Analoghi GLP-1: quale può essere il paziente tipo?

Giuseppe Defeudis MD, PhD
g.defeudis@unicampus.it

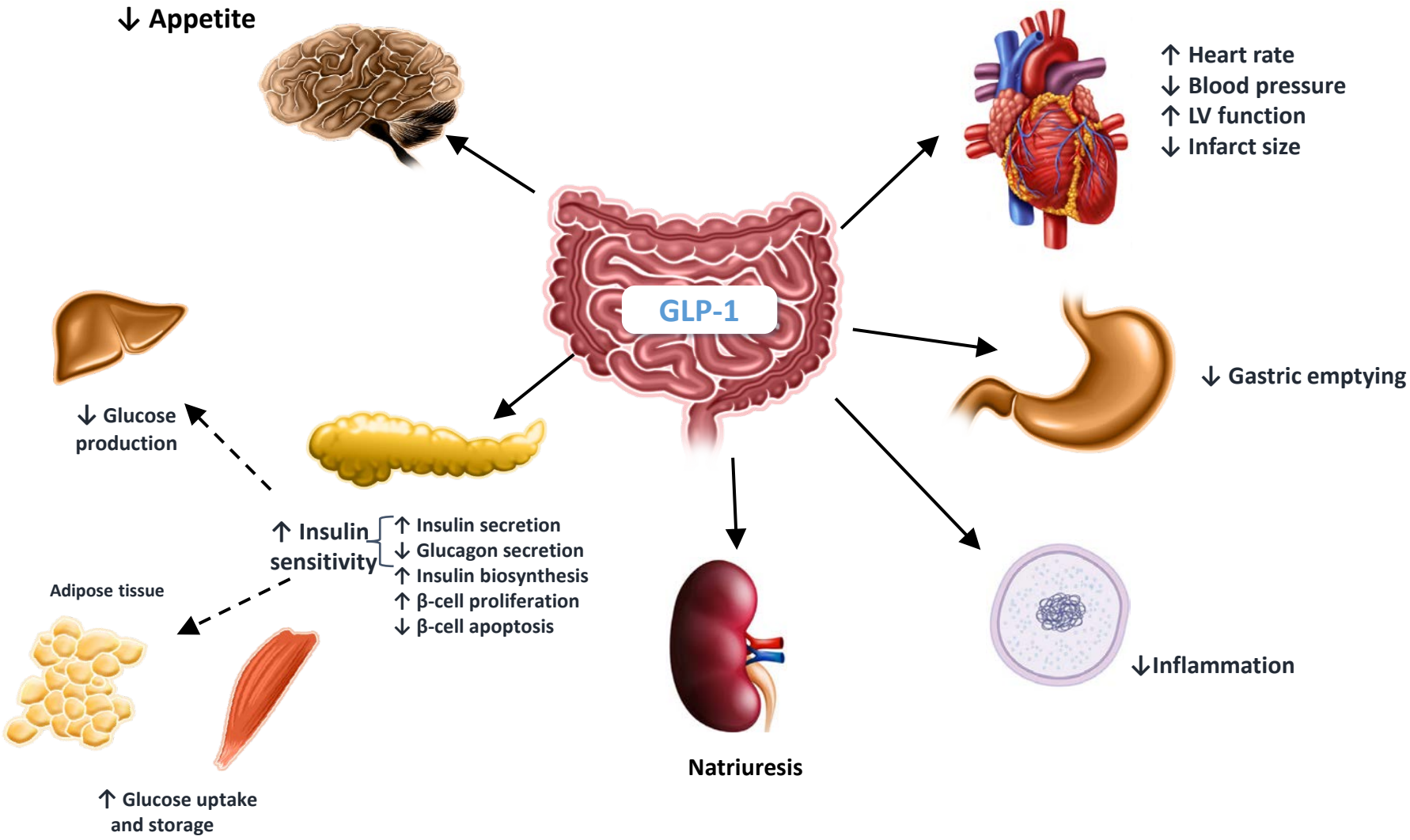
Unità di Endocrinologia e Malattie del Metabolismo, Dip. di Medicina
Università Campus Bio-Medico di Roma

AGENDA

GLP 1-RA

- background
- LG
- *effetto ipoglicemizzante*
- *effetto sulla safety CV e renale*
- *effetto sul rischio di ipoglicemie*
- *effetto anoressizzante*
- *Aderenza/Persistenza: Manegevolezza e Tolleranza*
- Associazioni
- Altri target
- Conclusioni

BACKGROUND: Physiologic Actions and Effects of GLP-1 RA



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.

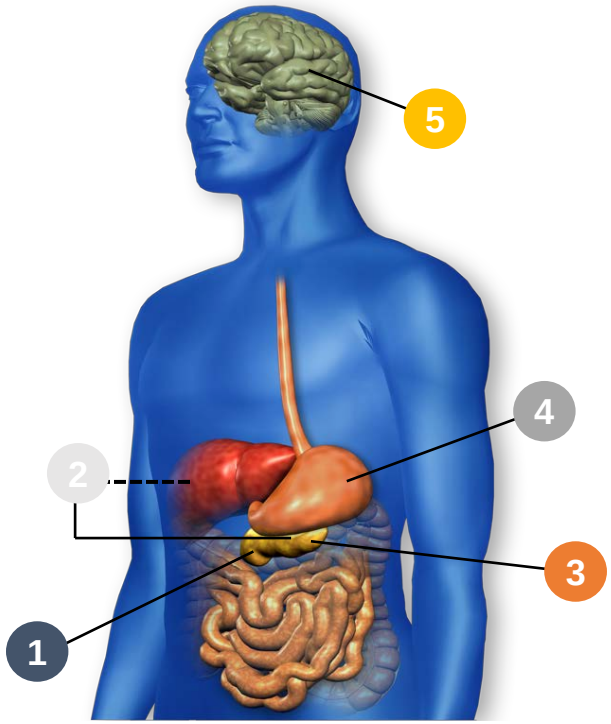
BACKGROUND: GLP-1R Agonism Addresses the Core Defects of T2D

Fasting state

1. Stimulates glucose-dependent insulin secretion[1]
2. Suppresses glucagon secretion, which decreases hepatic glucose production[2]

Fed state

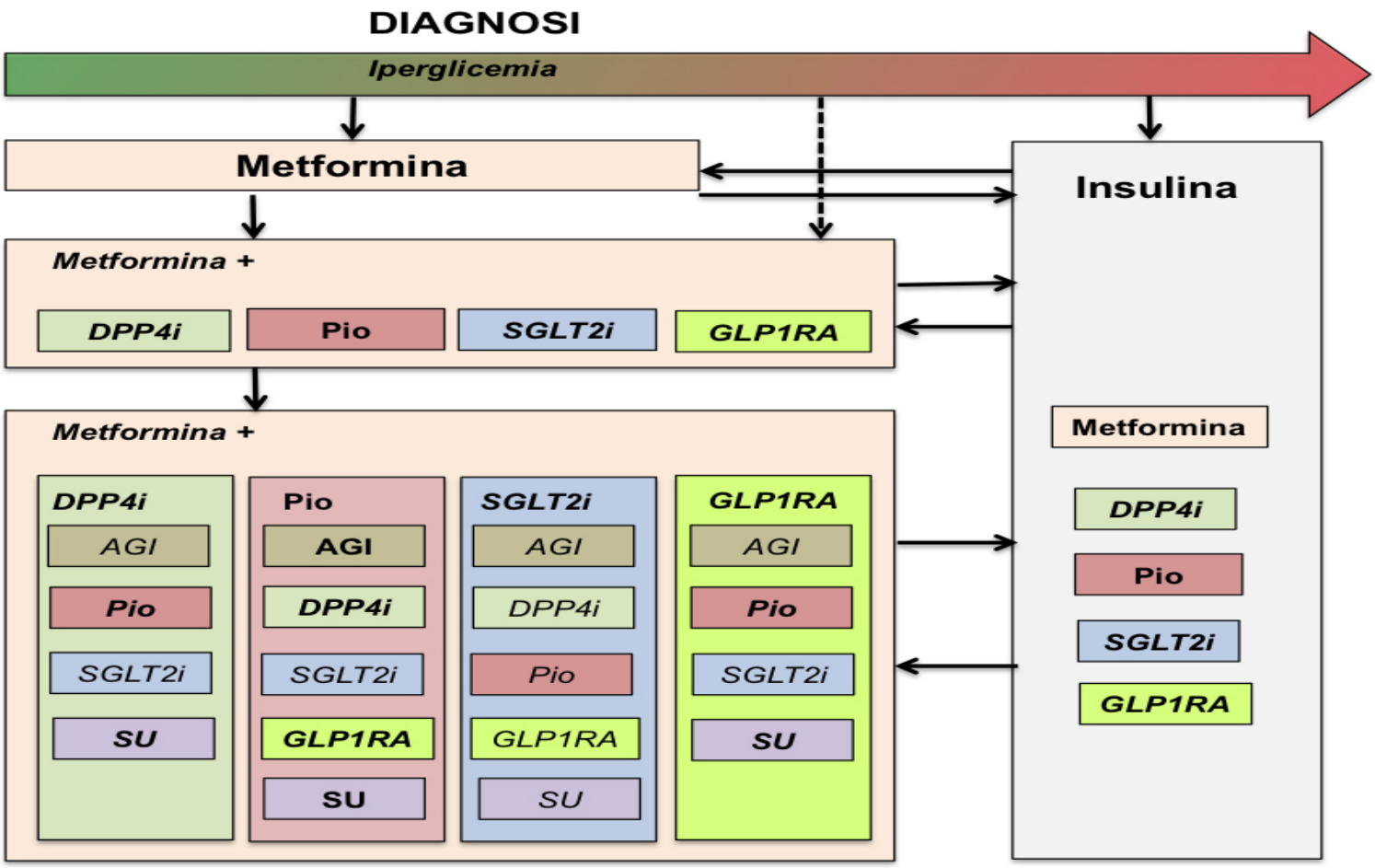
1. Stimulates glucose-dependent insulin secretion[1]
2. Suppresses postprandial glucagon secretion, which decreases hepatic glucose production[2]
3. Improves first-phase insulin response[3]
4. Slows gastric emptying[1]
5. Reduces food intake[4]



GLP-1R, glucagon-like peptide-1 receptor; T2DM, Type 2 diabetes mellitus

1. Drucker DJ. Diabetes 1998; Larsson H, et al. Acta Physiol Scand 1997; 3. Quddusi S, et al. Diabetes Care 2003; 4. Flint A, et al. J Clin Invest 1998.


STANDARD ITALIANI
PER LA CURA DEL
DIABETE MELLITO
2018


DIAGNOSI
Iperglicemia
Metformina
Insulina
Metformina +
DPP4i
Pio
SGLT2i
GLP1RA
Metformina +
DPP4i
AGI
Pio
SGLT2i
SU
Pio
AGI
DPP4i
SGLT2i
GLP1RA
SU
SGLT2i
AGI
DPP4i
Pio
GLP1RA
SU
GLP1RA
AGI
Pio
SGLT2i
SU
Metformina
DPP4i
Pio
SGLT2i
GLP1RA

ADA standards of care 2020

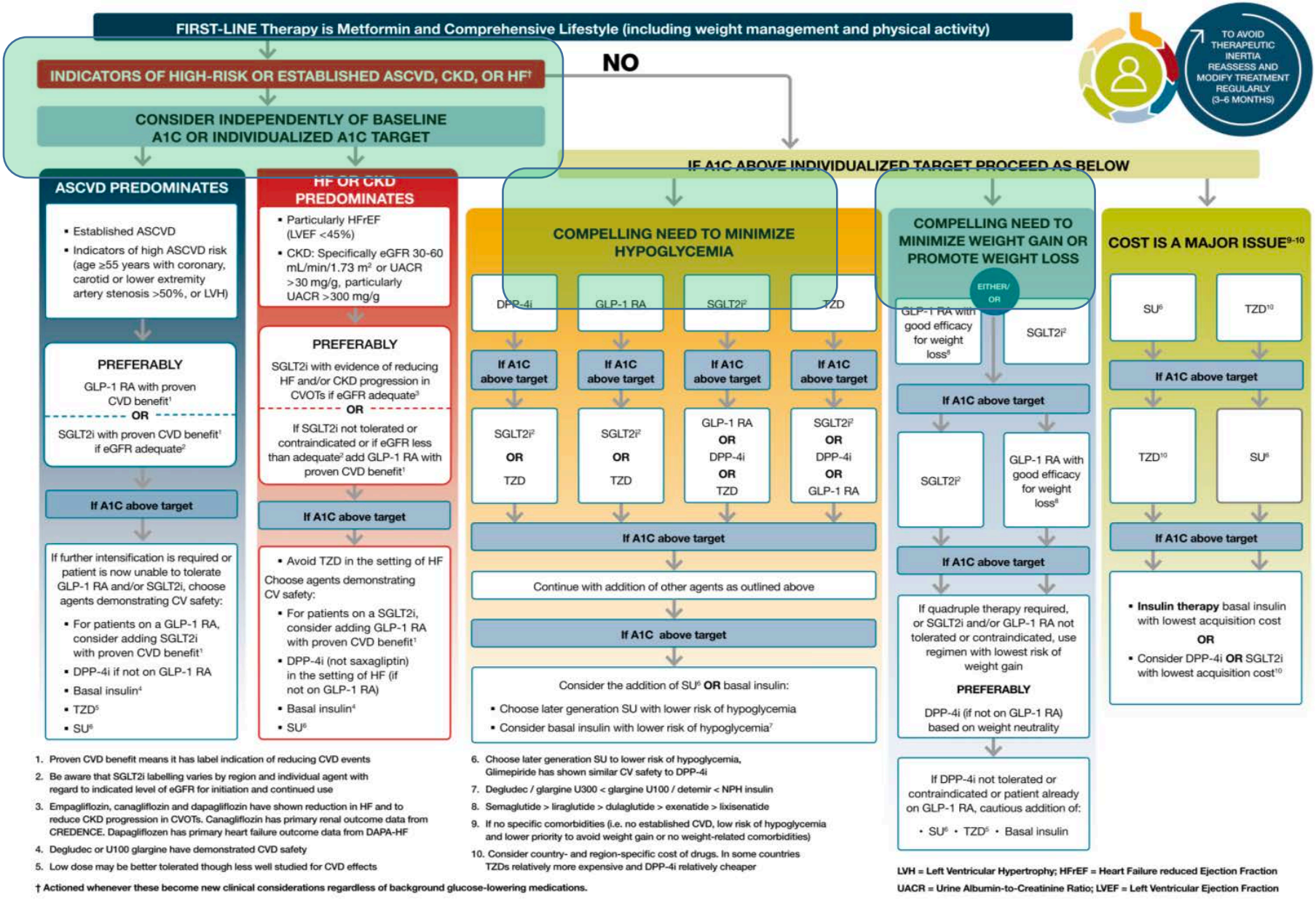


Figure 9.1—Glucose-lowering medication in type 2 diabetes: overall approach. For appropriate context, see **Fig. 4.1**. ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CVOTs, cardiovascular outcomes trials; DPP-4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; SGLT2i, sodium–glucose cotransporter 2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione. Adapted from Davies and colleagues (33,34).

Effetto Ipoglicemizzante

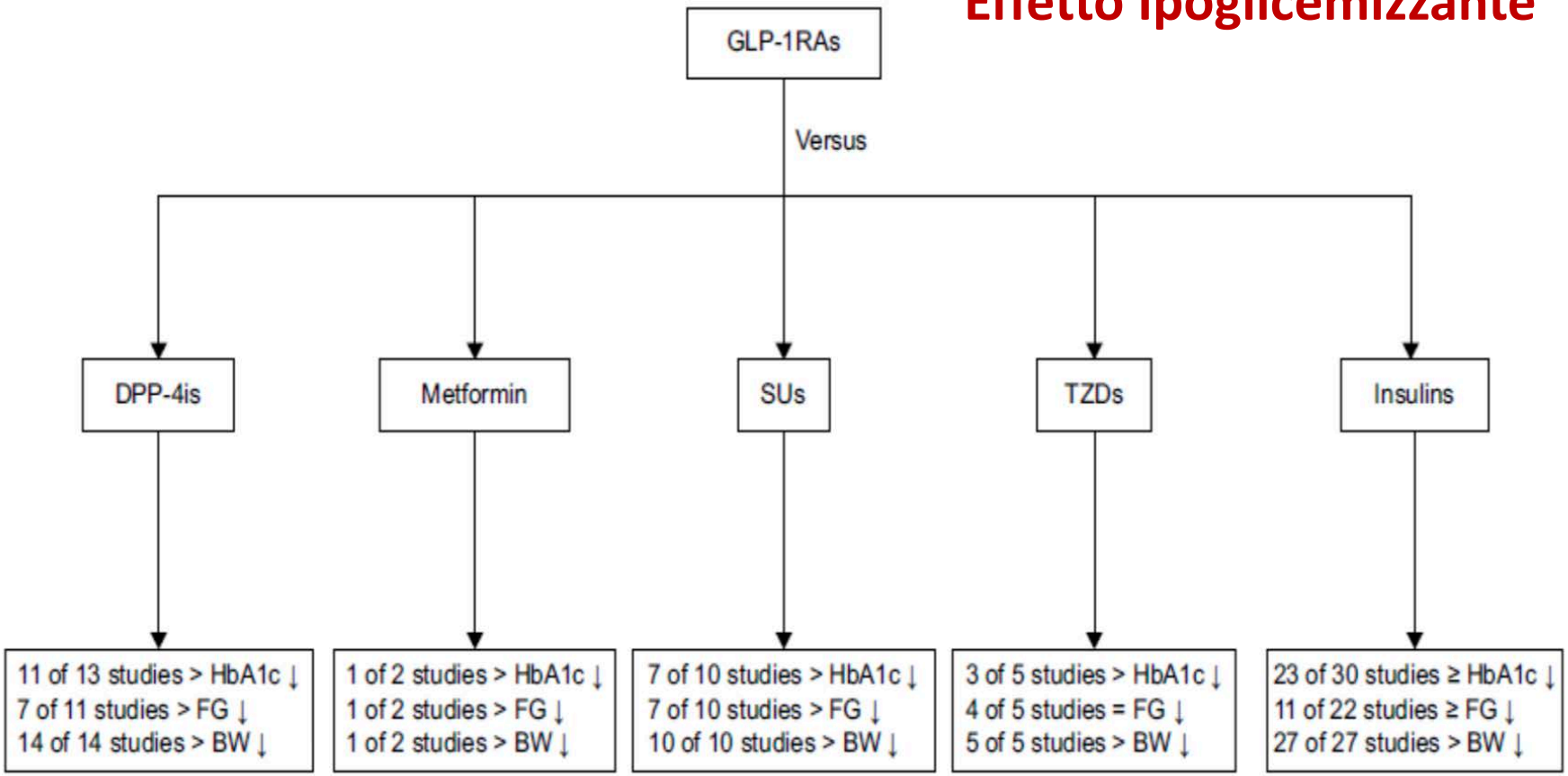
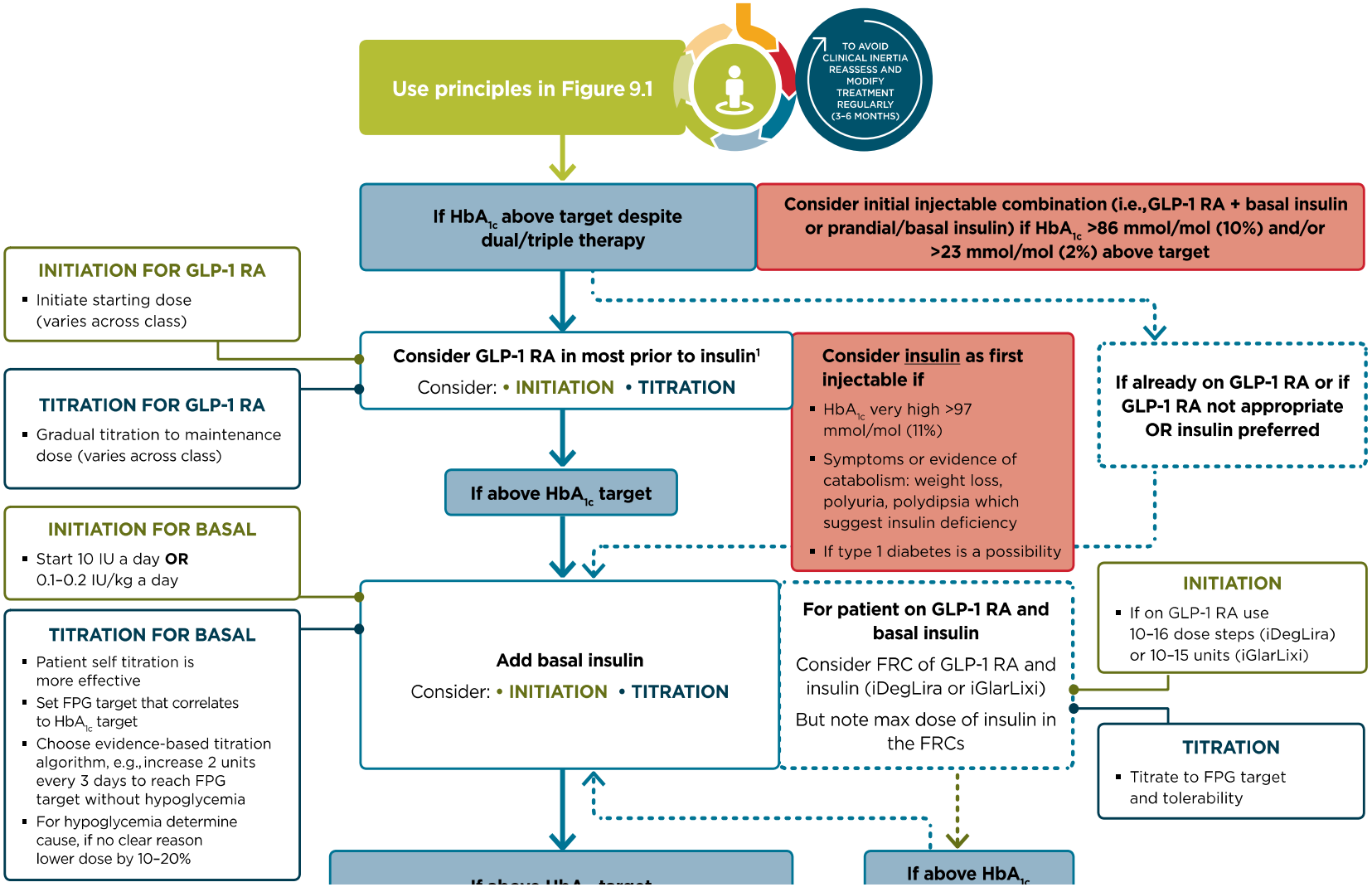


Figure 3 Comparison of efficacy of GLP-1RAs with other glucose-lowering treatments in type 2 diabetes. General trends in glycemic parameters and body weight (BW) in comparative trials of glucagon-like peptide-1 receptor agonists (GLP-1RAs) and other glucose-lowering therapies. The total number of studies includes studies that reported these parameters.

Abbreviations: DPP-4i, dipeptidyl peptidase-4 inhibitor; FG, fasting glucose; HbA1c, glycated hemoglobin; SU, sulfonylurea; TZD, thiazolidinedione.

da Russo G. AMD 2017

Standards of Medical Care in Diabetes—2020, Diabetes Care 43(Suppl. 1):S98–S110

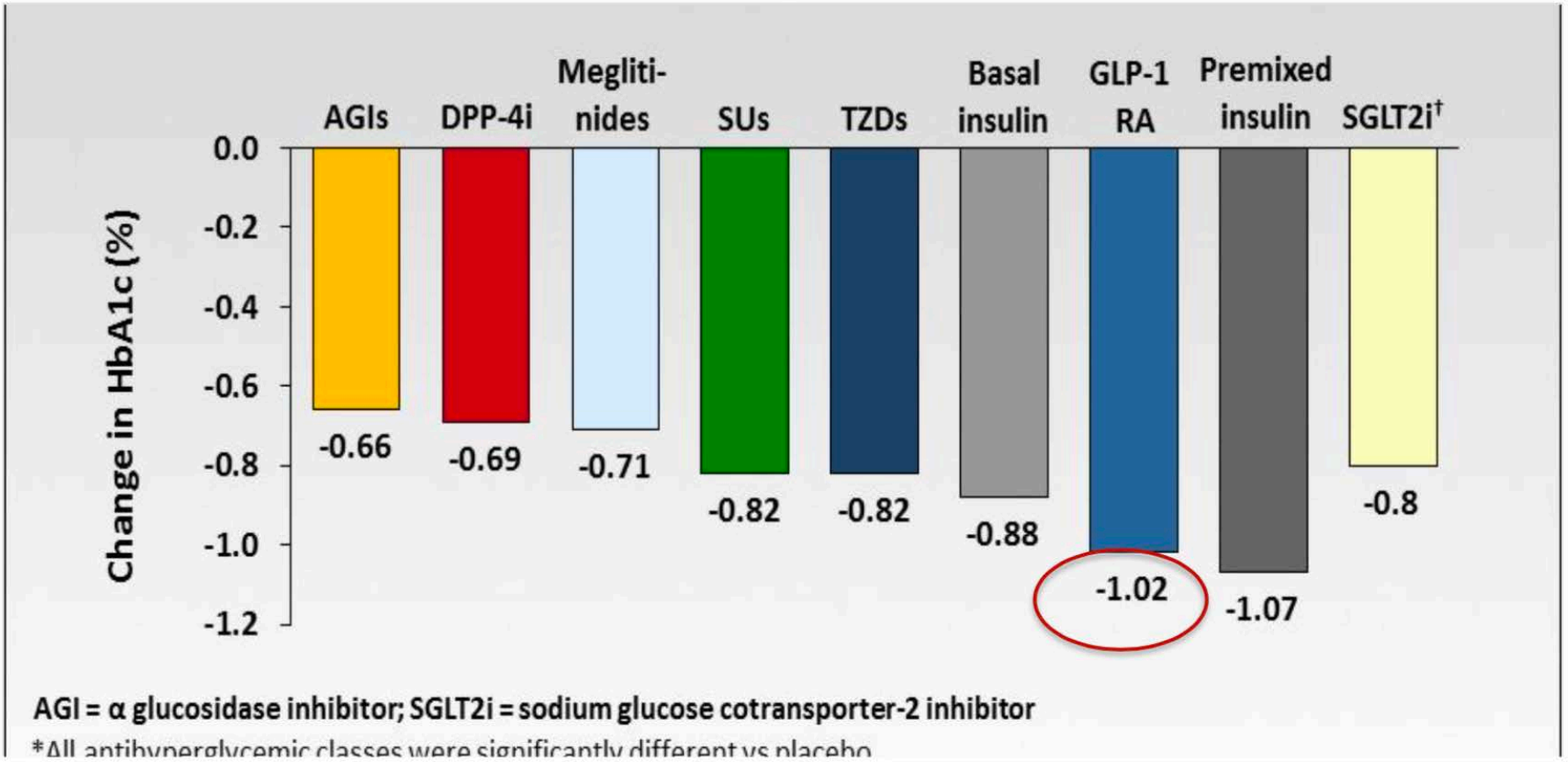


«Quando si è deciso di intensificare con un iniettivo, iniziare nella maggior parte dei casi con un GLP-1 RA invece che con la basale»

«L'insulina andrebbe considerata come primo iniettivo se HbA1c > 11% o in caso di sintomi di catabolismo»

Effetto Ipoglicemizzante

Network meta-analysis of pairwise comparisons of randomized controlled trials evaluating the use of anti-hyperglycemic agents in addition to metformin vs. placebo: mean change from baseline in A1C



da Russo G. AMD 2017

Liu S-C et al. Diabetes Obes and Metab 14: 810–820, 2012

[b] Fujita Y et al. J Diabetes Investing 5: 265-275, 2014

effetto sulla safety CV e renale
GLP-1 RA CVOTs

DIABETES RESEARCH AND CLINICAL PRACTICE 162 (2020) 108112

Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

ELSEVIER

International Diabetes Federation

Editorial

Invited review. Series: Implications of the recent CVOTs in type 2 diabetes
Which patients for GLP-1RA or SGLT-2 inhibitor?

*Angela Dardano, Roberto Miccoli, Cristina Bianchi, Giuseppe Daniele, Stefano Del Prato**

Table 2 – Cardiovascular outcomes in major trials with GLP-1 receptor agonists.

	ELIXA	LEADER	SUSTAIN-6	EXSCEL	HARMONY	REWIND	PIONEER-6
Drug tested	Lixisentide	Liraglutide	Semaglutide	Exenatide OW	Albiglutide	Dulaglutide	Oral Semaglutide
Subjects, n	6,068	9,340	3,297	14,752	9,463	9,901	3,183
Duration of follow-up	2.1 years	3.8 years	2.1 years	3.2 years	1.6 years	5.4 years	1.3 years
Baseline HbA1c, %	7.7	8.7	8.7	8.0	8.7	7.3	8.2
Cardiovascular risk, %	100	81.3	58.8	73.1	100	31.4	84.6
Main cardiovascular outcomes HR (95%CI)	Primary outcome 3P-MACE 1.02 (0.89–1.17) Non-inferior to placebo	Primary outcome 3P-MACE 0.87 (0.78–0.97) NNT = 53	Primary outcome 3P-MACE 0.74 (0.58–0.95) NNT = 44	Primary outcome 3P-MACE 0.91 (0.83–1.00) Non-inferior to placebo	Primary outcome 3P-MACE 0.78 (0.68–0.90) NNT = 50	Primary outcome 3P-MACE 0·88 (0·79–0·99) NNT = 72	Primary outcome 3P-MACE 0.79 (0.57–1.11) Non-inferior to placebo
Composite renal outcome measure including macroalbuminuriaHR (95%CI)	0.84 (0.68–1.02) –	0.78 (0.67–0.92) NNT = 67	0.64 (0.46–0.88) NNT = 44	0.88 (0.76–1.01) –	Not reported	0.85 (0.77–0.93) NNT = 38	Not reported

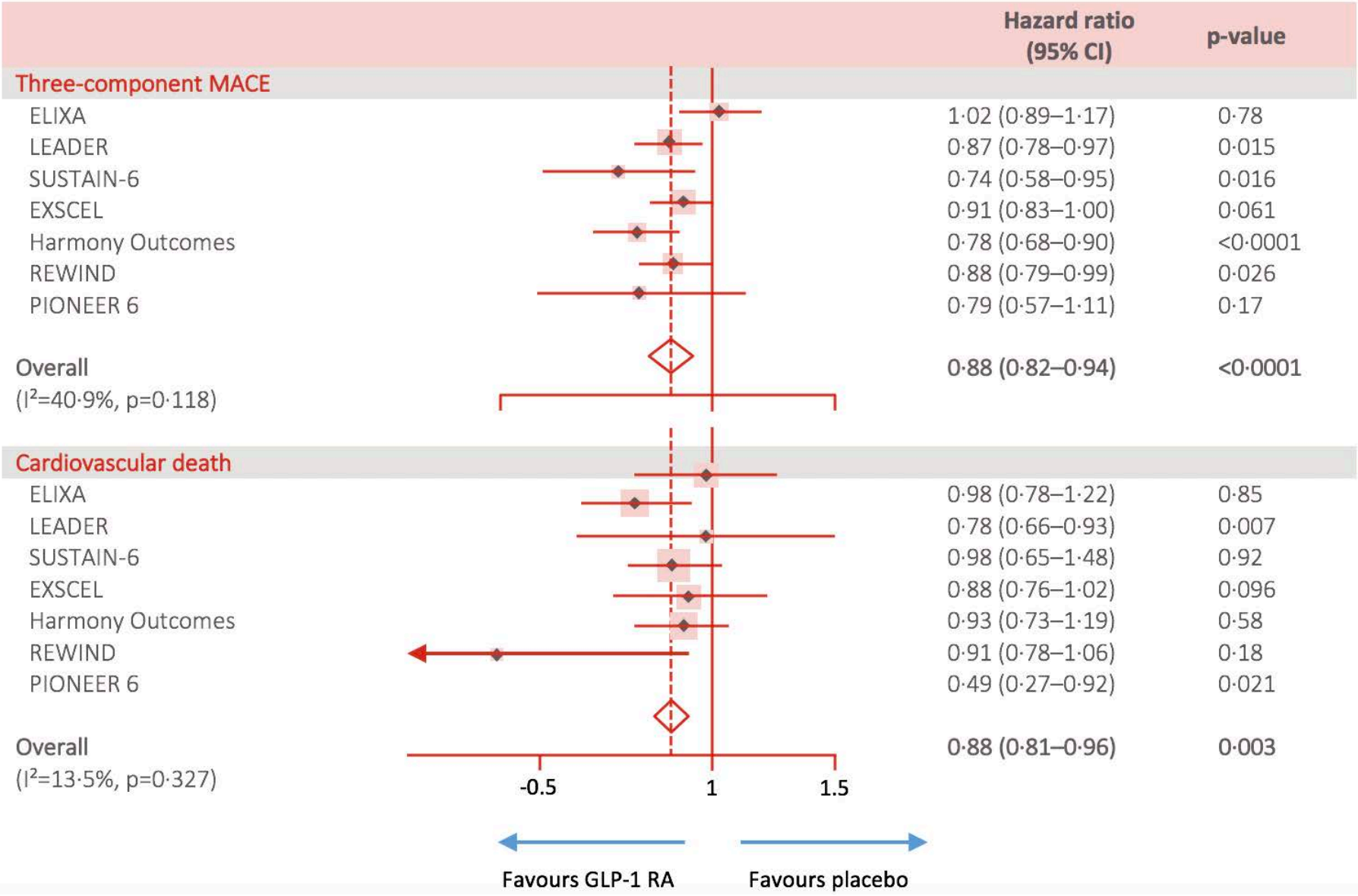
3P- MACE: 3-point major adverse cardiovascular events; NNT: number needed to treat.

Baseline characteristics across GLP-1 RA CVOTs

	ELIXA n=6068	LEADER n=9340	SUSTAIN 6 n=3297	EXSCEL n=14752	Harmony Outcomes n=9463	REWIND n=9901	PIONEER 6 n=3183
Drug	Lixi senatide	Lira glutide	Sema glutide	Exenatide	Albi glutide	Dula glutide	Sema glutide (oral)
Age (years)	60	64	65	62	64	66	66
Sex (%) - Men - Women	 69% 31%	 64% 36%	 61% 39%	 62% 38%	 69% 31%	 54% 46%	 68% 32%
BMI (kg/m^2)	30.1	32.5	32.8	32.7	32.3	32.3	32.3
Diabetes duration (years)	9.2	12.8	13.9	13.1	14.2	10.6	14.9
HbA_{1c} (%)	7.7	8.7	8.7	8.1	8.7	7.3	8.2
Established CVD (%)	100	81	83	73	100	31	85
History of HF (%)	22	18	24	16	20	9	12
Systolic blood pressure (mm Hg)	129	136	136	135	135	137	136
eGFR (mL/min per 1.73 m^2)	78	80	80	77	79	75	74

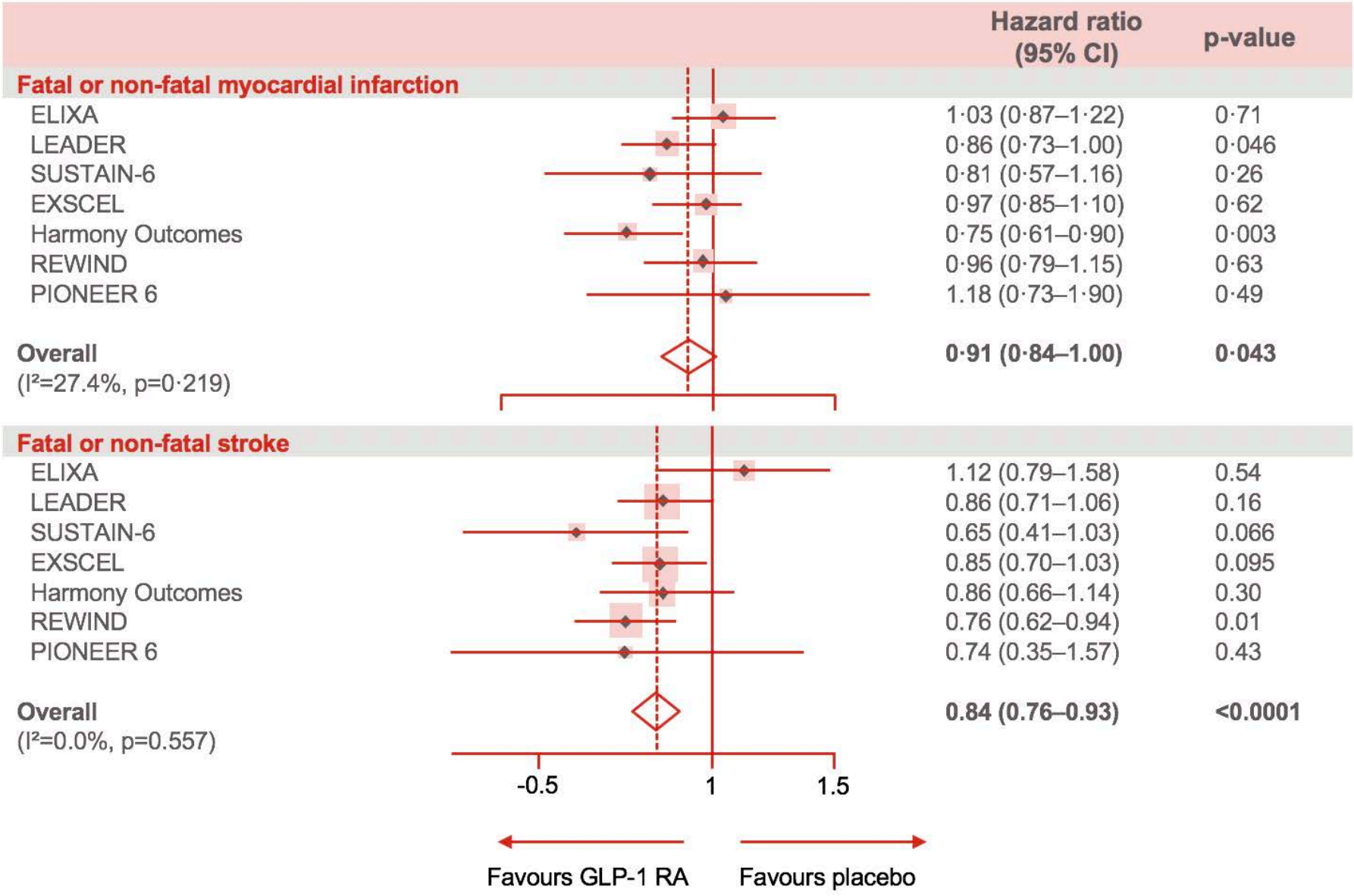
GLP-1 RA = glucagon-like peptide-1 receptor agonist; CVOT = cardiovascular outcomes trial; BMI = body mass index; CVD = cardiovascular disease; HF = heart failure.

Kristensen S et al. *Lancet Diabetes Endocrinol* 2019;7(10):776-785.



MACE = major adverse cardiovascular event; CV = cardiovascular; GLP-1 RA = glucagon-like peptide-1 receptor agonist; CI = confidence interval.

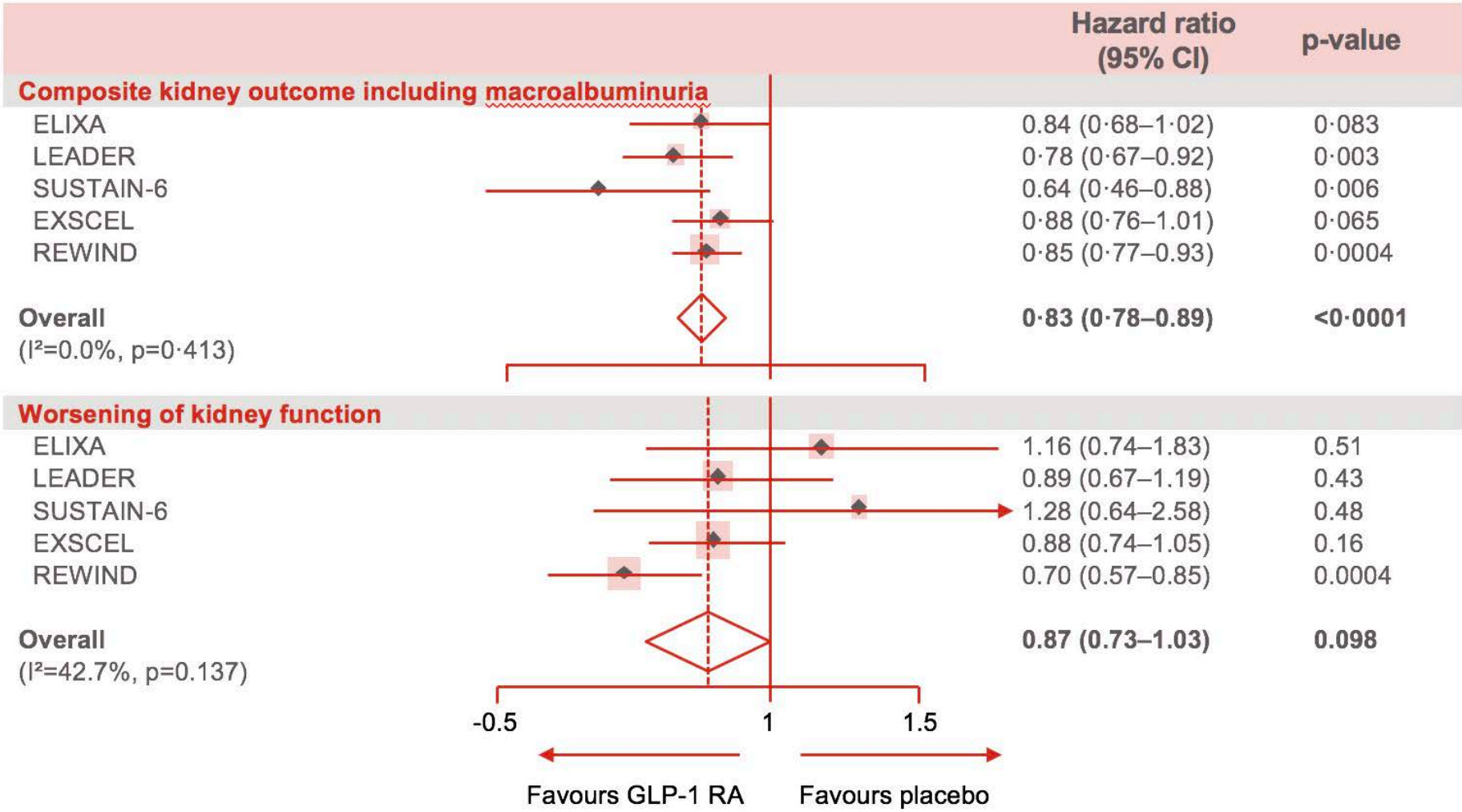
Kristensen S et al. *Lancet Diabetes Endocrinol* 2019;7(10):776-785.



MI = myocardial infarction; CV = cardiovascular; GLP-1 RA = glucagon-like peptide-1 receptor agonist; CI = confidence interval.

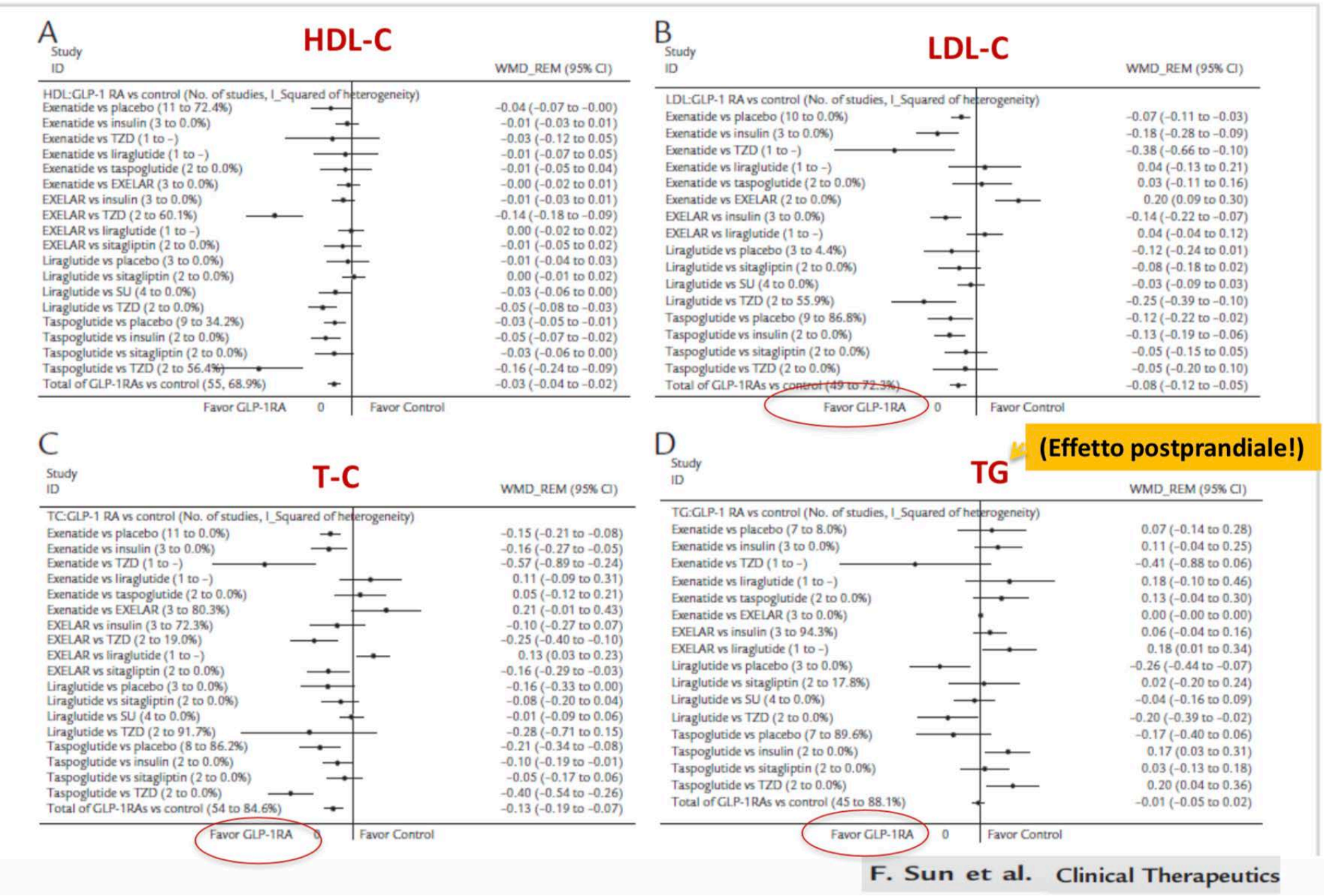
Kristensen S et al. *Lancet Diabetes Endocrinol* 2019;7(10):776-785.

GLP-1 RA - CKD



MACE = major adverse cardiovascular event; CV = cardiovascular; GLP-1 RA = glucagon-like peptide-1 receptor agonist; CI = confidence interval.

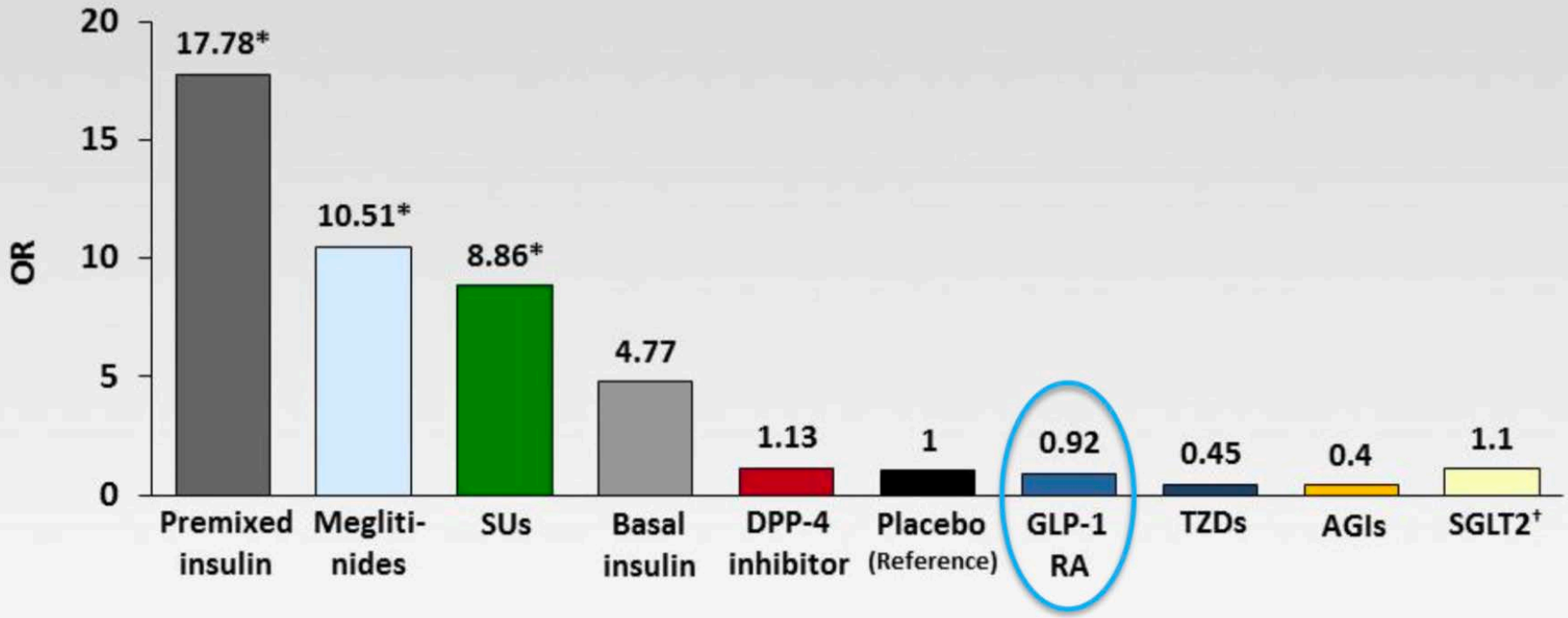
Kristensen S et al. *Lancet Diabetes Endocrinol* 2019;7(10):776-785.



da Russo G. AMD 2017

-Effetto sul rischio di ipoglicemie

Network meta-analysis of pairwise comparisons of randomized controlled trials evaluating the use of anti-hyperglycemic agents in addition to metformin vs. placebo: At least one event of overall hypoglycaemia (odds ratio)



*Statistically significant vs placebo.

†An estimate of hypoglycemia risk; SGLT2 inhibitors were not included in the network meta-analysis.[b]

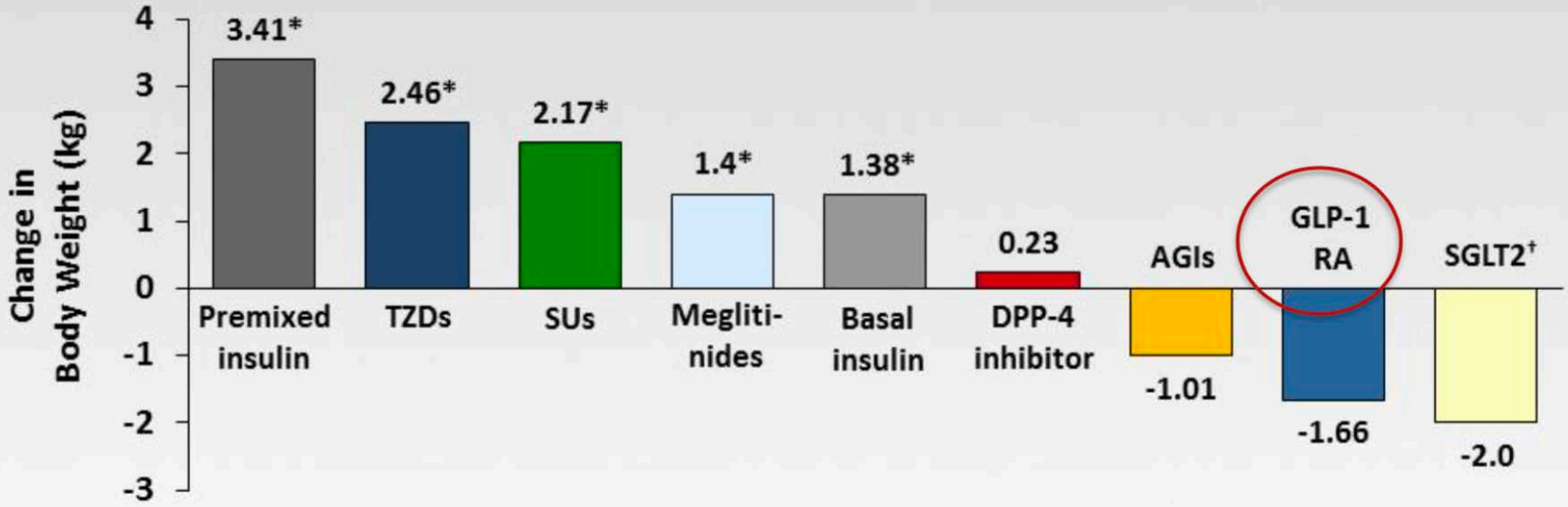
da Russo G. AMD 2017

Liu S-C et al. Diabetes Obes and Metab 14: 810–820, 2012

[b] Fujita Y et al. J Diabetes Investing 5: 265-275, 2014

Effetto anoressizzante

Network meta-analysis of pairwise comparisons of randomized controlled trials evaluating the use of anti-hyperglycemic agents in addition to metformin vs. placebo: Mean change from baseline in body weight



*Statistically significant vs placebo.

†An estimate of weight loss; SGLT2 inhibitors were not included in the network meta-analysis.[b]

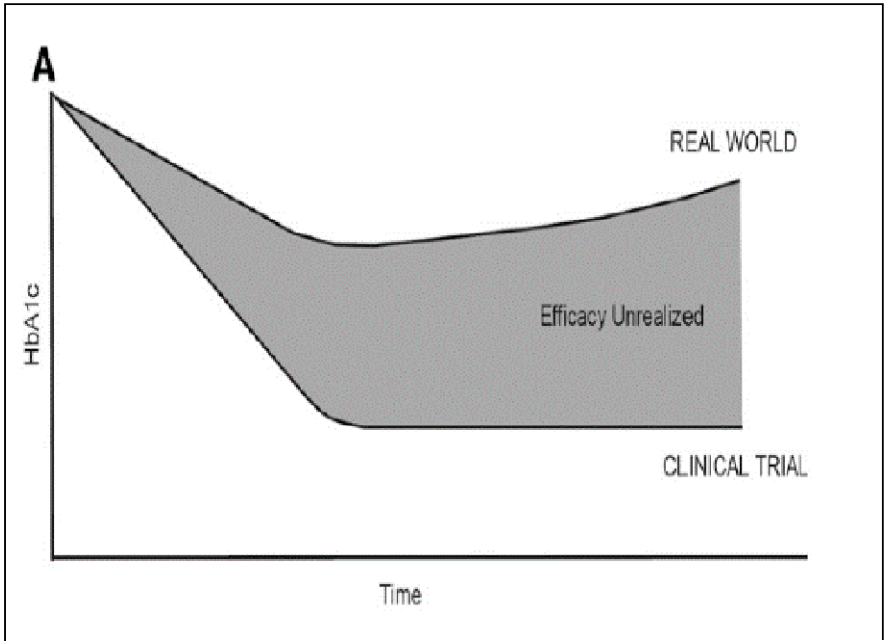
da Russo G. AMD 2017

Liu S-C et al. Diabetes Obes and Metab 14: 810–820, 2012

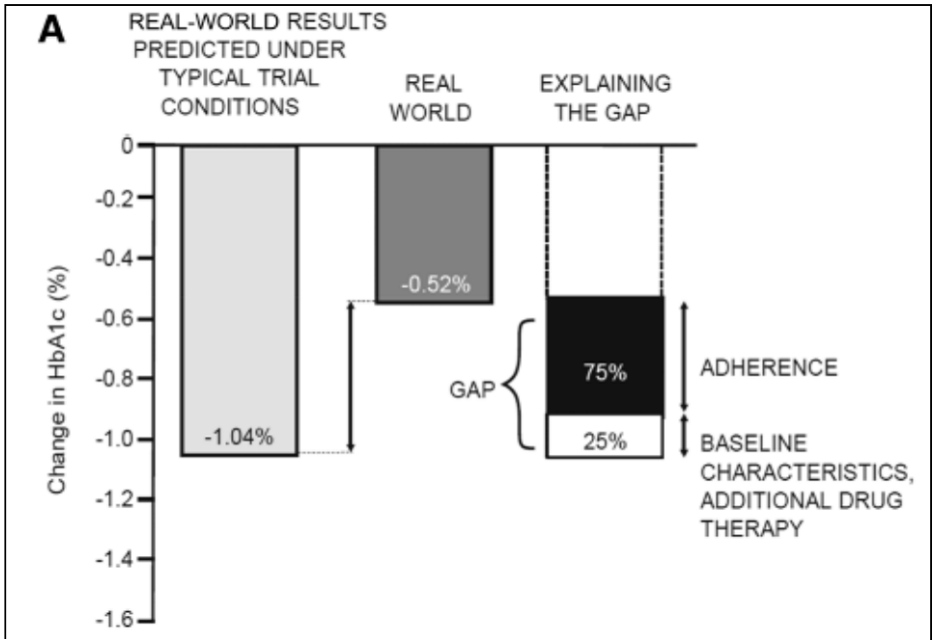
[b] Fujita Y et al. J Diabetes Investing 5: 265-275, 2014

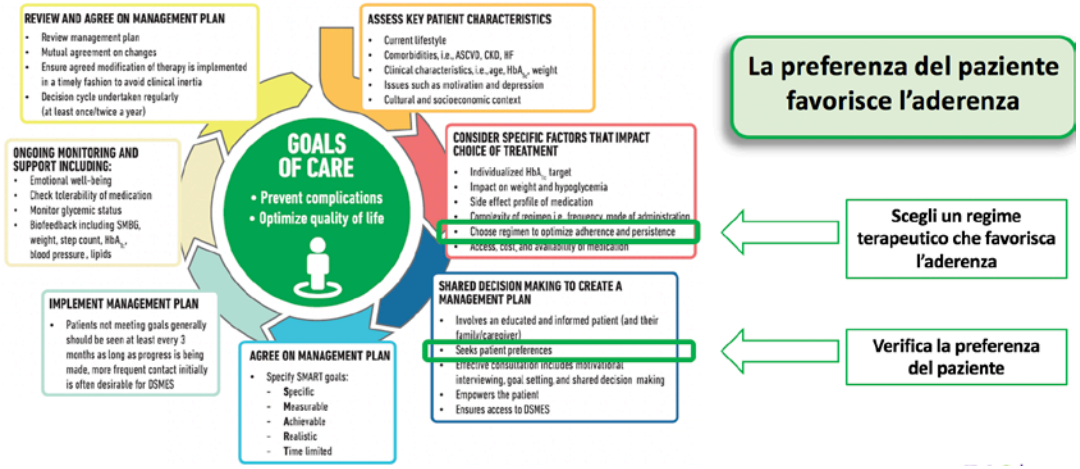
ADERENZA/PERSISTENZA: tolleranza e manegevolezza

Riduzione di HbA1c promessa nei trial clinici non realizzata nel Real World



La scarsa aderenza è la maggiore causa del GAP di efficacia sulla HbA1c tra trial clinici e Real World





La preferenza del paziente favorisce l'aderenza

Scegli un regime terapeutico che favorisca l'aderenza

Verifica la preferenza del paziente

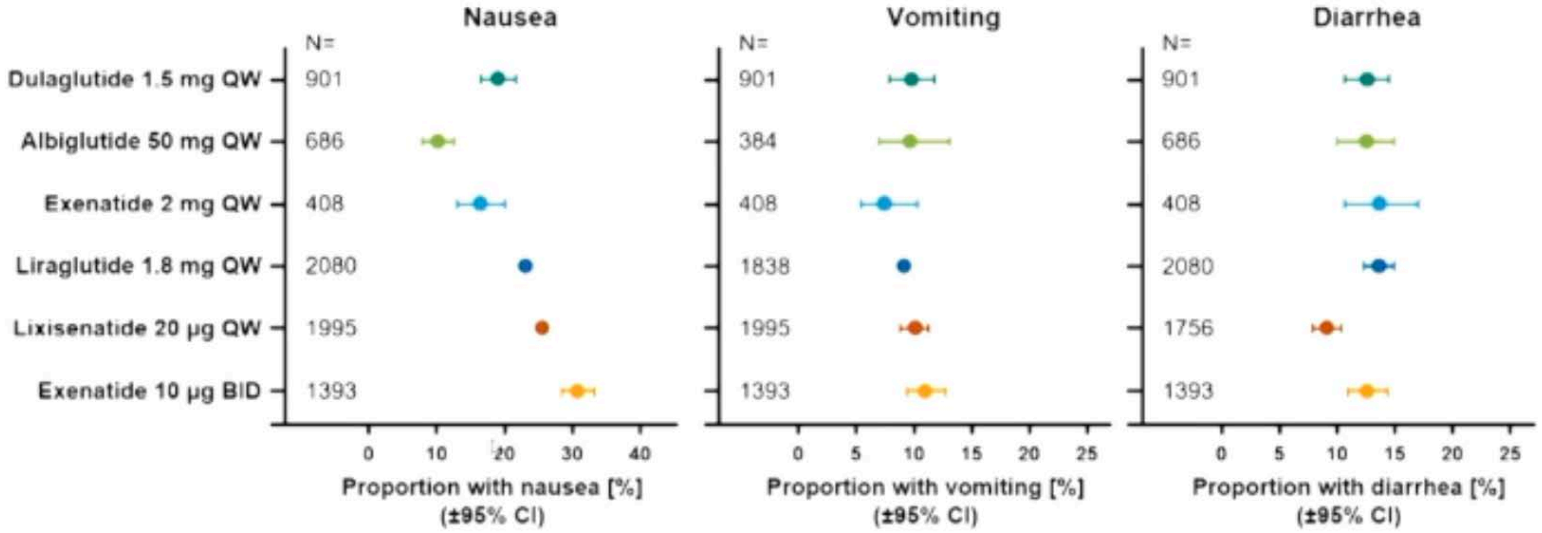
American Diabetes Association. EASD European Association for the Study of Diabetes

Inzucchi et al. diabetes care 2019

ADERENZA/PERSISTENZA: Tolleranza e manegevolezza

	GLP-1 receptor agonists								GLP-1 receptor agonist/ basal insulin fixed-dose combinations	
Pen devices for injection										
Drug name: Generic Commercial	Exenatide b.i.d. Byetta®	Lixisenatide Lyxumia®	Liraglutide Victoza®	Exenatide once weekly, Bydureon® (original)	Bydureon® BCise (improved)	Dulalgutide Trulicity®	Albiglutide Eperzan®, Tanzeum®	Semaglutide Ozempic®	IdegLira Xultophy®	iGlarLixi Soliqua®
Pen for single or multiple use?	multiple	multiple	multiple	single	single	single	single	multiple	multiple	multiple
Pen for pre-determined single dose/ variable dosing	single	single	variable (0.6, 1.2, or 1.8 mg)	single	single	single	single	single	variable, for titration	variable, for titration
Pen devices available (maximum dose)	5 or 10 µg	10 or 20 µg	1.8 mg	2 mg	2 mg	0.75 or 1.5 mg	30 or 50 mg	0.25, 0.5 or 1.0 mg	Up to 1.8 mg (plus insulin *degludec* up to 50 IU)	Up to 20 µg (plus insulin *glargine* up to 60 IU)
Resuspension before injection necessary?	no	no	no	yes	No, but thorrough mixing	no	yes	no	no	no

Nauck & Maier Eur J Endocrinol 2019



BID, twice daily; CI, confidence interval; GI, gastrointestinal; GLP-1 RA, glucagon-like peptide-1 receptor agonist; QW, once weekly

Bettege K, et al. *Diabetes Obes Metab*. 2017;19:336–47

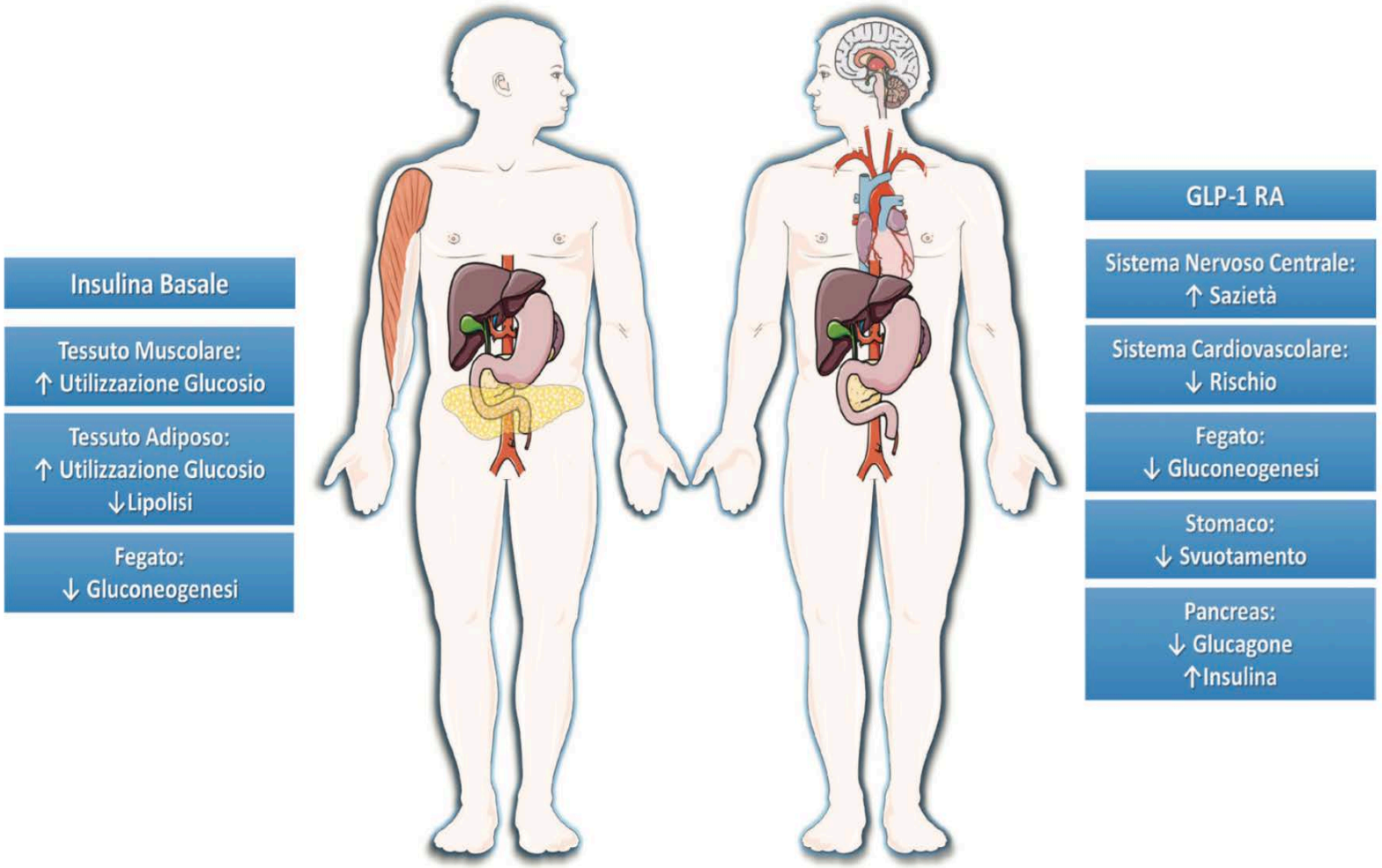
from Giorgino F. for Lilly Academy 2019

GI, gastrointestinal

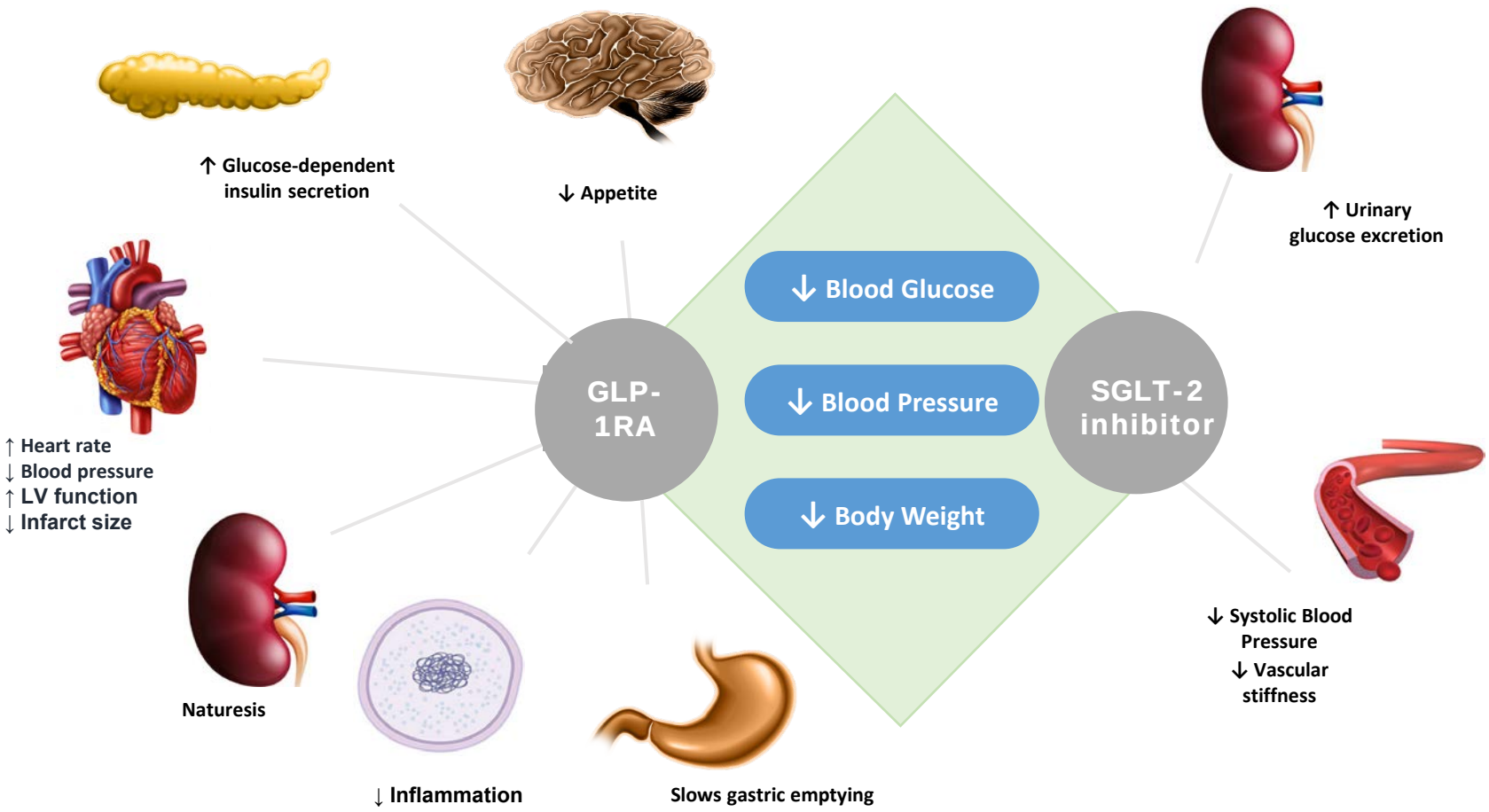
Reid TS. *Clin Diabetes*. 2013;31(4):148–57

Associazioni: iDegLira / iGlarLixi

Use of fixed dose GLP-1 RA+basal insulin combination appears therefore an excellent strategy of basal insulin intensification.



Associazioni: GLP1 RA and SGLT-2 Inhibitors



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

ALTRI TARGET

Farmaci per il trattamento del diabete e possibile effetto sulla fertilità maschile

Farmaco antidiabetico	Possibili effetti sulla fertilità (Si/No/Non Valutato - nv)
Inibitori dell'alfa glucosidasi (Acarbosio)	Nv
Biguanidi (Metformina)	Si
Inibitori del DPP-IV	Si
Glinidi (Repaglinide)	Si
Agonisti del GLP-1	Si
Insuline	Si
Inibitori del SGLT-2	Si/nv
Tiazolidinedioni (Pioglitazone)	Si
Sulfoniluree	Si

Defeudis G et al. Percorso terapeutico della coppia infertile, ed. 2019

Esposito K, Defeudis G et al, Consensus SID-SIE-SIAMS Complicanze andrologiche del diabete 2020_under construction

Fertilità maschile e analoghi GLP-1

- **Due trial in vivo su topi con exenatide**: rispetto al gruppo controllo →aumento della motilità spermatica → ridotta espressione delle citochine infiammatorie → diminuizione dei livelli circolanti di gonadotropine e rispettivamente stabilità o aumento dei valori di testosterone circolante

  (Tavares et al. 2019; Ahangarpour et al. 2014; Zhang et al. 2015).

- **Case report**: uomo di 35 anni trattato con liraglutide per 5 mesi: alterazione spermatogenesi e riduzione dei livelli di testosterone circolante.

  (Fontoura et al. 2014).

- Ad oggi l'EMA osservando i recenti trials sulla lixisenatide (clinical Study TDR11215) riferisce l'assenza di effetti significativi sulla spermatogenesi nell'uomo, dopo utilizzo al dosaggio attualmente indicato nel trattamento per il diabete (EMA. Europa).

Disfunzione erettile, ipogonadismo e GLP-1 RA

- **Studio in vivo su ratti**: ruolo protettivo della liraglutide sull'endotelio dei corpi cavernosi con il conseguente miglioramento della funzionalità erettile

(Yue et al. 2016)

- **Studio osservazionale retrospettivo**: effetto della liraglutide in soggetti obesi, con diabete tipo 2 ed ipogonadici, già in trattamento con metformina e con terapia sostitutiva con testosterone. Il gruppo con la liraglutide ha presentato maggiori benefici sulla funzionalità erettile, oltre che con l'incremento dei valori di testosterone.

(Giagulli et al. 2015)

CONCLUSIONI

	Metformina	Acarbose	GLP1RA	Gliflozine	Gliptine	Pioglitazone	SU/glinidi	Insulina basale	Insulina ba-sal-bolus
Riduzione HbA1c a breve termine (3-4 mesi)*	+++	+	+++	++	++	+	+++	+++	++++
Riduzione HbA1c a medio termine (1-2 anni)*	++	+	+++	++	++	++	++	+++	++++
Riduzione HbA1c a lungo termine (oltre 2 anni)*	++	+	+++	++	ND	+++	+	+++	++++
Riduzione peso corporeo	+/-	+/-	+++	++	-	-	-	-	-
Riduzione pressione arte-riosa	+/-	-	+	++	-	+	-	-	-
Riduzione morbilità e mor-talità cardiovascolare**	+/-	+/-	++[a]	+++[b]	-	++	-	-	-

* Derivata da studi di comparazione diretta con altri farmaci attivi. ** A parità di obiettivo glicemico perseguito. [a] Per liraglutide e semaglutide. [b] Per empagliflozin; per canagliflozin limitatamente alla morbilità. ND: dato non disponibile.

American Diabetes Association. Diabetes Care 2020 Jan;

	Efficacy	Hypoglycemia	Weight change	CV effects		Cost	Oral/SQ	Renal effects		Additional considerations
				ASCVD	HF			Progression of DKD	Dosing/use considerations*	
Metformin	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Low	Oral	Neutral	▪ Contraindicated with eGFR <30 mL/min/1.73 m²	▪ Gastrointestinal side effects common (diarrhea, nausea) ▪ Potential for B12 deficiency
SGLT-2 inhibitors	Intermediate	No	Loss	Benefit: empagliflozin†, canagliflozin	Benefit: empagliflozin†, canagliflozin, dapagliflozin‡	High	Oral	Benefit: canagliflozin§, empagliflozin, dapagliflozin	▪ Renal dose adjustment required (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin)	▪ **FDA Black Box:** Risk of amputation (**canagliflozin**) ▪ Risk of bone fractures (canagliflozin) ▪ DKA risk (all agents, rare in T2DM) ▪ Genitourinary infections ▪ Risk of volume depletion, hypotension ▪ ↑LDL cholesterol ▪ Risk of Fournier's gangrene
GLP-1 RAs	High	No	Loss	Neutral: lixisenatide Benefit: See label indication of reducing CVD events	Neutral	High	SQ; oral (semaglutide)	Benefit: liraglutide	▪ Renal dose adjustment required (exenatide, lixisenatide) ▪ Caution when initiating or increasing dose due to potential risk of acute kidney injury	▪ **FDA Black Box:** Risk of thyroid C-cell tumors (**liraglutide, albiglutide, dulaglutide, exenatide extended release**) ▪ Gastrointestinal side effects common (nausea, vomiting, diarrhea) ▪ Injection site reactions ▪ ?Acute pancreatitis risk
DPP-4 inhibitors	Intermediate	No	Neutral	Neutral	Potential risk: saxagliptin	High	Oral	Neutral	▪ Renal dose adjustment required (sitagliptin, saxagliptin, alogliptin); can be used in renal impairment ▪ No dose adjustment required for linagliptin	▪ Potential risk of acute pancreatitis ▪ Joint pain
Thiazolidinediones	High	No	Gain	Potential benefit: pioglitazone	Increased risk	Low	Oral	Neutral	▪ No dose adjustment required ▪ Generally not recommended in renal impairment due to potential for fluid retention	▪ **FDA Black Box:** Congestive heart failure (**pioglitazone, rosiglitazone**) ▪ Fluid retention (edema; heart failure) ▪ Benefit in NASH ▪ Risk of bone fractures ▪ Bladder cancer (pioglitazone) ▪ ↑LDL cholesterol (rosiglitazone)
Sulfonylureas (2nd generation)	High	Yes	Gain	Neutral	Neutral	Low	Oral	Neutral	▪ Glyburide: not recommended ▪ Glipizide and glimepiride: initiate conservatively to avoid hypoglycemia	▪ FDA Special Warning on increased risk of cardiovascular mortality based on studies of an older sulfonylurea (tolbutamide)
Insulin — Human insulin	Highest	Yes	Gain	Neutral	Neutral	Low	SQ; inhaled	Neutral	▪ Lower insulin doses required with a decrease in eGFR; titrate per clinical response	▪ Injection site reactions ▪ Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
Insulin — Analogs						High	SQ			

GLP-1 RAs	High	No	Loss	Neutral: lixisenatide Benefit: See label indication of reducing CVD events	Neutral	High	SQ; oral (semaglutide)	Benefit: liraglutide	▪ Renal dose adjustment required (exenatide, lixisenatide) ▪ Caution when initiating or increasing dose due to potential risk of acute kidney injury	▪ **FDA Black Box:** Risk of thyroid C-cell tumors (**liraglutide, albiglutide, dulaglutide, exenatide extended release**) ▪ Gastrointestinal side effects common (nausea, vomiting, diarrhea) ▪ Injection site reactions ▪ ?Acute pancreatitis risk

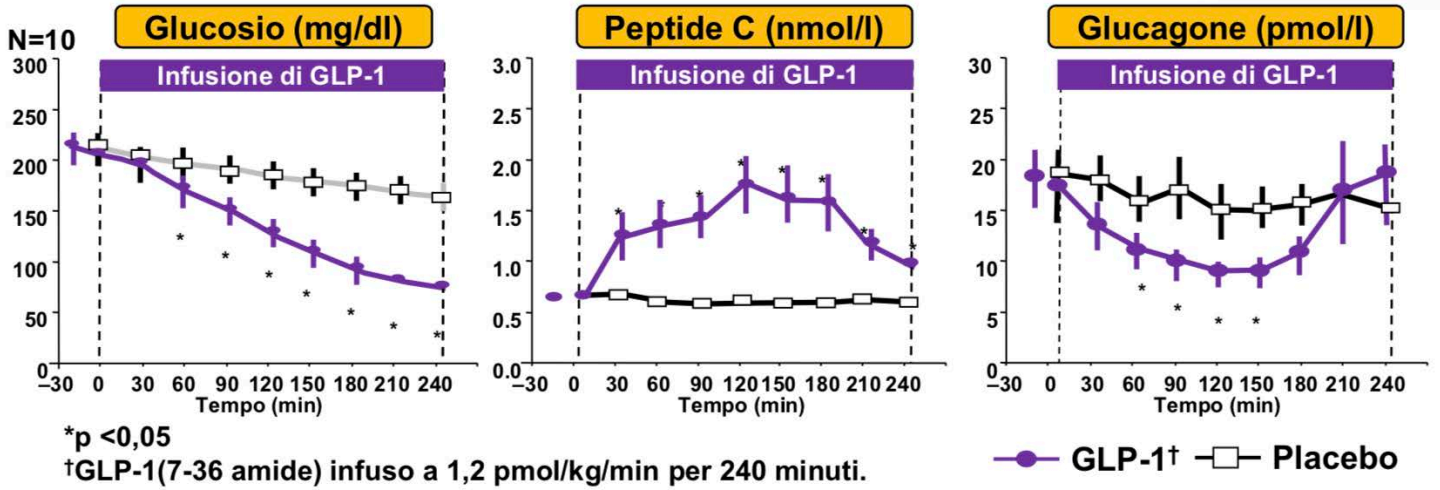
	GLP-1 Receptor Agonists
Pros	• Valuable efficacy profile • Weight loss • Blood pressure reduction • Negligible/low risk of hypoglycaemia • Cardiovascular protection • Renal protection (proven in LEADER trial) • Generally well tolerated • No increased risk for pancreatitis, pancreatic cancer or bone disease
Cons	• Less HbA1c lowering with short-acting agents • Gastrointestinal effects • Injectable therapy • Contraindicated in personal/family history of medullary thyroid cancer or MEN2 • Higher rate of worsening retinopathy (SUSTAIN-6) • Increased risk of bile duct and gallbladder disease • Not recommended or contraindicated in moderate to severe chronic kidney disease (exenatide and lixisenatide) • Cost

American Diabetes Association. Diabetes Care 2020 Jan

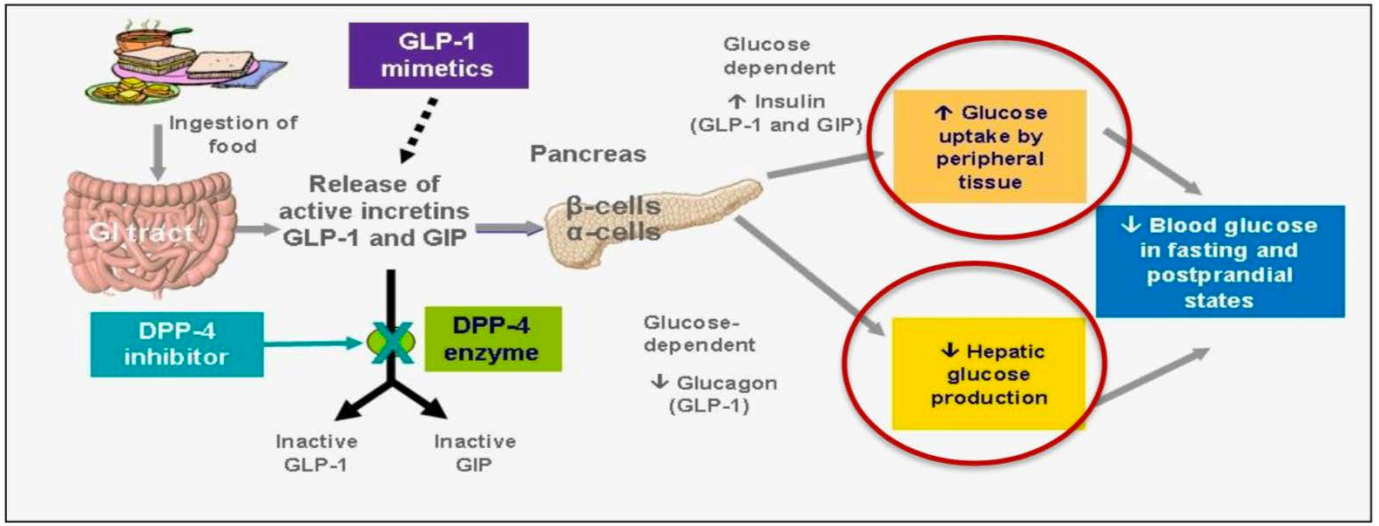
GRAZIE!

Giuseppe Defeudis MD, PhD
g.defeudis@unicampus.it

Unità di Endocrinologia e Malattie del Metabolismo, Dip. di Medicina
Università Campus Bio-Medico di Roma



Nauck MA et al. Diabetologia 1993;36:741



Drucker DJ. Cell Metab 2006; 3:153-65

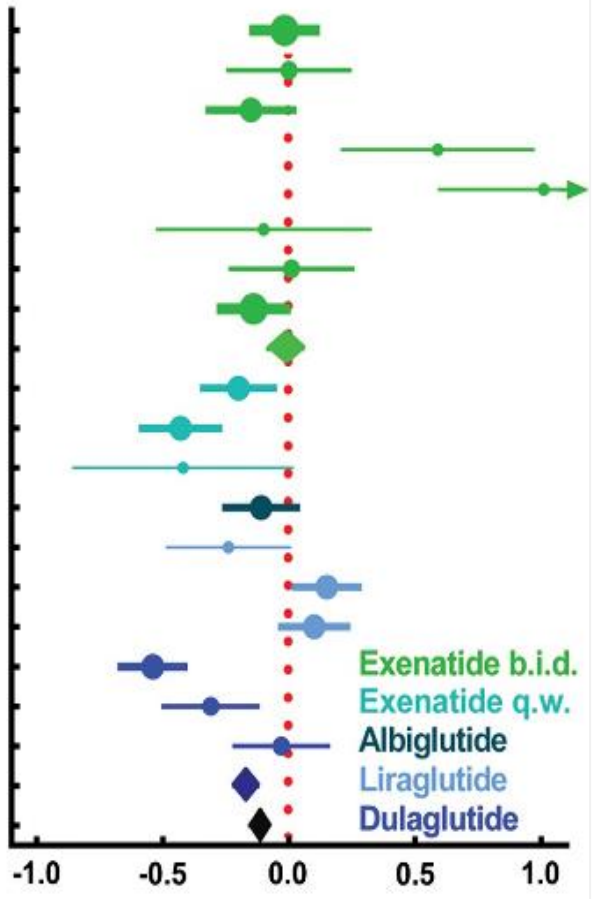
da RUSSO G. AMD 2017

… hanno impatto favorevole sul peso mentre l'insulina basale è generalmente accompagnata da aumento di peso e …

… sono associati ad un rischio più basso di ipoglicemie

A **GLP-1 RA versus insulin treatment (OGLM background)**

Study	Duration of action	Difference in means	Lower Limit	Upper Limit	Z-value	p-value
Heine et al. 2005 [44]	short	-0.02	-0.16	0.12	-0.24	0.81
Barnett et al. 2007 [33]	short	0.00	-0.25	0.25	0.00	1.00
Nauck et al. 2007 [47]	short	-0.15	-0.33	0.03	-1.63	0.10
Bergenstal et al. 2009 a [34]	short	0.59	0.21	0.97	3.02	0.0026
Bergenstal et al. 2009 b [34]	short	1.01	0.59	1.43	4.72	< 0.0001
Bunck et al. 2009 [35]	short	-0.10	-0.53	0.33	-0.46	0.65
Davies et al. 2009 [38]	short	0.01	-0.24	0.26	0.08	0.94
Gallwitz et al. 2011 [41]	short	-0.14	-0.29	0.01	-1.87	0.061
All short-acting GLP-1 RAs		**-0.02**	**-0.09**	**0.06**	**-0.39**	**0.70**
Diamant et al. 2010 [40]	long	-0.20	-0.35	-0.05	-2.57	0.010
Inagaki et al. 2012 [45]	long	-0.43	-0.60	-0.26	-5.08	< 0.0001
Davies et al. 2013 [37]	long	-0.42	-0.86	0.02	-1.87	0.061
Weissman et al. 2014 [50]	long	-0.11	-0.27	0.05	-1.39	0.16
Russell-Jones et al. 2009 [49]	long	-0.24	-0.49	0.01	-1.89	0.059
D'Alessio et al. 2015 [36]	long	0.15	0.01	0.29	2.12	0.034
Gough et al. 2015 [43]	long	0.10	-0.04	0.24	1.37	0.17
Araki et al. 2015 [32]	long	-0.54	-0.68	-0.40	-7.66	< 0.0001
Giorgino et al. 2015 a [42]	long	-0.31	-0.50	-0.12	-3.13	0.0018
Giorgino et al. 2015 b [42]	long	-0.03	-0.22	0.16	-0.30	0.76
All long-acting GLP-1 RAs		**-0.17**	**-0.22**	**-0.12**	**-6.24**	**< 0.0001**
All GLP-1 RAs		**-0.12**	**-0.16**	**-0.07**	**-5.30**	**< 0.0001**



M. El Aziz et al Diabetes Obes Metab. 2017 Feb;19(2):216-22

Evidence From CVOTs has Shown That Some Diabetes Agents Have Beneficial Effects on CV Outcomes

	EMPA-REG OUTCOME®[1]	CANVAS Program[2]	DECLARE-TIMI 58[3]	LEADER[4]	SUSTAIN-6[5]	HARMONY OUTCOMES[6]
3P-MACE	**HR 0.86** (95% CI 0.74, 0.99) *p*=0.04	**HR 0.86** (95% CI 0.75, 0.97) *p*=0.02†	HR 0.93 (95% CI 0.84, 1.03) *p*=0.17	**HR 0.87** (95% CI 0.78, 0.97) *p*=0.01	**HR 0.74** (95% CI 0.58, 0.95) *p*=0.02§	**HR 0.78** (95% CI 0.68, 0.90) *p*=0.0006
CV death	**HR 0.62** (95% CI 0.49, 0.77) *p*<0.001*	HR 0.87 (95% CI 0.72, 1.06)	HR 0.98 (95% CI 0.82, 1.17)	**HR 0.78** (95% CI 0.66, 0.93) *p*=0.007*	HR 0.98 (95% CI 0.65, 1.48) *p*=0.92	HR 0.93 (95% CI 0.73, 1.19) P=0.578*
HHF	**HR 0.65** (95% CI 0.50, 0.85) *p*=0.002*	**HR 0.67** (95% CI 0.52, 0.87)‡*	**HR 0.73** (95% CI 0.61–0.88)‡*	HR 0.87 (95% CI 0.73, 1.05) *p*=0.14	HR 1.11 (95% CI 0.77, 1.61) *p*=0.57	NR
CV death or HHF	**HR 0.66** (95% CI 0.55, 0.79) *p*<0.001*	**HR 0.78** (95% CI 0.67, 0.91) *p*=0.002*	**HR 0.83** (95% CI 0.73, 0.95) *p*=0.005	NR	NR	HR 0.85 (95% CI 0.70, 1.04) *p*=0.113*
Non-fatal stroke	HR 1.24 (95% CI 0.92, 1.67) *p*=0.16	HR 0.90 (95% CI 0.71, 1.15)	HR 1.01 (95% CI 0.84, 1.21)	HR 0.89 (95% CI 0.72, 1.11) *p*=0.30	**HR 0.61** (95% CI 0.38, 0.99) *p*=0.04*	NR
Fatal/Non-fatal MI	HR 0.87 (95% CI 0.70, 1.09) *p*=0.23	HR 0.89 (95% CI 0.73, 1.09)	HR 0.89 (95% CI 0.77, 1.01)	**HR 0.86** (95% CI 0.73, 1.00) *p*=0.046§	HR 0.74 (95% CI 0.51, 1.08) *p*=0.12	**HR 0.75** (95% CI 0.61, 0.90) *p*=0.003*

Albiglutide has now been withdrawn from the European market. Direct comparison of studies should be interpreted with caution as study design, populations and methodology differ. *p*-values are for superiority. *Nominal p-value; †Testing for superiority for 3P-MACE was part of the statistical analysis plan but not of the hierarchical testing strategy; ‡Exploratory outcome, no p-value reported – only nominal effect estimate given; §Testing for superiority was neither prespecified nor adjusted for multiplicity; Analysis not prespecified; includes fatal, non-fatal and silent MI.

3P-MACE = 3-point major adverse CV events; CV = cardiovascular; CVOTs = cardiovascular outcome trials; HHF = hospitalisation for heart failure; HR = hazard ratio; MI = myocardial infarction; NR = not reported.

[1]Zinman B, et al. *N Engl J Med* 2015;373:2117; [2]Neal B, et al. *N Engl J Med* 2017;377:644; [3]Wiviott SD, et al. *N Engl J Med* 2019;380:347;[4]Marso SP, et al. *N Engl J Med* 2016;375:1834;

[5]Marso SP, et al. *N Engl J Med* 2016;375:311; [6]Hernandez AF, et al. *Lancet* 2018;392(10157):1519