SID Società Italiana di Diabetologia
fondata nel 1964

AMD ASSOCIAZIONE MEDICI DIABETOLOGI
1974 ANNO DI FONDAZIONE

Congresso Interassociativo
SID-AMD
CALABRIA 2018

Nuove frontiere terapeutiche e innovazioni tecnologiche nella gestione della Malattia Diabetica.

Diabete 2.0: *un lungo sguardo verso il futuro*

04 - 05 MAGGIO 2018

Best Western Premier - Villa Fabiano Palace Hotel
RENDE (CS)

LA FUNZIONALITÀ RENALE NEL PAZIENTE ANZIANO DIABETICO: DALLA DIAGNOSI ALLA TERAPIA

Dott. Salvatore Pacenza
Responsabile SERVIZIO DI MALATTIE METABOLICHE E DIABETOLOGIA
P.O. "San Giovanni di Dio" - CROTONE

In un'ottica di trasparenza e di adeguamento agli standard internazionali in tema di potenziali conflitti di interessi, la SID ha deciso, a partire dal Congresso Nazionale di Padova, che a tutti i relatori dei corsi/congressi verrà fornita l'opportunità, prima dei loro interventi, di indicare le aziende produttrici di farmaci e/o diagnostici dalle quali ha ricevuto compensi o finanziamenti negli ultimi due anni.
A questo proposito, le aziende con le quali ha avuto tali rapporti sono:
Eli Lilly, Boehringer Ingelheim, Novo Nordisk, Guidotti.

Age-related structural and functional changes in the kidney

Structural changes	Functional changes
Reduced kidney size	Reduced RPF and GFR
Greater involvement of renal cortex	Decreased renal functional reserve
Decreased number of gromeruli	Abnormal renal vasodilatatory response
Arteriosclerosis	Limited sodium retention and K excretion
Arteriolar hyalinosis	Defect in urinary concentration
Gromerular sclerosis	Decreased EPOand renin production
Tubular atrophy	Reduced conversion of 25-OHD to 1,25-$(OH)^2$ D
Interstitial fibrosis	Decreased insulin clearance

25-OHD: 25-hydroxyvitamin D, 1,25-$(OH)_2$D: 1,25-dihydroxyvitamin D3 (calcitriol), EPO: erytropoietin, GFR: glomerular filtration rate, RPF: renal plasma flow.

Age-related carbohydrate metabolism disorders

Reduced insulin secretion	Increased resistance to insulin
Amyloid deposits in pancreatic islets	Increased fat mass (visceral)
Decreased amylin secretion	Reduced adiponectin
Abnormal pulsatile insulin secretion	Increased CPR, IL-6 and TNF-α
Reduced β cell sensitivity to incretins	Resistance to leptin
Decreased β cell response to different glucose stimuli (arginine)	Increased intracellular triglyceride content
Abnormal glucagon response to hypoglycaemia	Mitochondrial dysfunction

IL-6: interleukin 6, CPR: C-reactive protein, TNF-α: tumour necrosis factor alpha.

Albuminuria: biomarker use and major limitations

Biomarker use	Major limitations
DKD: albuminuria levels associated with faster e-GFR decline discordance between lowering albuminuria by treatment and clinical events	Not sensitive -low e-GFR present in half or more without increased albuminuria
CVD: indipendently predicts events and mortality	Nonstandardized measurement and reporting •Assays vary by 40% •Variably reported as concentration, ratio to creatinine or timed excretion Individual variability is large •Day-to-day variability 40% •Episodic increases with fever, urinary tract infection, exercise, congestive heart failure, hypertension, hyperglycemia, high-protein diet Categorical nomenclature does not reflect continous nature of associations with DKD and CVD risks •Moderately increased albuminuria (“microalbuminuria”) •Severely increased albuminuria (“macroalbuminuria”)

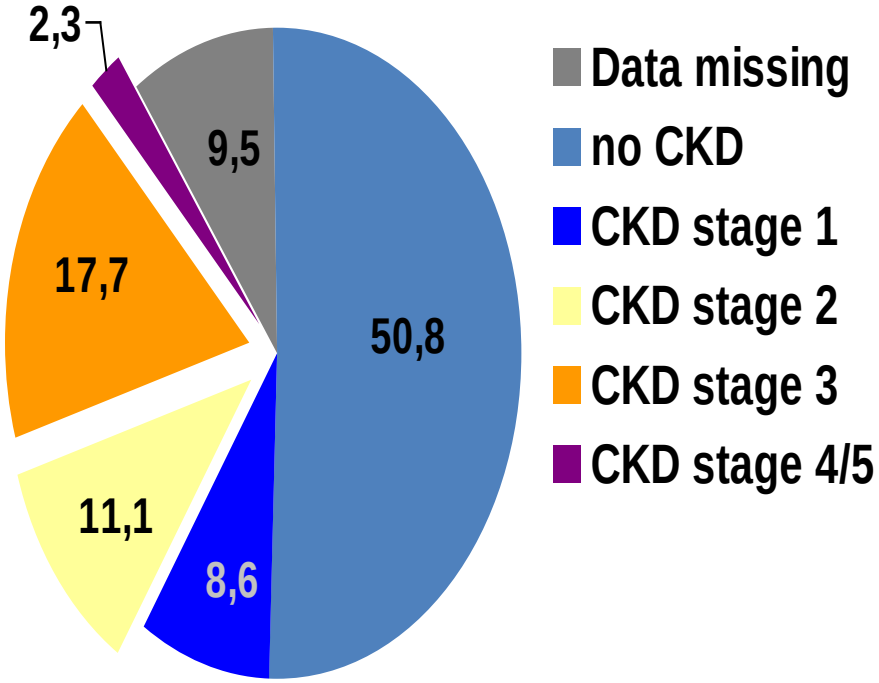
Table 2—Other cause(s) of CKD should be considered in the presence of any of the following circumstances

- Absence of diabetic retinopathy;
- Low or rapidly decreasing GFR;
- Rapidly increasing proteinuria or nephrotic syndrome;
- Refractory hypertension;
- Presence of active urinary sediment;
- Signs or symptoms of other systemic disease; or
- >30% reduction in GFR within 2–3 months after initiation of an ACE inhibitor or ARB.

Reproduced with permission from NKF (4).

Circa il 40% dei pazienti con Diabete T2 ha complicazioni renali†

La prevalenza di CKD prevalence è maggiore nei soggetti con diabete rispetto a quelli senza diabete (40.2% versus 15.4%)



CKD Stage	*eGFR (mL/min)*
No CKD	≥90*
1	≥90**
2	60–89
3	30–59
4	15–29
5	<15 or dialysis

* Normal kidney function, no sign of kidney damage
** Albuminuria – kidney damage

†Based on data from 1462 patients aged ≥20 years with T2DM who participated in the Fourth National Health and Nutrition Examination Survey (NHANES IV) from 1999 to 2004.

1. Koro CE, et al. *Clin Ther.* 2009;31:2608–17; 2. Saydah S, et al. *JAMA*. 2007;297(16):1767.

Almeno il 67% di tutti i pazienti con Diabete Tipo 2 hanno fattori di rischio cardiovascolari che % impattanto anche sulla funzionalità renale

Prevalence of risk factors for declining renal function:

	Risk factor		Prevalence in T2DM patients
1	Arterial Hypertensio n		67%[1]
2	Poor glycemic control*		63%[2]
3	Microalbuminuri a**		30%[3]
4	Dyslipidemia†		24%**[4,5]

Risk range is likely to be significantly higher than 67% due to overlap of risk factors in individuals

*Defined as not reaching the target HbA_{1c} of 7.0%[2]. **Defined as a urinary albumin-to-creatinine ratio ≥ 30 ug/mg
† defined as hypertriglyceridemia in male subjects

1. ADA National Diabetes Fact Sheet 2011. http://www.diabetes.org/diabetes-basics/diabetes-statistics (Accessed June 2011)
2. Saydah SH, et al. *JAMA*. 2004;291:335–342; 3. Cheung BMY, et al. *Am J Med.* 2009;122:443–53.
4. Mooradian A, *Nat Clin Pract Endocrinol Metab.* 2009:5;150–15; 5. Kannel WB. *Am Heart J.* 1985;110;1100–7.

OGNI INDIVIDUO HA IL DIRITTO DI NON SUBIRE DANNI DERIVANTI DAL CATTIVO FUNZIONAMENTO DEI SERVIZI SANITARI O DA ERRORI MEDICI

E

HA IL DIRITTO DI ACCEDERE A SERVIZI E TRATTAMENTI SANITARI CHE GARANTISCANO ELEVATI STANDARD DI SICUREZZA.

ART. 9 CARTA EUROPEA DIRITTI DEL MALATO

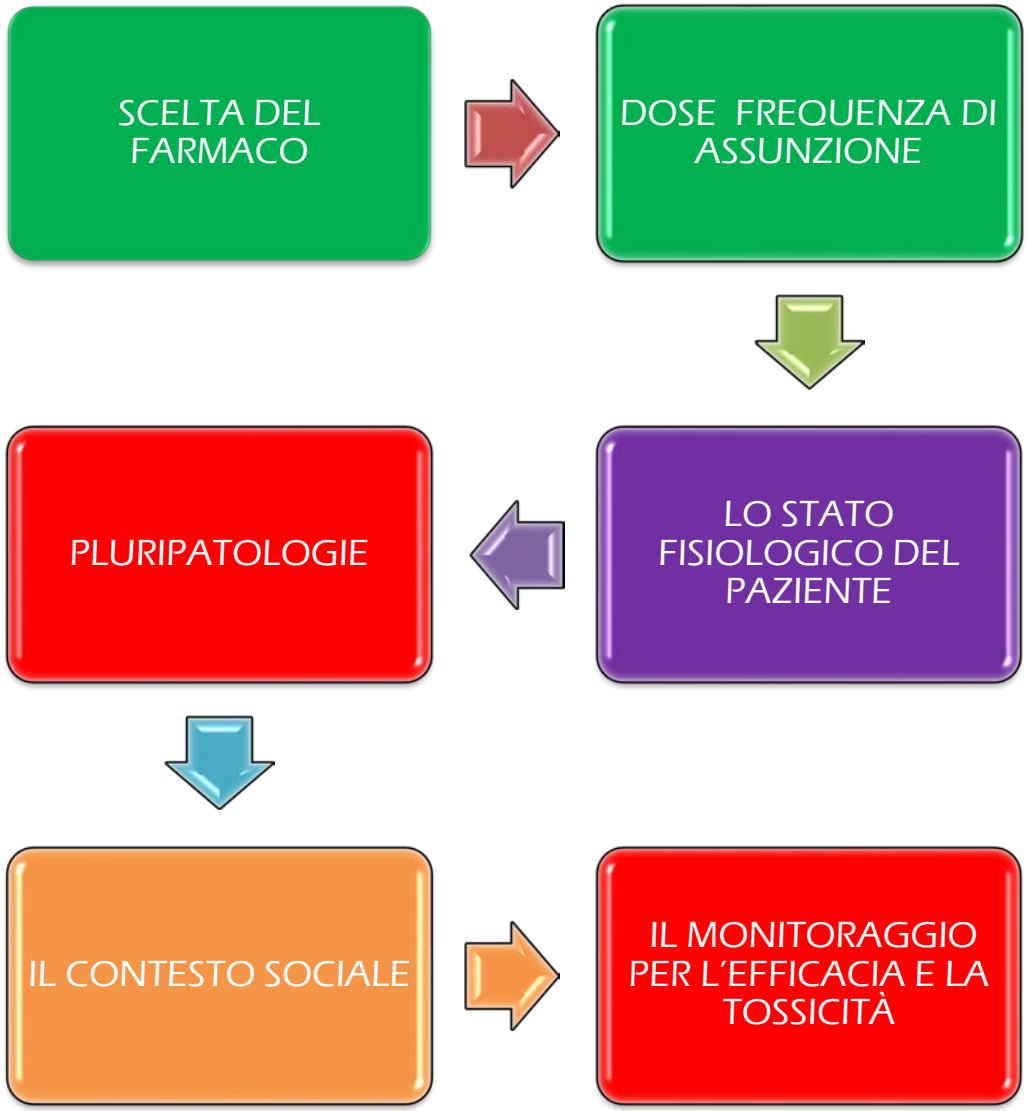
Le linee guida non sono tutte uguali

- L'attività del medico è costellata di linee, raccomandazioni e protocolli. quali sono obbligatori e quali no?

- **LE LINEE GUIDA E RACCOMANDAZIONI** definiscono direttive generali relative al compimento di una determinata operazione clinica, o per la conduzione di una specifica di atto diagnostico o terapeutico." per la loro genericità sono considerate delle indicazioni di massima da adattare al casi concreto.

- **PROTOCOLLI E CHECKLIST** indicano , in senso generale, un predefinito schema di comportamento **ed una sequenza di comportamenti assai ben definiti all'interno di un percorso clinico o terapeutico considerato fondamentale e/o obbligatorio** (es. procedura di controllo delle garze dopo un'operazione).

Prescrivere è difficile



Standard italiani per la cura del diabete mellito 2016

Metformina

Se non sufficiente, aggiungere alla metformina un secondo farmaco:

SU/Glinidi	Pioglitazone	Acarbose	*DPP4 inibitori*	*GLP1 agonisti*	*SGLT2 inibitori*	Insulina

Se non sufficiente, aggiungere un terzo farmaco:

SU/Glinidi	Pioglitazone	Acarbose	*DPP4 inibitori*	*GLP1 agonisti*	*SGLT2 inibitori*	Insulina
Pioglitazone	SU/Glinidi	Pioglitazone	Pioglitazone	Pioglitazone	*Pioglitazone*[1]	Pioglitazone
Acarbose	Acarbose	SU/Glinidi	SU/Glinidi	SU/Glinidi	*Acarbose*[1]	Acarbose
DPP4 inib.	*DPP4 inib.*	*SGLT2 inib.*[1]	*SGLT2 inib.*[1]	*SGLT2 inib.*[1]	*DPP4 inib.*[1]	*DPP4 inib.*
GLP1 agon.	*GLP1 agon.*	Insulina	Insulina	Insulina	*GLP1 agon.*[1]	*GLP1 agon.*
SGLT2 inib.[1]	*SGLT2 inib.*[1]				*SU/Glinidi*[1]	*SGLT2 inib.*
Insulina	Insulina				Insulina	SU/Glinidi

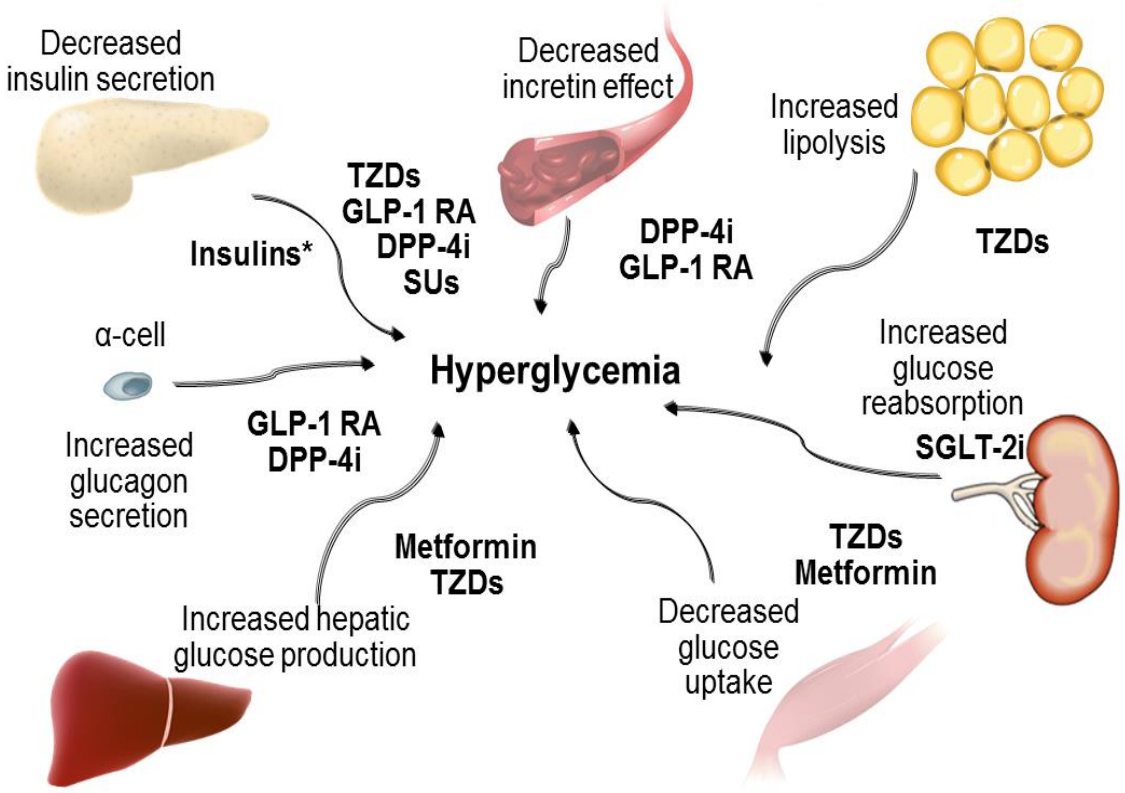
In caso di cattivo controllo con la triplice terapia, iniziare comunque la terapia insulinica, mantenendo la metformina:

Insulina

con l'eventuale aggiunta di:

SU/Glinidi	Pioglitazone	Acarbose	*DPP4 inib.*	*GLP1 agon.*	*SGLT2 inib.*

Target dei farmaci ipoglicemizzanti



*Exogenous insulin does not increase insulin secretion but does act as a substitute for decreased endogenous insulin

1. DeFronzo. *Diabetes* 2009;58:773-95
2. Freeman. *J Am Osteopath Assoc* 2009;109:26-36

DPP-4i=dipeptidyl peptidase-4 inhibitor
GLP-1 RA=glucagon-like peptide-1 receptor agonist
SGLT-2=sodium-glucose co-transporter-2
SU=sulfonylurea
TZD=thiazolidinedione

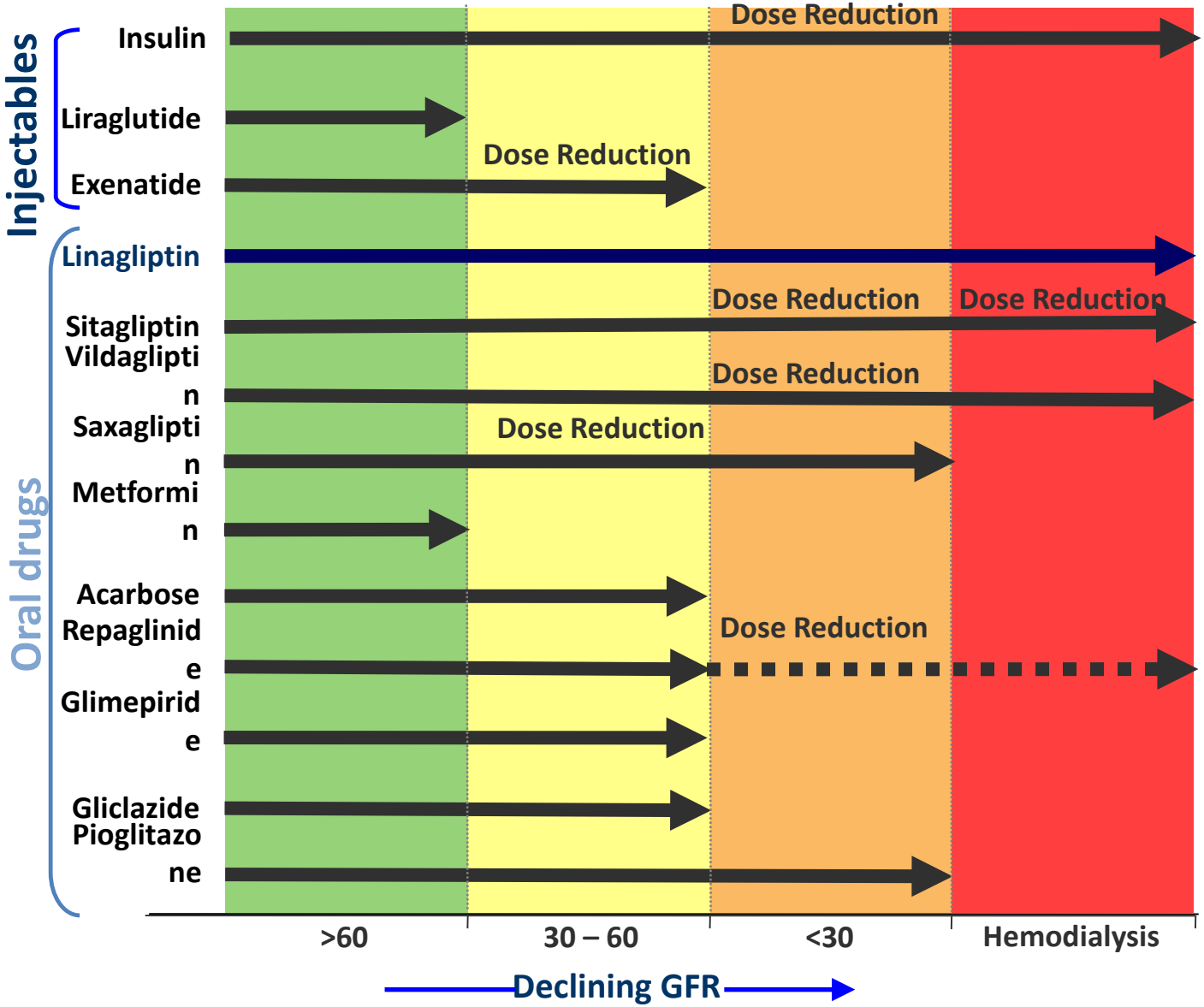
	Metfor-mina	Acarbosio	GLP-1	Gliflo-zina	Glip-tina	Pioglita-zone	SU/ glinide	Insulina basale	Insulina basal-bolus
Riduzione della HbA_{1c} a breve termine (3-6 mesi)*	+++	+	+++	++	++	+	+++	+++	++++
Riduzione della HbA_{1c} a medio termine (1-2 anni)*	++	+	+++	++	++	++	++	+++	++++
Riduzione della HbA_{1c} a lungo termine (oltre 2 anni)*	++	+	+++	++	ND	+++	+	+++	++++
Riduzione del peso corporeo	+/-	+/-	+++	++	-	-	-	-	-
Riduzione della pressione arteriosa	+/-	-	+	++	-	+	-	-	-
Riduzione della morbilità/mortalità CV**	++	-	-	+++	-	++	-	-	-

AMD - Standard italiani per la cura del diabete mellito 2016

	Metfor-mina	Acarbosio	Agon-sta GLP-1	Gliflo-zina	Glip-tina	Pioglita-zone	SU/ glinide	Insulina basale	Insulina basal-bolus
Interazioni con altri farmaci	-	-	-	-	-	+	+++	+++	++++
Ipoglicemie	-	-	-	-	-	-	++	+++	++++
Aumento di peso	-	-	-	-	-	++	+	+++	++++
Pancreatiti	-	-	+/-	-	+/-	-	-	-	-
Fratture	-	-	-	-/+[a]	-	+++	-	-	-
Scompenso cardiaco	-	-	-	-	-/+[b]	++	+	-	-
Disturbi gastrointe-stinali	++	+++	++	-/+	-	-	-	-	-
Infezioni genitali	-	-	-	+	-	-	-	-	-

AMD – SID. Standard italiani per la cura del diabete mellito 2016

Gli attuali trattamenti per diabete tipo 2 hanno limitazioni quando declina la funzionalità renale.



Adapted from: Schernthaner G, et al. *Nephrol Dial Transplant*. 2011;26(2):454–7 and respective EMEA SmPCs

Table 3—Recommended dose adjustments for noninsulin antihyperglycemic agents in DKD

Medication	In patients with impaired GFR	In dialysis patients
Biguanides		
Metformin	U.S. prescribing information states "do not use if serum creatinine ≥1.5 mg/dL in men, ≥1.4 mg/dL in women" British National Formulary and the Japanese Society of Nephrology recommend cessation if eGFR <30 mL/min/1.73 m^2	Contraindicated
Second-generation sulfonylureas		
Glipizide	No dose adjustment required	No dose adjustment required
Glimepiride	Initiate conservatively at 1 mg daily	Initiate conservatively at 1 mg daily
Glyburide	Avoid use	Avoid use
Meglitinides		
Repaglinide	Initiate conservatively at 0.5 mg with meals if eGFR <30 mL/min/1.73 m^2	No clear guidelines exist
Nateglinide	Initiate conservatively at 60 mg with meals if eGFR <30 mL/min/1.73 m^2	No clear guidelines exist
TZDs		
Pioglitazone	No dose adjustment required	15–30 mg daily has been used (190)
α-Glucosidase inhibitors		
Acarbose	Avoid if eGFR <30 mL/min/1.73 m^2	Avoid use
Miglitol	Avoid if eGFR <25 mL/min/1.73 m^2	Avoid use
GLP-1 receptor agonists		
Exenatide	Not recommended with eGFR <30 mL/min/1.73 m^2	Avoid use
Liraglutide	Not recommended with eGFR <60 mL/min/1.73 m^2	Manufacturer does not recommend use (currently under study)
Albiglutide	No dose adjustment required	No clear guidelines exist—limited clinical experience in severe impairment of kidney function
DPP-4 inhibitors		
Sitagliptin	100 mg daily if eGFR >50 mL/min/1.73 m^2 50 mg daily if eGFR 30–50 mL/min/1.73 m^2 25 mg daily if eGFR <30 mL/min/1.73 m^2	25 mg daily
Saxagliptin	5 mg daily if eGFR >50 mL/min/1.73 m^2 2.5 mg daily if eGFR ≤50 mL/min/1.73 m^2	2.5 mg daily
Linagliptin	No dose adjustment required	No dose adjustment required
Alogliptin	25 mg daily if eGFR >60 mL/min/1.73 m^2 12.5 mg daily if eGFR 30–60 mL/min/1.73 m^2 6.25 mg daily if eGFR <30 mL/min/1.73 m^2	6.25 mg daily
Amylinomimetics		
Pramlintide	No dose adjustment required with eGFR >30 mL/min/1.73 m^2	Avoid use

Table 4—Recommended dose adjustments for metformin based on eGFR

eGFR (mL/min/1.73 m^2)	Proposed action
≥60	No contraindication to metformin Monitor kidney function annually
<60 and ≥45	Continue use Increase monitoring of renal function (every 3–6 months)
<45 and ≥30	Prescribe metformin with caution Use lower dose (e.g., 50%, or half-maximal dose) Closely monitor renal function (every 3 months) Do not start new patients on metformin
<30	Stop metformin

Adapted with permission from ADA (83).

Table 5—Macronutrient recommendations in DKD

Organization	Lower ranges of dietary protein intake	Higher ranges of dietary protein intake	Carbohydrate	Fatty acids	Sodium
KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease (22)	0.8 g protein/kg/day in adults with diabetes and GFR <30 mL/min/1.73 m^2 with appropriate education	Avoid protein intake >1.3 g/kg/day in adults with CKD at risk for progression; specific comment for DKD not provided	Specific recommendation not provided	Specific recommendation not provided	Lower salt intake to <2 g of sodium per day (5 g of sodium chloride), unless contraindicated
KDOQI 2007 Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease (4)	Recommended dietary allowance of 0.8 g/kg body weight per day for people with DKD and CKD stages 1–4	Avoid high-protein diets defined as ≥20% of total daily calories	Specific recommendation not provided	Increase intake of omega-3 and omega-9 fatty acids	Reduction of intake 2.3 g/day as recommended by the DASH diet
ADA Standards of Medical Care in Diabetes—2014 (20) and Nutrition Therapy Recommendations for the Management of Adults With Diabetes (136)	Maintain usual level of dietary protein intake (136); approximated by reported studies surveying diet intake in people with diabetes to be approximately 16–18% of total calories (20)	Specific comment not provided	Specific recommendation for DKD not provided. For diabetes, include carbohydrates from vegetables, fruits, whole grains, legumes, and dairy products over intake from carbohydrates containing added sugar, fat, and sodium. Avoid beverages, products with high-fructose corn syrup, and sucrose	Total fat: individualized Omega-3: same recommendation as for general public. Cholesterol, saturated, *trans* fats: same as for general public Mono- and polyunsaturated fats: integrated to comment regarding potential benefits of a Mediterranean diet pattern	Specific recommendation for DKD not provided For individuals with diabetes, reduce sodium to <2,300 mg/day as recommended for the general public

Table 6—Approaches to incorporating diet patterns for diet management of DKD for type 1 and type 2 diabetes*

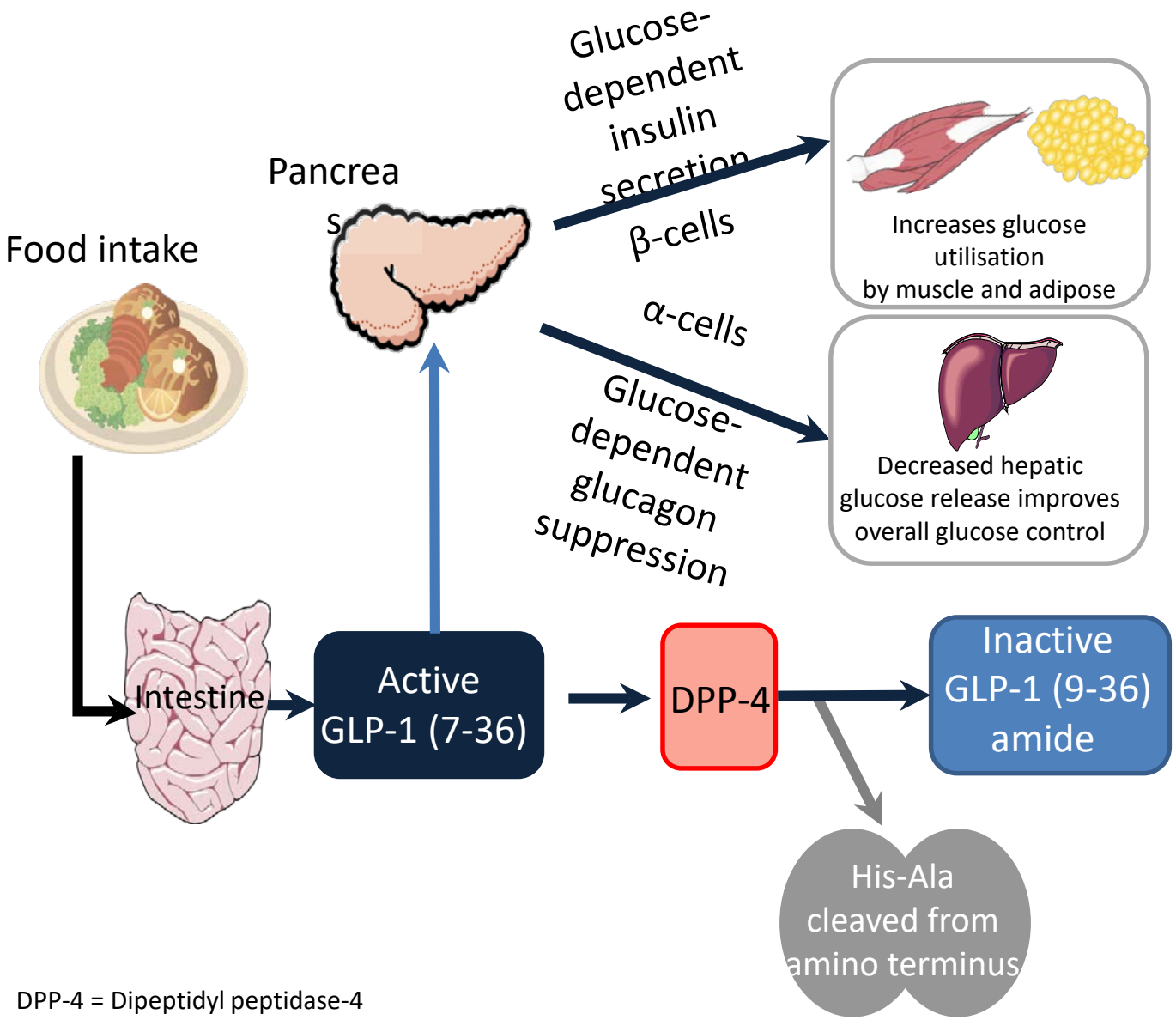
Nutrient	Concept	How?	What?	Quantity
Protein	Explore/sample plant proteins	Incorporate vegan protein sources into meal plan, de-emphasize intake of fatty animal protein sources such as marbled red meats, poultry products with skin, shellfish Dairy products: emphasize nonfat and low-fat versions in diet, sample nondairy milk products	Dried beans and peas Legumes Nuts and seeds Soy Quinoa Nonfat yogurts, milks, lower-fat cheese selections Include almond, rice, soy milk	Amount to maintain optimal glycemic control, as tolerated; maintain or obtain optimal nutritional status
Carbohydrates: complex	Explore/sample	Include high-fiber, whole-grain products, de-emphasize refined white flour—based products	Whole/mixed-grain breads, pastas, cereals; wild, brown rice types	Within carbohydrate counting/diabetes management plan, as tolerated
Fruits and vegetables	High-fiber fruits/vegetables	Include as part of meals snacks and different formats such as smoothies	Fresh fruits and vegetables of choice, fresh cooked vegetables ideal, precooked choices available without seasonings	6–8 servings per day as appropriate for meal plan and carbohydrate counting
Fat	Omega-9 and omega-3 fatty acids as a component of fat source	Enrich diet with olive oil, fish oil, and vegetarian sources of omega-3 fatty acids, de-emphasize saturated fat sources and generic vegetable oils that are enriched in omega-6 fatty acids	Include olive oil/canola oil—based margarines and fats, choose omega-3–enriched whole-grain breads and cereals when available	Within meal plan for calories and palatability
Sodium	Maximize approaches to lower sodium and salt intake	Reduce free salt use Use fresh cooked foods, purchase unseasoned options of foods, put sauces/flavorings on side	Use sodium-free fresh and dried herbs, spices, and herbal blends, when available	1,500–3,000 mg daily; transition toward lower range of intake
Weight management	If overweight, work on weight reduction	Decrease calories, increase calorie utilization through a regular exercise program, avoid excessively high-protein diets (i.e., >20% kcal from protein)	Balanced proportions of protein, carbohydrate, and fat within individualized approach to maintain euglycemia	Based on individually determined ideal/healthy body weight, gradual weight loss toward goal to allow for altered eating pattern, ongoing modifications in diet as weight goal approached and glycemia management

Table 7—Recommendations for multiple risk factor management in DKD (20,39,183,184)

Risk factor	General recommendations for diabetes	Modifications for DKD
Hyperlipidemia	Goal LDL <100 mg/dL or 30–40% reduction from baseline Treatment consists of dietary modifications Statins are recommended in patients with overt CVD and those over the age of 40 years with another risk factor for CVD For high-CVD-risk patients, <70 mg/dL is an option	No specific goal for LDL cholesterol, consider measuring lipids to assess adherence to medication regimen Treatment consists of dietary modifications Statin or statin-ezetimibe combination is recommended in patients with nondialysis-dependent CKD Reduced doses of statins are recommended for eGFR <60 mL/min/1.73 m^2 Initiation of statin therapy has not been shown to be beneficial in patients undergoing chronic dialysis treatment Statins may reduce CVD risk in kidney transplant recipients
Hypertension	Goal BP is <140/80 mmHg Treatment consists of lifestyle modifications and oral medications that generally should include RAAS blockers	Goal BP is <140/90 mmHg Goal BP is <130/80 mmHg if urine ACR >30 mg/g creatinine Goals for treatment are based primarily on studies of patients with nondiabetic CKD Treatment consists of lifestyle modifications and oral medications that usually include RAAS blockers Use of more than one RAAS blocker should generally be avoided
Hyperglycemia	Goal is A1C <7% A goal of <6.5% may be appropriate in early-onset diabetes in younger patients Treatment consists of lifestyle modification, oral medications, and injectable medications, including insulin	A1C <8% when GFR <60 mL/min/1.73 m^2 due to increased risks of hypoglycemia Imprecision of A1C with CKD strengthens reliance of SMBG in making treatment decisions Doses of insulin and other injectable and oral medications used to lower blood glucose often need to be reduced for eGFR <60 mL/min/1.73 m^2

DPP-4 Inibitori

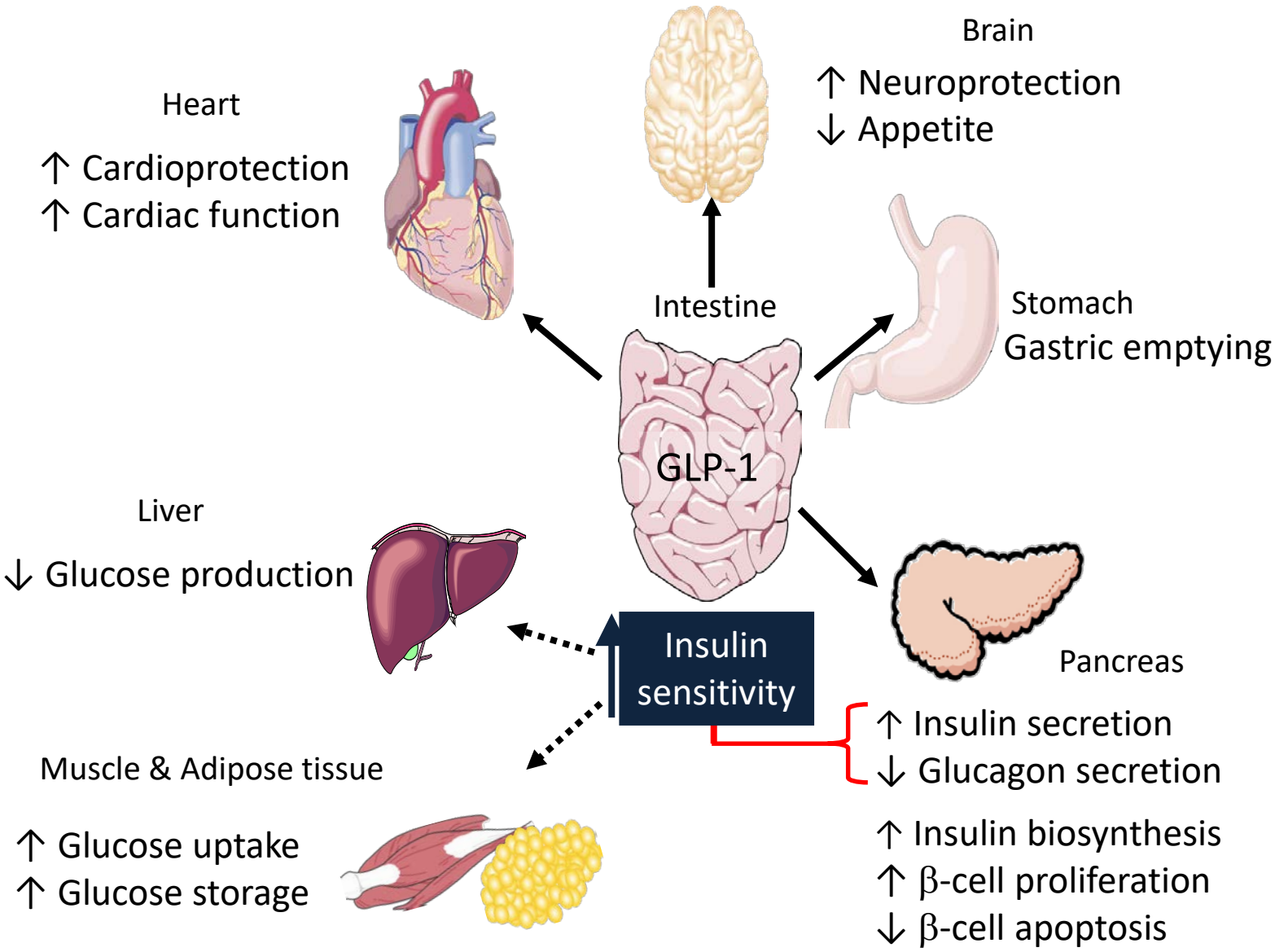
Glucagon-like-peptide (GLP) -1 è degradato da DPP-4



DPP-4 = Dipeptidyl peptidase-4

Adapted from Drucker DJ. *Expert Opin Invest Drugs*. 2003;12(1):87–100
Ahrén B. *Curr Diab Rep.* 2003;3:365–372

GLP-1 ha un‘ampia gamma di attività biologiche



Baggio & Drucker. *Gastroenterol.* 2007;132:2131–57.

Caratteristiche cliniche dei DPP-4 inibitori a confronto

Characteristics	Linagliptin[1]	Sitagliptin[2]	Vildagliptin[3]	Saxagliptin[4]
One dose fits all*	✓			
No dose adjustment in renal impairment	✓			
No dose adjustment in hepatic impairment	✓	✓		✓
No dose adjustment based on drug-drug-interactions	✓	✓	✓	
No drug-related monitoring of renal function	✓			
No skin toxicity in pre-clinical studies	✓	✓		
No liver toxicity	✓	✓		✓
No reports of decrease in renal function	✓		✓	✓

* Without limitations in renal or hepatic impairment: please consult the label before prescribing

1. Linagliptin US PI.
2. Sitagliptin US PI.
3. Vildagliptin EU SmPC
4. Saxagliptin US PI.

Caratteristiche farmacologiche dei DPP-4 inibitori a confronto

		Linagliptin 5 mg QD	Vildagliptin 100 mg QD	Vildagliptin 50 mg bid	Vildagliptin 5 mg QD	Vildagliptin 25 mg QD
Metabolism	Relevant organ for metabolism[1]	None	None	Liver	Liver	None
	Active metabolites	No	No	No	Yes	No
Excretion	Primary route of excretion	Bile & gut	Kidney	Kidney	Kidney	Kidney
	Share of renal excretion[2]	5%	87%	85%	75%	60 - 71%
Dosing and monitoring	Dose adjustment or limitations in RI[3]	No	Yes	Yes	Yes	Yes
	Drug-related monitoring	No	Kidney function	Kidney and liver function	Kidney function	Kidney function

1- If metabolized to a relevant degree
2- Including metabolites and unchanged drug; excretion after single dose administration of C14 labeled drug
3- As recommended in countries, where respective DPP-4 inhibitor is available

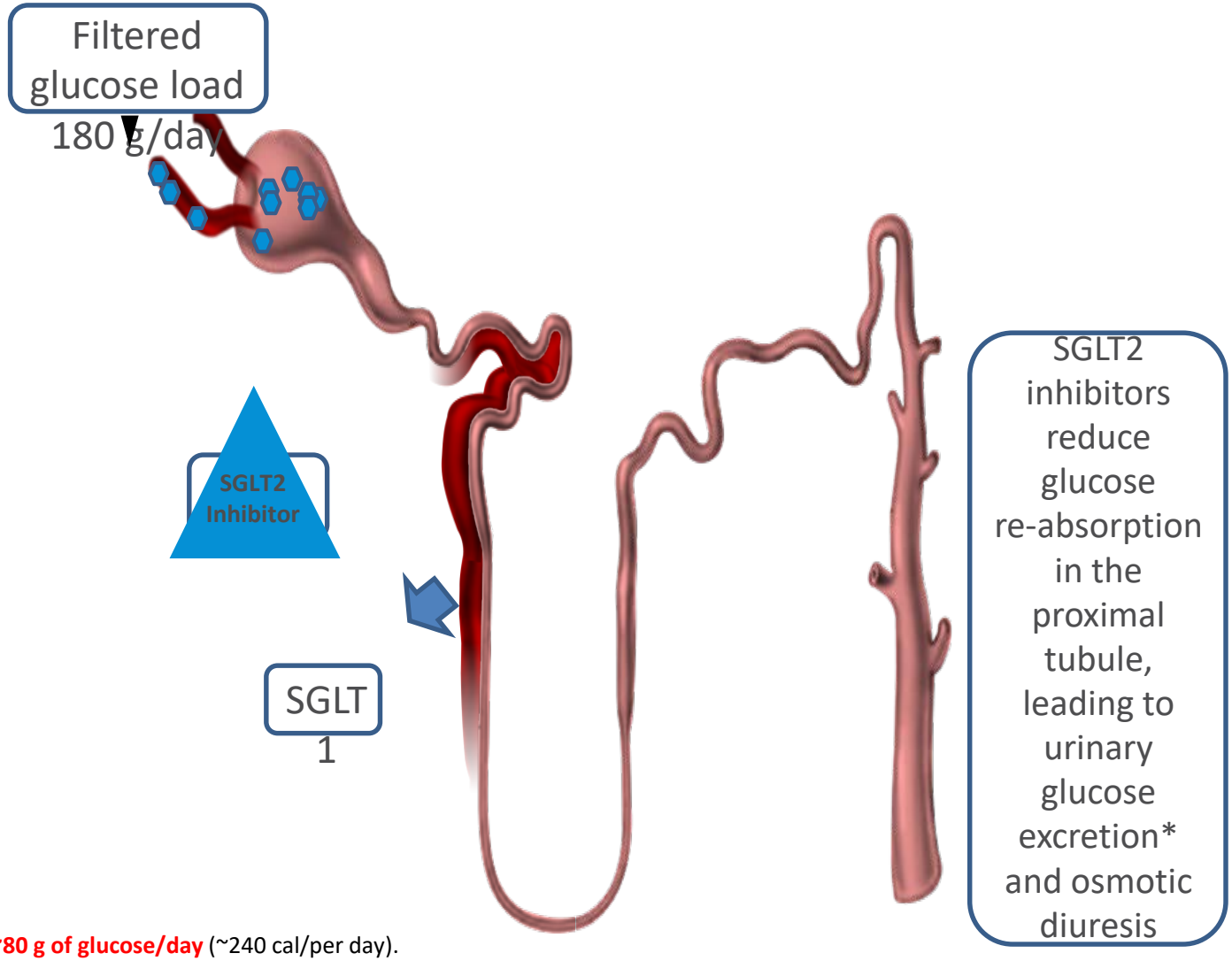
Linagliptin US PI; Saxagliptin US PI; Scheen AJ. *Diabetes Obes Metab*. 2010;12: 648–658; Deacon CF. *Diabetes Obes Metab*. 2011; 13: 7–18; Vincent et al. 2007, *Drug Metab Dispos* 35:533–538; He et al. 2009, *Drug Metab Dispos* 37:536–544; Christopher R et al. 2008 *Clin Ther* 30:513–527.

Struttura del GLP1 approvati e loro emivita

Exenatide BID	DPP-4 Resistant to DPP-4 HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS	$t_{1/2}$ = 3.3-4 hours and renal filtration
Liraglutide	DPP-4 Partial resistant to DPP-4 HAEGTFTSDVSSYLEGQAAKEFIAWLVRGRG Albumin C-16 free fatty acid derivative via a glutamoyl spacer	$t_{1/2}$ = 11-13 hours and multiple organ filtration
Exenatide QW	DPP-4 Resistant to DPP-4 HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS Poly (D,L lactic-co-glycolic acid) microspheres	Steady state over 6-7 weeks and renal filtration
Lixisenatide	DPP-4 Resistant to DPP-4 HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPSKKKKKK	$t_{1/2}$ = ~3 hours and renal filtration
Albiglutide	DPP-4 Resistant to DPP-4 Recombinant fusion protein linked to human albumin HGEGTFTSDVSSYLEGQAAKEFIAWLVKGR HGEGTFTSDVSSYLEGQAAKEFIAWLVKGR Albumin	$t_{1/2}$ = ~ 5 days and multiple organ filtration
Dulaglutide	DPP-4 Resistant to DPP-4 HGEGTFTSDVSSYLEEQAAKEFIAWLVKGGG HGEGTFTSDVSSYLEEQAAKEFIAWLVKGGG Modified IgG4 Fc domain Modified IgG4 Fc domain	$t_{1/2}$ = ~5 days

SGLT-2

Urinary glucose excretion via SGLT2 inhibition



***Loss of ~80 g of glucose/day** (~240 cal/per day).
Gerich JE. *Diabet Med*. 2010;27:136–142.

SGLT 2 inibitors selectivity

Drug	IC_{50} for human SGLT2 (nmol/L)	IC_{50} for human SGLT1 (nmol/L)	SGLT2 selectivity (fold)
Canagliflozin	4.4	684	155
Dapagliflozin	1.12	1,391	1,242
Empagliflozin	3.1	8,300	2,680
Ipragliflozin	7.38	1,876	254
Luseogliflozin	2.26	3,990	1,770
Tofogliflozin	2.9	8,444	2,912
Phrorizin	34.6	210	6

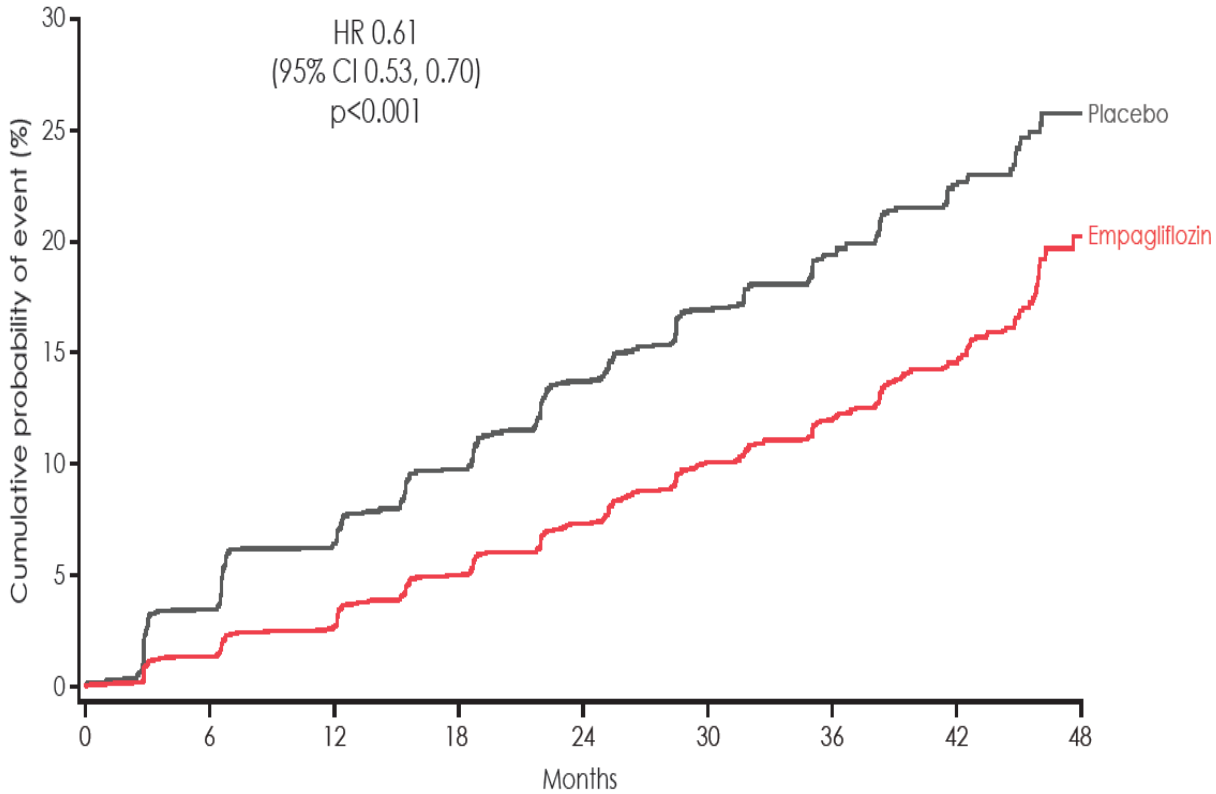
J Diabetes Invest 5(3) May 2014

Empagliflozin e funzione renale

- Dato il meccanismo d'azione, l'efficacia di empagliflozin è dipendente dalla funzione renale. Nessun aggiustamento della dose è richiesto per I pazienti con eGFR ≥60 ml/min/1.73 m2 or CrCl ≥60 ml/min.
- Empagliflozin non dovrebbe essere iniziato in pazienti con eGFR <60 ml/min/1.73 m2 o CrCl <60 ml/min. In che tollerano empagliflozin empagliflozin il cui eGFR scende persistentemente al di sotto di 60 ml/min/1.73 m2 o CrCl below 60 ml/min, la dose di empagliflozin dovrebbe essere aggiustata o mantenuta a 10 mg una volta al giorno. Empagliflozin dovrebbe essere interrotto quando eGFR is persistentemente al di sotto di 45 ml/min/1.73 m2 or CrCl persistentemente al di sotto di 45 ml/min (see sections 4.4, 4.8, 5.1, and 5.2).
- Empagliflozin non dovrebbe essere usato in pazienti con malattia renale allo stadio terminale (ESRD) o in pazienti in dialisi perché ci si aspetta che non sia efficace in questi pazienti

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002677/WC500168592.pdf

EMPAREG outcome: Incidenza di peggioramento della nefropatia



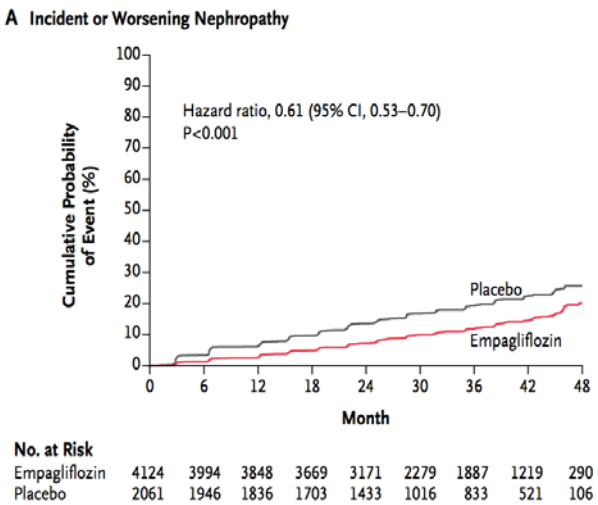
No. of patients									
Empagliflozin	4124	3994	3848	3669	3171	2279	1887	1219	290
Placebo	2061	1946	1836	1703	1433	1016	833	521	106

Wanner C et al. N Engl J Med 2016; 375:323-334

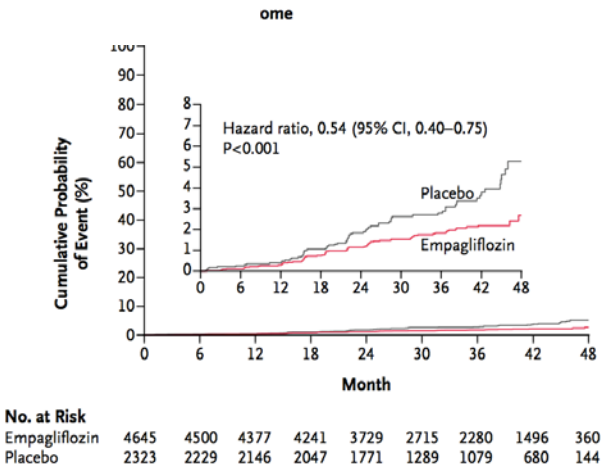
Kaplan-Meier estimate in patients treated with ≥1 dose of study drug.
Hazard ratios are based on Cox regression analyses.
HR, hazard ratio; CI, confidence interval. Pre-specified analyses.

Empagliflozin e Progressione della malattia renale in Type 2 Diabetes

Incident or Worsening Nephropathy



Renal Composite Outcome



New-onset or worsening nephropathy, including new onset of macroalbuminuria (UACR >300 mg/g)

reduction started very early with curves separating after 3 months

- 39 %

- 46 %

Composite outcome

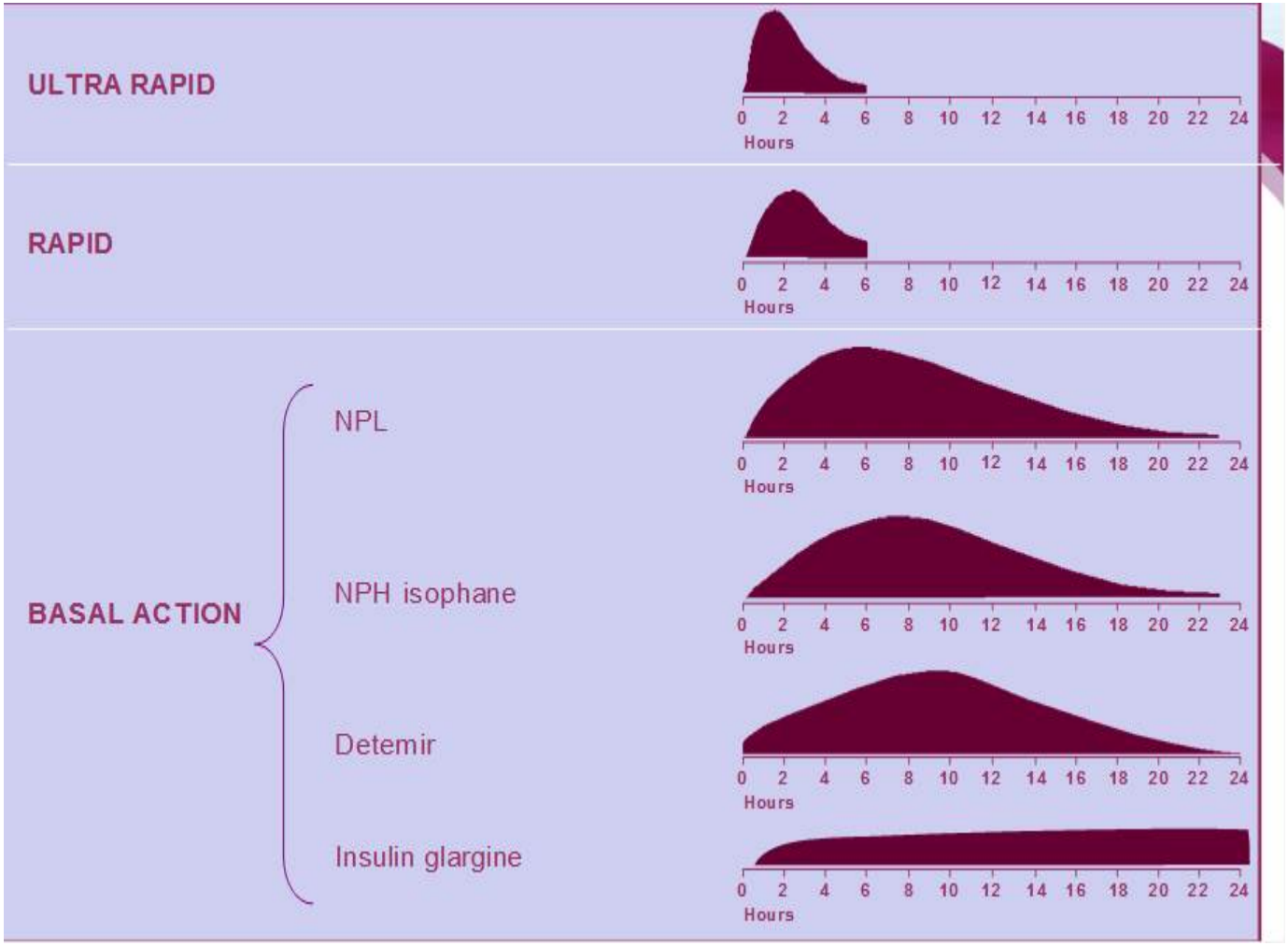
- Doubling of serum creatinine accompanied by an eGFR of 45 ml/min/1.73 m^2 or less
- Initiation of renal replacement therapy
- Death due to renal disease

Wanner C. et al. N Engl J Med 375: 323-334, **2016**

EMPAREG outcome: Conclusioni

In pazienti con diabete Tipo 2 e alto rischio cardiovascolare, empagliflozin usato in aggiunta alla terapia standard ha mostrato un rallentamento della progression della malattia renale e una significativa riduzione del rischio di eventi renali clinicamente rilevanti.

Terapia ipoglicemizzante: insuline



1. Skyler JS. Insulin treatment. In: Lebovitz HE, ed. Therapy for Diabetes Mellitus and Related Disorders. 3rd ed. Alexandria, VA: American Diabetes Association; 1998:186–203.

Insulin dose adjustment according to renal function

eGFR(ml/min/1.73 m^2)

Renal function	eGFR	Insulin dose adjustment
normal	120-90	NA
mild	90-60	No adjustment
moderate	60-30	25% dose reduction
Pre-ESRD	30-15	25% dose reduction
ESRD	15-0	50% dose reduction

American College of Physicians, 1994

Table 1 Baseline clinical characteristics by age groups

	All	< 65 years	65–75 years	> 75 years
	n = 157,595	*n = 58,238*	*n = 56,682*	*n = 42,675*
Male sex	89,290 (56.7%)	35,941 (61.7%)	32,469 (57.3%)	20,880 (48.9%)
Age (years)	68 ± 11	57 ± 7	70 ± 3	80 ± 4
Known duration of diabetes (years)	11 ± 9	8 ± 7	12 ± 9	15 ± 11
Serum creatinine (mg/dL)	0.98 ± 0.54	0.88 ± 0.43	0.99 ± 0.54	1.10 ± 0.63
eGFR (mL/min/1.73m^2)	76 ± 21	89 ± 18	74 ± 18	62 ± 19
Retinopathy	22,250 (14.1%)	6998 (12.0%)	8773 (15.5%)	6479 (15.2%)
BMI (Kg/m^2)	29.6 ± 5.3	30.4 ± 5.8	29.6 ± 5.1	28.4 ± 4.7
HbA1c (%)	7.2 ± 1.3	7.3 ± 1.4	7.2 ± 1.2	7.2 ± 1.2
HbA1c				
7.0–7.4%	26,576 (17.1%)	9002 (15.7%)	10,057 (18.0%)	7517 (17.9%)
7.5–8.5%	32,320 (20.8%)	11,265 (19.7%)	11,473 (20.5%)	9582 (22.8%)
> 8.5%	20,993 (13.5%)	9214 (16.1%)	6401 (11.4%)	5378 (12.8%)
Total cholesterol (mg/dL)	177 ± 39	181 ± 40	175 ± 37	176 ± 38
Triglycerides (mg/dL)	137 ± 90	147 ± 108	133 ± 82	128 ± 69
HDL (mg/dL)	50 ± 14	48 ± 14	50 ± 14	51 ± 15
LDL (mg/dL)	101 ± 33	104 ± 34	99 ± 32	100 ± 33
Systolic BP (mmHg)	137 ± 18	134 ± 18	139 ± 18	140 ± 19
Diastolic BP (mmHg)	78 ± 9	79 ± 9	78 ± 9	76 ± 9
Smokers	14,793 (16.7%)	8865 (25.2%)	4435 (14.1%)	1493 (6.9%)
Cardiovascular therapy				
Lipid-lowering treatment	90,690 (57.5%)	31,402 (53.9%)	35,490 (62.6%)	23,798 (55.8%)
Treatment with statins	83,342 (52.9%)	28,002 (48.1%)	32,928 (58.1%)	22,412 (52.5%)
Treatment with fibrates	4588 (2.9%)	2285 (3.9%)	1503 (2.7%)	800 (1.9%)
Antihypertensive treatment	112,424 (71.3%)	35,069 (60.2%)	43,031 (75.9%)	34,324 (80.4%)
Treatment with ACE-Is/ARBs	95,821 (60.8%)	30,460 (52.3%)	36,938 (65.2%)	28,423 (66.6%)
Aspirin	35,284 (22.4%)	9467 (16.3%)	14,278 (25.2%)	11,539 (27.0%)
Antidiabetic therapy				
Diet	8229 (5.2%)	3149 (5.4%)	3086 (5.4%)	1994 (4.7%)
Oral antidiabetic drugs	100,535 (63.8%)	39,150 (67.2%)	36,379 (64.2%)	25,006 (58.6%)

Table 2 Patients' characteristics by the presence of low estimated glomerular filtration and by age groups

	< 65 years			*65–75 years*			*> 75 years*		
	eGFR-	*eGFR+*		*eGFR-*	*eGFR+*		*eGFR-*	*eGFR+*	
	n = 54,297	*n = 3941*	*p*	*n = 44,378*	*n = 12,304*	*p*	*n = 23,754*	*n = 18,921*	*p*
Male sex	**33,640 (62.0%)**	**2301 (58.4%)**	**< 0.001**	**25,773 (58.1%)**	**6696 (54.4%)**	**< 0.001**	**12,262 (51.6%)**	**8618 (45.5%)**	**< 0.001**
Age (years)	**56 ± 7**	**60 ± 5**	**< 0.001**	**70 ± 3**	**71 ± 3**	**< 0.001**	**80 ± 4**	**81 ± 4**	**< 0.001**
Duration of diabetes (years)	**8 ± 7**	**11 ± 9**	**< 0.001**	**11 ± 9**	**14 ± 9**	**< 0.001**	**14 ± 10**	**16 ± 11**	**< 0.001**
Albuminuria	**13,031 (24.0%)**	**1855 (47.1%)**	**< 0.001**	**11,126 (25.1%)**	**5000 (40.6%)**	**< 0.001**	**6770 (28.5%)**	**7605 (40.2%)**	**< 0.001**
Retinopathy	**6073 (11.2%)**	**925 (23.5%)**	**< 0.001**	**6208 (14.0%)**	**2565 (20.8%)**	**< 0.001**	**3168 (13.3%)**	**3311 (17.5%)**	**< 0.001**
BMI (Kg/m^2)	**30.3 ± 5.7**	**31.8 ± 6.2**	**< 0.001**	**29.3 ± 5.0**	**30.5 ± 5.3**	**< 0.001**	**28.0 ± 4.6**	**28.8 ± 4.8**	**< 0.001**
HbA1c (%)	**7.3 ± 1.4**	**7.4 ± 1.5**	**< 0.001**	**7.1 ± 1.2**	**7.3 ± 1.3**	**< 0.001**	**7.2 ± 1.2**	**7.3 ± 1.3**	**< 0.001**
Triglycerides ≥150 mg/dl	**17,380 (33.8%)**	**1916 (52.0%)**	**< 0.001**	**10,902 (26.1%)**	**4792 (42.0%)**	**< 0.001**	**4696 (21.4%)**	**5781 (33.8%)**	**< 0.001**
HDL < 40/< 50 mg/dL (Male/Female)	**19,366 (38.3%)**	**1837 (51.1%)**	**< 0.001**	**12,780 (31.1%)**	**4939 (44.2%)**	**< 0.001**	**6188 (28.6%)**	**6998 (41.7%)**	**< 0.001**
LDL ≥100 mg/dL	**26,449 (52.8%)**	**1593 (45.1%)**	**< 0.001**	**18,723 (45.6%)**	**4820 (43.4%)**	**< 0.001**	10,034 (46.5%)	7676 (45.9%)	0.061
Blood Pressure ≥ 140/85 mmHg	**22,307 (47.6%)**	**1795 (54.0%)**	**< 0.001**	21,453 (56.1%)	5701 (56.0%)	0.130	**11,688 (58.8%)**	**8518 (56.6%)**	**< 0.001**
Smokers	**8406 (25.5%)**	**459 (20.4%)**	**< 0.001**	**3612 (14.5%)**	**823 (12.2%)**	**< 0.001**	**923 (7.7%)**	**570 (6.0%)**	**< 0.001**
Cardiovascular therapy									
Lipid-lowering treatment	**28,831 (53.1%)**	**2571 (65.2%)**	**< 0.001**	**27,130 (61.1%)**	**8360 (67.9%)**	**< 0.001**	**12,802 (53.9%)**	**10,996 (58.1%)**	**< 0.001**
Treatment with statins	**25,854 (47.6%)**	**2148 (54.5%)**	**< 0.001**	**25,456 (57.4%)**	**7472 (60.7%)**	**< 0.001**	**12,224 (51.5%)**	**10,188 (53.8%)**	**< 0.001**
Treatment with fibrates	**1982 (3.7%)**	**303 (7.7%)**	**< 0.001**	**927 (2.1%)**	**576 (4.7%)**	**< 0.001**	**310 (1.3%)**	**490 (2.6%)**	**< 0.001**
Antihypertensive treatment	**31,773 (58.5%)**	**3296 (83.6%)**	**< 0.001**	**32,412 (73.0%)**	**10,619 (86.3%)**	**< 0.001**	**18,098 (76.2%)**	**16,226 (85.8%)**	**< 0.001**
Treatment with ACE-Is/ARBs	**27,592 (50.8%)**	**2868 (72.8%)**	**< 0.001**	**27,773 (62.6%)**	**9165 (74.5%)**	**< 0.001**	**14,992 (63.1%)**	**13,431 (71.0%)**	**< 0.001**
Aspirin	**8470 (15.6%)**	**997 (25.3%)**	**< 0.001**	**10,745 (24.2%)**	**3533 (28.7%)**	**< 0.001**	**6079 (25.6%)**	**5460 (28.9%)**	**< 0.001**
Antidiabetic therapy									
Diet	**3010**	**139**	**< 0.001**	**2566**	**520**	**< 0.001**	**1262**	**732**	**< 0.001**

Table 3 Patients' characteristics by the presence of albuminuria and by age groups

	< 65 years			*65–75 years*			*> 75 years*		
	ALB-	*ALB+*		*ALB-*	*ALB+*		*ALB-*	*ALB+*	
	n = 43,352	*n = 14,886*	*p*	*n = 40,556*	*n = 16,126*	*p*	*n = 28,300*	*n = 14,375*	*p*
Male sex	**25,532 (58.9%)**	**10,409 (69.9%)**	**< 0.001**	**21,651 (53.4%)**	**10,818 (67.1%)**	**< 0.001**	**12,721 (45.0%)**	**8159 (56.8%)**	**< 0.001**
Age (years)	**56 ± 7**	**57 ± 7**	**< 0.001**	**70 ± 3**	**70 ± 3**	**< 0.001**	**80 ± 4**	**81 ± 4**	**< 0.001**
Duration of diabetes (years)	**8 ± 7**	**9 ± 8**	**< 0.001**	**12 ± 9**	**13 ± 9**	**< 0.001**	**14 ± 11**	**16 ± 11**	**< 0.001**
eGFR < 60 mL/min/1.73m^2	**2086 (4.8%)**	**1855 (12.5%)**	**< 0.001**	**7304 (18.0%)**	**5000 (31.0%)**	**< 0.001**	**11,316 (40.0%)**	**7605 (52.9%)**	**< 0.001**
Retinopathy	**4346 (10.0%)**	**2652 (17.8%)**	**< 0.001**	**5357 (13.2%)**	**3416 (21.2%)**	**< 0.001**	**3729 (13.2%)**	**2750 (19.1%)**	**< 0.001**
BMI (Kg/m^2)	**30.1 ± 5.7**	**31.1 ± 5.9**	**< 0.001**	**29.4 ± 5.1**	**30.0 ± 5.1**	**< 0.001**	**28.3 ± 4.7**	**28.5 ± 4.7**	**< 0.001**
HbA1c (%)	**7.2 ± 1.4**	**7.6 ± 1.6**	**< 0.001**	**7.1 ± 1.2**	**7.4 ± 1.3**	**< 0.001**	**7.1 ± 1.2**	**7.4 ± 1.3**	**< 0.001**
Triglycerides ≥150 mg/dl	**13,144 (32.0%)**	**6152 (43.7%)**	**< 0.001**	**10,438 (27.4%)**	**5256 (34.9%)**	**< 0.001**	**6453 (24.8%)**	**4024 (30.7%)**	**< 0.001**
HDL < 40/< 50 mg/dL (Male/Female)	**15,038 (37.3%)**	**6165 (44.4%)**	**< 0.001**	**12,114 (32.4%)**	**5605 (37.9%)**	**< 0.001**	**8308 (32.5%)**	**4878 (38.0%)**	**< 0.001**
LDL ≥100 mg/dL	**21,368 (53.4%)**	**6674 (49.1%)**	**< 0.001**	**17,237 (46.0%)**	**6306 (42.8%)**	**< 0.001**	**12,048 (47.3%)**	**5662 (44.2%)**	**< 0.001**
Blood Pressure ≥ 140/85 mmHg	**16,778 (45.2%)**	**7324 (56.3%)**	**< 0.001**	**18,392 (53.4%)**	**8762 (62.8%)**	**< 0.001**	**12,690 (55.1%)**	**7516 (63.2%)**	**< 0.001**
Smokers	**6062 (23.4%)**	**2803 (29.9%)**	**< 0.001**	**2863 (12.9%)**	**1572 (16.9%)**	**< 0.001**	**869 (6.1%)**	**624 (8.4%)**	**< 0.001**
Cardiovascular therapy									
Lipid-lowering treatment	**22,567 (52.1%)**	**8835 (59.4%)**	**< 0.001**	**24,821 (61.2%)**	**10,669 (66.2%)**	**< 0.001**	15,504 (54.8%)	8294 (57.7%)	0.072
Treatment with statins	**20,167 (46.5%)**	**7835 (52.6%)**	**< 0.001**	**23,040 (56.8%)**	**9888 (61.3%)**	**< 0.001**	14,616 (51.6%)	7796 (54.2%)	0.217
Treatment with fibrates	**1616 (3.7%)**	**669 (4.5%)**	**< 0.001**	1058 (2.6%)	445 (2.8%)	0.045	508 (1.8%)	292 (2.0%)	0.175
Antihypertensive treatment	**24,528 (56.6%)**	**10,541 (70.8%)**	**< 0.001**	**29,651 (73.1%)**	**13,380 (83.0%)**	**< 0.001**	**22,154 (78.3%)**	**12,170 (84.7%)**	**< 0.001**
Treatment with ACE-Is/ ARBs	**21,042 (48.5%)**	**9418 (63.3%)**	**< 0.001**	**25,256 (62.3%)**	**11,682 (72.4%)**	**< 0.001**	**18,282 (64.6%)**	**10,141 (70.5%)**	**< 0.001**
Aspirin	**6536 (15.1%)**	**2931 (19.7%)**	**< 0.001**	**9751 (24.0%)**	**4527 (28.1%)**	**< 0.001**	7468 (26.4%)	4071 (28.3%)	0.010
Antidiabetic therapy									
Diet	**2596 (6.0%)**	**553 (3.7%)**	**< 0.001**	**2445 (6.0%)**	**641 (4.0%)**	**< 0.001**	**1502 (5.3%)**	**492 (3.4%)**	**< 0.001**
Oral antidiabetic drugs	**29,916 (69.0%)**	**9234 (62.0%)**	**< 0.001**	**27,180 (67.0%)**	**9199 (57.0%)**	**< 0.001**	**17,437 (61.6%)**	**7569 (52.7%)**	**< 0.001**
Oral drugs and insulin	**6320 (14.6%)**	**3140 (21.1%)**	**< 0.001**	**6365 (15.7%)**	**3541 (22.0%)**	**< 0.001**	**4416 (15.6%)**	**2852 (19.8%)**	**< 0.001**
Insulin	**4520 (10.4%)**	**1959 (13.2%)**	**< 0.001**	**4566 (11.3%)**	**2745 (17.0%)**	**< 0.001**	**4945 (17.5%)**	**3462 (24.1%)**	**< 0.001**
Q Score									

Table 4 Multivariate odds ratios for estimated glomerular filtration rate < 60 mL/min/1.73 m^2 or albuminuria by age groups

	Overall	*p*	< 65 years	*p*	65–75 years	*p*	> 75 years	*p*
Model for eGFR < 60 mL/min/1.73 m^2								
Male sex	**0.85 (0.82–0.88)**	**< 0.001**	**0.83 (0.76–0.90)**	**< 0.001**	**0.84 (0.80–0.88)**	**< 0.001**	**0.86 (0.82–0.91)**	**< 0.001**
Age (×5 years)	**1.81 (1.79–1.83)**	**< 0.001**	**1.75 (1.67–1.82)**	**< 0.001**	**1.90 (1.82–1.99)**	**< 0.001**	**1.77 (1.72–1.83)**	**< 0.001**
BMI (× 5 Kg/m^2)	**1.19 (1.17–1.21)**	**< 0.001**	**1.13 (1.09–1.17)**	**< 0.001**	**1.18 (1.15–1.21)**	**< 0.001**	**1.23 (1.20–1.27)**	**< 0.001**
Albuminuria	**2.14 (2.06–2.22)**	**< 0.001**	**2.90 (2.66–3.17)**	**< 0.001**	**2.22 (2.10–2.35)**	**< 0.001**	**1.78 (1.68–1.88)**	**< 0.001**
HbA1c (×1%)	1.00 (0.99–1.02)	0.839	1.00 (0.97–1.03)	0.979	1.01 (0.99–1.03)	0.421	1.00 (0.98–1.02)	0.976
Triglycerides ≥150 mg/dl	**1.69 (1.63–1.76)**	**< 0.001**	**1.85 (1.70–2.02)**	**< 0.001**	**1.73 (1.64–1.83)**	**< 0.001**	**1.58 (1.49–1.67)**	**< 0.001**
HDL < 40/< 50 mg/dL (Male/Female)	**1.41 (1.36–1.46)**	**< 0.001**	**1.34 (1.23–1.46)**	**< 0.001**	**1.39 (1.32–1.47)**	**< 0.001**	**1.48 (1.40–1.56)**	**< 0.001**
LDL ≥100 mg/dL	**0.88 (0.86–0.91)**	**< 0.001**	**0.80 (0.74–0.87)**	**< 0.001**	**0.90 (0.85–0.94)**	**< 0.001**	**0.91 (0.87–0.96)**	**< 0.001**
Blood Pressure ≥ 140/85 mmHg	**0.87 (0.84–0.90)**	**< 0.001**	1.00 (0.92–1.09)	0.969	**0.86 (0.82–0.91)**	**< 0.001**	**0.84 (0.79–0.88)**	**< 0.001**
Smoking[a]	**0.79 (0.74–0.84)**	**< 0.001**	**0.73 (0.64–0.83)**	**< 0.001**	**0.81 (0.73–0.90)**	**< 0.001**	0.82 (0.71–0.94)	0.004
Model for Albuminuria								
Male sex	**2.09 (2.02–2.15)**	**< 0.001**	**1.94 (1.83–2.05)**	**< 0.001**	**2.30 (2.18–2.42)**	**< 0.001**	**2.05 (1.93–2.17)**	**< 0.001**
Age (×5 years)	**1.07 (1.06–1.08)**	**< 0.001**	**1.02 (1.01–1.04)**	**0.011**	**1.08 (1.04–1.13)**	**< 0.001**	**1.16 (1.11–1.20)**	**< 0.001**
BMI (×5 Kg/m^2)	**1.11 (1.09–1.12)**	**< 0.001**	**1.14 (1.12–1.17)**	**< 0.001**	**1.11 (1.09–1.14)**	**< 0.001**	1.05 (1.02–1.08)	0.003
eGFR< 60 mL/min/1.73 m^2	**2.19 (2.11–2.27)**	**< 0.001**	**2.99 (2.74–3.27)**	**< 0.001**	**2.27 (2.14–2.40)**	**< 0.001**	**1.82 (1.72–1.93)**	**< 0.001**
HbA1c (×1%)	**1.22 (1.20–1.23)**	**< 0.001**	**1.21 (1.19–1.23)**	**< 0.001**	**1.24 (1.21–1.27)**	**< 0.001**	**1.19 (1.16–1.22)**	**< 0.001**
Triglycerides ≥150 mg/dl	**1.26 (1.22–1.31)**	**< 0.001**	**1.40 (1.33–1.48)**	**< 0.001**	**1.19 (1.13–1.26)**	**< 0.001**	**1.19 (1.11–1.27)**	**< 0.001**
HDL < 40/< 50 mg/dL (Male/Female)	**1.19 (1.15–1.23)**	**< 0.001**	**1.18 (1.11–1.24)**	**< 0.001**	**1.21 (1.14–1.28)**	**< 0.001**	**1.18 (1.11–1.26)**	**< 0.001**
LDL ≥100 mg/dL	**0.92 (0.89–0.95)**	**< 0.001**	**0.89 (0.85–0.94)**	**< 0.001**	0.94 (0.89–0.98)	0.010	0.92 (0.87–0.97)	0.002
Blood Pressure ≥ 140/85 mmHg	**1.47 (1.42–1.51)**	**< 0.001**	**1.49 (1.41–1.57)**	**< 0.001**	**1.45 (1.37–1.52)**	**< 0.001**	**1.47 (1.38–1.56)**	**< 0.001**
Smoking[a]	**1.60 (1.52–1.68)**	**< 0.001**	**1.58 (1.47–1.70)**	**< 0.001**	**1.68 (1.54–1.84)**	**< 0.001**	**1.55 (1.35–1.79)**	**< 0.001**

The bold values refers to significant ($p < 0.001$) associations. Complete case analysis performed including patients for which all data were observed. Overall group included 115,493 patients: 23,973 (20.8%) with eGFR< 60 mL/min/1.73m^2 and 33,598 (29.1% with albuminuria). Group with < 65 years included 43,945 patients: 2844 (6.5%) with eGFR< 60 mL/min/1.73m^2 and 11,401 (25.9%) with albuminuria. Group with 65–75 years included 42,248 patients: 8746 (20.7%) with eGFR< 60 mL/min/1.73m^2 and 12,170 (28.8%) with albuminuria. Group with > 75 years included 29,300 patients: 12,383 (42.26%) with eGFR< 60 mL/min/1.73m^2 and 10,027 (34.2%) with albuminuria

[a]Models including smoking status was analysed in 67,276 patients (27,431 with < 65 years, 24,249 with 65–75, and 15,596 with > 75 years)

Grazie per l’attenzione