Update sulla gestione clinica del paziente con DM tipo 2

Dr. Andrea Da Porto

Ambulatorio di Diabetologia
SOC Clinica Medica
Azienda Ospedaliera-Universitaria Integrata Udine

Agenda

- ✓ Diabete, malattia cardiovascolare e malattia renale
- ✓ Obiettivi di cura ed approccio multifattoriale al paziente
- ✓ Snodi decisionali nella scelta del farmaco
- ✓ DPP4-Inibitori, SGLT2-Inibitori, Agonisti Recettoriali del GLP1 raccomandazioni di pratica clinica

The NEW ENGLAND JOURNAL of MEDICINE

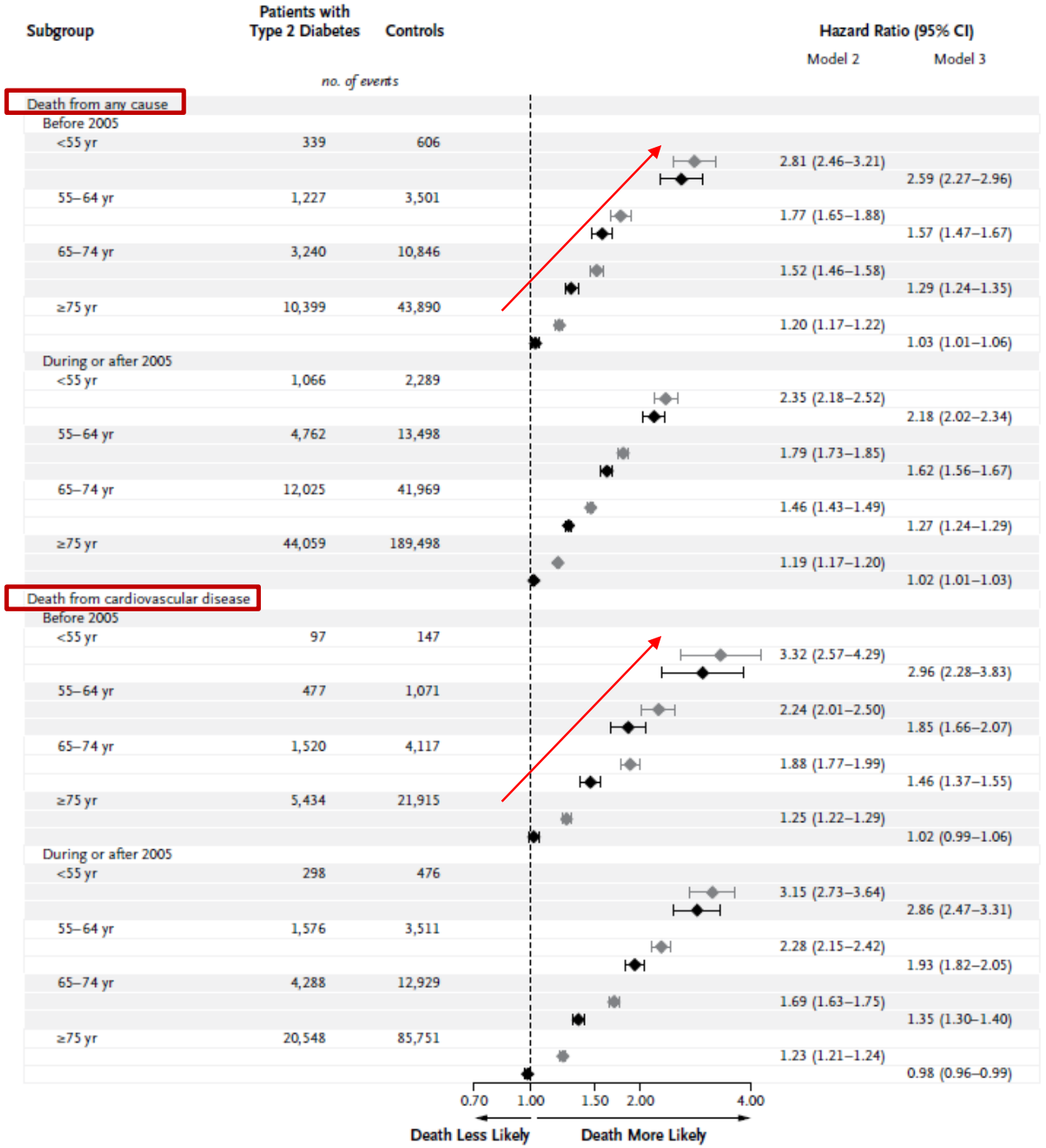
ORIGINAL ARTICLE

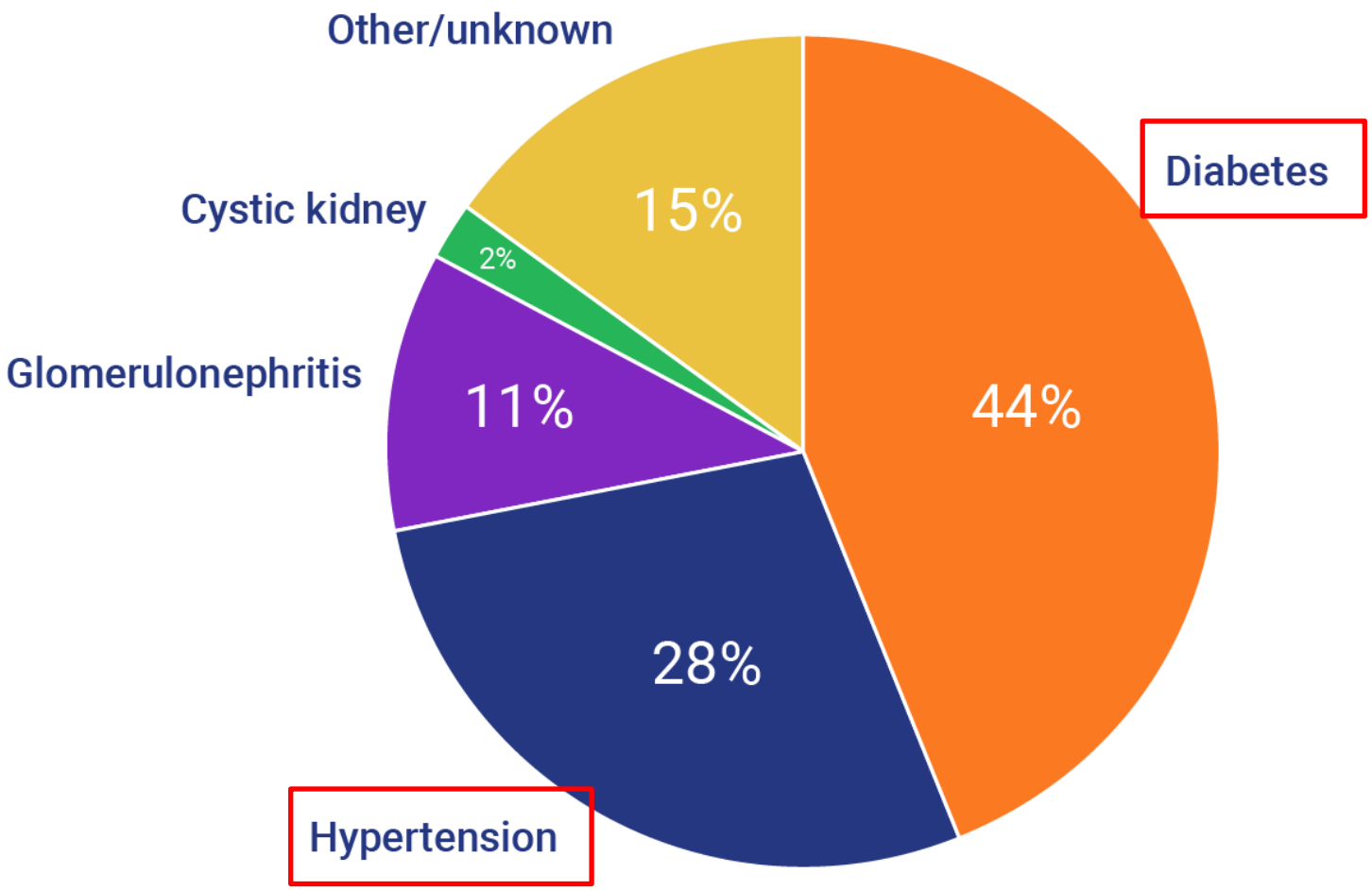
Excess Mortality among Persons with Type 2 Diabetes

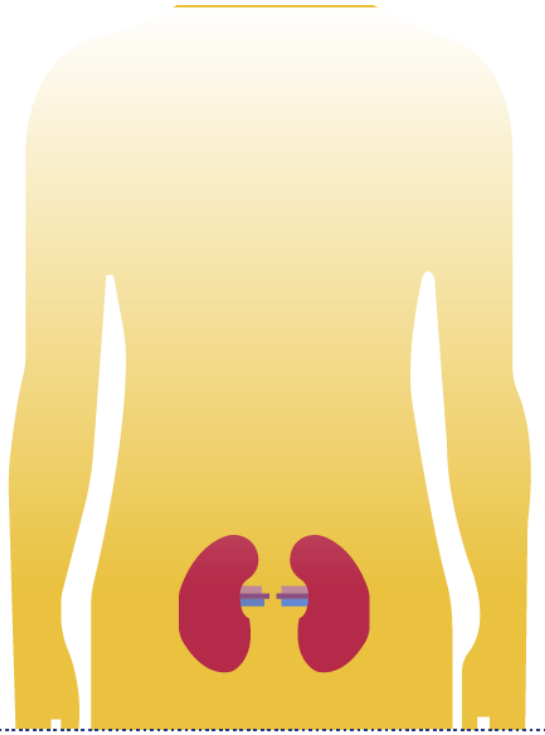
Mauro Tancredi, M.D., Annika Rosengren, M.D., Ann-Marie Svensson, Ph.D., Mikhail Kosiborod, M.D., Aldina Pivodic, M.Sc., Soffia Gudbjörnsdottir, M.D., Ph.D., Hans Wedel, Ph.D., Mark Clements, M.D., Ph.D., Sofia Dahlqvist, and Marcus Lind, M.D., Ph.D.

Più precocemente esordisce il diabete maggiore è l'incremento del rischio di

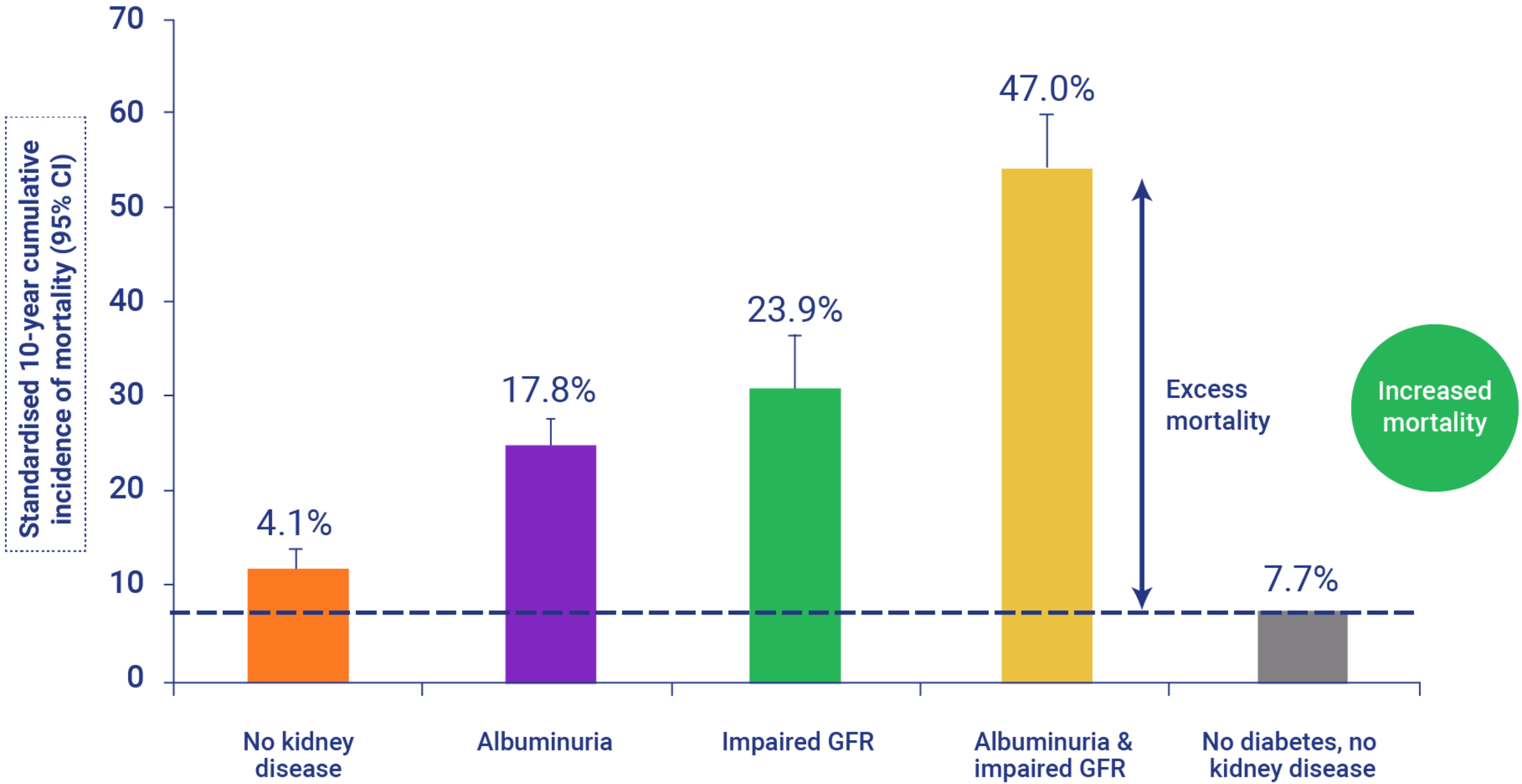
Mortalità per tutte le cause
Mortalità Cardiovascolare





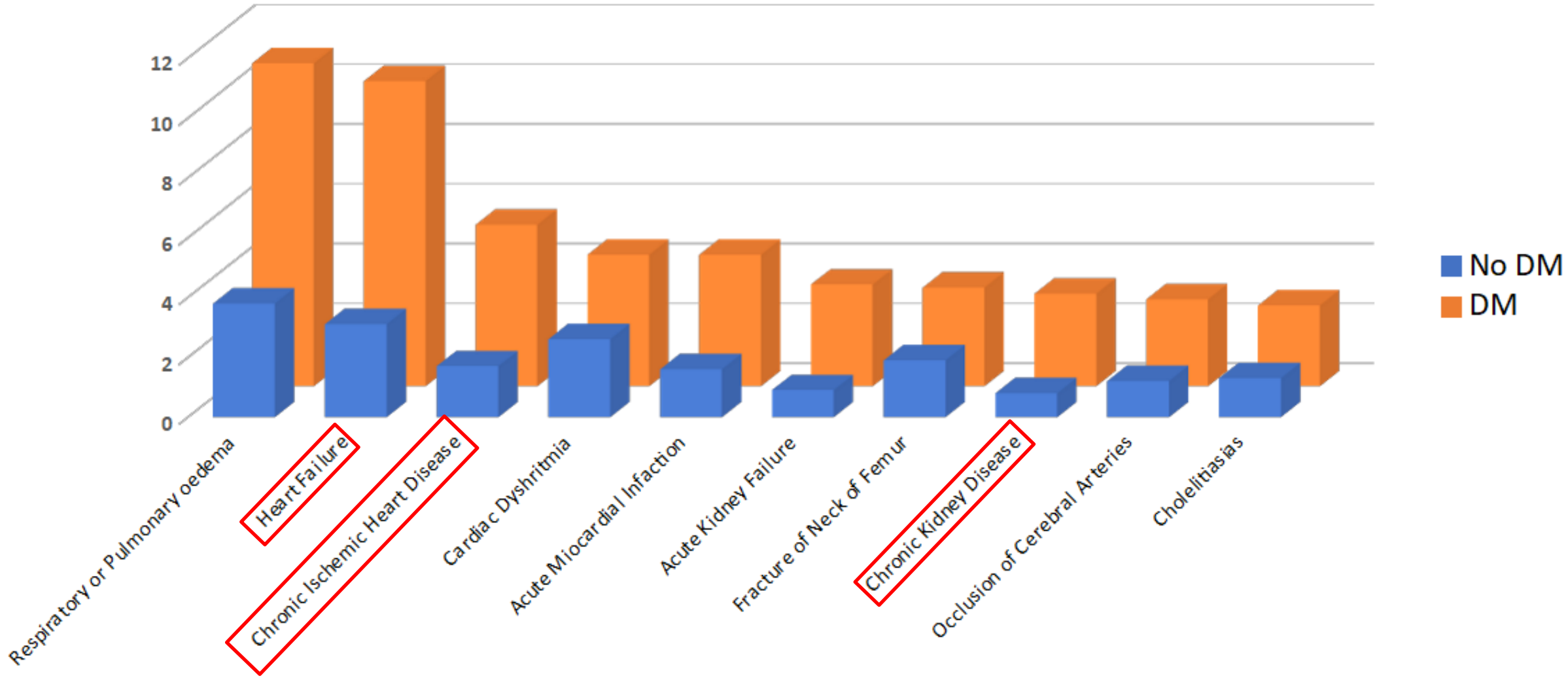


Diabetes is the leading cause of end-stage renal disease



J Am Soc Nephrol. 2013 Feb;24(2):302-8

Number of Subjects with at least one primary diagnosis of selected diseases in discharge medical reports (data are presented per 1000 subjects with or without diabetes)



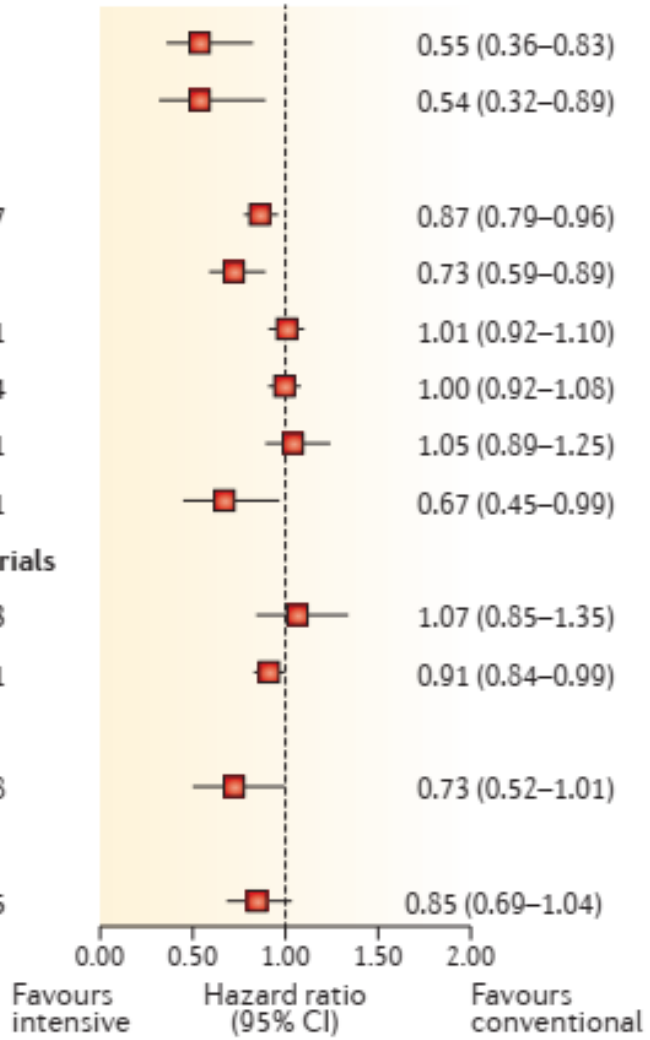
Bonora E. et al, BMJ Open Diab Res Care 2020; 8:e001191

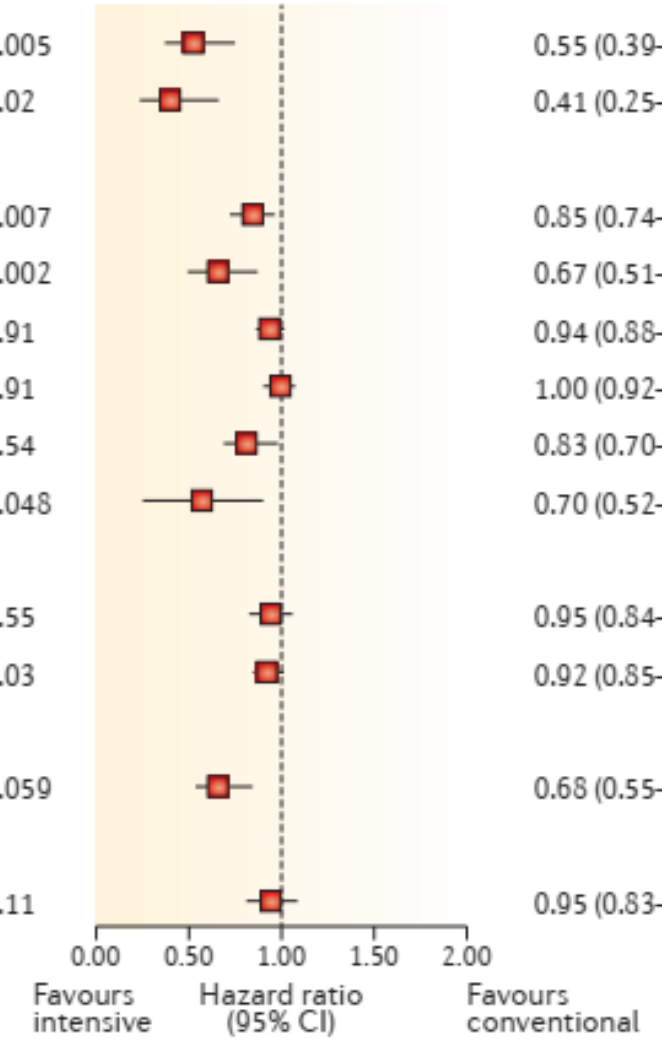
Cosa possiamo fare?

Mortalità Totale

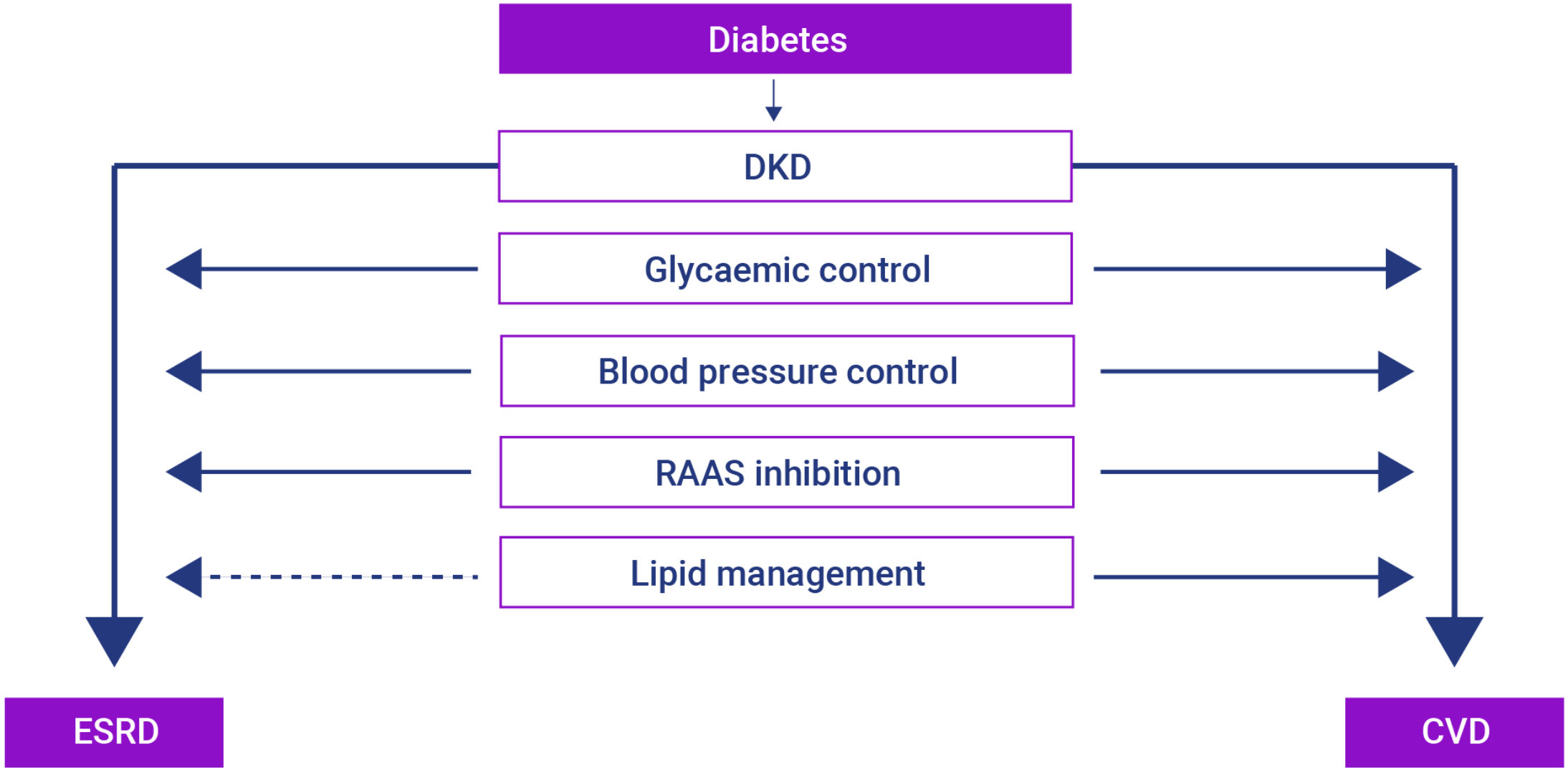
Eventi CV

Trial	Years	*n* (at start)	All cause mortality	HR (95% CI)	*P*	Incident cardiovascular events	HR (95% CI)	*P*
Multifactorial intervention trial								
Steno-2[1]	21	160		0.55 (0.36–0.83)	0.005		0.55 (0.39–0.77)	<0.001
Steno-2[4]	13.3	160		0.54 (0.32–0.89)	0.02		0.41 (0.25–0.67)	<0.001
Glucose lowering intervention trials								
UKPDS (SU-insulin group)[3]	10	3,867		0.87 (0.79–0.96)	0.007		0.85 (0.74–0.97)	0.01
UKPDS (metform group)[3]	10	753		0.73 (0.59–0.89)	0.002		0.67 (0.51–0.89)	0.005
ACCORDION[5]	9	8,601		1.01 (0.92–1.10)	0.91		0.94 (0.88–1.00)	0.05
ADVANCE-ON[6]	10	8,494		1.00 (0.92–1.08)	0.91		1.00 (0.92–1.08)	0.93
VADT[7]	11.8	1,791		1.05 (0.89–1.25)	0.54		0.83 (0.70–0.99)	0.04
DCCT/EDIC[2]	30	1,441		0.67 (0.45–0.99)	0.048		0.70 (0.52–0.93)	0.016
Blood pressure lowering intervention trials								
ACCORD BP[8]	4.7	4,733		1.07 (0.85–1.35)	0.55		0.95 (0.84–1.07)	0.4
ADVANCE ON[6]	10	8,491		0.91 (0.84–0.99)	0.03		0.92 (0.85–1.00)	0.06
Lipid lowering intervention trial								
CARDS[9]	3.9	2,838		0.73 (0.52–1.01)	0.059		0.68 (0.55–0.85)	0.001
Intensive lifestyle intervention trial								
LOOK AHEAD[10]	9.5	5,145		0.85 (0.69–1.04)	0.11		0.95 (0.83–1.09)	0.51





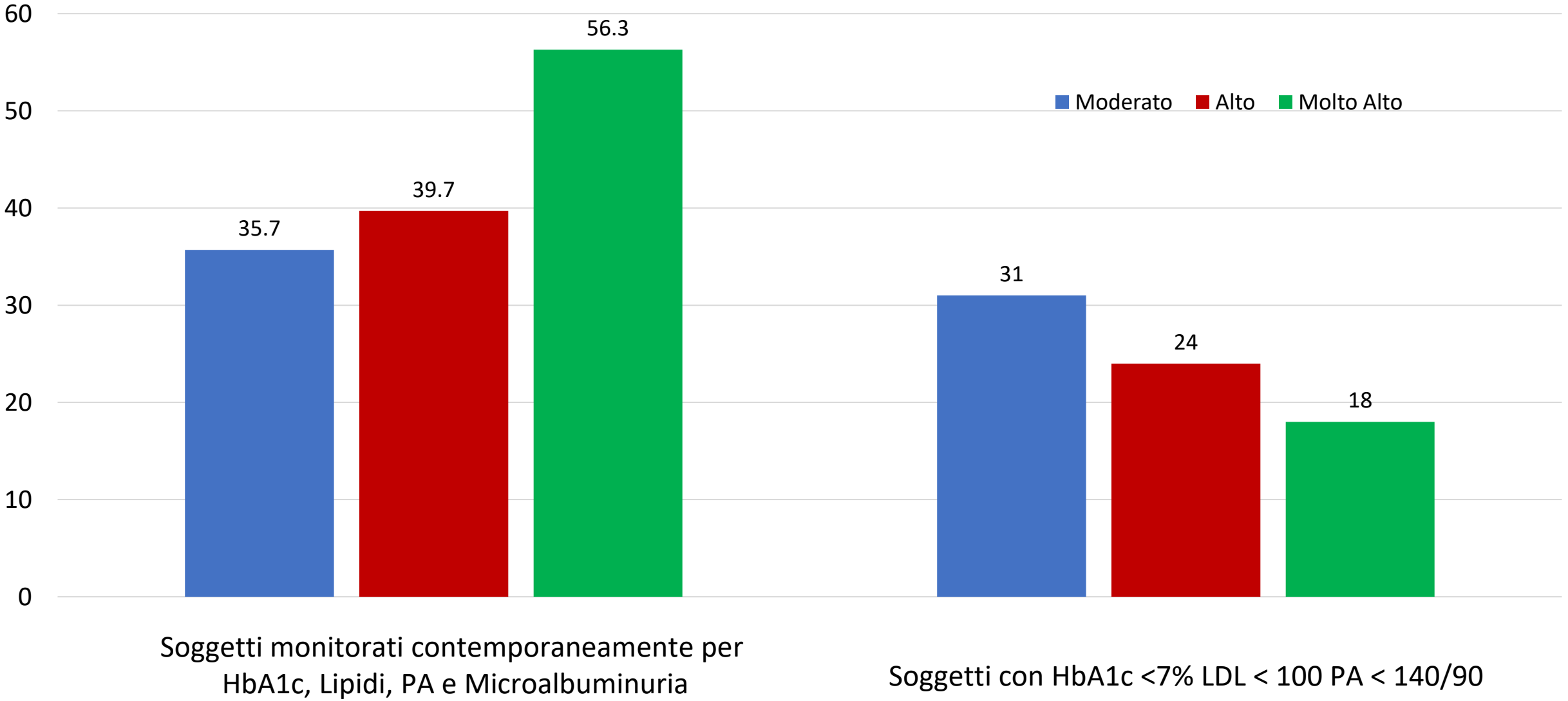
Nature Reviews Endocrinology, 12(12), 692–694.


Diabetes
DKD
Glycaemic control
Blood pressure control
RAAS inhibition
Lipid management
ESRD
CVD

Risk factor	Target
BP	• Target SBP 130 mmHg for most adults, <130 mmHg if tolerated, but not <120 mmHg • Less-stringent targets, SBP 130 - 139 in older patients (aged >65 years)
Glycaemic control: HbA1c	• HbA1c target for most adults is <7.0% (<53 mmol/mol) • More-stringent HbA1c goals of <6.5% (48 mmol/mol) may be suggested on a personalized basis if this can be achieved without significant hypoglycaemia or other adverse effects of treatment • Less-stringent HbA1c goals of <8% (64 mmol/mol) or ≤9% (75 mmol/mol) may be adequate for elderly patients (see *section 6.2.1*)
Lipid profile: LDL-C	• In patients with DM at very high CV risk,[a] target LDL-C to <1.4 mmol/L (<55 mg/dL) • In patients with DM at high risk,[a] target LDL-C to <1.8 mmol/L (<70 mg/dL) • In patients with DM at moderate CV risk,[a] aim for an LDL-C target of <2.5 mmol/L (<100 mg/dL)
Platelet inhibition	In DM patients at high/very high CV risk
Smoking	Cessation obligatory
Physical activity	Moderate-to-vigorous, ≥150 min/week, combined aerobic and resistance training
Weight	Aim for weight stabilization in overweight or obese patients with DM, based on calorie balance, and weight reduction in subjects with IGT, to prevent the development of DM.
Dietary habits	Reduction of caloric intake is recommended in obese patients with T2DM to lower body weight; there is no ideal percentage of calories from carbohydrate, protein, and fat for all people with DM.

European Heart Journal. doi:10.1093/eurheartj/ehz486

Annali AMD 2020: Controllo FDR CV



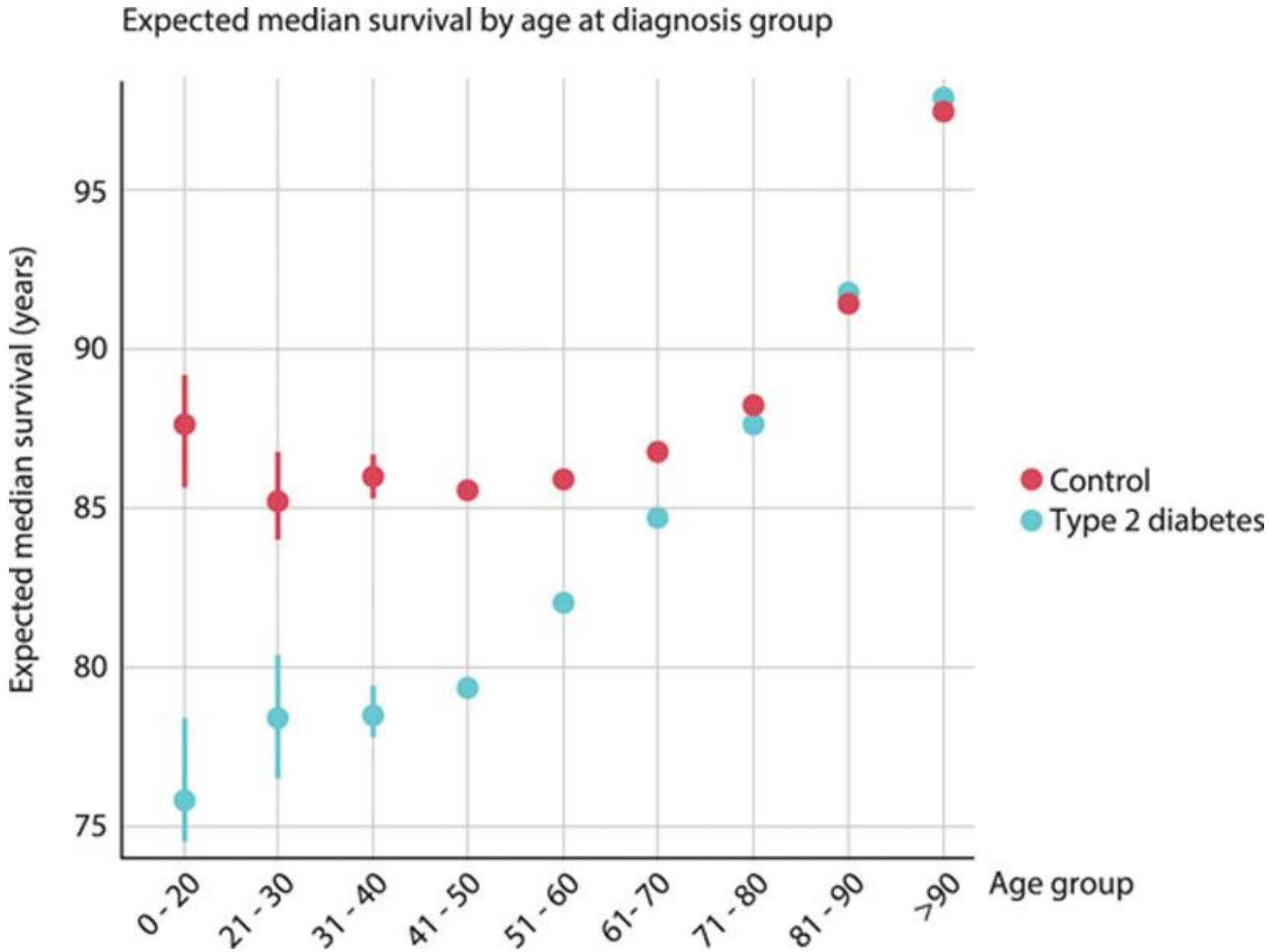
	Early diabetes		Late diabetes	
	ASCVD	Non-ASCVD CHF	ASCVD	Non-ASCVD CHF
HbA1c lowering	++	0	+	0
Blood Pressure lowering	++	+	+++	++
LDL lowering	+++	0	++++	0
Multifactorial interventions	+++++	+	++++	++
Aspirin	±	0	++	0
RAAS blockers	++	+	+++	+++
Beta Blockers	0	0	++	++
ILI	+	0	0	0
GLP-1 RA	+++?	0	++	±
SGLT2 inhibitors	±?	+?	++	++++

Pre-diabetes

Diagnosis diabetes

Diabetes duration 10-15 years

Stratificazione del paziente come momento fondamentale della scelta terapeutica



https://doi.org/10.1161/CIRCULATIONAHA.118.037885

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

CV Risk > 10% / Year

CV Risk 5-10% / Year

CV Risk < 5% / Year

B) Proteinuria, renal impairment defined as eGFR <30 mL/min/1.73 m, left ventricular hypertrophy, or retinopathy.
C) Age, hypertension, dyslipidemia, smoking, obesity.

European Heart Journal. doi:10.1093/eurheartj/ehz486

Tabella 3 Definizione di scompenso cardiaco con frazione di eiezione ridotta, lievemente ridotta e preservata

Tipo di SC		HFrEF	HFmrEF	HFpEF
CRITERI	1	Sintomi ± segni[a]	Sintomi ± segni[a]	Sintomi ± segni[a]
	2	FEVS ≤40%	FEVS 41-49%[b]	FEVS ≥50%
	3	–	–	Evidenza oggettiva di anomalie cardiache funzionali e/o strutturali suggestive della presenza di disfunzione diastolica VS/elevate pressioni di riempimento VS, inclusi elevati livelli dei peptidi natriuretici[c]

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012

GFR categories (ml/min per 1.73m²) description and range				Persistent albuminuria categories description and range		
				A1	A2	A3
				Normal to midly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300mg/g 3-30 mg/mmol	>300mg/g >30 mg/mmol
	G1	Normal or high	>90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD)
Yellow: moderately increased risk
Orange: high risk
Red: very high risk

Nat Rev Dis Primers. 2015 Jul 30;1:15018.

L’ Anziano con Diabete: Fragilità

2 – IN FORMA

Persone che **non hanno sintomi della malattia attivi**, ma che sono meno in forma rispetto alle persone della categoria 1. Praticano spesso sport o sono **a volte** molto attive, a seconda della stagione

3 – SE LA CAVA BENE

Persone, i cui **problemi medici sono ben monitorati**, ma **non sono però regolarmente attive** al di fuori della normale deambulazione quotidiana esterna.

4 – SE LA CAVA ABBASTANZA BENE

Anche se **non** dipendenti dall'aiuto degli altri nella vita quotidiana, queste persone sono spesso limitate nelle loro attività **a causa di sintomi di malattia**. Spesso lamentano di sentirsi "rallentati" e / o stanchi durante il giorno.

5 – LEGGERMENTE FRAGILE

Persone spesso evidentemente rallentate nei **movimenti** e nelle **attività** più impegnative **della vita quotidiana** (ad es. gestione delle finanze, locomozione, lavori domestici pesanti, gestione dei farmaci) e **hanno bisogno di aiuto**. Sono in genere sempre più limitate nello shopping, nella deambulazione autonoma, nella preparazione dei pasti e nei lavori domestici.

6 – MODERATAMENTE FRAGILE

Queste persone hanno bisogno **di assistenza in tutte le attività esterne alla casa** e nella **gestione delle finanze**. Spesso hanno difficoltà a salire le scale, hanno bisogno di **aiuto per lavarsi** e possono avere bisogno di aiuto per vestirsi.

7 – MOLTO FRAGILE

Completamente dipendenti per la cura personale, per qualunque tipo di causa (fisica o cognitiva). Tuttavia, sembrano stabili e non ad alto rischio di morte (entro ~ 6 mesi).

8 – FRAGILITA' MOLTO GRAVE

Queste persone **si avvicinano al decesso e sono completamente dipendenti dagli altri**. Se si ammalassero di qualsiasi malattia, molto probabilmente non riuscirebbero a riprendersi.

9 - MALATO TERMINALE

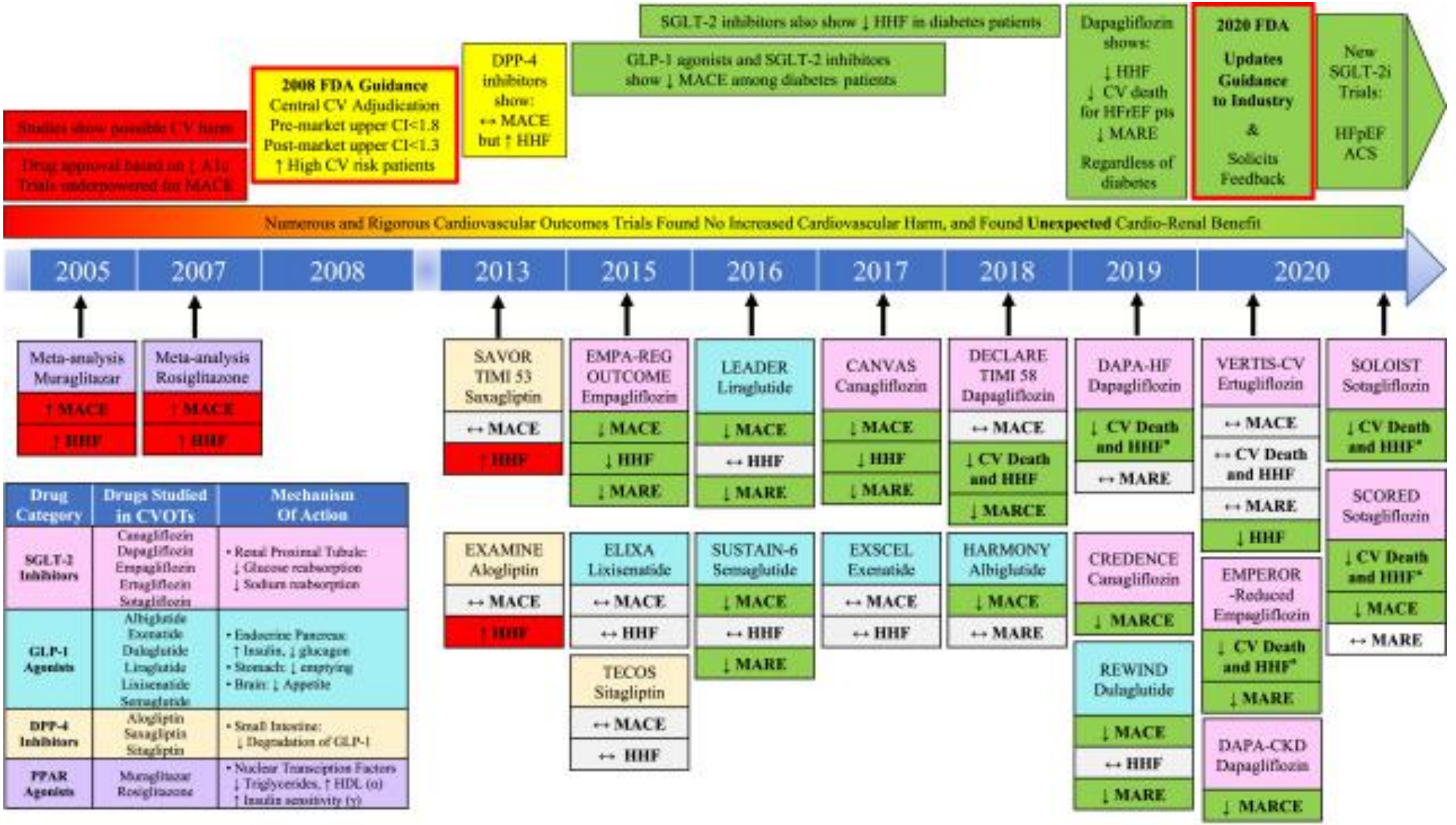
Queste persone hanno **un'aspettativa di vita <6 mesi** e si avvicinano alla fine della vita, anche se la loro condizione non è così marcatamente visibile.

Condizione estremamente eterogenea

- ✓ Durata malattia
- ✓ Complicanze
- ✓ Comorbilità
- ✓ Sindromi geriatriche
- ✓ Contesto sociale, economico
- ✓ Aspettativa di vita

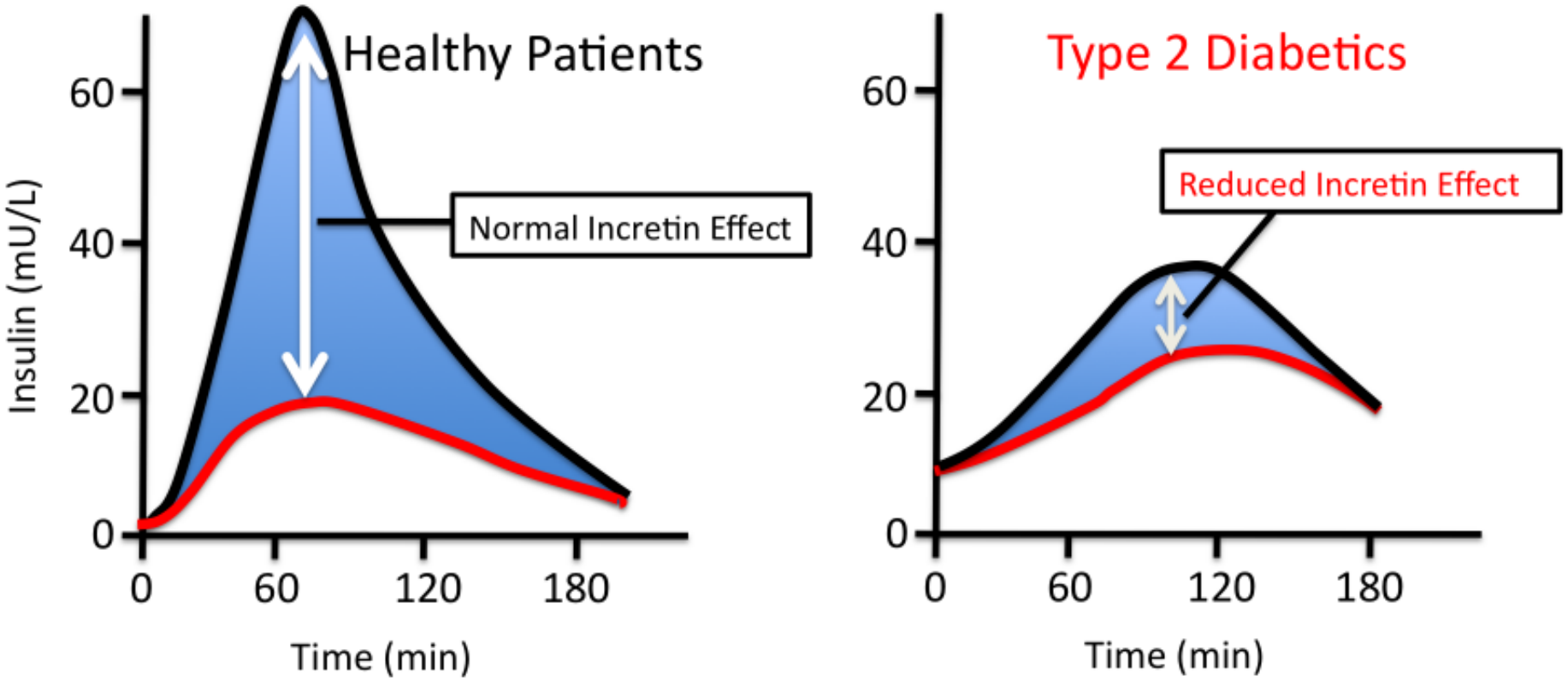
Rockwood K et al. CMAJ 2005;173:489-495

Quale terapia è appropriata



Drug Category	Drugs Studied in CVOTs	Mechanism Of Action
SGLT-2 Inhibitors	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin Sotagliflozin	• Renal Proximal Tubule: ↓ Glucose reabsorption ↓ Sodium reabsorption
GLP-1 Agonists	Albiglutide Exenatide Dulaglutide Liraglutide Lixisenatide Semaglutide	• Endocrine Pancreas: ↑ Insulin, ↓ glucagon • Stomach: ↓ emptying • Brain: ↓ Appetite
DPP-4 Inhibitors	Alogliptin Saxagliptin Sitagliptin	• Small Intestine: ↓ Degradation of GLP-1
PPAR Agonists	Muraglitazar Rosiglitazone	• Nuclear Transcription Factors ↓ Triglycerides, ↑ HDL (α) ↑ Insulin sensitivity (γ)

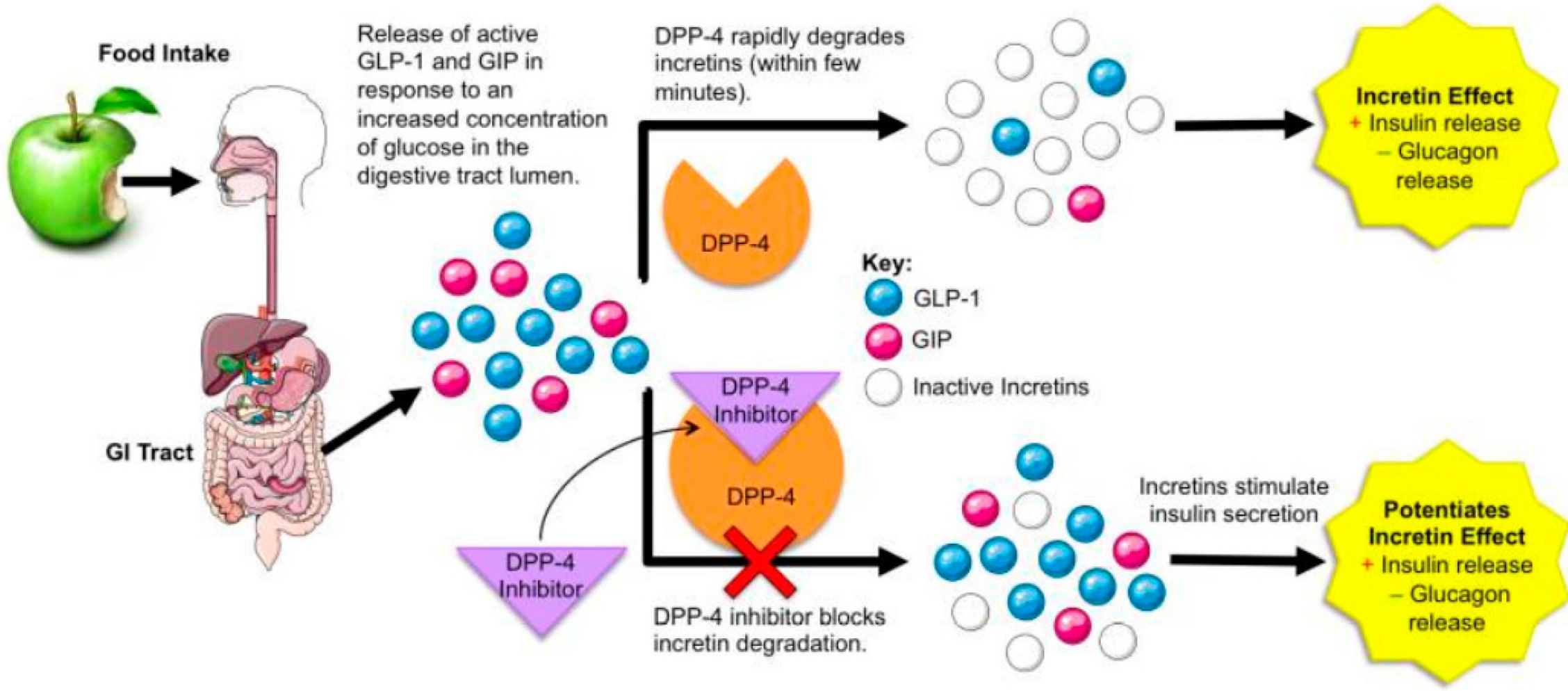
Diabetes & The "Incretin Effect"

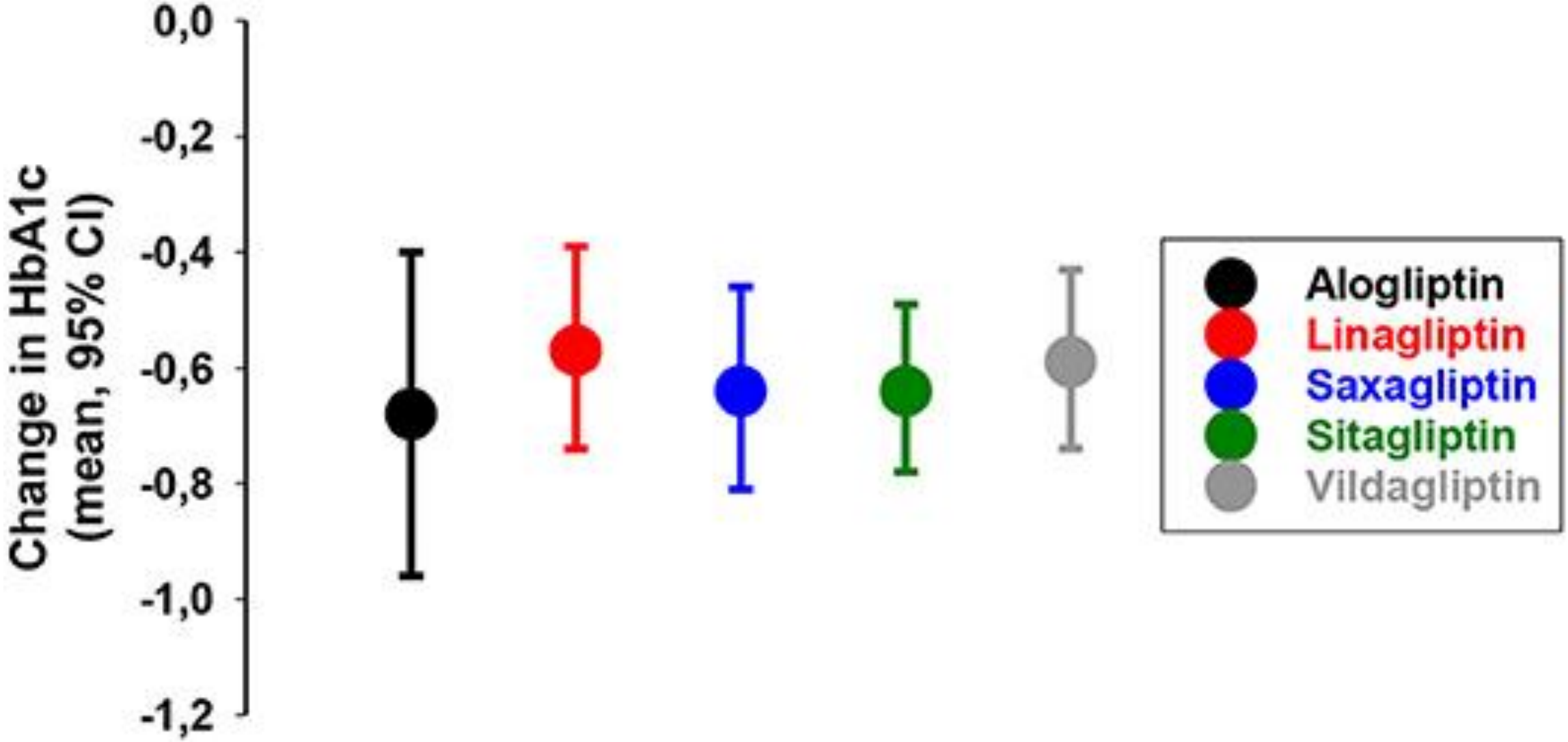


Oral Glucose (50 g/400 ml)

Isoglycemic IV Glucose Infusion

Nauck M et al.
Diabetologia (1986) 29:46-52


Food Intake
GI Tract
Release of active GLP-1 and GIP in response to an increased concentration of glucose in the digestive tract lumen.
DPP-4 rapidly degrades incretins (within few minutes).
DPP-4
DPP-4 Inhibitor
DPP-4
DPP-4 Inhibitor
DPP-4 inhibitor blocks incretin degradation.
Key:
GLP-1
GIP
Inactive Incretins
Incretin Effect
+ Insulin release
– Glucagon release
Incretins stimulate insulin secretion
Potentiates Incretin Effect
+ Insulin release
– Glucagon release


Change in HbA1c
(mean, 95% CI)
0,0
-0,2
-0,4
-0,6
-0,8
-1,0
-1,2
Alogliptin
Linagliptin
Saxagliptin
Sitagliptin
Vildagliptin

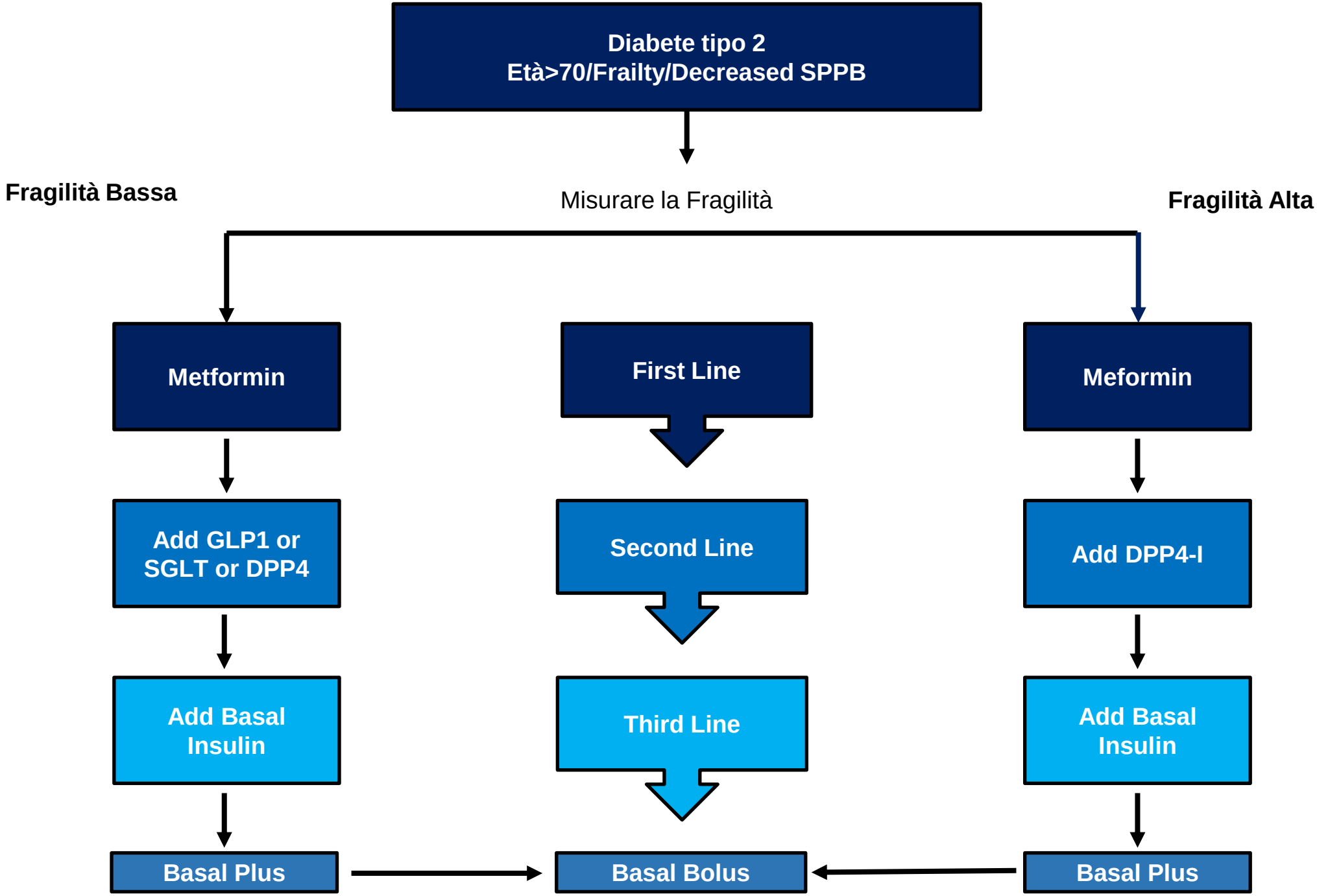
DPP4i Sicurezza

- ✓ Generalmente «SAFE»
- ✓ Utilizzabili in tutte le classi di IRC (con appropriate accortezze)
- ✓ Trascurabile rischio di Ipoglicemia
- ✓ Alcune molecole utilizzabili anche in insufficenza epatica avanzata (linagliptin)
- ✓ Poche interazioni farmacologiche
- ✓ Minimo incremento infezione respiratorie superiori (trascurabile)
- ✓ Manifetazioni allergiche minori (cutanee) in pazienti predisposti
- ✓ Accettabile sicurezza CV

DPP4i effetti sugli eventi CV o Renali

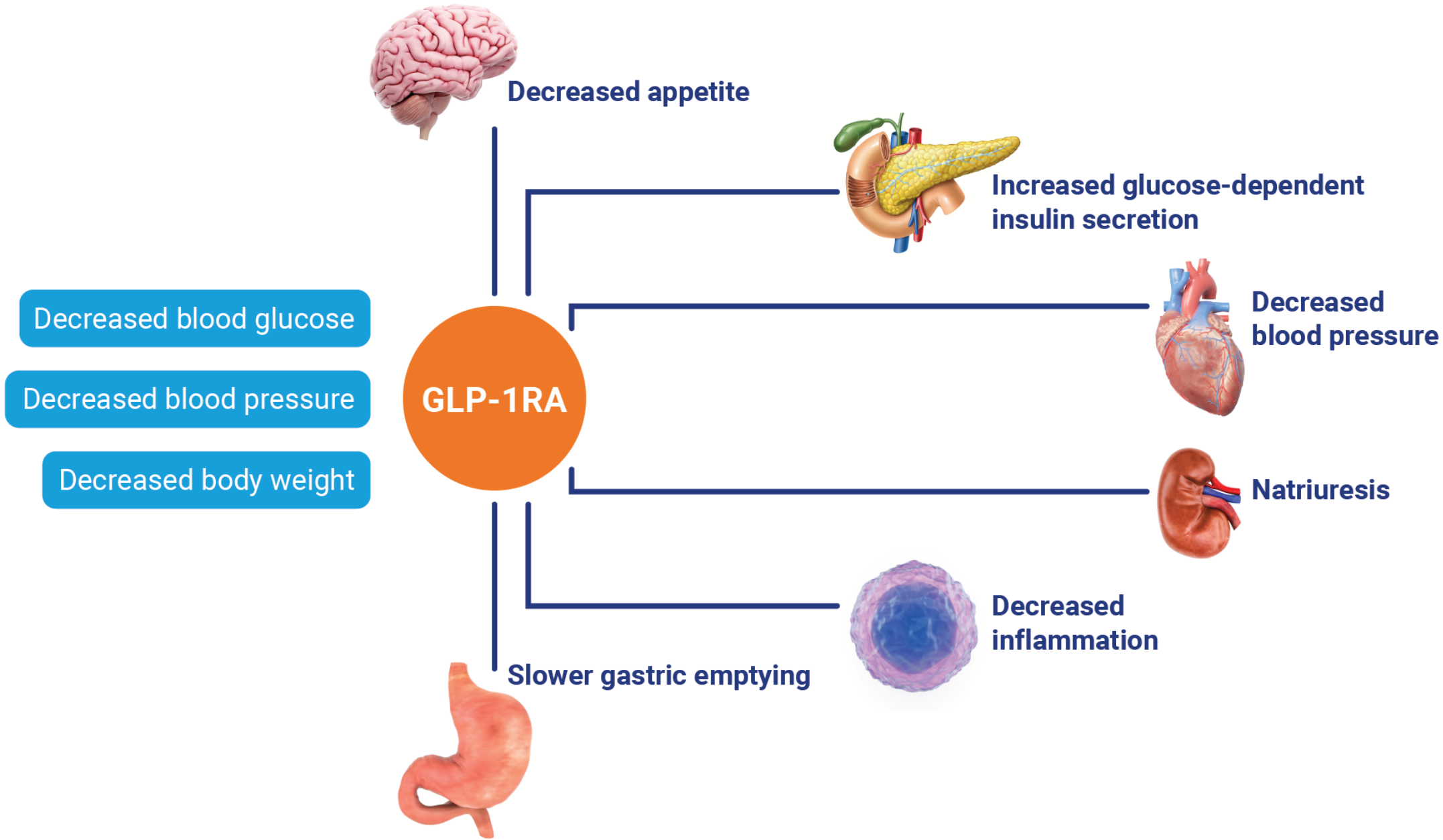
DPP-4 inhibitor	Name of trial	Number of subjects	Median follow up period (year)	Hazard ratio for primary endpoint (95% CI*)	References
Saxagliptin	SAVOR-TIMI	16,492	2.1	1.00 (0.89; 1.12)	(94)
Alogliptin	EXAMINE	5,280	1.5	0.96 (0.76; 1.16)	(95)
Sitagliptin	TECOS	14,671	3.0	0.98 (0.88; 1.09)	(96)
Linagliptin	CARMELINA	6,979	2.2	1.02 (0.89; 1.17)	(97)
Linagliptin	CAROLINA	6,033**	6.0**	Not reported	(98)

*CI, confidence interval. **These results reported in a press release from Boehringer Ingelheim, February 19, 2019.
Primary endpoint: composite of cardiovascular death, myocardial infarction, or ischemic stroke (94), composite of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke (95), composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for unstable angina (96), or time to first occurrence of the composite of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke (97), respectively.

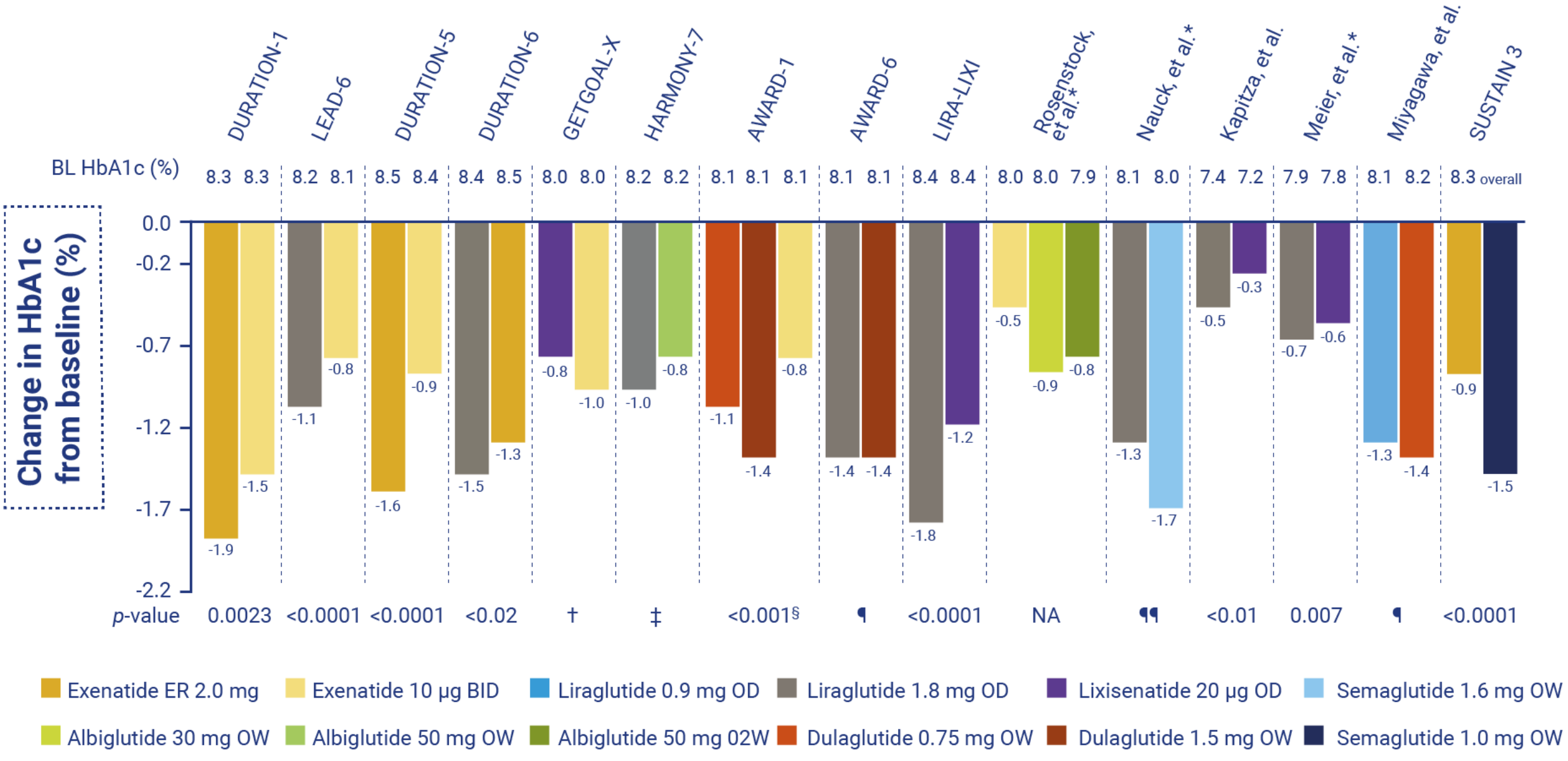

Diabete tipo 2
Età>70/Frailty/Decreased SPPB
Misurare la Fragilità
Fragilità Bassa
Fragilità Alta
Metformin
Add GLP1 or SGLT or DPP4
Add Basal Insulin
Basal Plus
First Line
Second Line
Third Line
Basal Bolus
Meformin
Add DPP4-I
Add Basal Insulin
Basal Plus

Agonisti recettoriali del GLP1

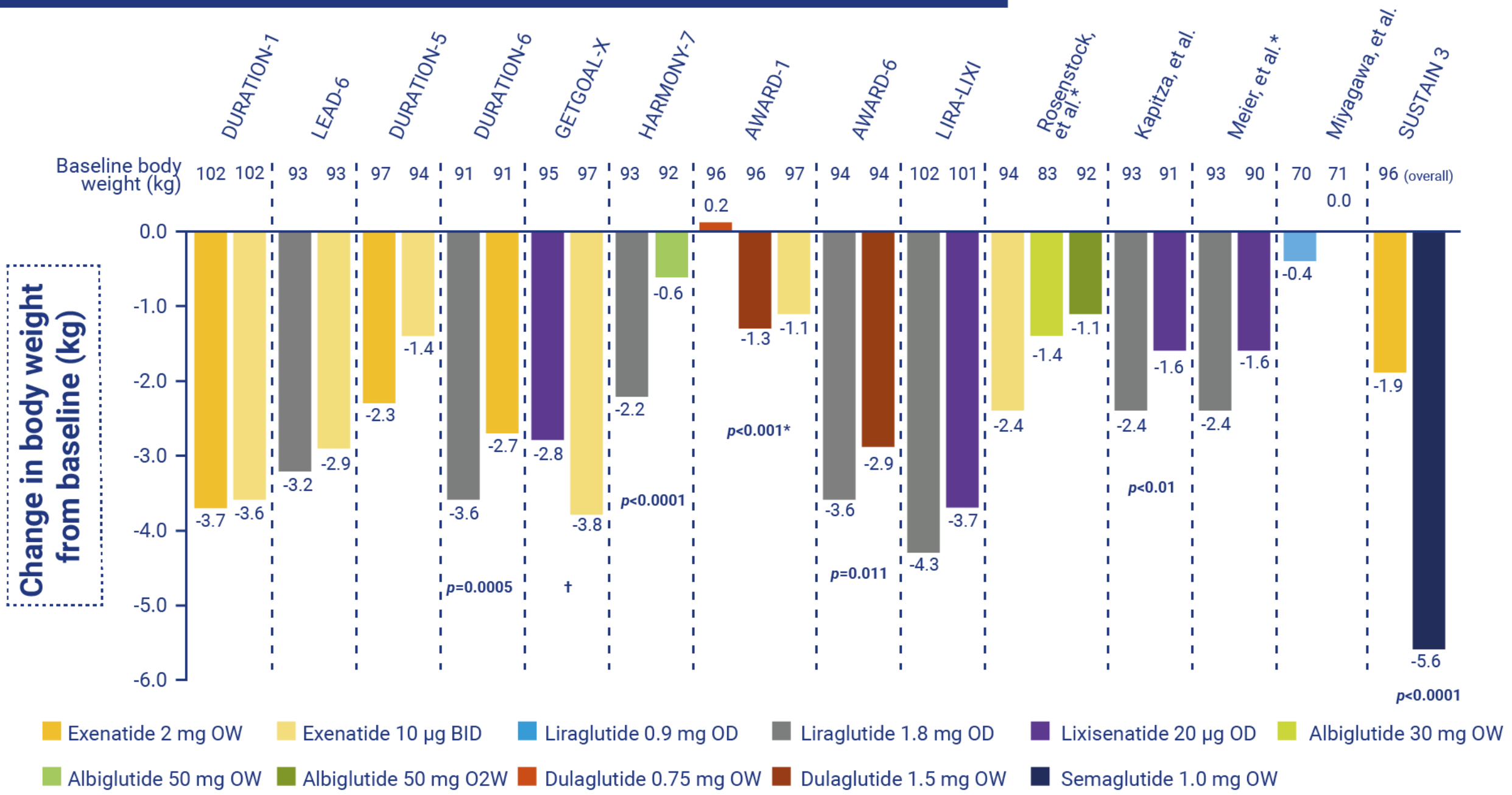
How GLP-1RAs benefit people with type 2 diabetes



Effect on HbA1c of different GLP-1RAs in head-to-head trials



Effect on body weight of different GLP-1RAs in head-to-head trials



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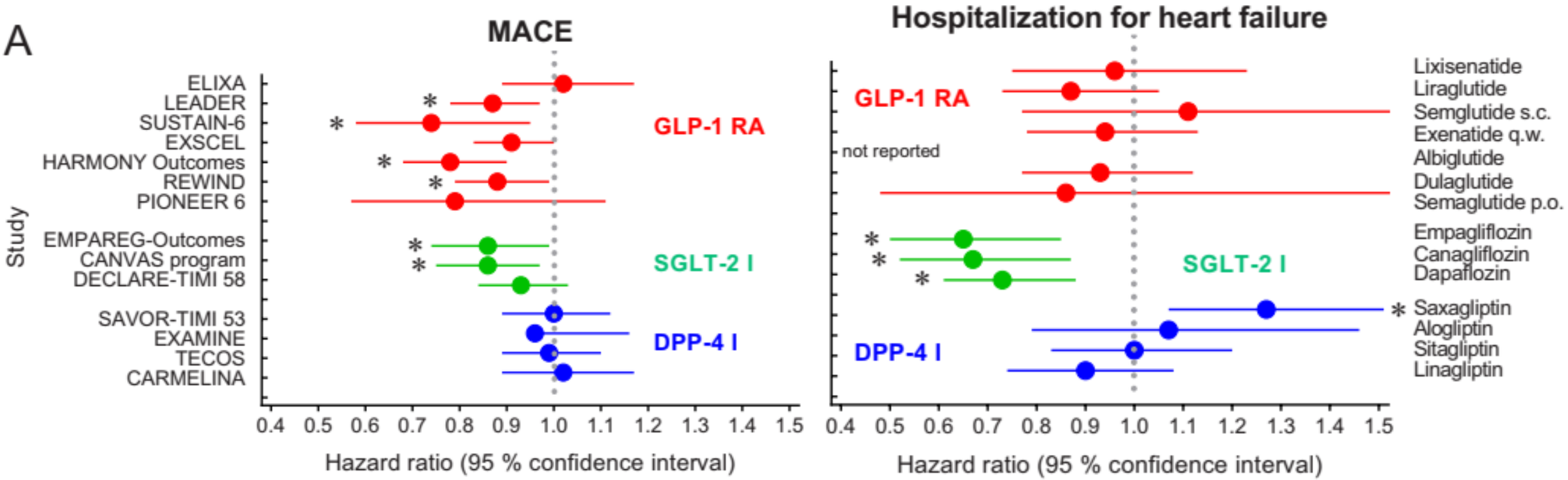
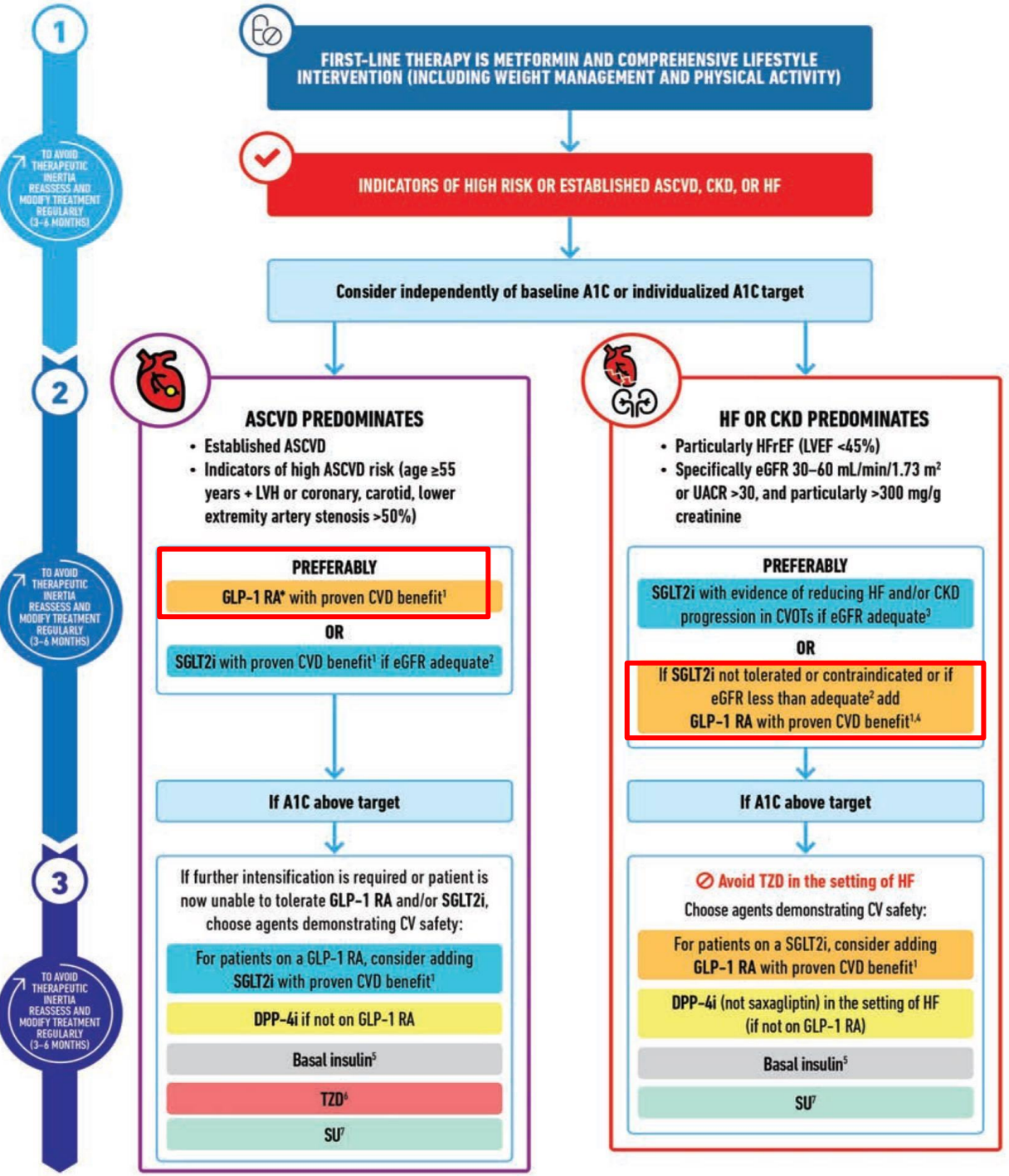
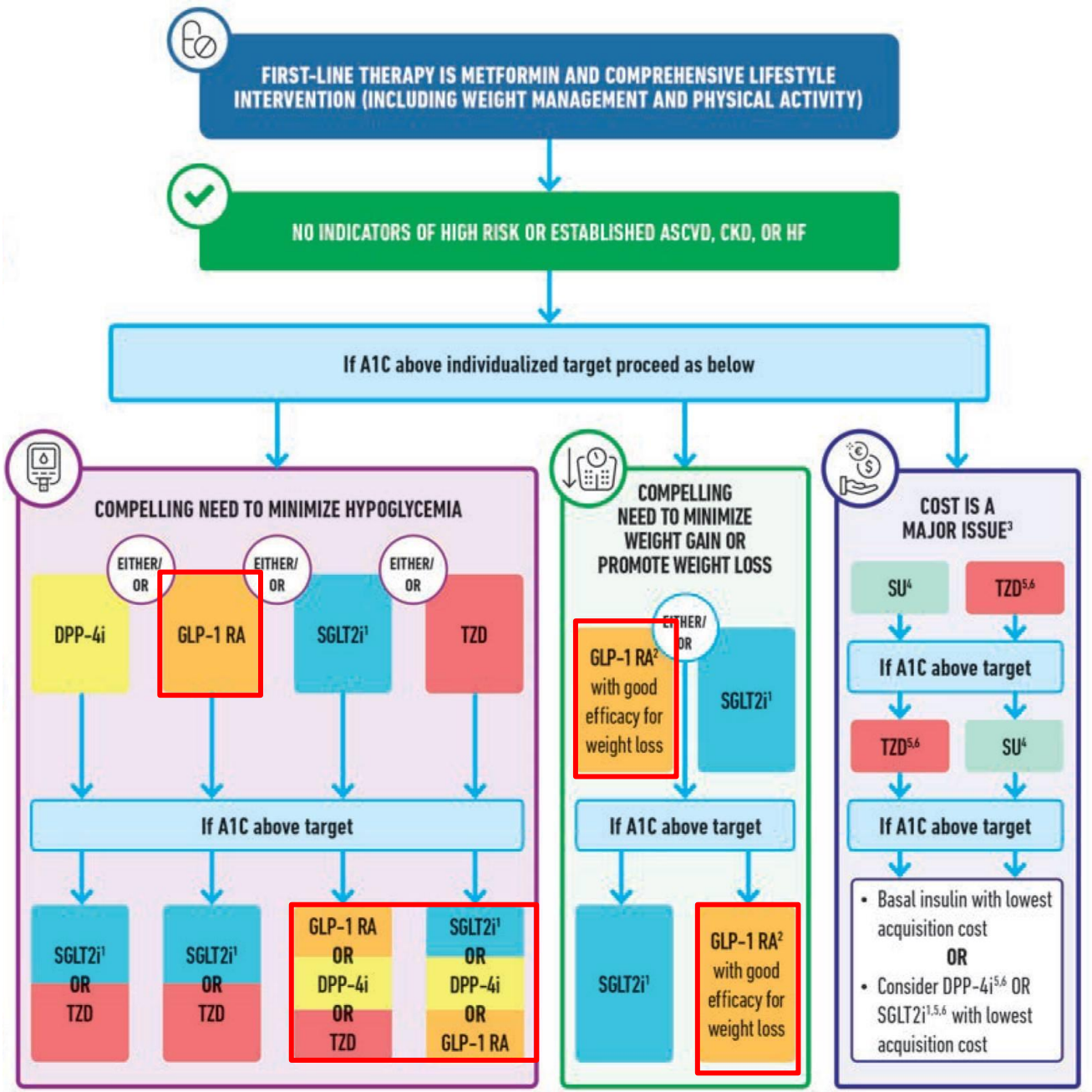

MACE
Hospitalization for heart failure
Study
ELIXA
LEADER
SUSTAIN-6
EXSCEL
HARMONY Outcomes
REWIND
PIONEER 6
EMPAREG-Outcomes
CANVAS program
DECLARE-TIMI 58
SAVOR-TIMI 53
EXAMINE
TECOS
CARMELINA
GLP-1 RA
SGLT-2 I
DPP-4 I
not reported
Lixisenatide
Liraglutide
Semglutide s.c.
Exenatide q.w.
Albiglutide
Dulaglutide
Semaglutide p.o.
Empagliflozin
Canagliflozin
Dapaflozin
Saxagliptin
Alogliptin
Sitagliptin
Linagliptin
0.4 0.5 0.6 0.7 0.8 0.9 1.0 1.1 1.2 1.3 1.4 1.5
Hazard ratio (95 % confidence interval)

Agonisti Recettoriali del GLP1

- ✓ Indicazioni
- ✓ Controindicazioni
- ✓ Somministrazione SC
- ✓ Educazione al Device
- ✓ Siti di Iniezione
- ✓ Educazione ai comuni effetti collaterali prevenibili all’avvio della terapia
- ✓ Adattamento dosaggio in IRC o Insufficienza Epatica





glucose-lowering medication if there is a compelling need to minimize hypoglycemia, there is a

GLP1-RA: Avvio e titolazione

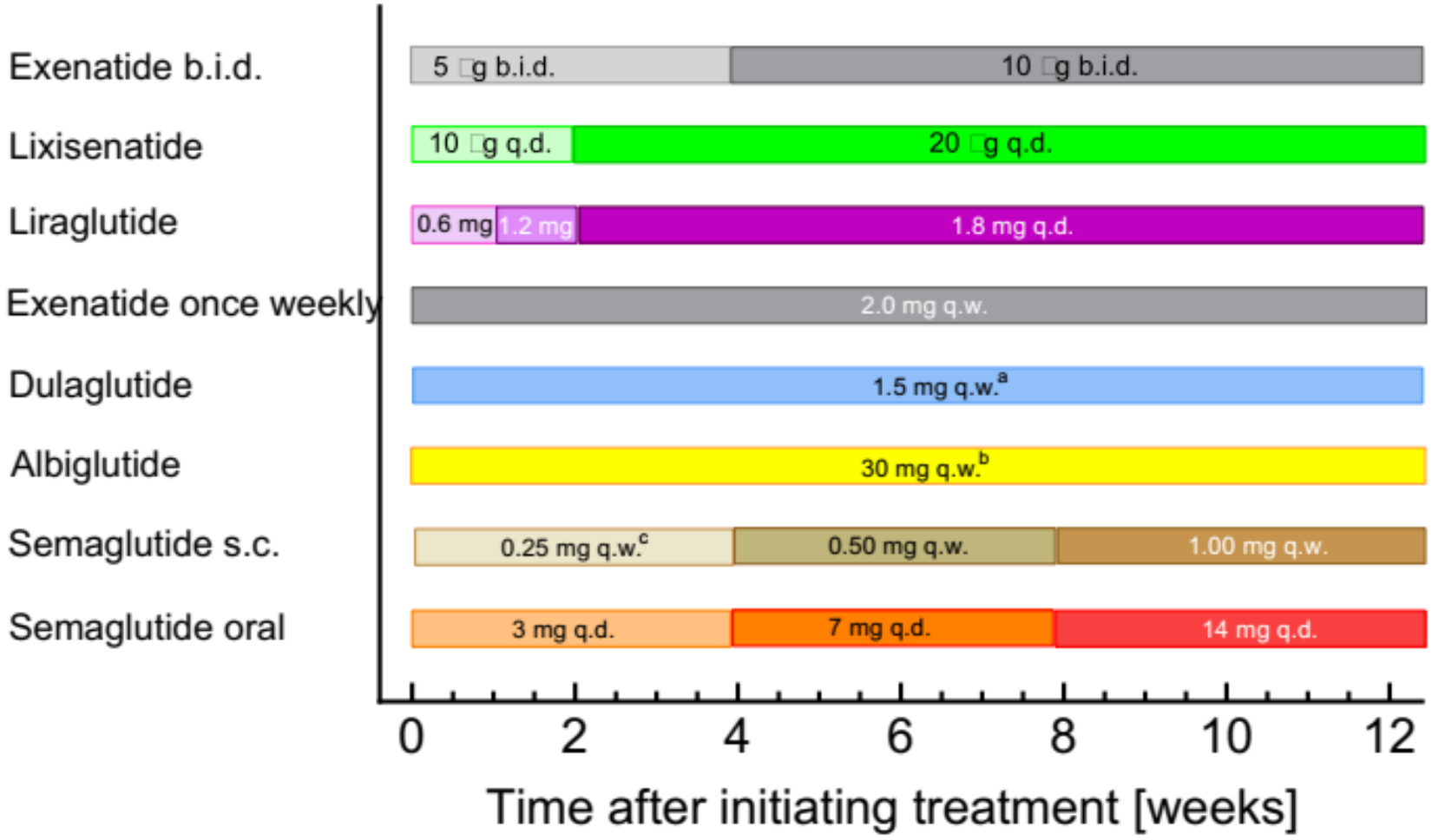


Figura 6 | Raccomandazioni per la titolazione degli agonisti del recettore GLP-1 attualmente approvati. Da:[13].

GLP1-RA: Controindicazioni

Table 1. Recommended use of GLP-1 receptor agonists in chronic kidney disease.

GLP-1 receptor agonist	Renal function (eGFR in mL/min/1.73 m²)
Exenatide immediate-release (twice-daily)	Avoid if eGFR <30
Liraglutide	Can use down to eGFR 15
Exenatide modified-release (once-weekly)	Avoid if eGFR <50
Lixisenatide	Avoid if eGFR <30, caution if eGFR 30–50
Dulaglutide	Can use down to eGFR 15
Semaglutide	Can use down to eGFR 15

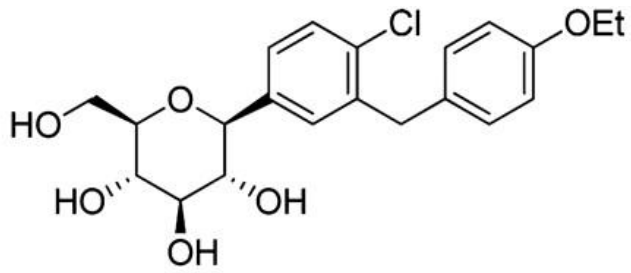
eGFR=estimated glomerular filtration rate; GLP-1=glucagon-like peptide-1.

Box 1. Who should not receive a GLP-1 receptor agonist?

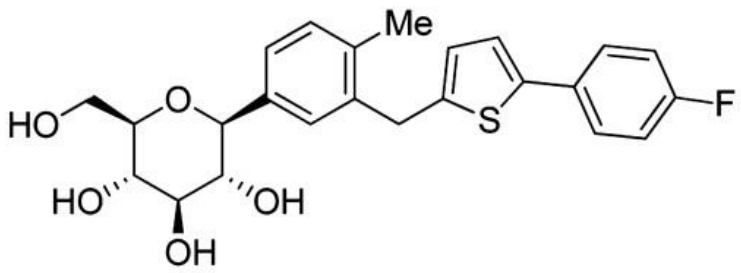
- Type 1 diabetes.
- Pregnancy and breastfeeding.
- Severe gastrointestinal disease (e.g. inflammatory bowel disease).
- Diabetic gastroparesis.
- History of pancreatitis.
- Caution if high risk of pancreatitis (e.g. gallstones, alcohol excess, hypertriglyceridaemia).
- History of medullary thyroid cancer or multiple endocrine neoplasia (MEN) type 2.
- Caution in renal impairment – see *Table 1.*

https://www.pcdsociety.org/resources/details/glp-1-receptor-agonists-type-2-diabetes-underused-asset-updated-january-2021

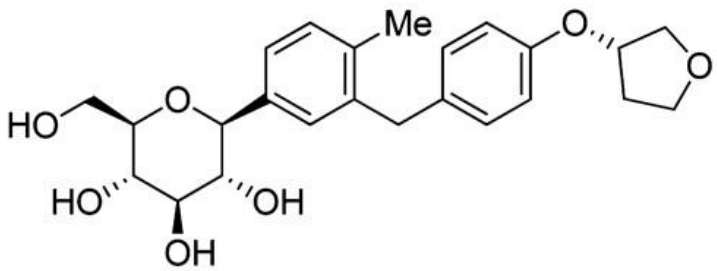
SGLT2 inibitori



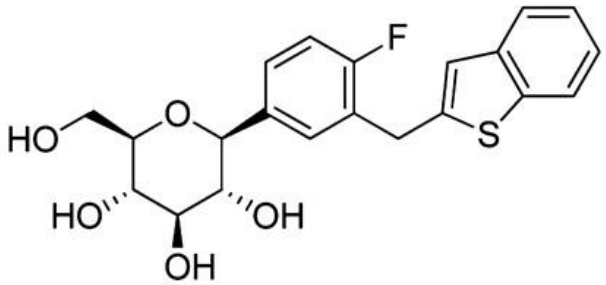
1, Dapagliflozin



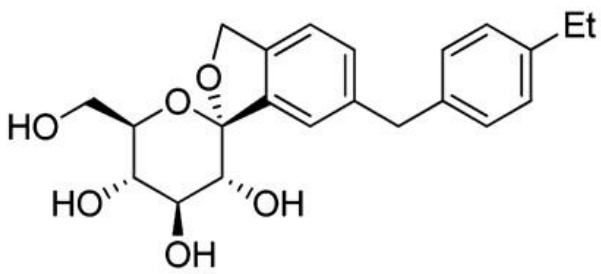
2, Canagliflozin



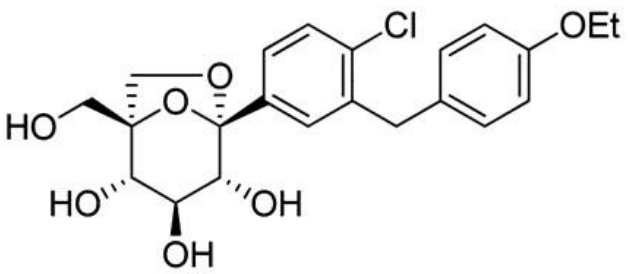
3, Empagliflozin/BI 10773



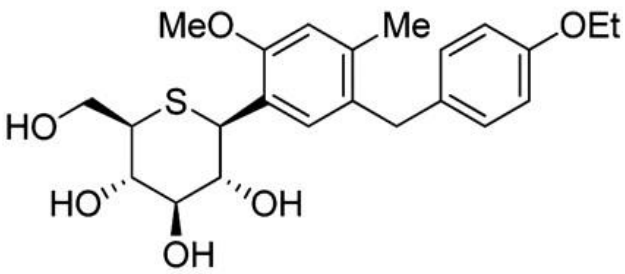
4, Ipragliflozin/ASP-1941



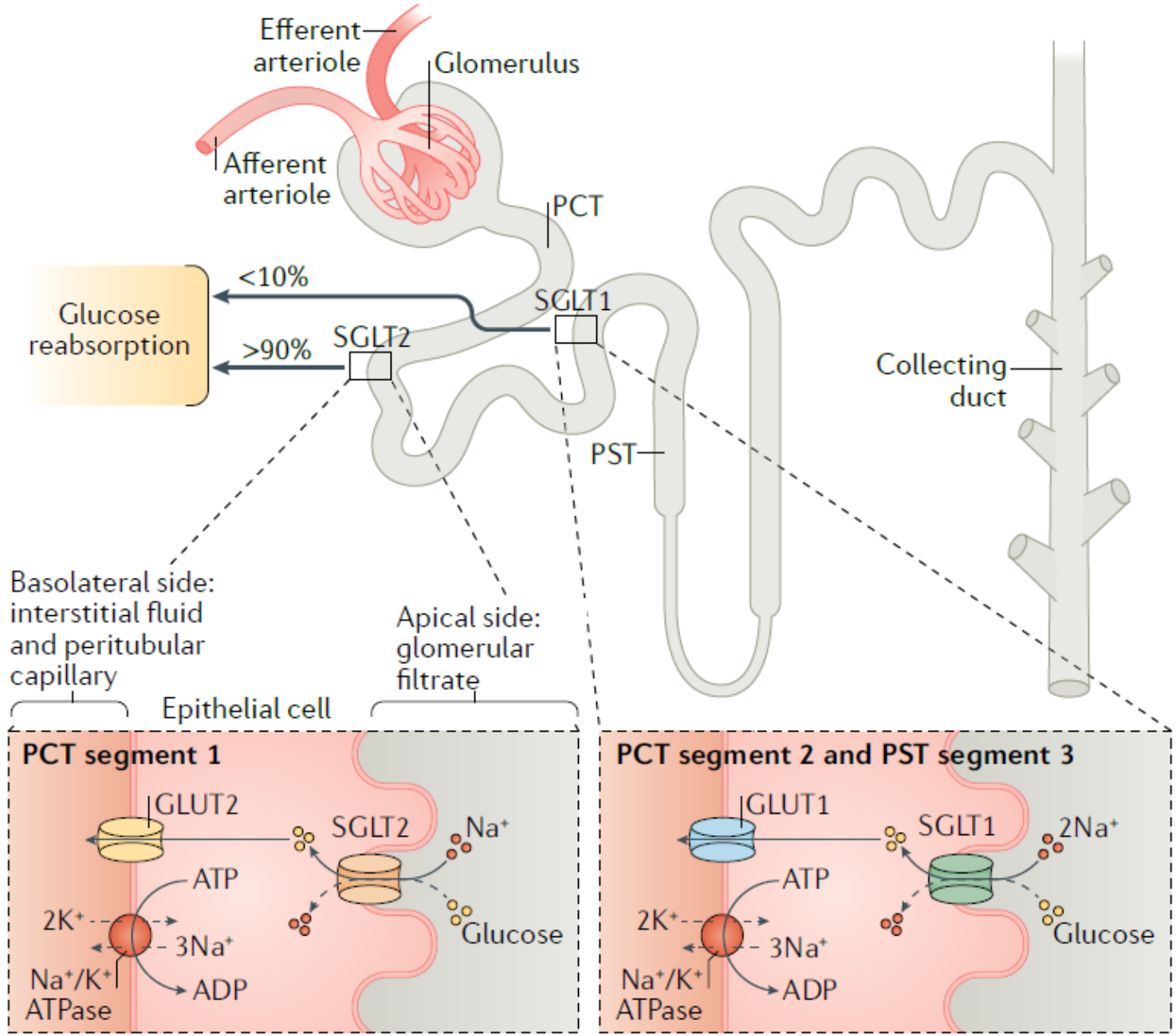
5, Tofogliflozin/CSG-452



6, PF-04971729



7, TS-071


Efferent arteriole
Glomerulus
Afferent arteriole
PCT
<10%
Glucose reabsorption
>90%
SGLT2
SGLT1
Collecting duct
PST
Basolateral side: interstitial fluid and peritubular capillary
Epithelial cell
Apical side: glomerular filtrate
PCT segment 1
GLUT2
SGLT2
Na+
ATP
2K+
3Na+
Glucose
Na+/K+ ATPase
ADP
PCT segment 2 and PST segment 3
GLUT1
SGLT1
2Na+
ATP
2K+
3Na+
Glucose
Na+/K+ ATPase
ADP

SGLT2: effetti su peso e glicata, dati dei RCT

	No. studies	No. participants (SGLT2i vs placebo)	WMD from baseline	95% CI	*P*-value
Weight change from baseline (kg)					
Dapagliflozin	20	2,954/2,971	−1.92*	−2.11, −1.72	<0.001
Canagliflozin	11	2,781/2,551	−2.30*	−2.73, −1.88	<0.001
Empagliflozin	13	2,495/2,288	−1.95*	−2.07, −1.83	<0.001
Ipragliflozin	4	370/237	−1.72*	−1.90, −1.54	<0.001
Tofogliflozin	2	122/122	−2.15*	−2.82, −1.48	<0.001
Total	51	8,710/8,151	−2.01*	−2.18, −1.83	<0.001
HbA1c change from baseline (%)					
Dapagliflozin	20	2,954/2,971	−0.58*	−0.65, −0.52	<0.001
Canagliflozin	11	2,781/2,551	−0.75*	−0.82, −0.68	<0.001
Empagliflozin	13	2,495/2,288	−0.64*	−0.71, −0.56	<0.001
Ipragliflozin	4	370/237	−0.68*	−1.02, −0.35	<0.001
Tofogliflozin	2	122/122	−0.73*	−0.77, −0.69	<0.001
Total	51	8,710/8,151	−0.64*	−0.68, −0.60	<0.001

*$P < 0.001$. CI, confidence interval; HBA1c, glycated hemoglobin; SGLT2, sodium-glucose cotransporter 2; WMD, weighted mean difference.

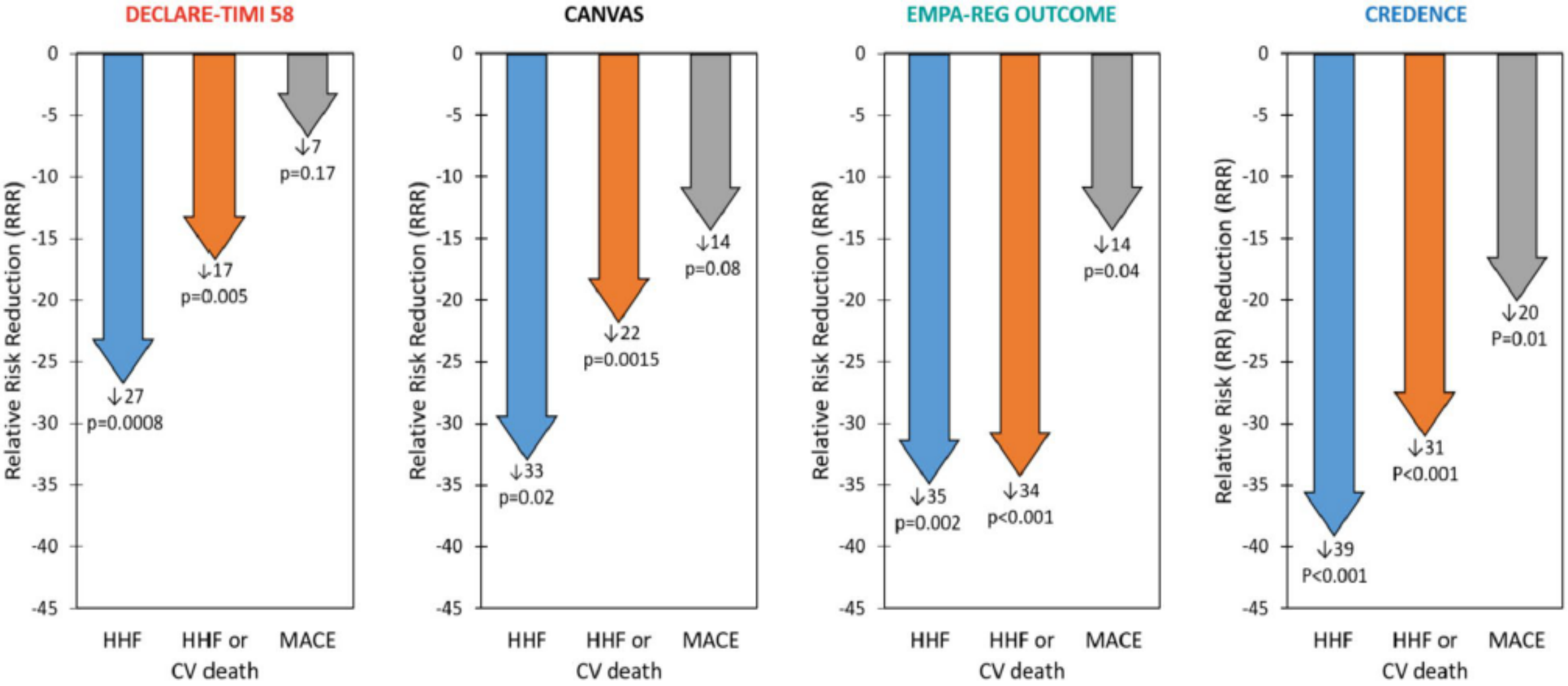
J Diabetes Investig 2017; 8: 510–517

Protezione Cardio-Renale

Evidenze Dirette e Indirette

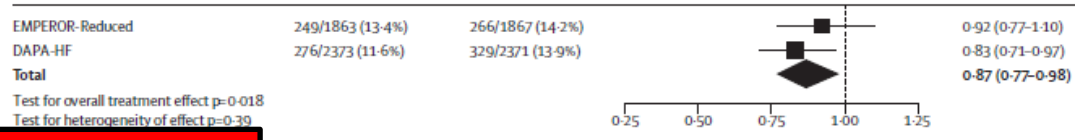
1. **CVOTs**: studi ad Hoc per valutare la sicurezza CV degli ipoglicemizzanti, spesso precedenti alla commercializzazione (EMPAREG, DECLARE-TIMI38, CANVAS, VERTIS)
2. **Heart Failure Trials:** disegnati per valutare l'efficacia di SGLT2-i su pazienti ad alto rischio CV (DAPA-HF, EMPEROR-Reduced ecc)
3. **Kidney Outcome Trials:** (Creedence, DAPA-CKD, EMPA-Kidney) disegnati per valutare l'efficacia di SGLT2-i sulla progressione della malattia renale

CVOT's

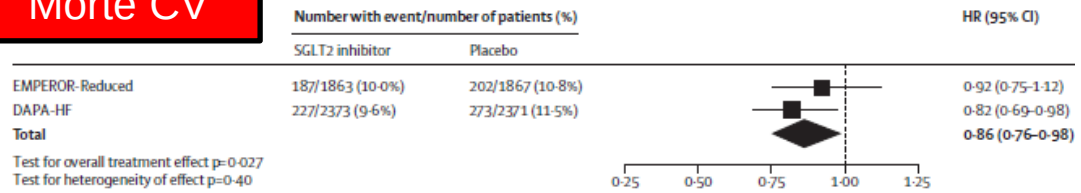


Cardiovasc Diabetol **18,** 99 (2019)

Mortalità T

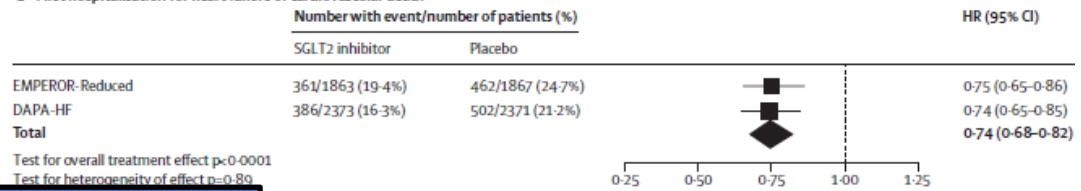


Morte CV

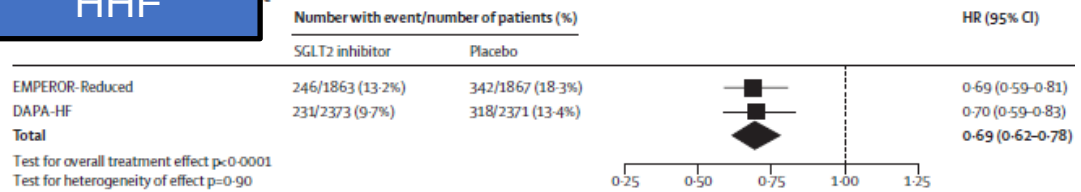


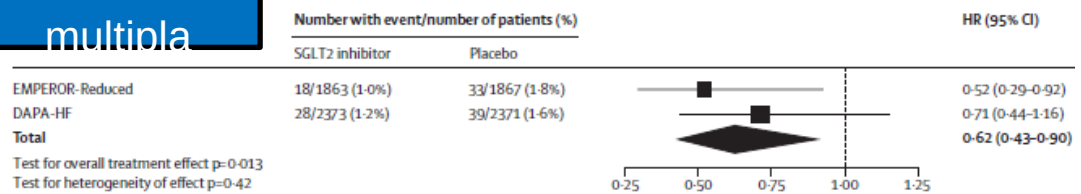
C First hospitalisation for heart failure or cardiovascular death

HHF



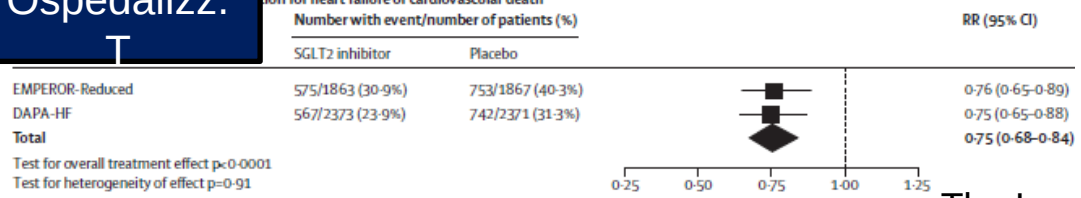
HHF multipla



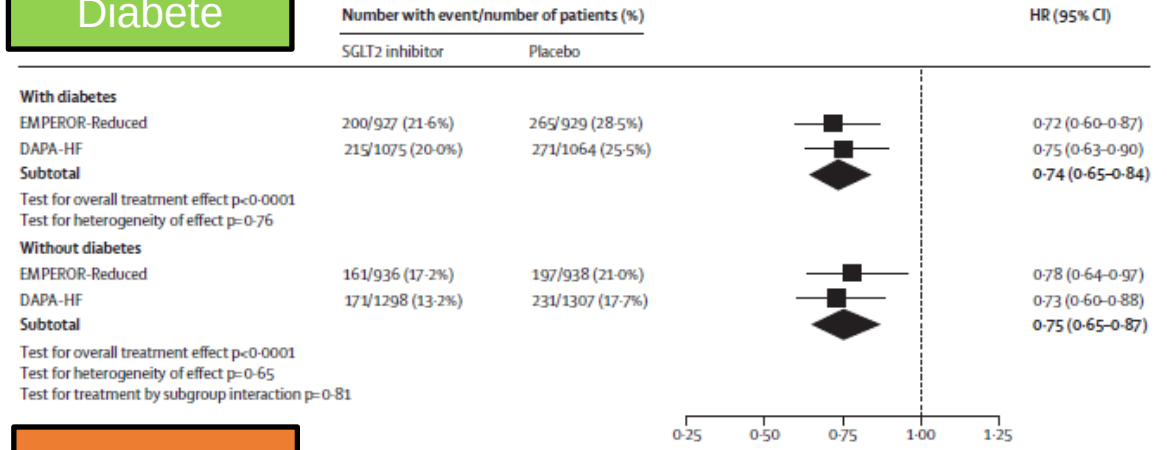


Ospedalizz. T

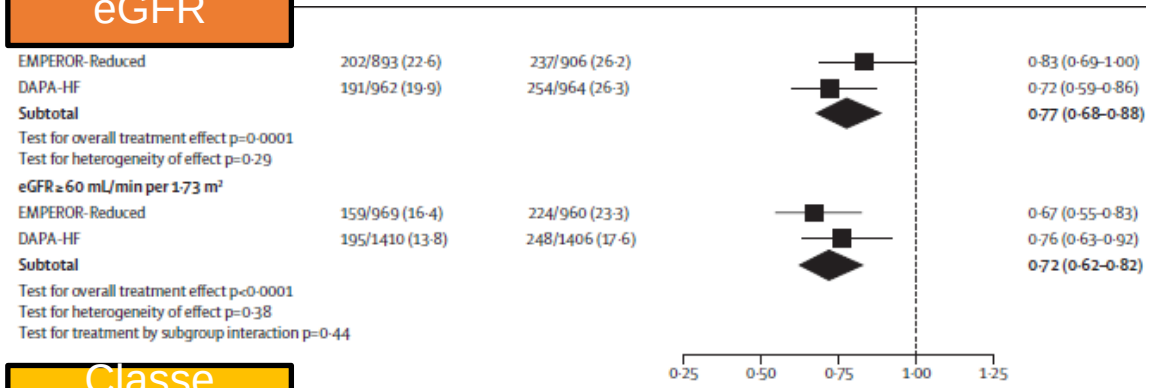
ion for heart failure or cardiovascular death



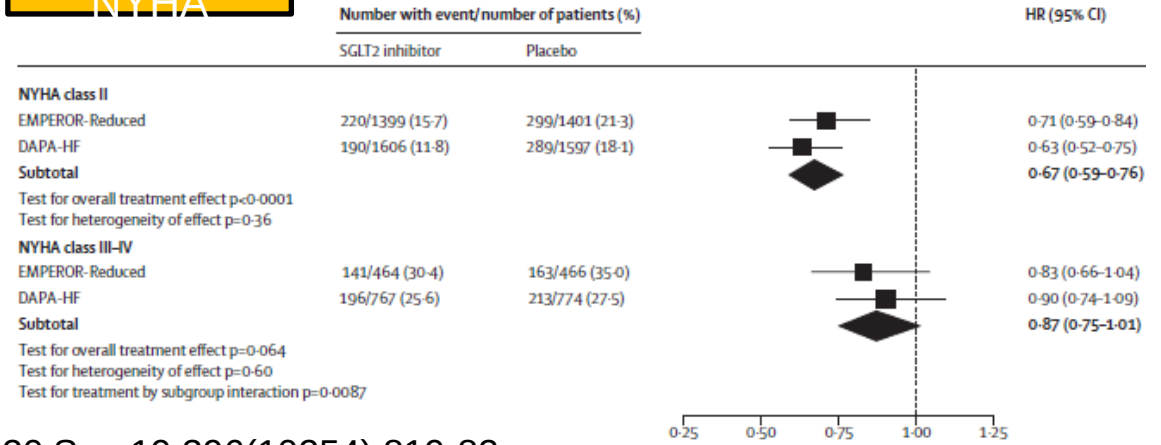
Diabete



eGFR



Classe NYHA



The Lancet. 2020 Sep 19;396(10254):819-82

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012

GFR categories (ml/min per 1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	<15			

Green, low risk (if no other markers of kidney disease, no CKD); yellow, moderately increased risk; orange, high risk; red, very high risk.

CREDENCE
GFR ≥ 30 to ≤ 90 and
UCAR ≥ 300 mg/g

DAPA-CKD
GFR ≥ 25 to ≤75
UCAR ≥ 200 mg/g

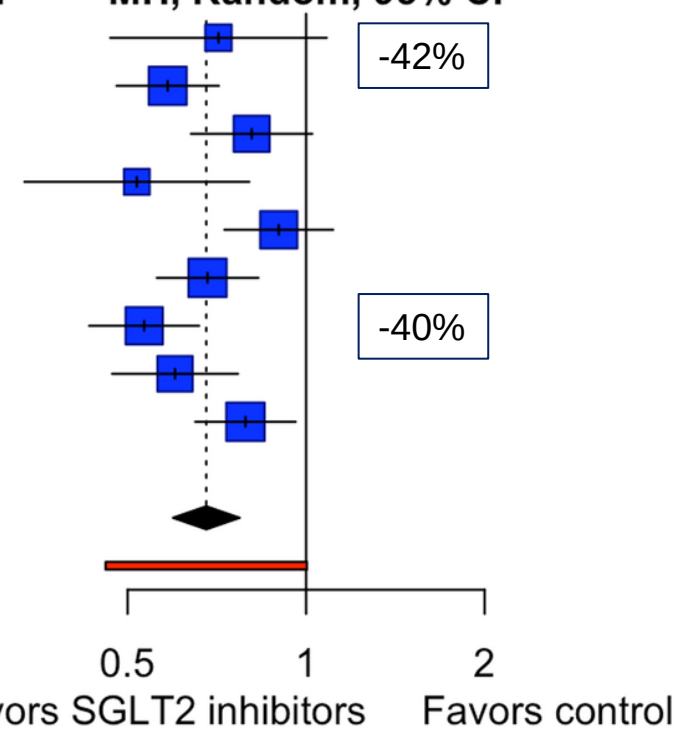
EMPA-KIDNEY
GFR ≥ 20 to ≤ 45 and
GFR ≥ 45 to ≤ 90
UCAR ≥ 200 mg/g

SGLT2-I and Renal Outcomes

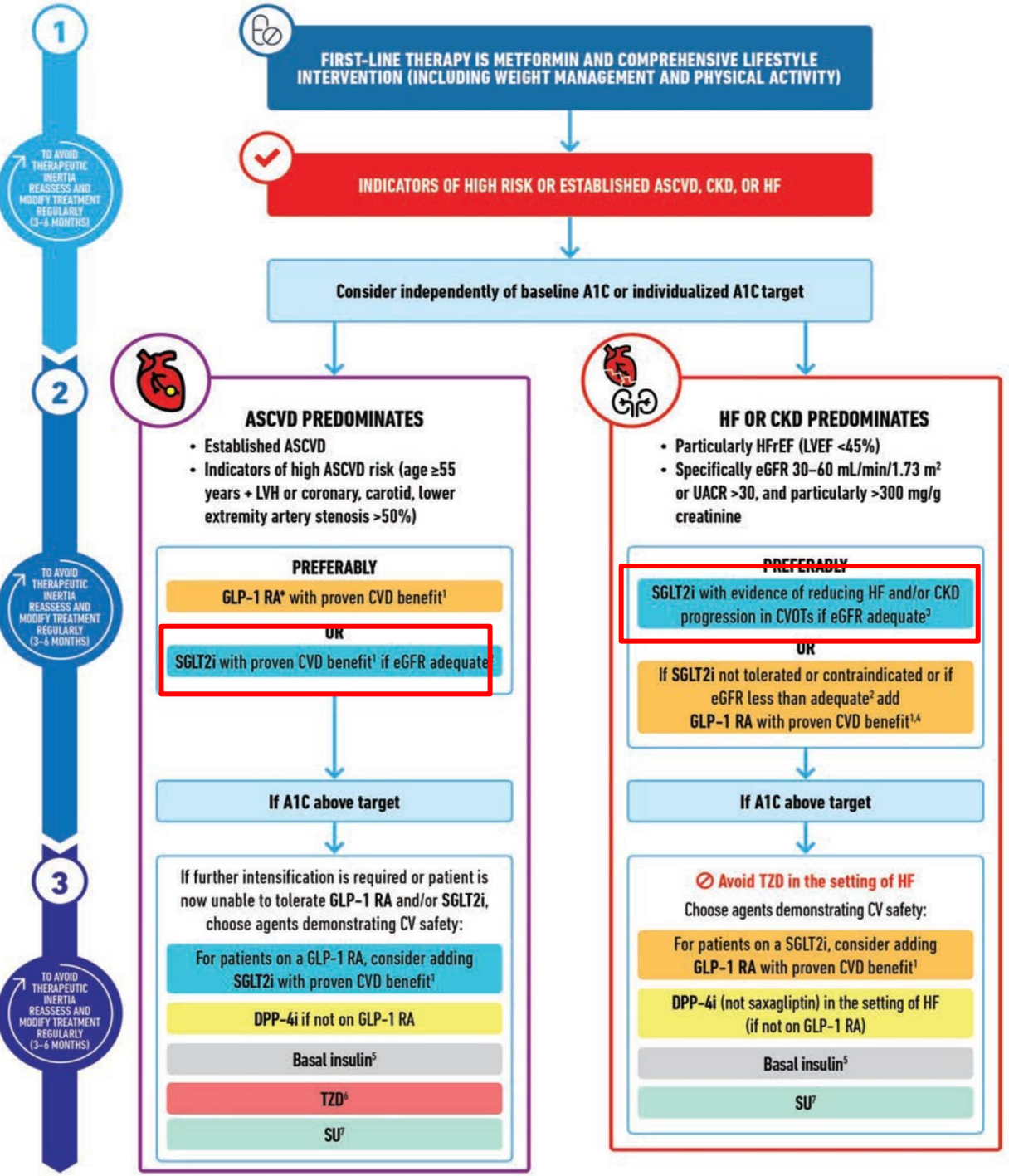
Heart Fail Rev (2021). https://doi.org/10.1007/s10741-021-10083-z

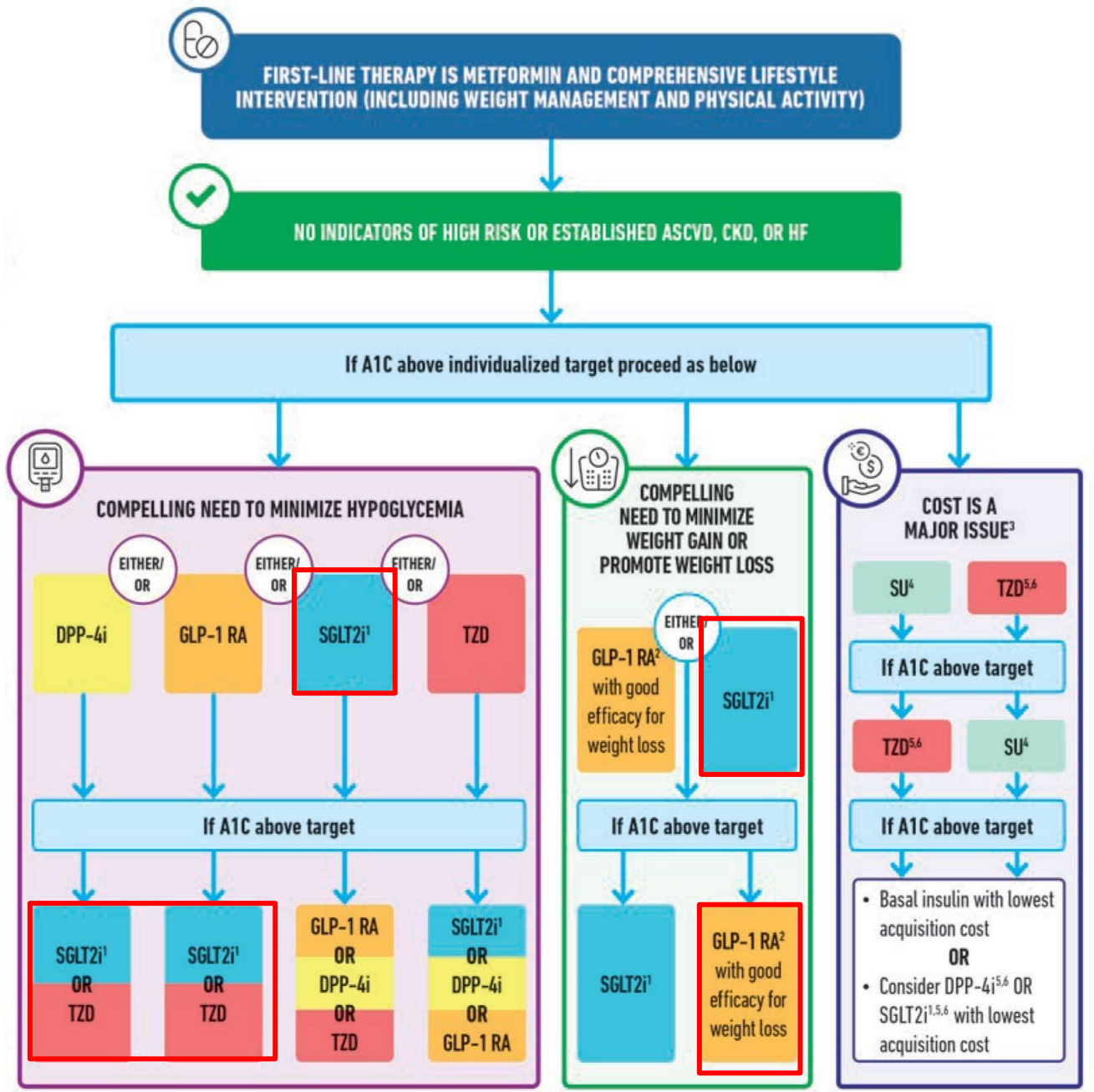
Study	SGLT2 inhibitors Events	Total	Control Events	Total	Weight	Risk Ratio MH, Random, 95% CI
SCORD 2020	37	5292	52	5292	6.3%	0.71 [0.47; 1.08]
Heerspink / DAPA-CKD 2020	142	2152	243	2152	13.1%	0.58 [0.48; 0.71]
Cannon / VERTIS CV 2020	175	5499	108	2747	11.7%	0.81 [0.64; 1.02]
Packer / EMPEROR-Reduced 2020	30	1863	58	1867	6.0%	0.52 [0.34; 0.80]
McMurray / DAPA-HF 2019	153	2373	170	2371	12.6%	0.90 [0.73; 1.11]
Perkovic / CREDENCE 2019	153	2202	224	2199	13.2%	0.68 [0.56; 0.83]
Wiviott / DECLARE–TIMI 58 2019	127	8582	238	8578	12.5%	0.53 [0.43; 0.66]
Neal / CANVAS 2017	113	5795	141	4347	11.3%	0.60 [0.47; 0.77]
Zinman / EMPA-REG OUTCOME 2015	246	4687	155	2333	13.3%	0.79 [0.65; 0.96]
Total (95% CI)		**38445**		**31886**	**100.0%**	**0.68 [0.60; 0.77]**
Prediction interval						**[0.46; 1.00]**

Heterogeneity: $Tau^2 = 0.0229$; $Chi^2 = 20.86$, df = 8 ($P < 0.01$); $I^2 = 62\%$
Test for overall effect: Z = -5.87 ($P < 0.01$)



- 32% RR Outcome Compostito di ESRD, Trapianto Renale, Morte per Cause Renali

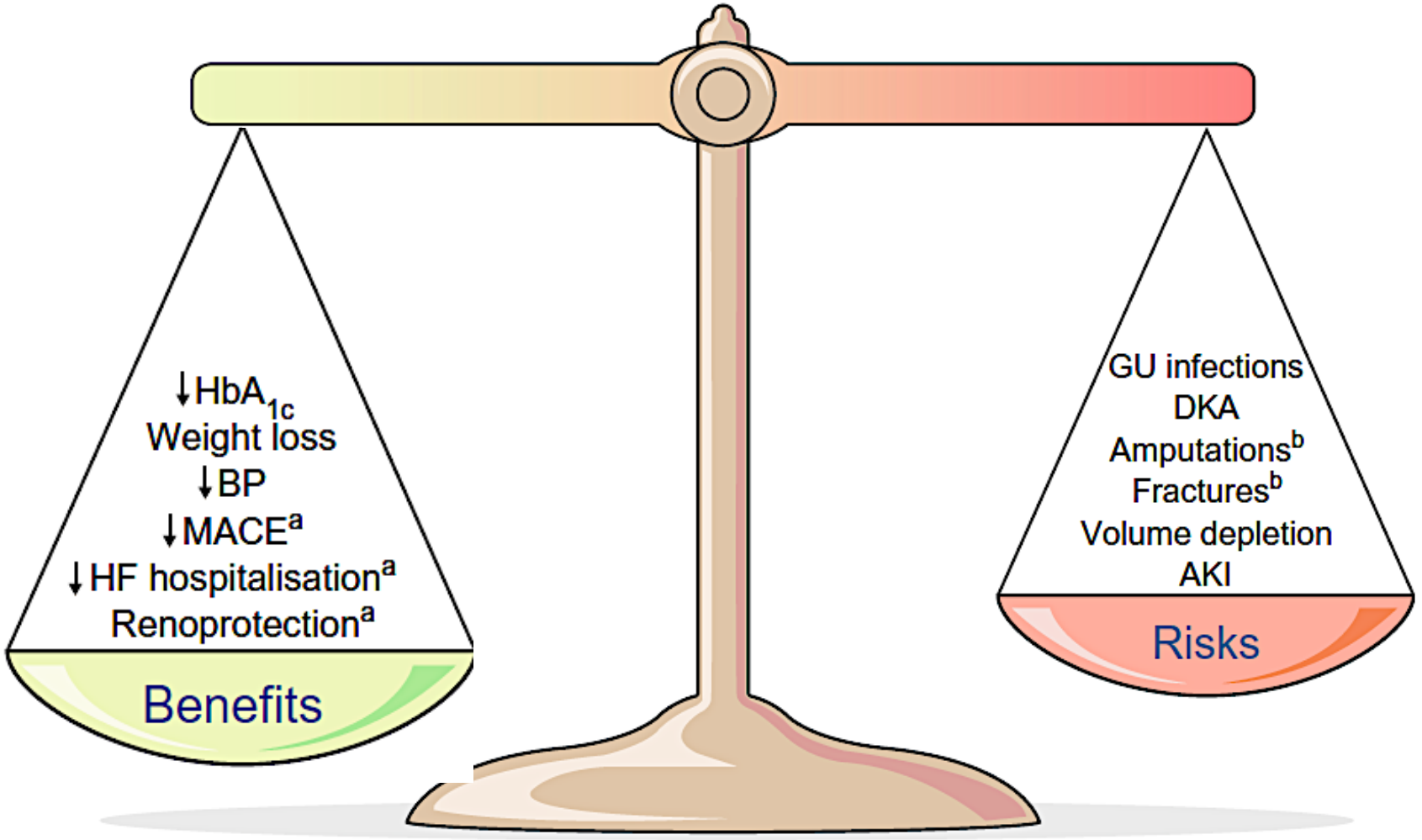




glucose-lowering medication if there is a compelling need to minimize hypoglycemia, there is a

VFG fino a (mL/min*1.73 m^2)	90	80	70	60	50	40	30	20	15	dialisi
GLP1-RA										
Dulaglutide										
Exenatide										
Exenatide LAR										
Liraglutide										
Lixisenatide										
Semaglutide s.c.										
Semaglutide orale										
Insulina umana/analoghi dell'insulina										
Metformina										
Pioglitazone										
Repaglinide										
SGLT2i										
Canagliflozin[b]										
Dapagliflozin[c]										
Empagliflozin[d]										
Ertugliflozin[d]										
Sulfoniluree										

Use of SGLT2 inhibitors in type 2 diabetes: weighing the risks and



Lupsa BC, Inzucchi SE., Diabetologia 61: 2118-2125, 2018

Infezioni Micotiche Genitali

Table 2. Incidence of GMIs in Randomized Controlled Clinical Trials.[5-8]

	Canagliflozin[a]		Dapagliflozin[b]		Empagliflozin[c]		Ertugliflozin[d]	
	100 mg	300 mg	5 mg	10 mg	10 mg	25 mg	5 mg	15 mg
GMIs (%)	7.4	7.8	5.7	4.8	4.1	3.7	6.4	8.0
Female GMIs (%)	10.6	11.6	8.4	6.9	5.4	6.4	9.1	12.2
Male GMIs (%)	4.2	3.8	2.8	2.7	3.1	1.6	3.7	4.2

Abbreviation: GMI, genital mycotic infection.
[a]Data obtained from a pool of 4 placebo-controlled, 26-week clinical trials between 2012 and 2017.
[b]Data obtained from a pool of 12 placebo-controlled clinical trials ranging from 12 to 24 weeks between 2014 and 2019.
[c]Data obtained from a pool of four 24-week and one 18-week placebo-controlled clinical trials between 2013 and 2018.
[d]Data obtained from a pool of three 26-week placebo-controlled trials between 2015 and 2018.

- ✓ 3- to 4-fold increased incidence of GMIs is considered a classwide effect of SGLT2 inhibitors.
- ✓ When candidiasis occurs, it is often mild and responsive to treatment and often does not require discontinuation of drug.
- ✓ Female sex and a prior history of GMIs are factors associated with the highest risk.
- ✓ ***Personal hygiene advice can reduce the infection risk*.**

Annals of Pharmacotherapy 2021, Vol. 55(4) 543–548

Infezioni Urinarie

Acta Diabetologica (2018) 55:503–514
https://doi.org/10.1007/s00592-018-1116-0

ORIGINAL ARTICLE

SGLT-2 inhibitors and the risk of infections: a systematic review and meta-analysis of randomized controlled trials

Robert Puckrin[1] · Marie-Philippe Saltiel[2] · Pauline Reynier[3] · Laurent Azoulay[3,4,5] · Oriana H. Y. Yu[6] · Kristian B. Filion[2,3,5]

Received: 6 December 2017 / Accepted: 9 February 2018 / Published online: 27 February 2018

Abstract

Aims There is concern about the infection-related safety profile of sodium–glucose co-transporter 2 (SGLT-2) inhibitors. We aimed to determine the effect of SGLT-2 inhibitors on genitourinary and other infections via systematic review and meta-analysis of randomized controlled trials (RCTs).

Methods We conducted a systematic search of Medline, EMBASE, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov to identify double-blinded RCTs enrolling ≥ 50 patients with type 2 diabetes which compared an SGLT-2 inhibitor to placebo or active comparator. Two independent reviewers extracted data and appraised study quality. Data were pooled using random-effects models.

Results Eighty-six RCTs enrolling 50,880 patients were included. SGLT-2 inhibitors increased the risk of genital infections compared to placebo (relative risk [RR] 3.37, 95% CI 2.89–3.93, I^2 0%) and active comparator (RR 3.89, 95% CI 3.14–4.82, I^2 0.3%). The risk of urinary tract infection (UTI) was not increased with SGLT-2 inhibitors compared to placebo (RR 1.03, 95% CI 0.96–1.11, I^2 0%) or active comparator (RR 1.08, 95% CI 0.93–1.25, I^2 22%). In drug-specific analyses, only dapagliflozin 10 mg daily was associated with a significantly increased risk of UTI compared to placebo (RR 1.33, 95% CI 1.10–1.61, I^2 0%). SGLT-2 inhibitors were associated with a reduced risk of gastroenteritis (RR 0.38, 95% CI 0.20–0.72, I^2 0%) but did not affect the risk of respiratory tract infections.

Conclusions/interpretation SGLT-2 inhibitors are associated with an increased risk of genital tract infections. Although there is no association overall between SGLT-2 inhibitors and UTI, higher doses of dapagliflozin are associated with an increased risk.

Metanalisi di 86 RCTs per un totale di 50,880 patient.

SGLT-2 inhibitors **increased the risk of genital infections** compared to placebo (relative risk [RR] 3.37, 95% CI 2.89–3.93) and active comparator (RR 3.89, 95% CI 3.14–4.82,).

The **risk of urinary tract infection (UTI) was not increased** with SGLT-2 inhibitors compared to placebo (RR 1.03, 95% CI 0.96–1.11) or active comparator (RR 1.08, 95% CI 0.93–1.25)

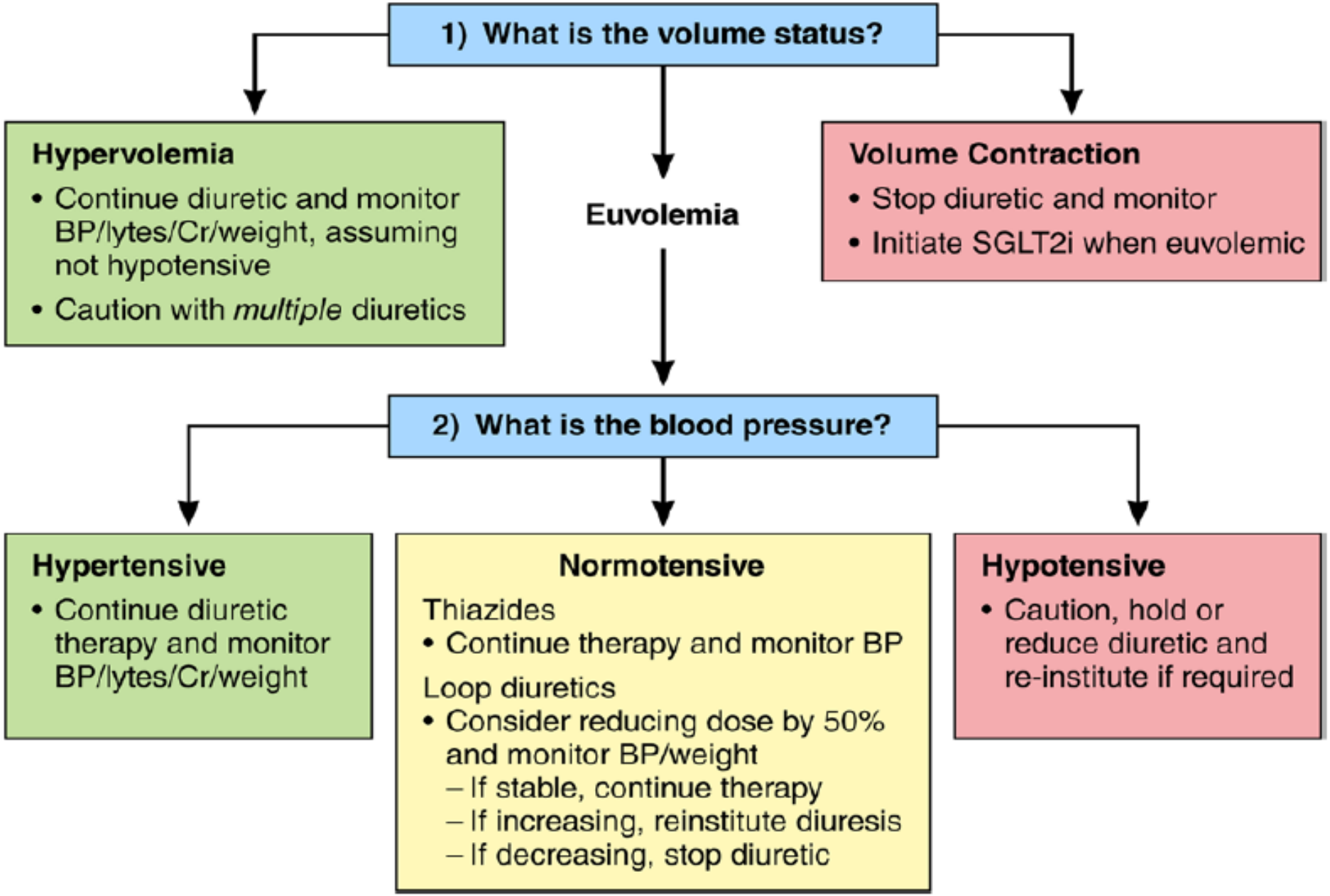
Acta Diabetol. 2018;55:503-514.

Deplezione di Volume: a Chi?

SGLT2 inibitori possono causare deplezione di volume

- ✓ Ipotensione
- ✓ Ortostatismo
- ✓ AKI
- ✓ Sincope
- ✓ Disidratazione

Attenzione a pazienti fragili, può essere necessaria rimodulazione della terapia diuretica o antipertensiva



Nephrol Dial Transplant. 2020;35(Suppl 1):i3-i12.

Chetoacidosi Euglicemica: Fattori di Rischio

- ✓ T1D including latent autoimmune diabetes in adults
- ✓ T2D with insulin deficiency (long standing)
- ✓ Excessive reduction in exogenous insulin dose or insulin cessation
- ✓ Diabetes due to pancreatic disease (pancreasectomy-Chronic Pancreatitis)
- ✓ Fasting, including during the perioperative state
- ✓ Very low carbohydrate diet
- ✓ Hypovolaemia
- ✓ Excessive alcohol consumption (daily consumption and/or binge drinking)
- ✓ Metabolic stress including acute infection, surgery, myocardial infarction, pancreatitis, and intensive exercise

Milder TY et al., Drug Safety 43: 1211-1221, 2020

Chetoacidosi Euglicemica: preveniamola

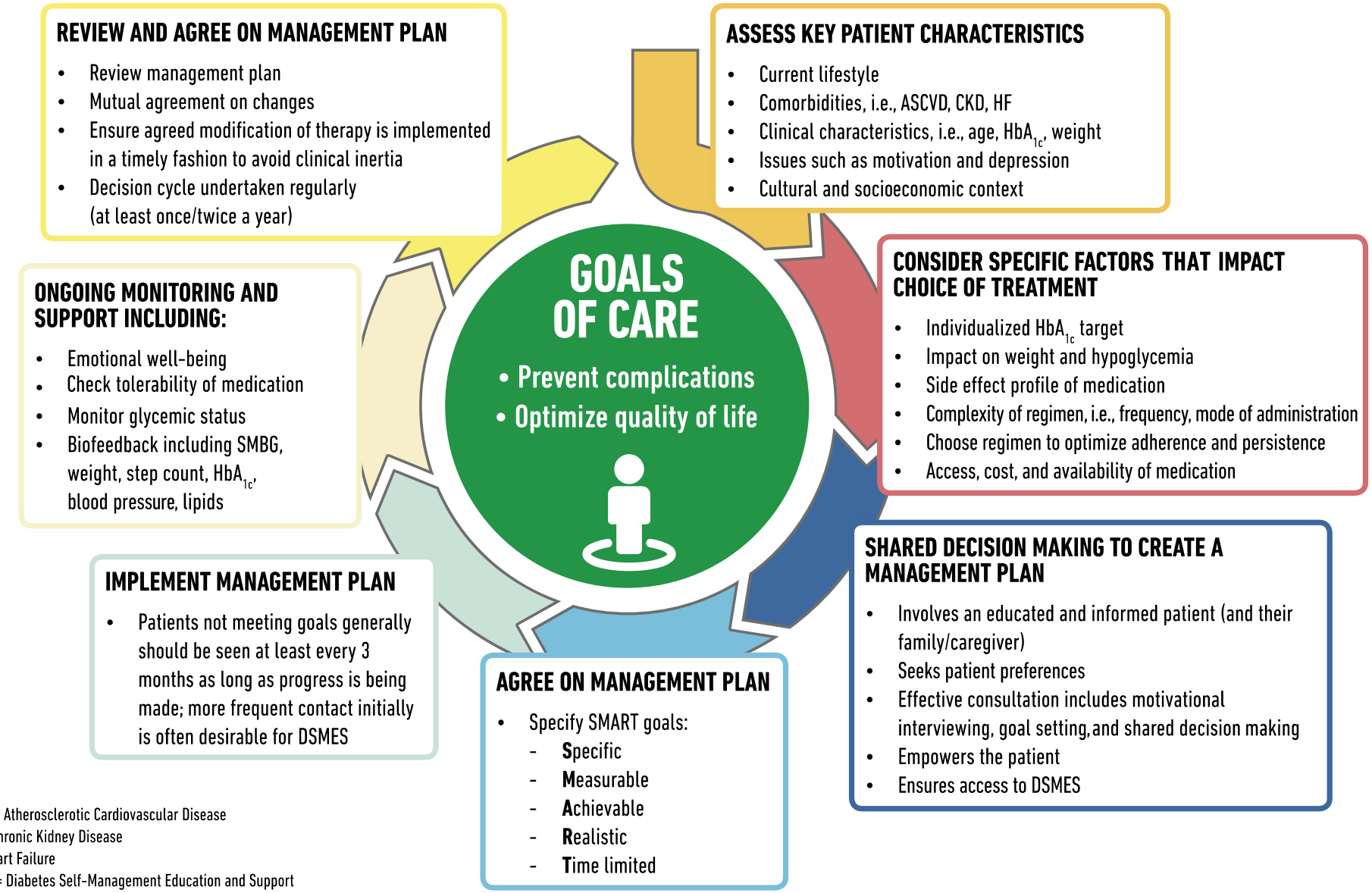
- **Prescrizione appropriata tenendo bene a mente i fattori di rischio**
- Attenzione a ridurre le dosi di insulina quando si avvia un SGLT2 inibitore
- Informare ed Educare il paziente dei fattori di rischio per SGLT2 inhibitor-associated DKA,

  1. Malattia acuta intercorrente o ipovolemia → Sick Day Plan
  2. Riconoscere i sintomi (nausea, vomito, dolore addominale, tachipnea)
  3. Rivolgersi al medico in caso di dubbi

- Sospendere SGLT2 inibitore almeno 3 giorni prima di un intervento chirurgico o in caso di esami diagnostici che necessitino di un digiuno prolungato.

Milder TY et al., Drug Safety 43: 1211-1221, 2020

DECISION CYCLE FOR PATIENT-CENTERED GLYCEMIC MANAGEMENT IN TYPE 2 DIABETES



ASCVD = Atherosclerotic Cardiovascular Disease
CKD = Chronic Kidney Disease
HF = Heart Failure
DSMES = Diabetes Self-Management Education and Support
SMBG = Self-Monitored Blood Glucose

Davies M. Diabetes Care. 2020;41:2669-2701.