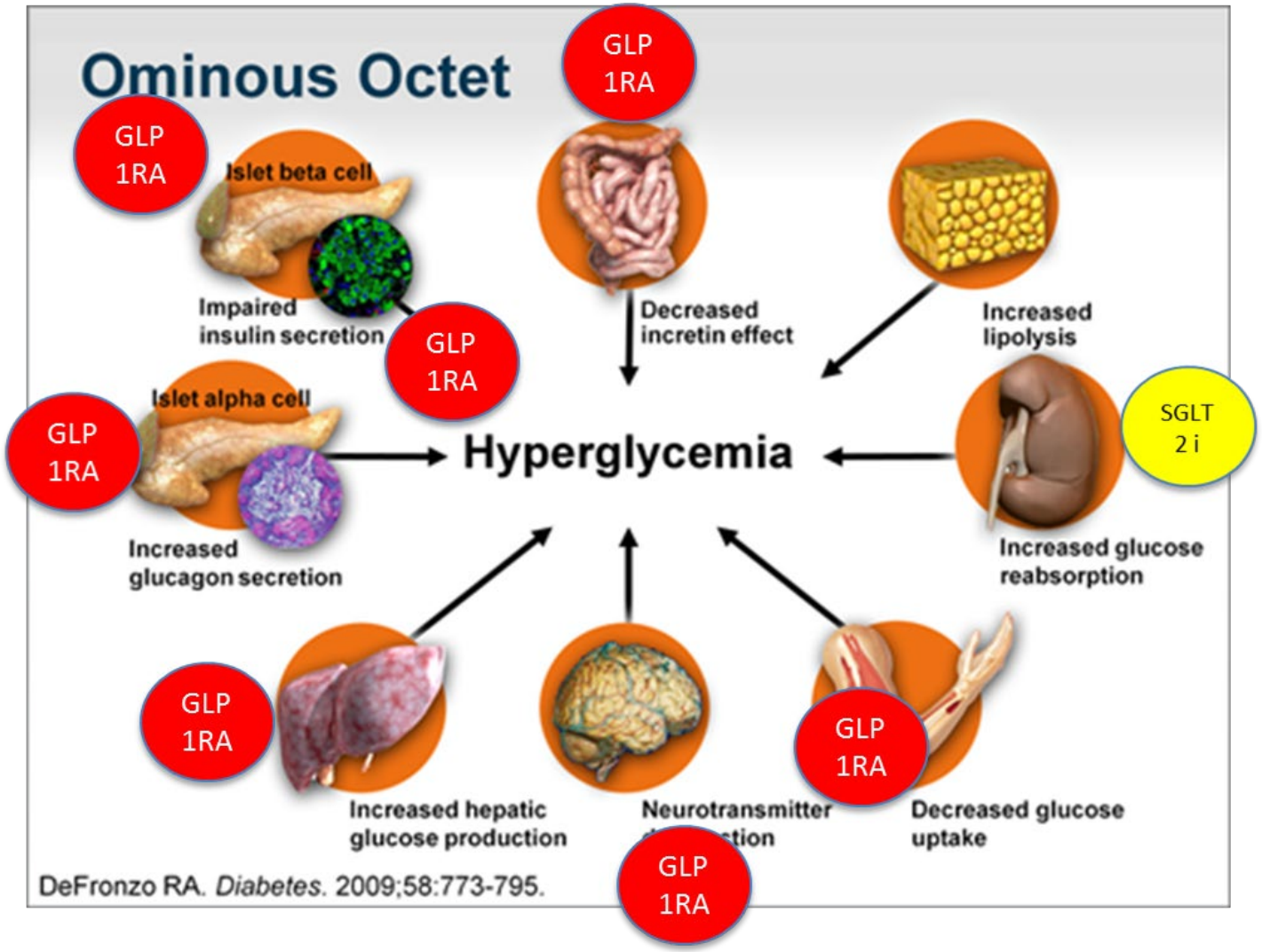
* For illustrative purposes only.

1. Bays H. *Curr Med Res Opin*. 2009;25;671-681. 2. Abdul-Ghani MA et al. *Endocr Pract*. 2008;14:782-790. 3. Marsenic O. *Am J Kidney Dis*. 2009;53:875-883. 4. Mather A et al. *Kidney Int*. 2011;79(suppl 120):S1-S6. 5. FARXIGA PI. 6. Inzucchi SE. *Diab Vasc Dis Res*. 2015;12(2):90-100. 7. Asano T et al. *Curr Med Chem.* 2004;11:2717-2724.

GLP1 RA and SGLT-2 Inhibitors Address a Broad Range of Pathophysiologic Defects Associated With T2D[1-10]



1. Drucker DJ *Diabetes*. 2015;64:317-326. 2. Campbell JE et al. *Cell Metab.* 2013;17:819-837. 3. Baggio LL et al. *Gastroenterology*. 2007;132:2131-2157. 4. Ussher JR et al. *Circ Res.* 2014;114:1788-1803 5. Bays H. *Curr Med Res Opin*. 2009;25;671-681. 6. Abdul-Ghani MA et al. *Endocr Pract*. 2008;14:782-790. 7. Marsenic O. *Am J Kidney Dis*. 2009;53:875-883. 8. Mather A et al. *Kidney Int*. 2011;79(suppl 120):S1-S6. 9. FARXIGA PI. 6. Inzucchi SE. *Diab Vasc Dis Res*. 2015;12(2):90-100. 10. Asano T et al. *Curr Med Chem.* 2004;11:2717-2724


Ominous Octet
GLP 1RA
Islet beta cell
Impaired insulin secretion
GLP 1RA
GLP 1RA
Decreased incretin effect
Increased lipolysis
Islet alpha cell
GLP 1RA
Hyperglycemia
SGLT 2 i
Increased glucagon secretion
Increased glucose reabsorption
GLP 1RA
Increased hepatic glucose production
Neurotransmitter
GLP 1RA
Decreased glucose uptake
GLP 1RA
DeFronzo RA. Diabetes. 2009;58:773-795.

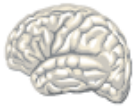
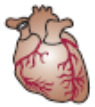
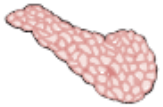
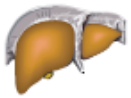
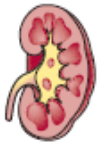
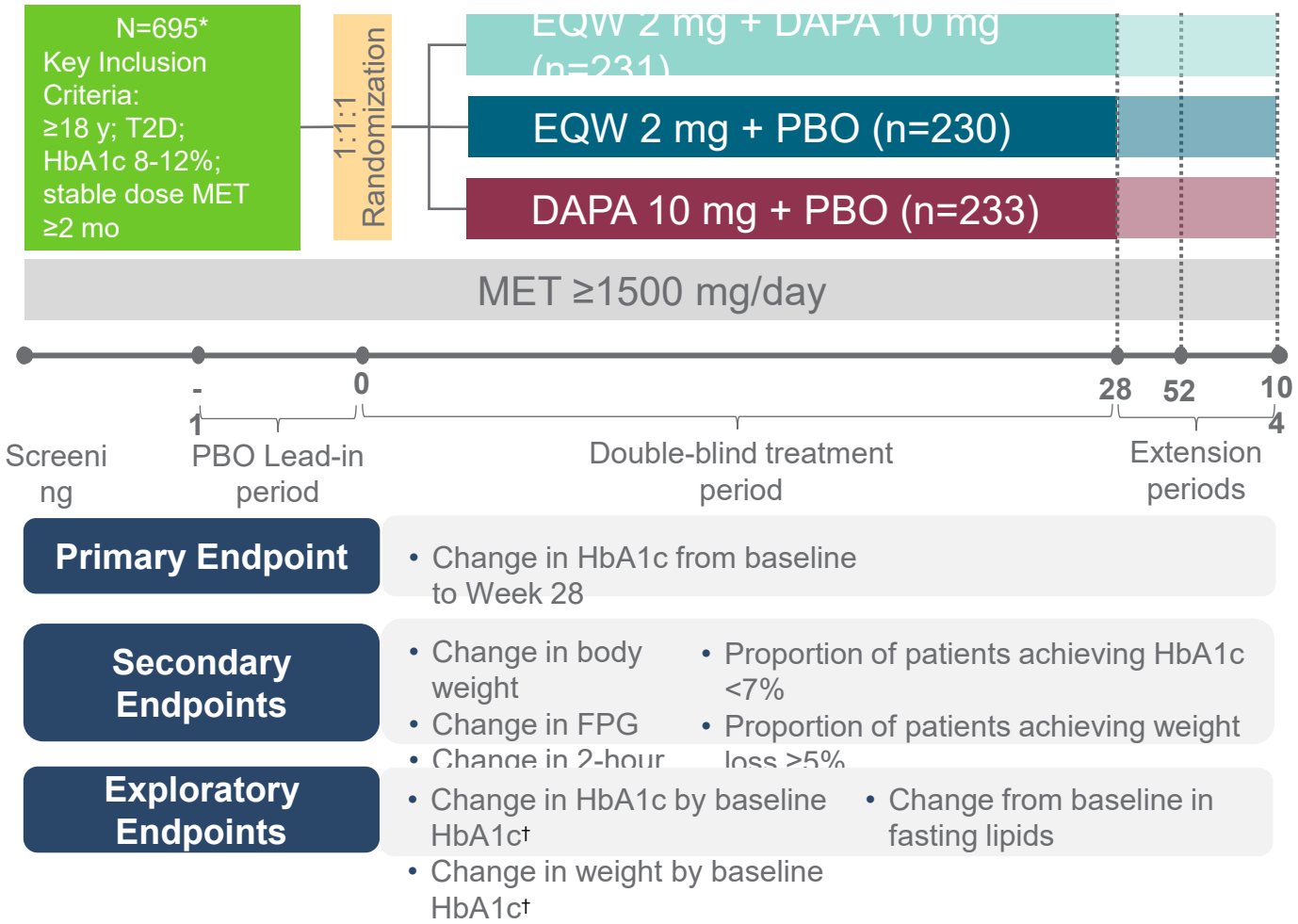
	GLP-1 receptor agonist		SGLT2 inhibitor	Combination therapy
Appetite	↓		↑ (?)	↓
Bodyweight	↓		↓	↓↓
Ischaemic cardiovascular events	↓		↓	↓↓
Heart failure events	↔		↓	↓
Insulin secretion	↑		↓	↑
Glucagon secretion	↓		↑	↔
Hepatic glucose output	↓		↑	↔
Ketone body production	↓ (?)		↑	↔
Glucose uptake (insulin-mediated)	↑ (?)		↑	↑↑
Diuresis, natiruresis	↑ (acutely)		↑	↑
Urinary glucose excretion	↔		↑	↑
Renoprotection	↔		↑	↑

Figure: **Effects of GLP-1 receptor agonists and SGLT2 inhibitors alone and in combination**
Schematic diagram showing qualitative effects at the level of the CNS, the heart, the endocrine pancreas (β cells, insulin secretion; α cells, glucagon secretion), the liver, and the kidney. Question marks signify some uncertainty about the significance of the effect indicated by the neighbouring arrow. Effects of combination therapy are based on findings from Frias and colleagues' study[1] or on inference from mechanistic studies. GLP-1=glucagon-like peptide-1. SGLT2=sodium-glucose cotransporter-2.

Nauck M.A., Mejer H, 2016 GLP-1 receptor agonists and SGLT2 inhibitors: a couple at last? Lancet Diabetes Endocrinol. 2016 Dec;4(12):963-964

DURATION-8: 28-Week, Multinational, Double-blind, Phase III Study With 2 Extension Periods[1,2]



* Includes 1 patient who was wrongly randomized but did not receive treatment; †Prespecified subgroup analysis.

Note: Study was not powered to compare the individual treatment of EQW alone and DAPA alone.

1. Guja C et al. Presented at: EASD Congress; September 11-15, 2017; Lisbon, Portugal. 2. Frías JP et al. Published correction for article and supplementary appendix. *Lancet Diabetes Endocrinol.* 2016;4:1004-1016.

Dulaglutide as Add-on Therapy to SGLT-2 Inhibitors in Patients With Inadequately Controlled Type 2 Diabetes (AWARD-10): A 24-Week, Randomised, Double-Blind, Placebo-Controlled Trial

- Bernhard Ludvik, MD[1]*; Juan P. Frias, MD[2]*; Francisco J. Tinahones, MD[3]; Julio Wainstein, MD[4]; Honghua Jiang, PhD[5]; Kenneth E. Robertson, PharmD, RPh[5]; Luis-Emilio Garcia-Perez, MD[5]; D. Bradley Woodward, MD[5]; Zvonko Milicevic, MD[6]

The AWARD-10 study was designed to assess the effects of once weekly dulaglutide (1·5 mg and 0·75 mg) on HbA1c, weight, FSG, and safety, when added on to stable doses of an SGLT-2i ± metformin in patients with inadequately controlled type 2 diabetes

[1]Medical Department and Karl Landsteiner Institute for Obesity and Metabolic Disorders, Rudolfstiftung Hospital, Vienna, Austria; [2]National Research Institute, Metro Medical Mall, Los Angeles, USA; [3]Hospital Universitario Virgen de la Victoria, Málaga and CIBER

Vienna, Austria

Ludvik et al. *Lancet Diabetes Endocrinol* 2018.

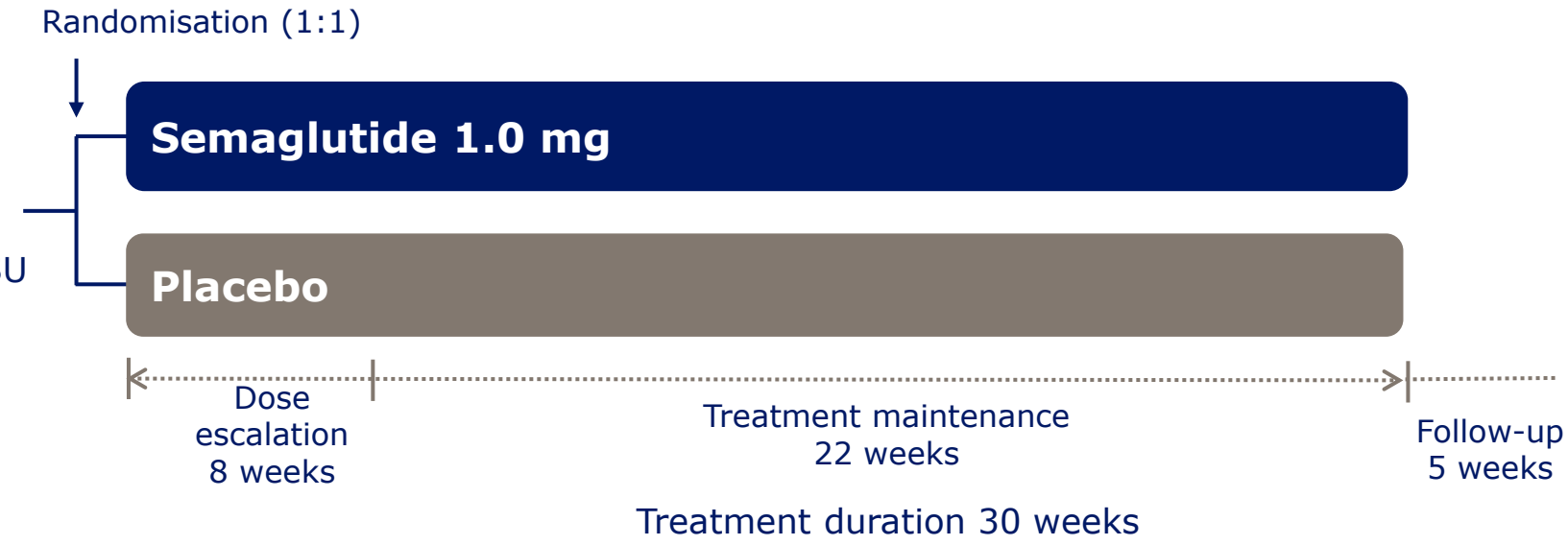
Ludvik et al. *Lancet Diabetes Endocrinol* 2018.

SUSTAIN 9

TRIAL DESIGN

302 patients with T2D

- Age ≥18 years*
- HbA_{1c} 7.0–10.0%†
- Stable treatment with SGLT-2 inhibitor‡ ± MET or SU
- eGFR ≥60 mL/min/1.73 m^2



Trial information

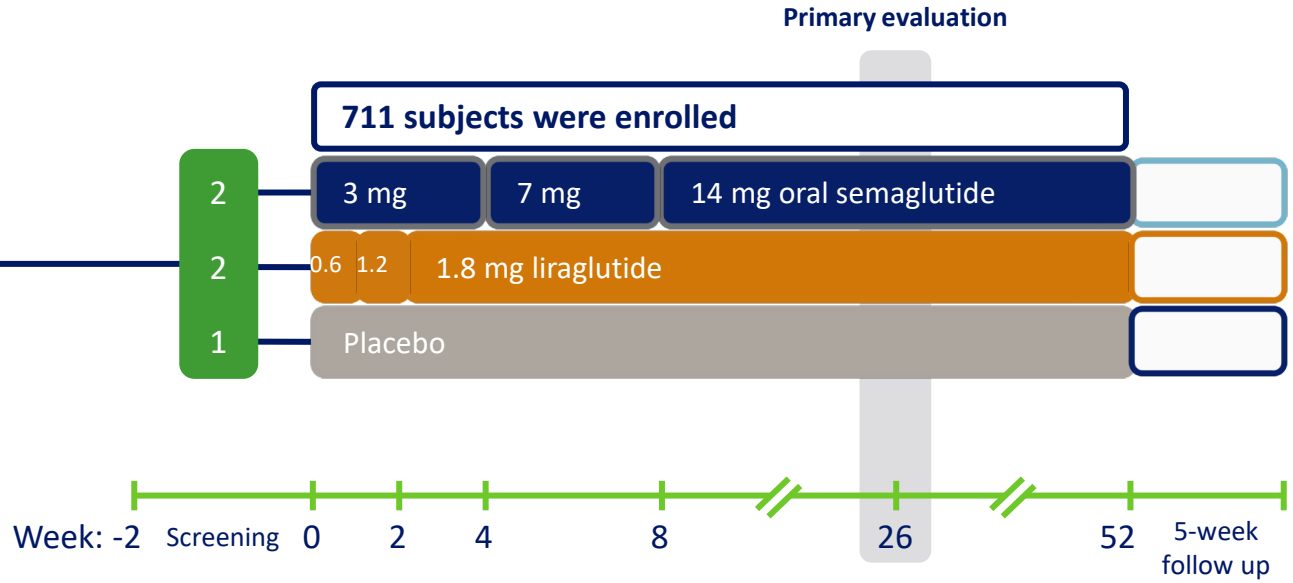
- Randomised, double-blind, placebo-controlled, parallel-group, multicentre, multinational, two-armed trial
- Conducted in six countries (Austria, Canada, Japan, Norway, Russian Federation, USA)
- Randomisation was stratified by background medication with SU (yes/no) and country (Japan/other)
- Semaglutide dose escalation from 0.25 mg, doubled every 4 weeks until maintenance dose achieved

*In Japan, the minimum age for enrolment was ≥20 years. †53–86 mmol/mol. ‡Stable treatment with SGLT-1 inhibitor was defined as having started SGLT-2 inhibitor treatment at least 90 days before screening.
eGFR, estimated glomerular filtration rate; MET, metformin; SGLT-2, sodium–glucose cotransporter-2; SU, sulphonylurea.
Zinman B et al. *Lancet Diabetes Endocrinol* 2019;7:356–67.

PIONEER 4 vs OD liraglutide
trial design

Key inclusion criteria

- Age ≥18 years
- T2D ≥90 days
- Stable doses of metformin or metformin ± SGLT2i for ≥90 days
- HbA_{1c} 7.0–9.5%



Trial information

- Randomised, double-blinded, double-dummy, active- and placebo-controlled, parallel-group, multicentre, multinational trial with three arms

Primary endpoint

- Change from baseline to week 26 in HbA_{1c}

Key secondary endpoints

- Change from baseline to week 26 in body weight*
- Change from baseline to week 52 in HbA_{1c} and body weight

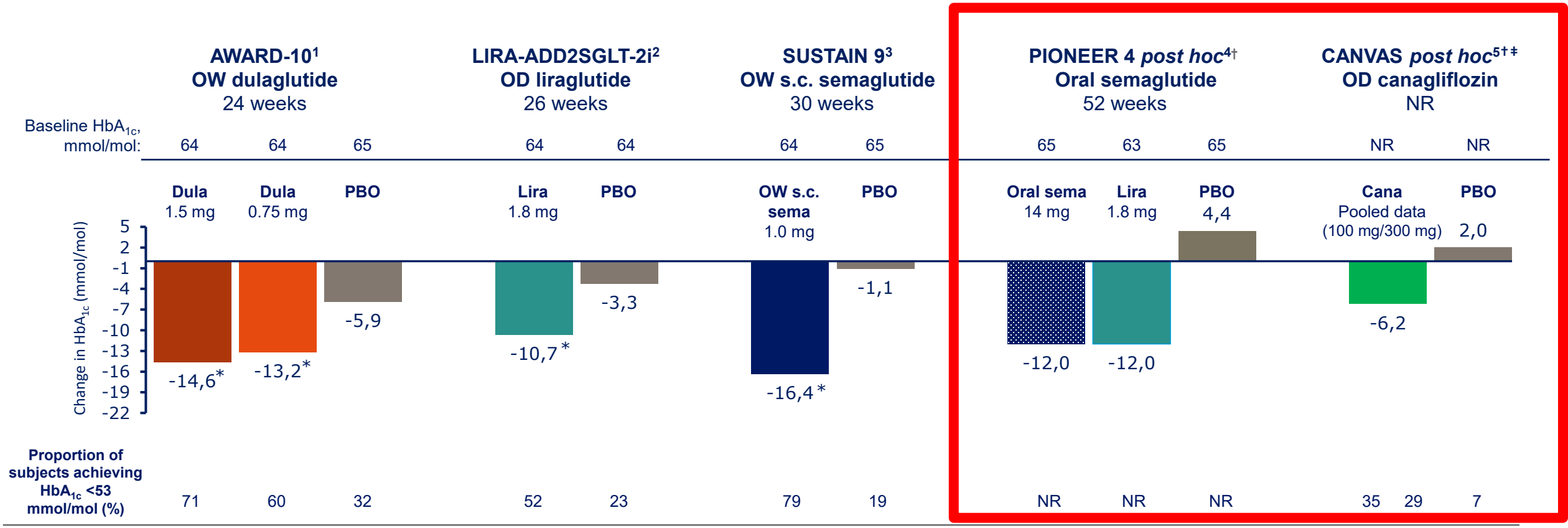
*Confirmatory secondary endpoint.
SGLT2i, sodium-glucose co-transporter-2 inhibitor.
Pratley R et al. *Lancet.* 2019;394:39–50.

Which RCTs have reported?

	GLP-1RA added to SGLT-2i			SGLT-2i added to GLP-1RA	Simultaneous initiation	
	AWARD-10[1]	Lira-Add2SGLT-2i[2]	SUSTAIN 9[3]	PIONEER 4[4*]	CANVAS[5,6*]	DURATION-8[7†]	Abdul-Ghani et al.[8]
Study treatment	Dulaglutide 1.5 mg or 0.75 mg	Liraglutide 1.8 mg ± metformin	OW s.c. semaglutide 1.0 mg	Oral semaglutide 14 mg	Canagliflozin 100 mg or 300 mg	Exenatide 2.0 mg + dapagliflozin 10 mg, or exenatide 2.0 mg + placebo, or dapagliflozin 10 mg + placebo	Canagliflozin 300 mg only, liraglutide 1.8 mg only or canagliflozin 300 mg + liraglutide 1.8 mg
Background therapy	Canagliflozin 100 mg or dapagliflozin 5 mg or empagliflozin 10 mg	Empagliflozin or dapagliflozin or canagliflozin (all doses)	Empagliflozin or dapagliflozin or canagliflozin (all doses)‡	Metformin ± SGLT-2i	**GLP-1RA:** Exenatide or liraglutide **OR** **DPP-4i:**§ sitagliptin or vildagliptin or saxagliptin	Metformin monotherapy	–
Comparator treatment	Placebo	Placebo	Placebo	Placebo	Placebo	–	–

*Post hoc analyses. †Exploratory analysis; ‡Three main background therapies; other SGLT-2is, only available in Japan, were used in a small number of subjects; §One patient was taking both sitagliptin and vildagliptin.
DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; OW, once weekly; RCT, randomised controlled trial; s.c., subcutaneous; SGLT-2i, sodium–glucose cotransporter-2 inhibitor.
1. Ludvik B et al. Lancet Diabetes Endocrinol 2018;6:370–81; 2. Blonde L et al. Diabetes Obes Metab 2020;22(6):929–37; 3. Zinman B et al. Lancet Diabetes Endocrinol 2019;7:356–67; 4. Pratley R et al. Presented at the American Diabetes Association 80th Scientific Sessions Virtual Meeting, 12–16 June 2020. Poster 927-P; 5. Fulcher G et al. Diabetes Obes Metab 2016;18:82–91; 6. Arnott C et al. Int J Cardiol 2020;318:126–9;; 7. Frías JP et al. Lancet Diabetes Endocrinol 2016;4:1004–16; 8. Abdul-Ghani M et al. Diabetes 2018;67(Suppl 1):109-OR.

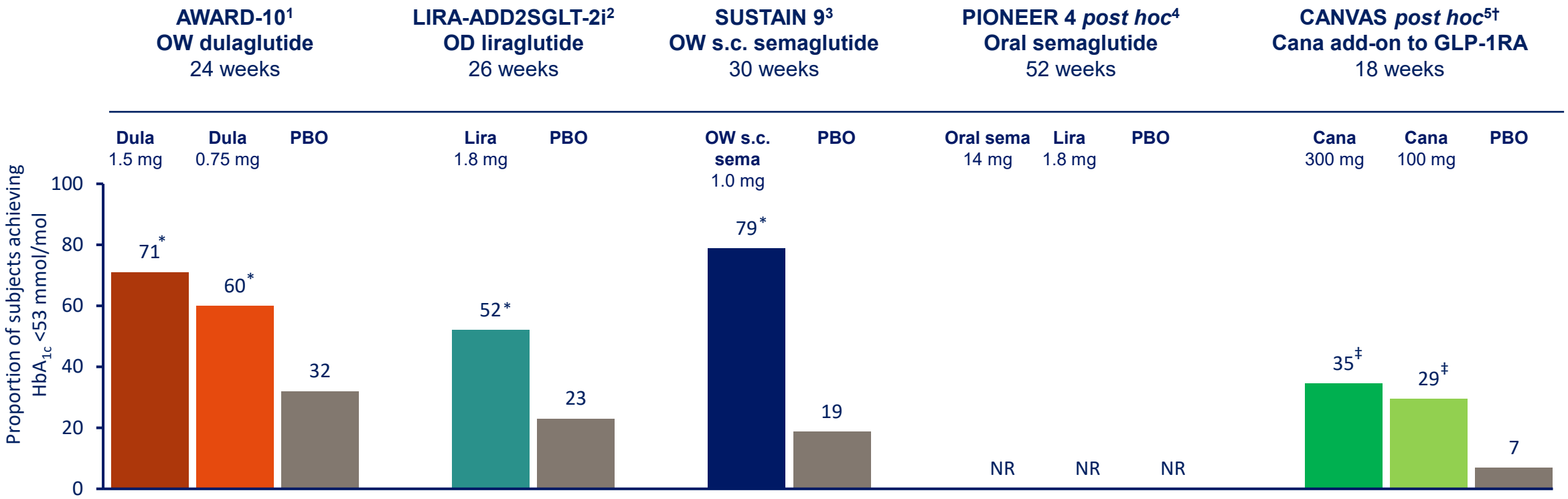
GLP-1RA or SGLT-2i as sequential add-on treatment: RCTs
KEY RESULTS: CHANGE IN HbA_{1c}



*Statistically significant vs placebo; †Statistical significance not reported. ‡Data from the CANVAS Programme (CANVAS and CANVAS-R).
Cana, canagliflozin; Dula, dulaglutide; GLP-1RA, glucagon-like peptide-1 receptor agonist; Lira, liraglutide; NR, not reported; OD, once daily; OW, once weekly; PBO, placebo; RCT, randomised controlled trial; s.c., subcutaneous;
Sema, semaglutide; SGLT-2i, sodium–glucose cotransporter-2 inhibitor.

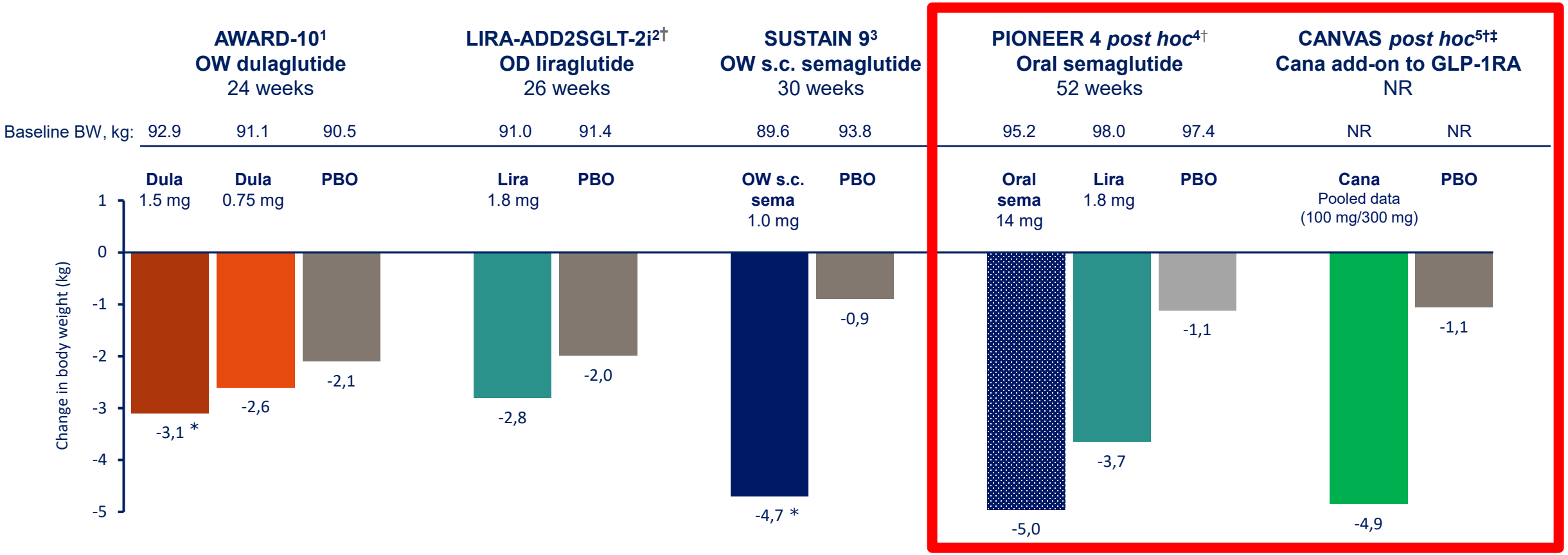
1. Ludvik B et al. Lancet Diabetes Endocrinol 2018;6:370–81; 2. Blonde L et al. Diabetes Obes Metab 2020;22(6):929–37; 3. Zinman B et al. Lancet Diabetes Endocrinol 2019;7:356–67; 4. Pratley R et al. Presented at the American Diabetes Association 80th Scientific Sessions Virtual Meeting, 12–16 June 2020. Poster 927-P; 5. Arnott C et al. Int J Cardiol 2020;318:126–9.

GLP-1RA or SGLT-2i as sequential add-on treatment: RCTs
PROPORTION OF SUBJECTS ACHIEVING HbA_{1c} <53 mmol/mol



*Statistically significant vs placebo. †Interim post hoc analysis from the CANVAS trial only. ‡Statistical significance not reported.
Cana, canagliflozin; Dula, dulaglutide; GLP-1RA, glucagon-like peptide-1 receptor agonist; Lira, liraglutide; OD, once daily; OW, once weekly; PBO, placebo; RCT, randomised controlled trial; s.c., subcutaneous; sema, semaglutide;
SGLT-2i, sodium–glucose cotransporter-2 inhibitor. 1. Ludvik B et al. Lancet Diabetes Endocrinol 2018;6:370–81; 2. Blonde L et al. Diabetes Obes Metab 2020;22(6):929–37. [OR22-1]; 3. Zinman B et al. Lancet Diabetes Endocrinol 2019;7:356–67;
4. Pratley R et al. Presented at the American Diabetes Association 80th Scientific Sessions Virtual Meeting, 12–16 June 2020. Poster 927-P; 5. Fulcher G et al. Diabetes Obes Metab 2016;18:82–9.

GLP-1RA or SGLT-2i as sequential add-on treatment: RCTs
KEY RESULTS: CHANGE IN BODY WEIGHT

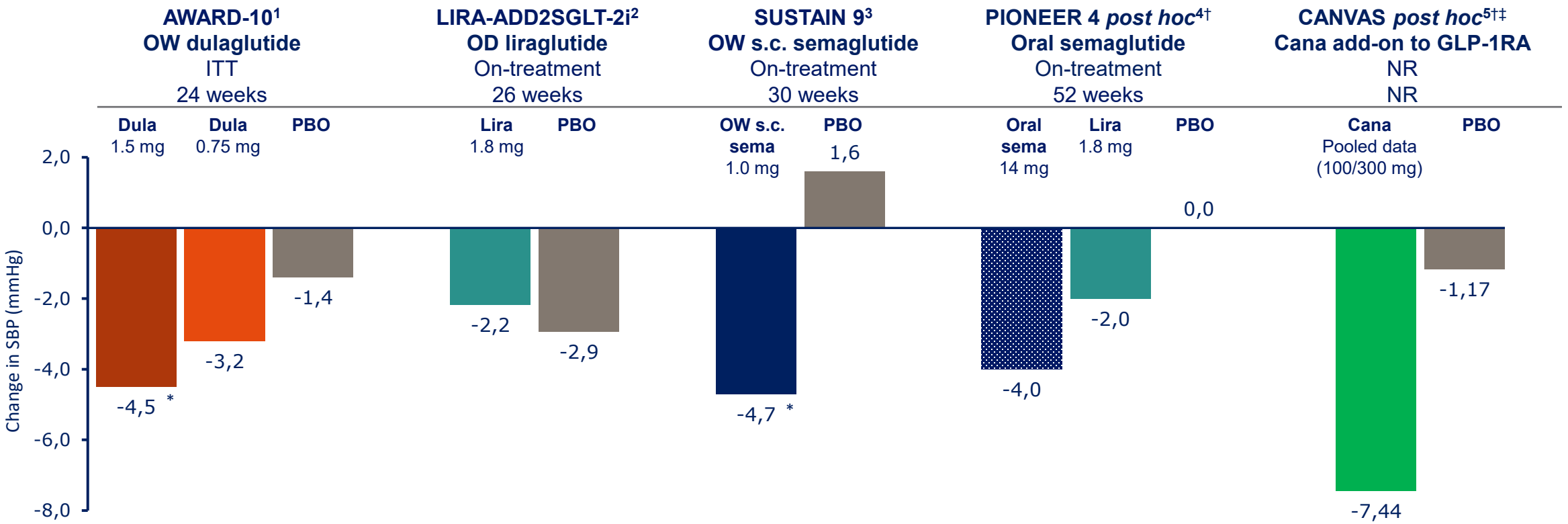


*Statistically significant vs placebo. †Statistical significance not reported. ‡Data from the CANVAS Programme (CANVAS and CANVAS-R).
BW, body weight; Cana, canagliflozin; Dula, dulaglutide; GLP-1RA, glucagon-like peptide-1 receptor agonist; Lira, liraglutide; NR, not reported; OD, once daily; OW, once weekly; PBO, placebo; RCT, randomised controlled trial;
s.c., subcutaneous; Sema, semaglutide; SGLT-2i, sodium–glucose cotransporter-2 inhibitor.

1. Ludvik B et al. Lancet Diabetes Endocrinol 2018;6:370–81; 2. Blonde L et al. Diabetes Obes Metab 2020;22(6):929–37; 3. Zinman B et al. Lancet Diabetes Endocrinol 2019;7:356–67; 4. Pratley R et al. Presented at the American Diabetes Association 80th Scientific Sessions Virtual Meeting, 12–16 June 2020. Poster 927-P; 5. Arnott C et al. Int J Cardiol 2020;318:126–9.

GLP-1RA or SGLT-2i as sequential add-on treatment: RCTs

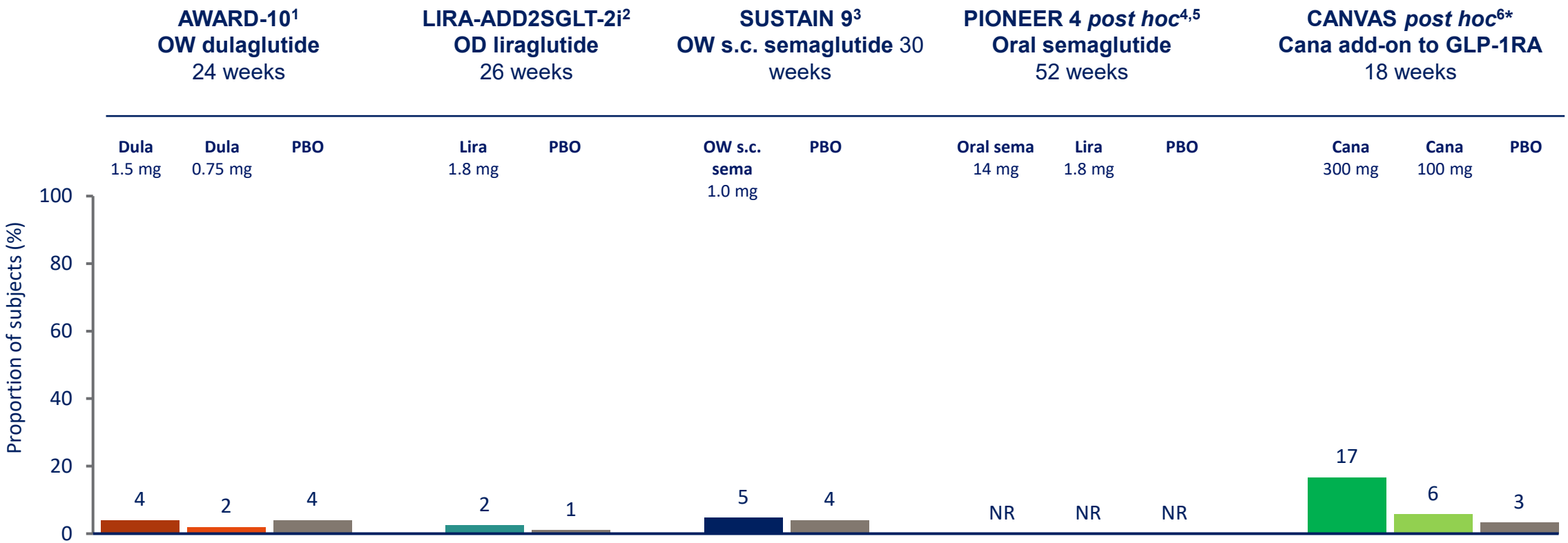
CHANGE IN SYSTOLIC BLOOD PRESSURE



*Statistically significant vs placebo. †Statistical significance not reported. ‡Data from the CANVAS Programme (CANVAS and CANVAS-R).
Cana, canagliflozin; Dula, dulaglutide; GLP-1RA, glucagon-like peptide-1 receptor agonist; ITT, intention-to-treat; Lira, liraglutide; NR, not reported; OD, once daily; OW, once weekly; PBO, placebo; RCT, randomised controlled trial; s.c., subcutaneous; Sema, semaglutide; SBP, systolic blood pressure; SGLT-2i, sodium–glucose co-transporter-2 inhibitor.

1. Ludvik B et al. Lancet Diabetes Endocrinol 2018;6:370–81; 2. Blonde L et al. Diabetes Obes Metab 2020;22(6):929–37; 3. Zinman B et al. Lancet Diabetes Endocrinol 2019;7:356–67; 4. Pratley R et al. Presented at the American Diabetes Association 80th Scientific Sessions Virtual Meeting, 12–16 June 2020. Poster 927-P; 5. Arnott C et al. Int J Cardiol 2020;318:126–9.

GLP-1RA or SGLT-2i as sequential add-on treatment: RCTs
PROPORTION OF SUBJECTS REPORTING SERIOUS ADVERSE EVENTS



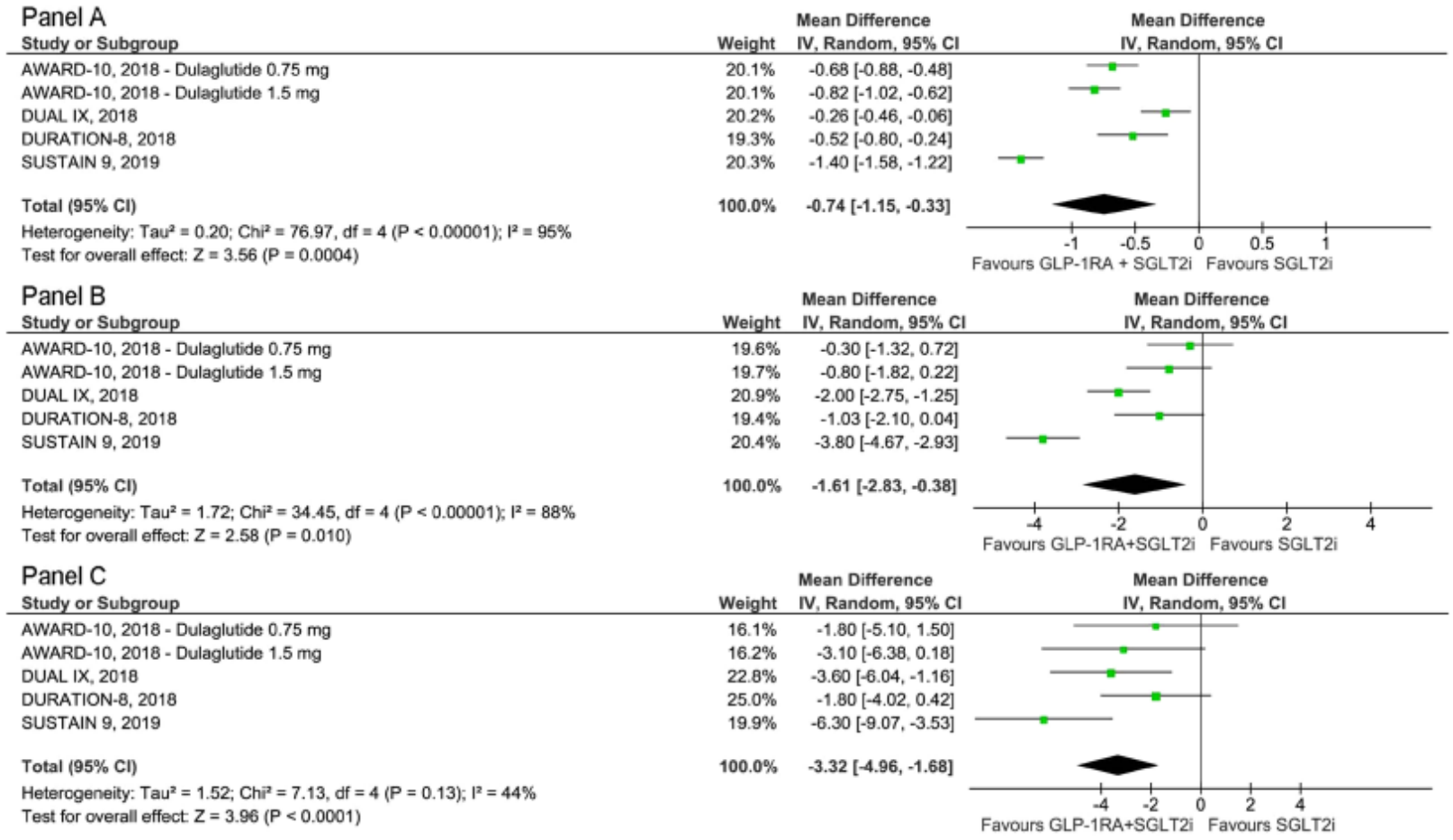
*Interim post hoc analysis from the CANVAS trial only.

Cana, canagliflozin; Dula, dulaglutide; GLP-1RA, glucagon-like peptide-1 receptor agonist; Lira, liraglutide; NR, not reported; OD, once daily; OW, once weekly; PBO, placebo; RCT, randomised controlled trial; s.c., subcutaneous;

Sema, semaglutide; SGLT-2i, sodium–glucose co-transporter-2 inhibitor. 1. Ludvik B et al. Lancet Diabetes Endocrinol 2018;6:370–81; 2. Blonde L et al. Diabetes Obes Metab 2020;22(6):929–37; 3. Zinman B et al. Lancet Diabetes Endocrinol 2019;7:356–67; 4. Pratley R et al. Presented at the American Diabetes Association 80th Scientific Sessions Virtual Meeting, 12–16 June 2020. Poster 927-P; 5. Pratley R et al. Lancet 2019;394:39–50; 6. Fulcher G et al. Diabetes Obes Metab 2016;18:82–9.

Efficacy and safety of GLP-1 receptor agonists as add-on to SGLT2 inhibitors in type 2 diabetes mellitus: A meta-analysis

Marco Castellana, Angelo Cignarelli, Francesco Brescia, Sebastio Perrini, Annalisa Natalicchio, Luigi Laviola & Francesco Giorgino*



HbA1c

Body weight

SBP

Real-world evidence: SGLT-2i add-on to GLP-1RA

Publication	Trial design (duration)	Subjects, N	Change from baseline to end of treatment		Safety	Summary
			HbA_{1c}, mmol/mol unless otherwise stated	Body weight, kg		
Saroka et al. 2015 (full publication)[1§]	Pre-post observational study Cana (100 or 300 mg) as add-on to GLP-1RA (10.7±2.9 m)	75	–4.3**‡ (±9.6)	–4.6**‡ (±4.3)	AEs: 17.3% subjects Discontinuation [AEs]: 5.3% (hypotension, yeast infection, UTIs, dry mouth)	**Canagliflozin reduced HbA_{1c} and body weight significantly further when added to GLP-1RA, and was generally well tolerated**
McGovern et al. 2015 (abstract only)[2§]	Retrospective, systematic case-note audit to evaluate BW Dapa as add-on to GLP-1RA vs dapa without GLP-1RA (12 m)	88	Comparable between groups	Dapa only: –3.0 (±2.4) Dapa+GLP-1RA: –7.2# (±3.1)	NR	**Combination of dapagliflozin and GLP-1RA resulted in additional weight loss compared with dapagliflozin alone**
Bashir et al. 2016 (abstract only)[3§]	Observational study Dapa as add-on to GLP-1RA (6±2 m)	14	From 88±18 at BL to 72±15*	From 106.7±12.3 at BL to 102.7±9.3*	NR	**Adding an SGLT-2i to GLP-1RA therapy was associated with significant reductions in HbA_{1c} and weight over a 6-month period**
Curtis et al. 2016 (full publication)[4§]	Retrospective, observational case-note review SGLT-2i as add-on to GLP-1RA (20 w and 48 w)	14 at 20 w 11 at 48 w	At 20 w: –26** At 48 w: –25**	At 20 w: –2.6 At 48 w: –5.47	Most common AEs included UTIs (3 subjects) and polydipsia (1 subject)	**Add-on with an SGLT-2i to a GLP-1RA further reduced HbA_{1c} and weight**
Gorgojo-Martínez et al. 2017 (full publication)[5§]	Retrospective, observational study Dapa added to diabetes multitherapy including GLP-1RA (6 m and 12 m)	109	Dapa+GLP-1RA (6 m): –5.6*** Dapa+GLP-1RA (12 m): –3.7***	Dapa+GLP-1RA (6 m): –2.3*** Dapa+GLP-1RA (12 m): –2.4***	Similar discontinuation and hypoglycaemia rates 1 death (non-GLP-1RA group)	**Dapagliflozin added GLP1-RA treatment, induced a further significant, albeit modest improvement in HbA_{1c} and a further weight loss**

*p<0.05, **p<0.001 and ***p<0.0001 all vs baseline; #p<0.05 vs comparator; ‡No significant difference between cana doses. $Includes some subjects on SGLT-2i+DPP-4i, results for these subjects not shown. §Study involved SGLT-2i added to GLP-1RA. The values preceded by ± signs refer to standard deviations (except for Bashir et al 2016, which does not explain the meaning of the sign).

AE, adverse event; BL, baseline; BW, body weight; Cana/cana, canagliflozin; Dapa/dapa, dapagliflozin; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like receptor-1 agonist; m, months; NR, not reported; SGLT-2i, sodium–glucose cotransporter-2 inhibitor; UTI, urinary tract infection; w, weeks.

1. Saroka RM et al. Endocr Pract 2015;21:1315–22; 2. McGovern AP et al. Diabet Med 2015;32:2–3; 3. Bashir J et al. Diabet Med 2016;33:165–6; 4. Curtis L et al. Pract Diabetes 2016;33:129–32; 5. Gorgojo-Martínez JJ et al. Nutr Metab Cardiovasc Dis 2017;27:129–37.

Real-world evidence: SGLT-2i and GLP-1RA initiated simultaneously or sequentially

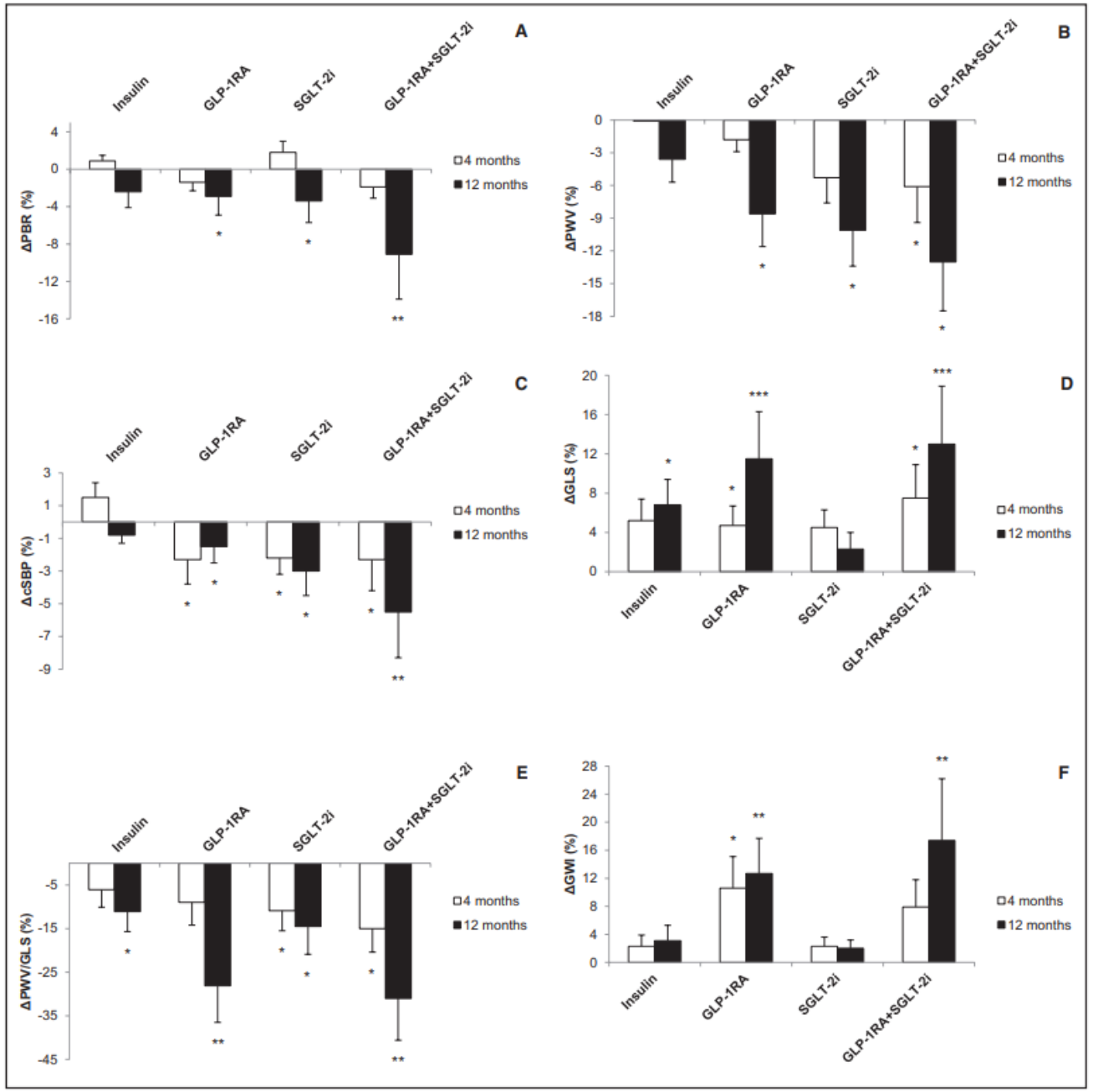
Publication	Trial design (duration)	Subjects, N	Change from baseline to end of treatment		Safety	Summary
			HbA_{1c}, mmol/mol	Body weight, kg		
†Pappas et al. 2016 (abstract only)[1]	Lira+dapa in combination vs dapa add-on to lira (6 m)	54	Lira+dapa: –21.4* (±9.0) Dapa added to lira: –15.3 (±7.4)	Lira+dapa: –6.68* (±2.59) Dapa added to lira: –4.55 (±2.06)	NR	**Simultaneous initiation yielded better glycaemic control and weight loss than sequential addition**
†Sotiropoulos et al. 2017 (abstract only)[2]	Lira+dapa in combination vs dapa add-on to lira (12 m)	63	Lira+dapa: –21.6* (±9.2) Dapa added to lira: –15.8 (±8.2)	Lira+dapa: –8.15* (±2.93) Dapa added to lira: –5.02 (±2.11)	NR	
Goncalves & Bell 2017[3]; Goncalves & Bell 2018[4]	Retrospective, observational study Lira+SGLT-2i in combination vs SGLT-2i add-on to lira (retrospective of electronic prescriptions)	33 46	Lira+SGLT-2i: –21.9** SGLT-2i add-on to lira: –9.8**	Lira+SGLT-2i: –10** SGLT-2i add-on to lira: –4**	NR	
Diaz-Trastoy et al. 2020[5]	Retrospective search of eRx for patients receiving GLP-1RA+SGLT-2i in combination (3 visits, mean duration 16.4 m)	212	SGLT-2i+GLP-1RA: –12.0**	SGLT-2i+GLP-1RA: –3.5**	AEs: 9.0% Most common AEs were genital infections (3.8%) and polyuria (2.4%) of all subjects).‡ No cases of ketoacidosis, fractures, or amputations were reported	**Simultaneous/ sequential initiation yielded significant reductions in HbA_{1c} and body weight vs baseline**

†The two abstracts are likely part of the same study (not stated in abstracts). *p<0.05 vs comparator; **p<0.001 vs baseline. ‡Proportion of subjects with AEs calculated from number of subjects with event and total subjects.

The values preceded by ± signs are not defined in the publications. AE, adverse event; Dapa/dapa, dapagliflozin; eRX, electronic prescription; GLP-1RA, glucagon-like receptor-1 agonist; lira, liraglutide; m, month; NR, not reported;

SGLT-2i, sodium–glucose cotransporter-2 inhibitor; w, week. 1. Pappas S et al. Diabetologia 2016;59(Suppl 1):S1–S581; 2. Sotiropoulos A et al. Presented at the 77th American Diabetes Association Scientific Sessions, 9–13 June 2017, San Diego, CA, USA. A304: 1142–P; 3. Goncalves E and Bell DSH. Diabetes Obes Metab 2017;19:909–11; 4. Goncalves E and Bell DSH. Diabetes Ther 2018;9:919–26; 5. Díaz-Trastoy O et al. Clin Ther 2020; 42:e1–e12.

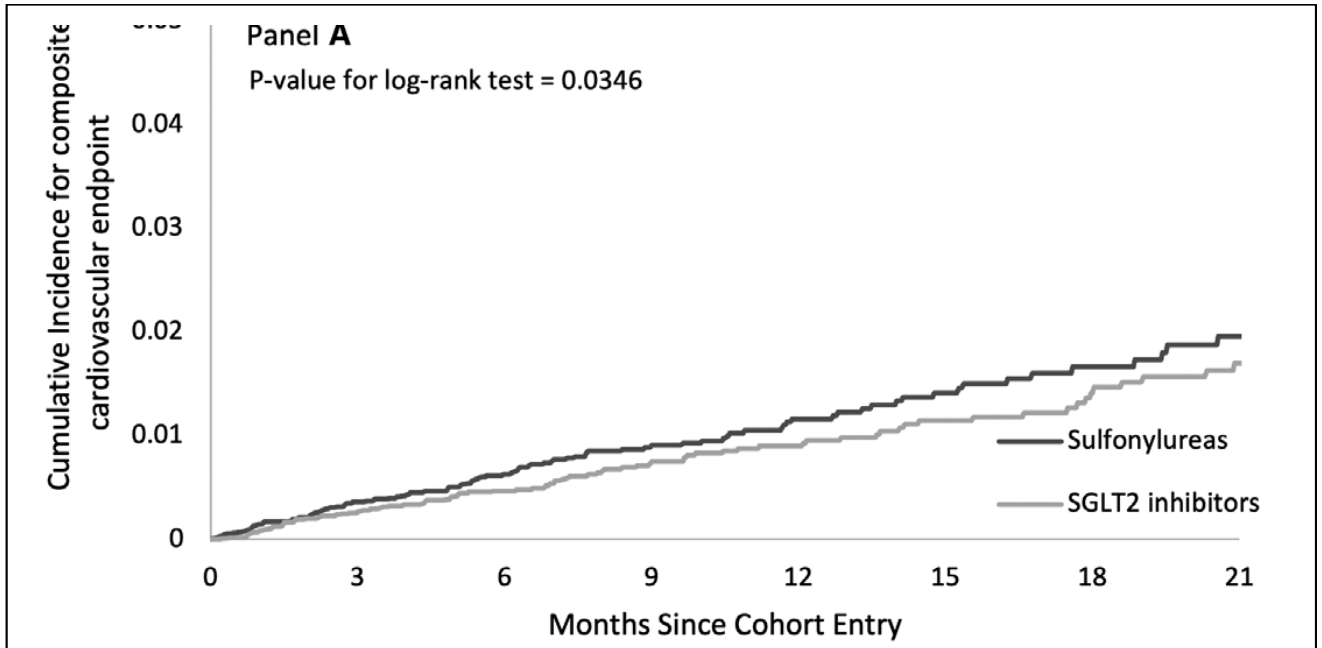
Miglioramento dei marcatori vascolari e del lavoro cardiaco effettivo in pazienti con T2DM trattati con associazione GLP-1 RA +SGLT2i rispetto alle singoli classi ed all'insulina basale.



Ikonomidis I et al. J Am Heart Assoc. 2020;9:e015716

Riduzione significativa del MACE in pazienti con T2DM trattati con l'associazione GLP-1 RA+SGLT2i rispetto a quelli trattati con GLP-1 RA + sulfoniluree nella real life

Studio osservazionale su 3 registri americani (Optum, MarketScan, Medicare) con due coorti comparabili (propensity-score match) di 12584 pazienti l'una.



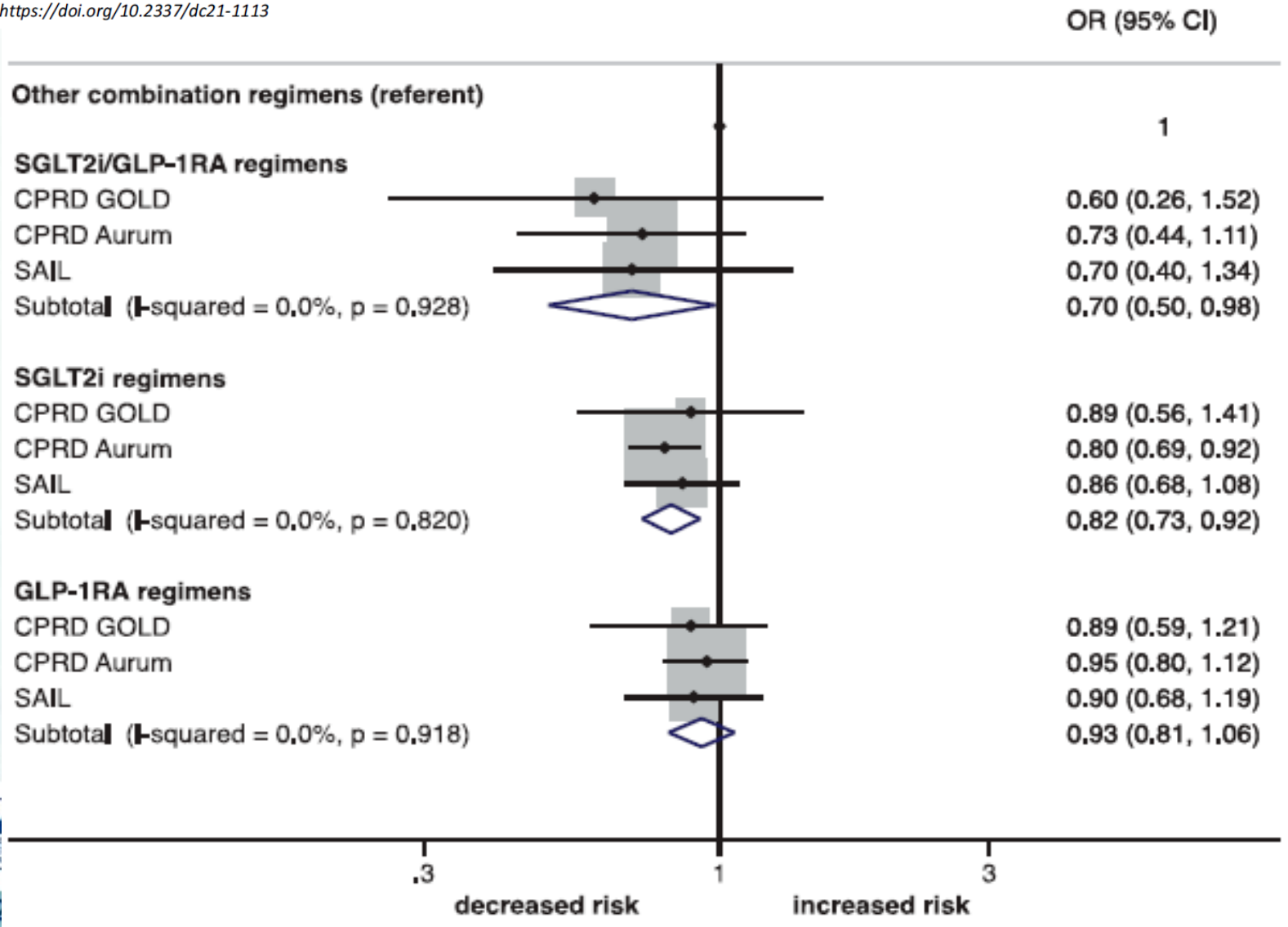
At risk (months), n	0	3	6	9	12	15	18	21
SU	12 584	10 576	7542	5050	3375	2342	1603	1111
SGLT2i	12 584	12 574	10 727	7710	5308	3779	2726	1508

Dave C et al. Circulation. 2021;143:770–779

Primary Prevention of Cardiovascular and Heart Failure Events With SGLT2 Inhibitors, GLP-1 Receptor Agonists, and Their Combination in Type 2 Diabetes

Associazione tra uso di SGLT2i e G1ra comparata con altri regimi terapeutici di combinazione e di rischio di MACE in prevenzione primaria

Diabetes Care 2022;45:909–918 | https://doi.org/10.2337/dc21-1113



AWARE 2- PREMESSA

- SONO STATI RECLUTATI **570** PAZIENTI IN TERAPIA CON SGLT2 i +/- ALTRE TERAPIE A CUI E' STATO AGGIUNTO UN GLP1-RA SETTIMANALE PERCHE' NON BEN COMPENSATI O PER I QUALI UNA TERAPIA DI COMBINAZIONE POTEVA APPORTARE UN BENEFICIO AGGIUNTIVO SUL PROFILO DI RISCHIO CARDIORENALE

- AD OGGI **271** PAZIENTI HANNO RICEVUTO UNA VISITA DI FOLLOW-UP A 6 MESI

- I RESTANTI FU VERRANNO COMPLETATI ENTRO IL 2022

LA STRATIFICAZIONE DEL RISCHIO CARDIOVASCOLARE SECONDO ESC-EASD 2019

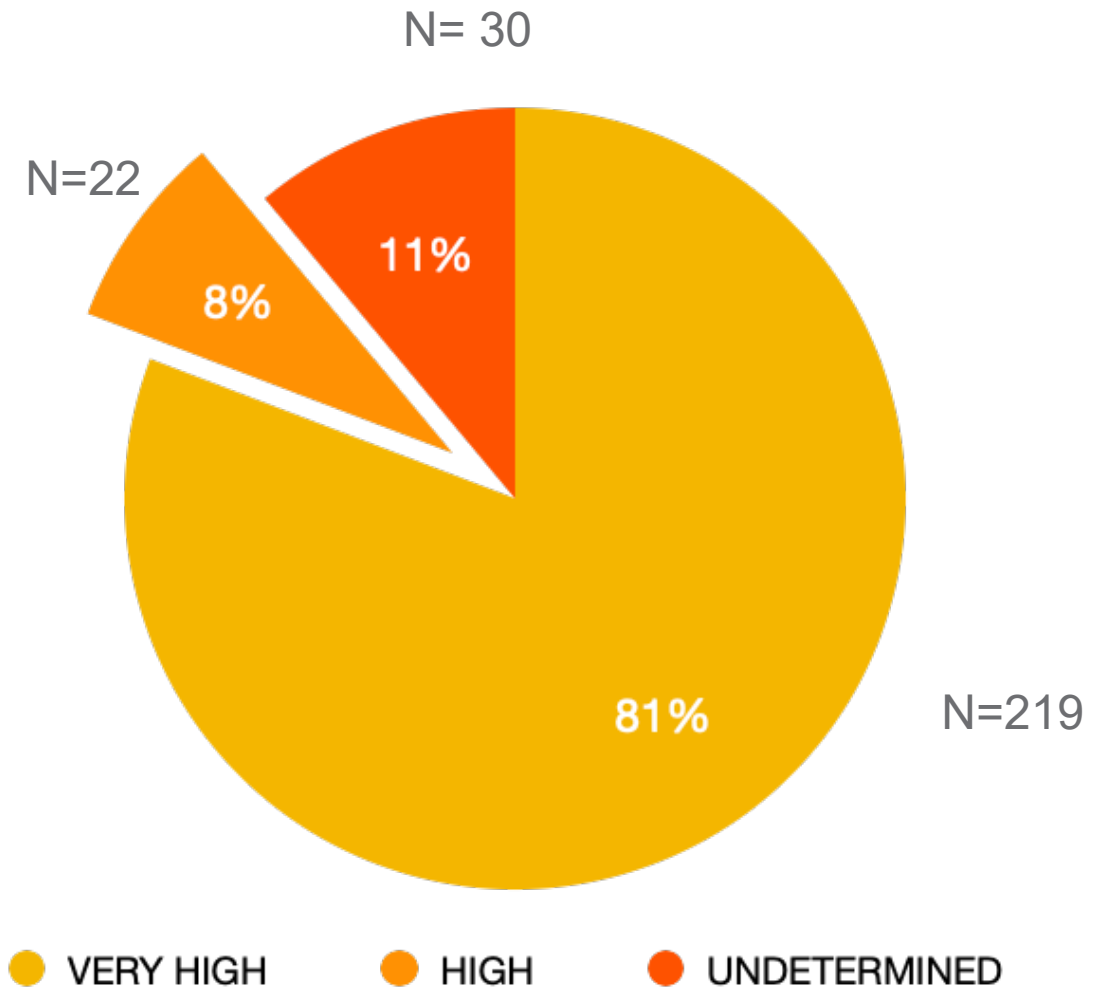
Very high-risk	Patients with DM **and** established CVD **or** other target organ damage[a] **or** three or more major risk factors[b] **or** early onset T1DM of long duration (>20 years)
High-risk	Patients with DM duration ≥10 years without target organ damage[a] plus any other additional risk factor[b]
Moderate-risk	Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors

e-GFR ≤ 30mL/min/1.73 m²

[a] proteinuria, renal impairment defined as eGFR≥30mL/min/1.73m².
[b] age, hypertension, dyslipidemia, smoking, obesity.

European Heart Journal 2019 doi/10.1093/eurheartj/ezh486

DISTRIBUZIONE DEI 271 PAZIENTI CON FU NELLE CATEGORIE DI RISCHIO



PARAMETRI AL BASALE E A 6 MESI NEI PAZIENTI CON FU

PAZIENTI	N°	GLICATA MEDIA BASALE	GLICATA MEDIA 6 MESI
TOTALE	**271**	**7,7**	**7,0**

-0,7

PAZIENTI	N°	BMI BASALE	BMI 6 MESI
TOTALE	**271**	**30**	**28,9**

-1,1

PAZIENTI	N°	PESO MEDIO (KG) BASALE	PESO MEDIO (KG) 6 MESI
TOTALE	**271**	**83,9**	**80,9**

-3

SOTTOGRUPPO PAZIENTI CHE SOSPENDONO L' INSULINA BASALE

PAZIENTI	N°	GLICATA MEDIA BASALE	GLICATA MEDIA 6 MESI
TOTALE	**22**	**7,3**	**7,1**

-0,2

PAZIENTI	N°	BMI BASALE	BMI 6 MESI
TOTALE	**22**	**27,4**	**26,3**

-1,1

PAZIENTI	N°	PESO (KG) BASALE	PESO(KG) 6 MESI
TOTALE	**22**	**76,2**	**73,2**

-3

SOTTOGRUPPO PAZIENTI CHE SOSPENDONO LA SULFANILUREA

PAZIENTI	N°	GLICATA MEDIA BASALE	GLICATA MEDIA 6 MESI
TOTALE	**15**	**8,0**	**6,9**

-1,1

PAZIENTI	N°	BMI BASALE	BMI 6 MESI
TOTALE	**15**	**29,1**	**27,7**

-1,4

PAZIENTI	N°	PESO BASALE	PESO 6 MESI
TOTALE	**15**	**78,2**	**74,5**

-3,7

Associazione SGLT2i + GLP1ra: quando e per quali pazienti?

- In pazienti con patologia cardiovascolare o renale e già in terapia con una delle due classi di farmaci, che necessitano di intensificare il controllo glicemico
- Pazienti con scompenso metabolico in cui è prioritario il calo ponderale
- In pazienti a rischio di ipoglicemia e già in a terapia con una delle due classi di famaci, in sostituzione ad altre terapia ipoglicemizzanti (SU, insulina)
- In pazienti affetti da patologia cardiovascolare associata a scompenso cardiaco e/o nefropatia

INDIPENDENDEMENTE DAI VALORI DI EMOGLOBINA GLICATA

NEW PARADIGM: MANAGEMENT OF THE CARDIOMETABOLIC CONTINUUM

Italian Guidelines for **Diabetes** Management 2021

	T2DM patients **without** previous CV event	T2DM patients **with** previous CV event	T2DM patients with previous **CV event and HF**
1° line	Metformin	Met	SGLT2i
2° line	GLP1RA, SGLT2i	GLP1RA, SGLT2i	GLP1RA, Metformin*
3° line	DPP4i, Aca, Pio, Ins	DPP4i, Aca, Pio, Ins	DPP4i**, Aca, Ins