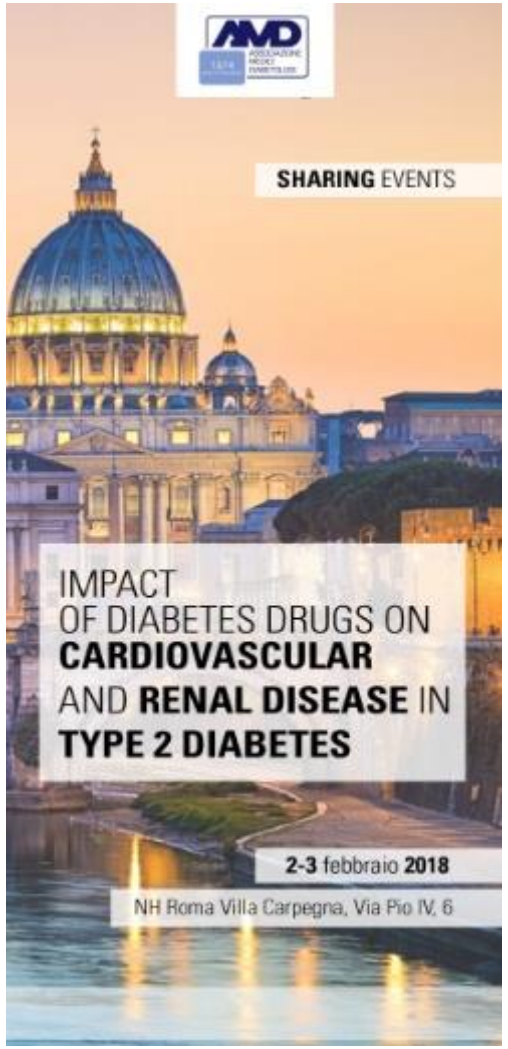


EFFETTO DEI NUOVI FARMACI SUL RENE

Inibitori DPP4

Marco Gallo

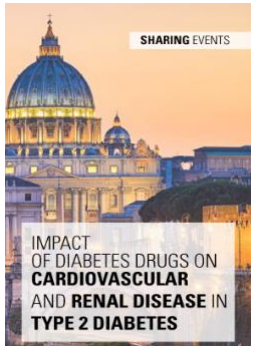
SCDU Endocrinologia Oncologica, AOU Città della Salute e della Scienza di Torino - Molinette - COES

conflitti d’interesse

Il relatore dichiara che negli ultimi due anni ha avuto i seguenti rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario:

- AstraZeneca
- Janssen
- Sanofi

inibitori DPP4 e rene



- efficacia e sicurezza
- effetti CV
- dialisi & trapianto
- endpoint renali

inibitori DPP4 e rene

- **efficacia e sicurezza**
- effetti CV
- dialisi & trapianto
- endpoint renali

Efficacy and safety of DPP-4 inhibitors in patients with type 2 diabetes: Meta-analysis of placebo-controlled randomized clinical trials

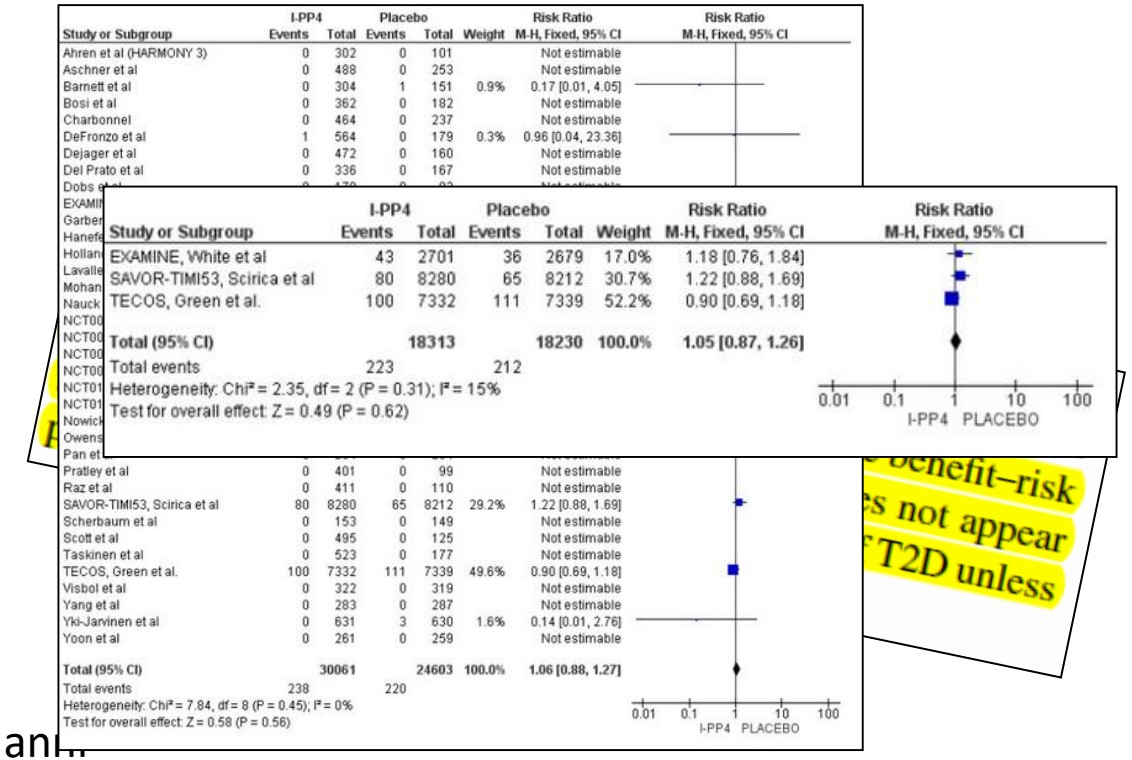
36 RCT in doppio cieco DPP4i vs placebo, 54.664 pz (30.061 DPP4i)

Nessuna differenza significativa per

- mortalità per tutte le cause (RR 1.03, 95% CI 0.95–1.12)
- mortalità CV (1.02, 95% CI 0.92–1.12)
- IMA (0.98, 95% CI = 0.89–1.08)
- stroke (1.02, 95% CI 0.88–1.17)
- **insufficienza renale*** (1.06, 95% CI 0.88–1.27)
- ipoglicemie severe (1.14, 95% CI 0.95–1.36)
- ca pancreas (0.54, 95% CI 0.28–1.04)

RR aumentato per

- insufficienza cardiaca (1.13, 95% CI 1.01–1.26)
- pancreatite acuta (1.57, 95% CI 1.03–2.39) – NNH: 653 a 3 anni



*doubling of serum creatinine levels

Rehman MB et al., *Diab & Metab* 2017

Systematic Literature Review of DPP-4 Inhibitors in Patients with Type 2 Diabetes Mellitus and Renal Impairment

[enale?

- revisione sistematica su efficacia e sicurezza
- 7 studi di durata >12 settimane su >50 pz con alterata fx renale
- età M: 64-70 anni
- in terapia insulinica al basale: 53-86% (eccez. sitagliptin)
- maggior parte su pz bianchi (eccez. sitagliptin)
- no dati su ESDR (eccez. saxagliptin)

Thomas MC et al., *Diab Ther* 2016

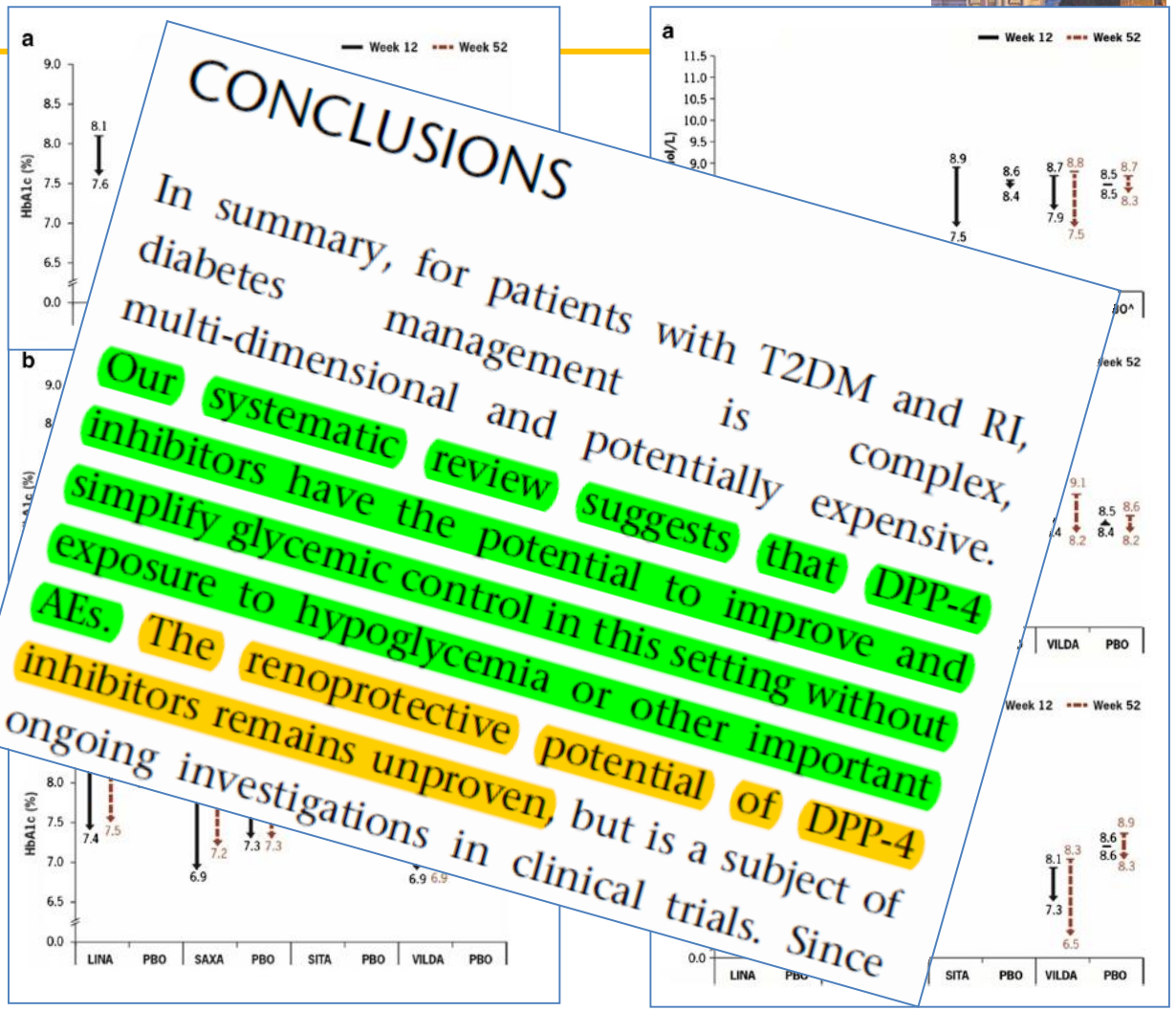
Systematic Literature Review of DPP-4 Inhibitors in Patients with Type 2 Diabetes Mellitus and Renal Impairment

efficacia simile vs pz con normale fx renale

- HbA1c -0.5%~
- FPG -20mg/dl~
- ↓ maggiore se IR severa
  - prolungamento T½ GLP1?
  - riduzione emivita emazie?

safety

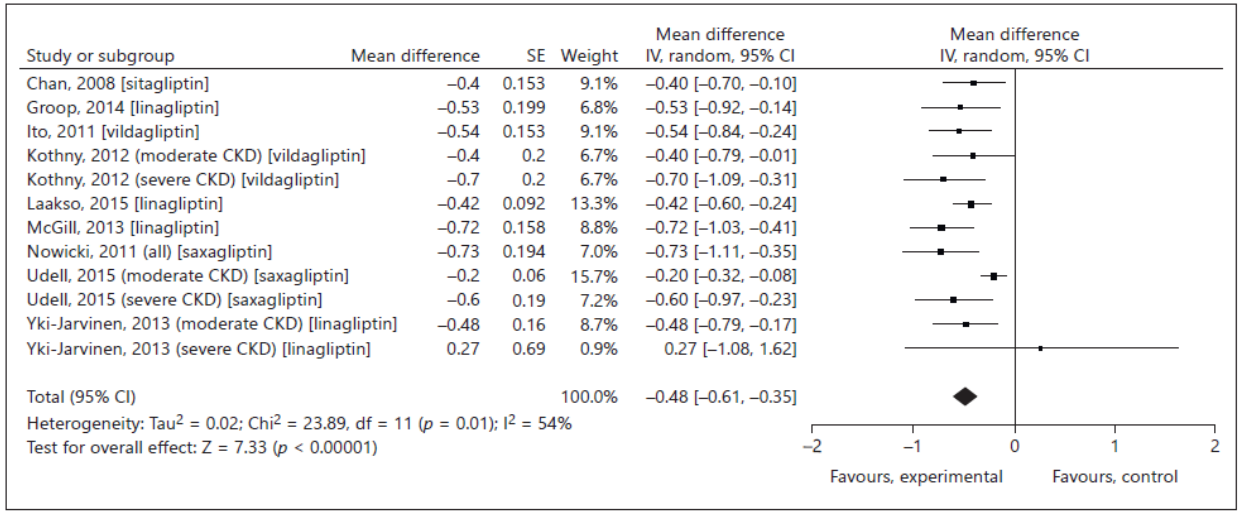
- Incidenza simile AE vs placebo
  - (SAVOR TIMI 53!)
- Incidenza simile ipoglicemie
  - riduzione gluconeogenesi
  - restrizioni alimentari
  - prolungamento az insulina e secretagoghi
- Lieve riduzione eGFR simile vs placebo



Thomas MC et al., *Diab Ther* 2016

Dipeptidyl Peptidase-4 Inhibitors in Chronic Kidney Disease: A Systematic Review of Randomized Clinical Trials

- revisione sistematica e metanalisi random effects su efficacia, sicurezza e tollerabilità
- 12 RCT comprendenti pz con ↓ funzione renale: 4403 pz con CKD e 239 in dialisi
- 4 RCT sita, 4 studi lina, 2 saxa, 2 vilda
- riduzione HbA1c -0.48 (95% CI da -0.61 a -0.35), partendo da 6-8.5%
- **non** aumento AE, ipoglicemie o mortalità



Study or subgroup	Mean difference	SE	Weight	Mean difference IV, random, 95% CI
Chan, 2008 [sitagliptin]	–0.4	0.153	9.1%	–0.40 [–0.70, –0.10]
Groop, 2014 [linagliptin]	–0.53	0.199	6.8%	–0.53 [–0.92, –0.14]
Ito, 2011 [vildagliptin]	–0.54	0.153	9.1%	–0.54 [–0.84, –0.24]
Kothny, 2012 (moderate CKD) [vildagliptin]	–0.4	0.2	6.7%	–0.40 [–0.79, –0.01]
Kothny, 2012 (severe CKD) [vildagliptin]	–0.7	0.2	6.7%	–0.70 [–1.09, –0.31]
Laakso, 2015 [linagliptin]	–0.42	0.092	13.3%	–0.42 [–0.60, –0.24]
McGill, 2013 [linagliptin]	–0.72	0.158	8.8%	–0.72 [–1.03, –0.41]
Nowicki, 2011 (all) [saxagliptin]	–0.73	0.194	7.0%	–0.73 [–1.11, –0.35]
Udell, 2015 (moderate CKD) [saxagliptin]	–0.2	0.06	15.7%	–0.20 [–0.32, –0.08]
Udell, 2015 (severe CKD) [saxagliptin]	–0.6	0.19	7.2%	–0.60 [–0.97, –0.23]
Yki-Jarvinen, 2013 (moderate CKD) [linagliptin]	–0.48	0.16	8.7%	–0.48 [–0.79, –0.17]
Yki-Jarvinen, 2013 (severe CKD) [linagliptin]	0.27	0.69	0.9%	0.27 [–1.08, 1.62]
Total (95% CI)			100.0%	–0.48 [–0.61, –0.35]

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 23.89$, df = 11 ($p = 0.01$); $I^2 = 54\%$
Test for overall effect: Z = 7.33 ($p < 0.00001$)

Walker SR et al., *Nephron* 2017

Dipeptidyl Peptidase-4 Inhibitors in Chronic Kidney Disease: A Systematic Review of Randomized Clinical Trials

Study or subgroup	DPP-4 Events	DPP-4 Total	Control Events	Control T	Risk ratio M-H, random, 95% CI	Risk ratio M-H, random, 95% CI
Chan, 2008 [sitagliptin]	8	65	1			
Arjona Ferreira, 2013 (CKD) [sitagliptin]	8	210	11			
Arjona Ferreira, 2013 (ESRD) [sitagliptin]	5	64	6			
Groop, 2014 [linagliptin]	1	68				
Kothny, 2012 (moderate CKD) [vildagliptin]	32	122				
Kothny, 2012 (severe CKD) [vildagliptin]	17	94				
Laakso, 2015 [linagliptin]	3	113				
McGill, 2013 [linagliptin]	7	68				
Udell, 2015 (moderate CKD) [saxagliptin]	212	1,122				
Udell, 2015 (severe CKD) [saxagliptin]	36	172				
Yki-Jarvinen, 2013 [linagliptin]	2	62				
Total (95% CI)		2,160				
Total events	331					
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 9.70$, df = 10 ($p = 0.4$						
Test for overall effect: Z = 0.01 ($p = 0.99$)						

CV events

low risk of bias did not alter these findings. **Conclusions:** DPP-4 inhibitors can lower HbA1C without increasing the risk of cardiovascular or other major adverse events in patients with CKD. Few studies reported critical adverse events such as heart failure and hypersensitivity. If compared with other oral antiglycemic drugs, the effect of DPP-4 inhibitors is limited; however, their low risk of hypoglycemia may favor their use in patients with CKD. **Summary:** This systematic review of DPP-4 inhibitors in CKD suggests that they reduce HbA1C by about 0.5%. Furthermore, there was not any increase in the risk for significant adverse events. More research is needed to determine the safety and efficacy of

Study or subgroup	Risk ratio M-H, random, 95% CI	Risk ratio M-H, random, 95% CI
	.05, 0.74]	
	0.20, 0.67]	
	[0.18, 1.89]	
	[0.41, 4.44]	
	lot estimable	
	56 [0.90, 2.69]	
	.05 [0.53, 2.10]	
	0.89 [0.75, 1.07]	
	1.29 [1.11, 1.51]	
	0.84 [0.27, 2.67]	
	0.77 [0.43, 1.38]	
	1.92 [0.64, 5.78]	
Udell, 2015 (mo	1.88 [1.25, 2.82]	
Udell, 2015 (severe CKD) [sa	0.64 [0.27, 1.52]	
Total (95% CI)	0.96 [0.73, 1.26]	
Total events	313	
Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 43.39$, df = 12 ($p < 0.0001$); $I^2 = 72\%$		
Test for overall effect: Z = 0.30 ($p = 0.76$)		

0.01 0.1 1 10 100
Favours, experimental Favours, control

ipoglicemie

Walker SR et al., *Nephron* 2017

AMD – Terapia personalizzata

http://www.aemmedi.it/algoritmi_it_2017/ Scegliere la caratteristica principale del paziente con diabete di tipo 2:

Tabella sinottica per l'uso della terapia antidiabetica nell'insufficienza renale

Farmaco	VFG 60-89 ml/min	VFG 30-59 ml/min	VFG 15-29 ml/min	VFG <15 ml/min	Dialisi
Metformina	Dose normale	Dose ridotta, monitoraggio	No	No	No
Glibenclamide	Dose ridotta, monitoraggio	Dose ridotta, monitoraggio	No	No	No
Gliclazide	Dose Normale	Dose ridotta, monitoraggio	No	No	No
Glimepiride	Dose normale	Dose ridotta, monitoraggio	No	No	No
Glipizide	Dose normale	Dose ridotta, monitoraggio	No	No	No
Gliquidone	Dose normale	Dose ridotta, monitoraggio	No	No	No
Repaglinide	Dose normale	Attenzione alla titolazione	No	No	No
Pioglitazone*	Dose normale	Dose normale	Dose normale	No	No
Acarbose	Dose normale	Dose normale	No	No	No
Alogliptin**	Dose normale	12,5 mg uid	6,5 mg uid	6,5 mg uid	6,5 mg uid
Linagliptin	Dose normale	Dose normale	Dose normale	Dose normale	Dose normale
Saxagliptin	Dose normale	2,5 mg uid	Cautela (esperienza limitata)	No	No
Sitagliptin	Dose normale	50 mg uid	25 mg uid	25 mg uid	25 mg uid
Vildagliptin	Dose normale	50 mg uid	50 mg uid	50 mg uid	Cautela (esperienza limitata)
Canagliflozin**	Dose normale	no	no	no	no
Dapagliflozin**	Dose normale	No	No	No	No
Albiglutide**	Dose normale	Dose normale	No (scarsa esperienza)	No (scarsa esperienza)	No (scarsa esperienza)
Exenatide	Dose normale	5 µg (10 µg con cautela)	No	No	No
Exenatide LAR	Dose normale	No	No	No	No
Liraglutide	Dose normale	Dose normale	No (nessuna esperienza)	No	No
Lixisenatide	Dose normale	Cautela (scarsa esperienza)	No (nessuna esperienza)	No (nessuna esperienza)	No (nessuna esperienza)
Insulina	Dose normale	Possibile riduzione fabbisogno	Possibile riduzione fabbisogno	Possibile riduzione fabbisogno	Possibile riduzione fabbisogno

* Può causare ritenzione idrica che può esacerbare o precipitare una insufficienza cardiaca.

M Gallo

AMD – Terapia personalizzata

http://www.aemmedi.it/algoritmi_it_2017/

Cari Soci,

si comunica che gli **algoritmi terapeutici online di AMD** sono stati integrati con uno schema interattivo che guida nella scelta nel paziente complesso il cui fenotipo comprende aspetti previsti da due o più algoritmi.

Vai alla **Scelta dell'algoritmo nel paziente complesso**.

Un cordiale saluto

Il gruppo Terapia personalizzata

Scegliere la caratteristica principale del paziente con diabete di tipo 2:

ALGORITMO A	ALGORITMO B	ALGORITMO C	ALGORITMO D	ALGORITMO E	ALGORITMO F	ALGORITMO G
HbA_{1c} ≥75 mmol/mol (≥9%)	BMI <30 e HbA_{1c} 48-75 mmol/mol (tra 6,5 e <9%)	BMI ≥30 e HbA_{1c} 48-75 mmol/mol (tra 6,5 e <9%)	Rischio professionale per possibili ipoglicemie	IRC e HbA_{1c} 48-75 mmol/mol (tra 6,5 e <9%)	Anziano fragile con iperglicemia lieve/moderata (HbA… <75	Paziente con DT2, pregressa SCA e iperglicemia lieve/moderata

Scelta dell'algoritmo nel paziente complesso

Questo algoritmo guida nella scelta per i pazienti il cui fenotipo comprende aspetti previsti da due o più algoritmi.
(si prega di completare sempre TUTTE le opzioni proposte)

HbA_{1c} ≥9,0%
- ○ Sì
- ◉ No

Paziente fragile
- ◉ Sì
- ○ No

Rischio professionale
- ◉ Sì
- ○ No

Pregressa SCA
- ◉ Sì
- ○ No

IRC
- ◉ Sì
- ○ No

Nel caso di GFR 30-60:
Metformina + DPP4-I oppure acarbosio

Nel caso di GFR <30:
DPP4-I

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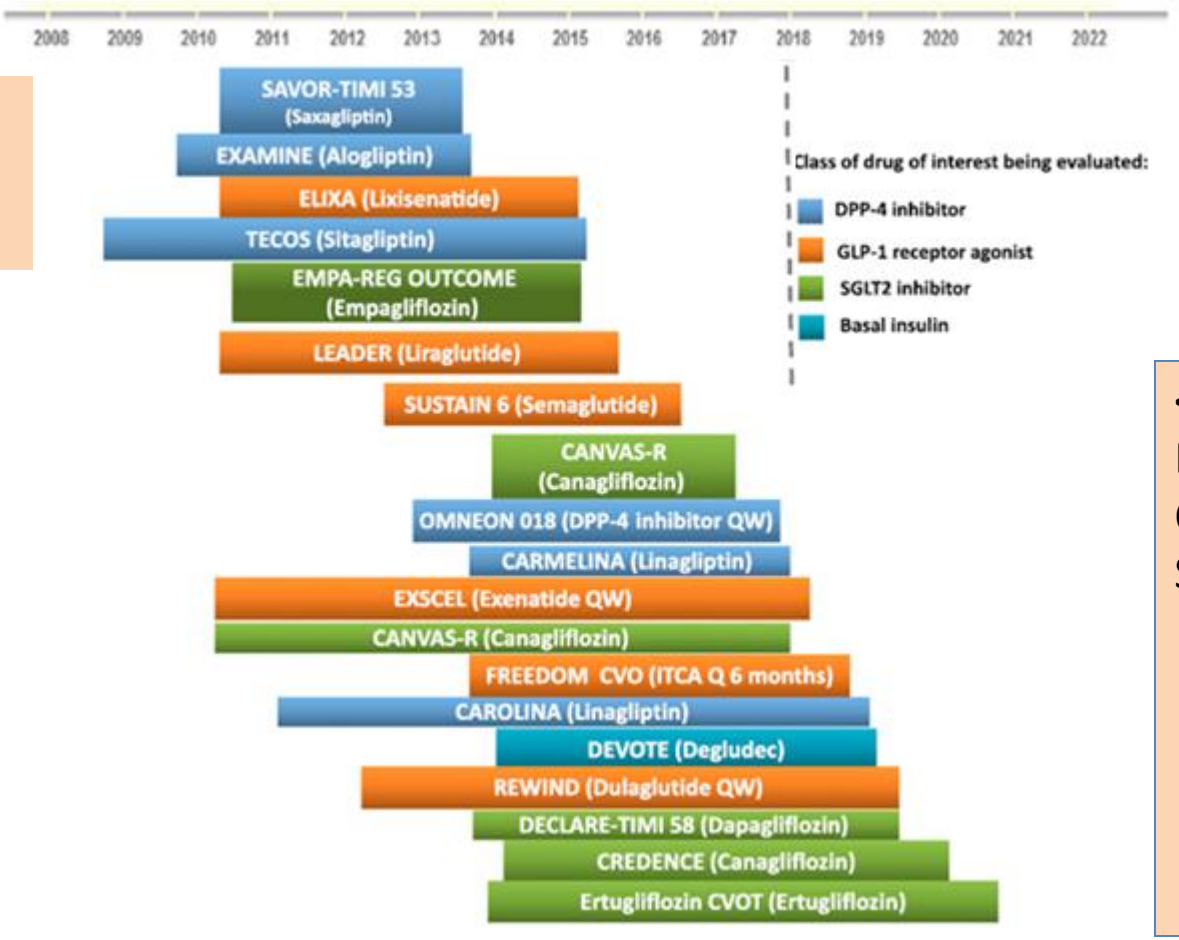
inibitori DPP4 e rene

- efficacia e sicurezza
- **effetti CV**
- ESRD - dialisi
- endpoint renali

cardiovascular safety of all new ADDs

demonstrated through:
- **pooled analyses of phase III studies**
- or **specifically designed trials**



<2008
Breve termine
Obiettivo: HbA1c
Soggetti "sani"

>2008
Obiettivo: sicurezza CV
Soggetti ad alto rischio
(età avanzata, lunga durata DM, insuff renale)

DPP-4i: i grandi trial CV

saxagliptin:

16% con eGFR ≤ 50 ml/min/1.73m^2

criterio esclusione: ESRD, dialisi, trapianto rene, creat > 6mg/ml

sitagliptin:

23% con eGFR < 60 ml/min/1.73m^2

criterio esclusione: eGFR < 30ml/min

alogliptin:

29% con eGFR < 60 ml/min/1.73m^2

criterio esclusione: dialisi entro 14 gg

DPP-4i: i grandi trial CV

Effect of Sitagliptin on Kidney Function and Respective Cardiovascular Outcomes in Type 2 Diabetes: Outcomes From TECOS

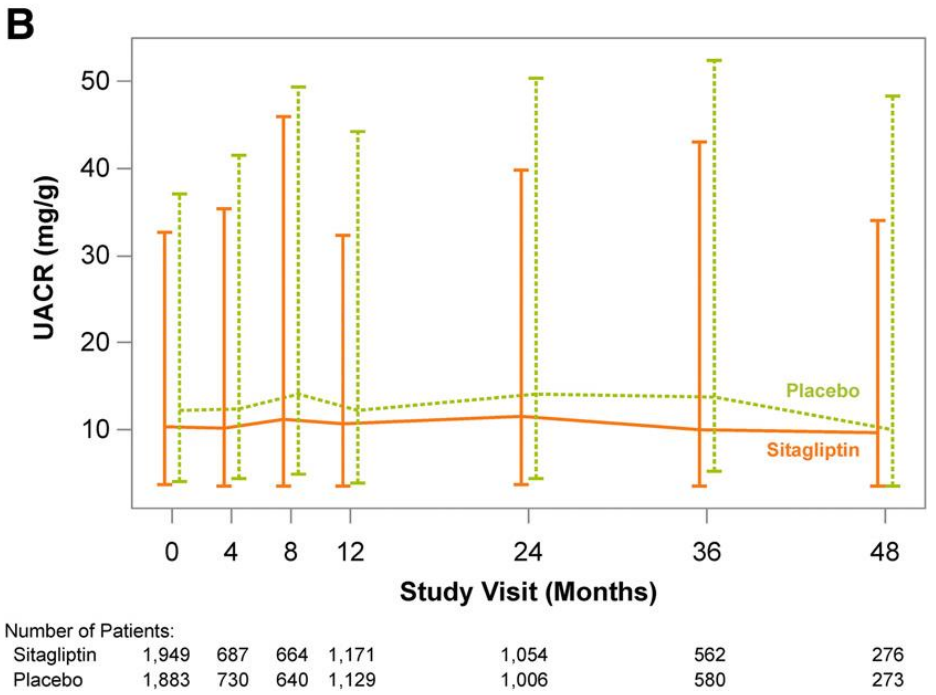
Diabetes Care 2016;39:2304–2310 | DOI: 10.2337/dc16-1415

TECOS: 14.671 pz ad alto rischio CV – HbA1c 6,5-8,0%

- esclusi pz con eGFR <30ml/min
- CKD 3324 pz (23%), età M 69 anni, ♂ 62%
- CKD associata a peggiori outcome CV

confronto: eGFR >90, 60-89, 45-59 o 30-44ml/min

- MACE: aumento progressivo nei 4 sottogruppi



efficacia?

sita: impatto neutro su outcome CV e renali

Cornel JH et al., *Diab Care* 2017

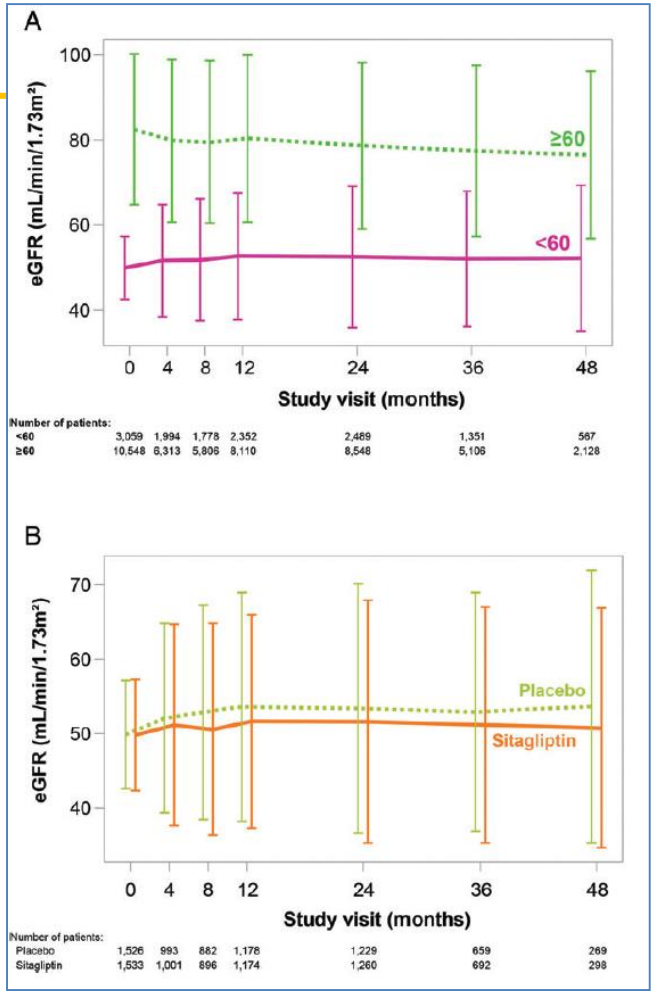
Safety of sitagliptin in patients with type 2 diabetes and chronic kidney disease: outcomes from TECOS

TECOS: 14.671 pz ad alto rischio CV – HbA1c 6,5-8,0%

- esclusi pz con eGFR <30ml/min
- CKD 3324 pz (23%), età M 69 anni, m 62%
- CKD associata a peggiori outcome CV

confronto: eGFR <60ml/min vs >60ml/min

- durata M DM 13,7 anni
- mediana follow up: 2,8 anni (!)



safety?

ipoglicemie: più frequenti nel gruppo CKD, senza differenze sita *vs* placebo

progressione CKD: nessuna differenza sita *vs* placebo

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Engel SS et al., *Diab Ob & Metab* 2017

Effects of DPP-4 inhibitors on cardiovascular outcomes in patients with type 2 diabetes and end-stage renal disease☆

Shang-Yih Chan [a,1], Shuo-Ming Ou [b,c,1], Yung-Tai Chen [c,d,e,*,2], Chia-Jen Shih [d,f,g,**,2]

ESRD: criterio esclusione TECOS e SAVOR-TIMI

- studio osservazionale su 3556 pz Taiwan con T2DM e ESRD trattati con DPP4-i (2009-2013)
- appaiati 1:1 a pz non trattato con DPP4i sec score di propensione
- **outcome primari:** mortalità tutte le cause, MACE (IMA, ictus ischemico)
- **outcome secondari:** ricoveri per CHF, ipoglicemie
- **risultati:** riduzione mortalità totale, MACE e ictus ischemico

Incidence and risks of all-cause mortality, myocardial infarction, stroke, hospitalization for heart failure, and hypoglycemia after propensity score matching.

	DPP-4 inhibitor user			DPP-4 inhibitor non-user			Crude	
	No. of events	Person-Years	Incidence rate*	No. of events	Person-Years	Incidence rate*	Hazard ratio (95% CI)	*P*
All-cause mortality	629	6228	100.99	1110	4501	246.60	0.43 (0.39–0.47)	<0.001
MACEs†	298	5980	49.83	291	4335	67.12	0.76 (0.65–0.90)	0.001
Myocardial infarction	167	6094	27.40	155	4416	35.10	0.81 (0.65–1.01)	0.059
Ischemic stroke	149	6103	24.41	143	4419	32.36	0.77 (0.61–0.97)	0.024
Heart failure	110	5987	18.37	72	4343	16.58	1.14 (0.85–1.54)	0.389
Hypoglycemia	200	5991	33.39	163	4373	37.28	0.95 (0.77–1.17)	0.617

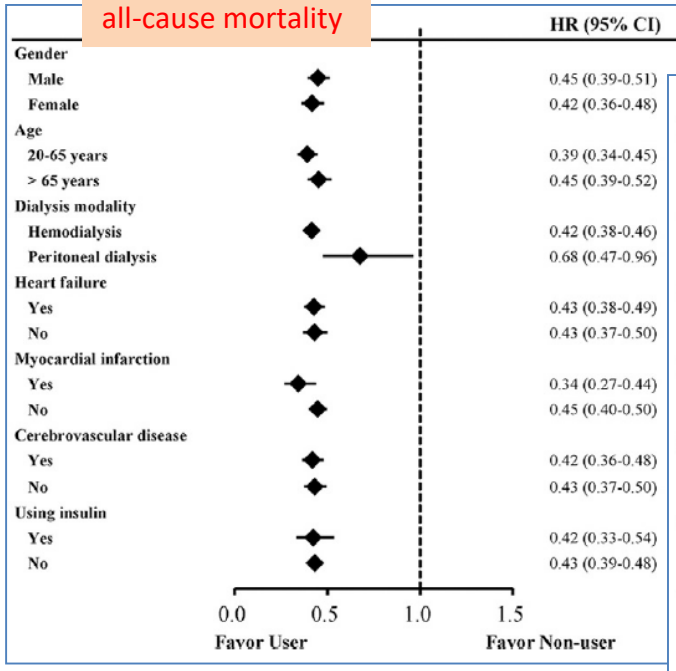
Shang-Yih C et al., *Int J Cardiol* 2016

Effects of DPP-4 inhibitors on cardiovascular outcomes in patients with type 2 diabetes and end-stage renal disease☆

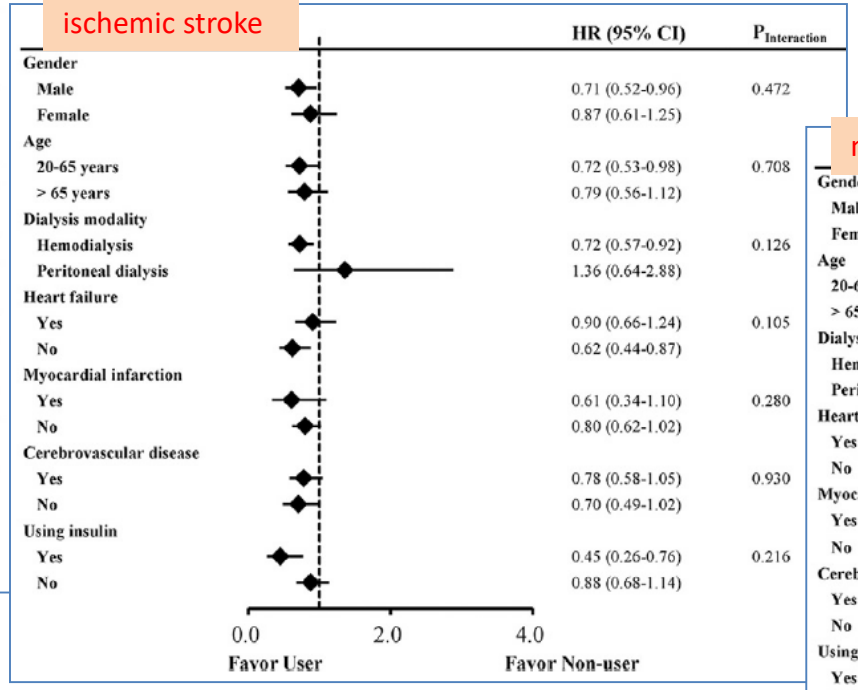
Shang-Yih Chan [a,1], Shuo-Ming Ou [b,c,1], Yung-Tai Chen [c,d,e,*,2], Chia-Jen Shih [d,f,g,**,2]

risultati confermati nell'**analisi per sottogruppi** (età, sesso, comorbilità, insulina, tipo dialisi)

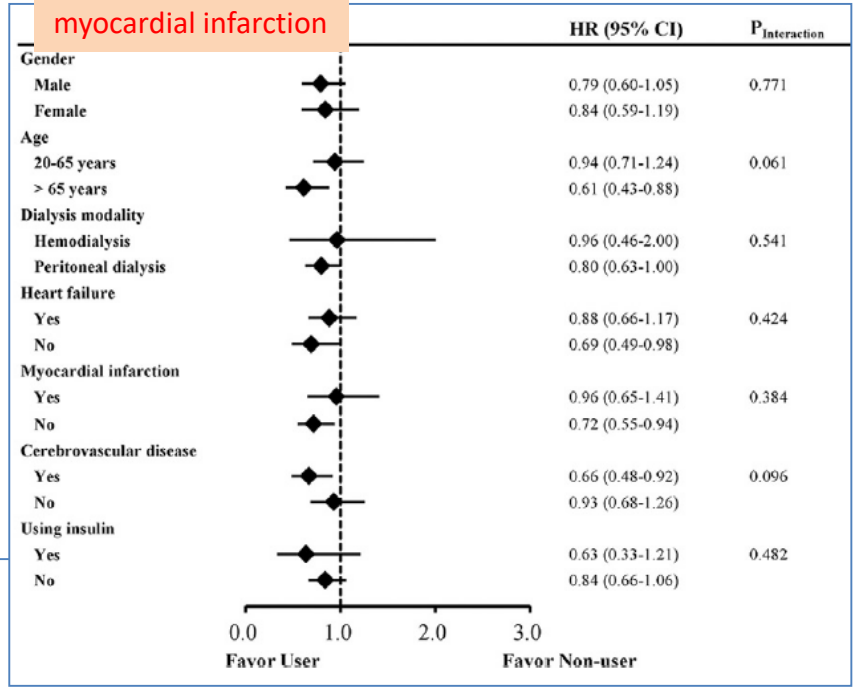
all-cause mortality



ischemic stroke



myocardial infarction



Shang-Yih C et al., *Int J Cardiol* 2016

inibitori DPP4 e rene

- efficacia e sicurezza
- effetti CV
- **dialisi & trapianto**
- endpoint renali

DPP-4 Inhibitors in Diabetic Patients with Chronic Kidney Disease and End-Stage Kidney Disease on Dialysis in Clinical Practice

Dialisi: criterio esclusione TECOS, EXAMINE, SAVOR-TIMI

- Tra i pochi antidiabetici utilizzabili in dialisi (ev. modulando dose)
- Efficacia simile vs pz con normale fx renale
- Non influenzano fx renale
- No ↑ ipoglicemie
- Uso albumina glicata?

					GFR (ml/min)	Major metabolic	
DPP-4 inhibitor	Comparator	Patient group	Duration	Details of treatment	Glycemic control	Other factors	Hypoglycemia
Sitagliptin [38]	Glipizide	HD, PD	54 weeks	Monotherapy with sitagliptin or glipizide. Sitagliptin group (n = 129; HD = 71.9%, PD = 28.1%). Glipizide group (n = 65; HD = 64.6%, PD = 35.4%).	HbA1c: sitagliptin group –0.72% vs. glipizide group –0.87% (NS). FPG: sitagliptin group –26.6 mg/dl vs. glipizide group –31.2 mg/dl (NS).		Symptomatic hypoglycemia: sitagliptin group 6.3% vs. glipizide group 10.8% (NS). Severe hypoglycemia: sitagliptin group 0% vs. glipizide group 7.7%.
Vildagliptin [39]	Current standard care	HD	24 weeks	Vildagliptin group (n = 30): add 50–100 mg/day to current standard care. Control group (n = 21): current standard care.	HbA1c: decrease from 6.7 to 6.1% ($p < 0.0001$). GA: decrease from 24.5 to 20.5% ($p < 0.0001$). PPG: decrease from 186 to 140 mg/dl ($p < 0.0001$).		None of the cases.
Vildagliptin [40]	None (single-arm)	HD	24 weeks	Monotherapy with vildagliptin: drug naïve (n = 16); switch from α-GI (n = 5); switch from mitiglinide (n = 2).	GA: decrease from 23.8 to 21.2% ($p < 0.001$). PPG (2 h): decrease from 206 to 159 mg/dl ($p < 0.001$).	Increase in GLP-1 level. Decrease in glucagon level.	None of the cases.
Alogliptin [41]	None (single-arm)	HD	2 years	n = 16, monotherapy with alogliptin 6.25 mg daily.	HbA1c: decrease from 7.1 to 5.8% ($p < 0.05$). GA: decrease from 22.5 to 19.6% ($p < 0.05$).	Increase in GLP-1 level.	None of the cases.
Alogliptin [42]	None (single-arm)	HD	48 weeks	Add 6.25 mg daily alogliptin to current standard care (n = 30): drug naïve (n = 15); α-GI (n = 8); mitiglinide (n = 5); α-GI + mitiglinide (n = 2)	HbA1c: decrease from 7.1% to 6.3% ($p < 0.0001$). GA: decrease from 25.6 to 20.7% ($p < 0.0001$). PPG: decrease from 212 mg/dl to 156 mg/dl ($p < 0.0001$).		None of the cases.
Linagliptin [43]	None (single-arm)	HD	24 weeks	n = 21, monotherapy with linagliptin 5 mg daily.	GA: decrease from 21.3 to 18.0% ($p < 0.05$).	Increase in GLP-1 level. Decrease in PGE2 and IL-6 levels.	None of the cases.
Teneligliptin [44]	Current standard care	HD	28 weeks	Teneligliptin group (n = 16): drug naïve (n = 7); switch from α-GI and/or vildagliptin (n = 9). Control group (n = 29): current standard care.	HbA1c: –0.57% compared to control group (NS). GA: –3.1% compared to control group ($p < 0.05$). PPG: NS compared to control group.	Increase in C-peptide level.	None of the cases.

Abe M & Okada K, *Chron Kidney Dis* 2015

Glucose-lowering agents for treating pre-existing and new-onset diabetes in kidney transplant recipients (Review)

Lo C, Jun M, Badve SV, Pilmore H, White SL, Hawley C, Cass A, Perkovic V, Zoungas S

Three studies with a total of 115 transplant recipients examined the use of DPP4 inhibitors for new-onset diabetes after transplantation. Evidence for the treatment effect of DPP4 inhibitors on transplant or graft survival, HbA1c and fasting blood glucose levels, all cause mortality, and adverse events including hypoglycaemia was of low quality. One study comparing vildagliptin to placebo and another comparing sitagliptin to placebo showed no difference in transplant or graft survival over two to four months of follow-up. One study comparing vildagliptin to placebo showed no significant change in estimated glomerular filtration rate from baseline (1.9 ± 10.3 mL/min/1.73 m^2, P = 0.48 and 2.1 ± 6.1 mL/min/1.73 m^2, P = 0.22) and no deaths, in either treatment group over three months of follow-up. One study comparing vildagliptin to placebo showed a lower HbA1c level (mean ± SD) (6.3 ± 0.5% versus versus 6.7 ± 0.6%, P = 0.03) and trend towards a greater lowering of fasting blood glucose (-0.91 ± -0.92 mmol/L versus vs -0.19 ± 1.16 mmol/L, P = 0.08) with vildagliptin. One study comparing sitagliptin to insulin glargine showed an equivalent lowering of HbA1c (-0.6 ± 0.5% versus -0.6 ± 0.6%, P = NS) and fasting blood glucose (4.92 ± 1.42 versus 4.76 ± 1.09 mmol/L, P = NS) with sitagliptin. For the outcome of hypoglycaemia, one study comparing vildagliptin to placebo reported no episodes of hypoglycaemia, one study comparing sitagliptin to insulin glargine reported fewer episodes of hypoglycaemia with sitagliptin (3/28 patients; 10.7% versus 5/28; 17.9%) and one cross-over study of sitagliptin and placebo reported two episodes of asymptomatic moderate hypoglycaemia (2 to 3.9 mmol/L) when sitagliptin was administered with glipizide. All three studies reported no drug interactions between DPP4 inhibitors and the immunosuppressive agents taken.

Outcomes	Impact	No. of participants (studies)	Quality of the evidence (GRADE)
Transplant or graft survival Follow-up: range 2 months to 3 months	One study compared vildagliptin to placebo on patients with NODAT and there was no difference in transplant or graft survival on correspondence with the authors. The other study was a cross-over RCT with 100% graft survival reported by the authors on correspondence	70 (2)	⊕⊕◯◯ LOW [1,2]
Kidney function: creatinine levels, eGFR, albuminuria Follow-up: 3 months	One study compared vildagliptin to placebo and there was no significant change in eGFR from baseline in either group (1.9 ±10.3 mL/min/1.73 m^2, P = 0.48 and 2.1 ± 6.1 mL/min/1.73 m^2, P = 0.22). Both groups did not develop proteinuria or albuminuria. The other study was a cross-over RCT comparing sitagliptin to placebo and no proteinuria or albuminuria developed in either intervention group during the study	70 (2)	⊕⊕◯◯ LOW [1,2]

Cochrane Library

Cochrane Database of Systematic Reviews

Glucose-lowering agents for treating pre-existing and new-onset diabetes in kidney transplant recipients (Review)

Lo C, Jun M, Badve SV, Pilmore H, White SL, Hawley C, Cass A, Perkovic V, Zoungas S

What did we find?

We found seven studies which together included 399 kidney transplant recipients. Four studies were undertaken in patients with pre-existing type 1 or type 2 diabetes; three of these examined more versus less intensive insulin treatment, and one compared pioglitazone and insulin treatment to insulin treatment alone. Three studies were undertaken in patients with new-onset diabetes after transplantation, and studied the effectiveness and safety of DPP-4 inhibitors. From these studies, the effects of more compared to less intensive insulin treatment on survival of the kidney transplant, control of diabetes, and survival of the patient, as well as treatment side-effects, are not well understood. The effects of using DPP4 inhibitors and pioglitazone on survival of the kidney transplant, control of diabetes and survival of the patient and possible side-effects are also uncertain.

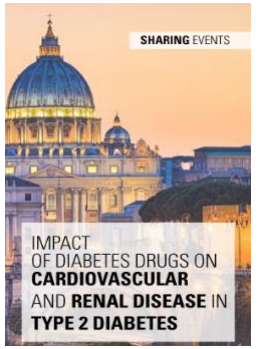
Cochrane Library

Cochrane Database of Systematic Reviews

Authors' conclusions

Evidence concerning the efficacy and safety of glucose-lowering agents for treating pre-existing and new-onset diabetes in kidney transplant recipients is limited. Existing studies examine more intensive versus less intensive insulin therapy, and the use of DPP4 inhibitors and pioglitazone. The safety and efficacy of more intensive compared to less intensive insulin therapy is very uncertain and the safety and efficacy of DPP4 inhibitors and pioglitazone is uncertain, due to data being limited and of poor quality. Additional RCTs are required to clarify the safety and efficacy of current glucose-lowering agents for kidney transplant recipients with diabetes.

inibitori DPP4 e rene



- efficacia e sicurezza
- effetti CV
- dialisi & trapianto
- **endpoint renali**

effetti renali dei DPP4-i: presupposti

- **GLP1-R e GIP-R** espressi non solo nel pancreas
  - Confermata espressione in glomeruli e tubulo prox. nei roditori, a. renali nell'uomo
  - Sovraespressione in reni di topi sottoposti a dieta iperlipidica o a stimoli flogistici
  - Controversa espressione in glomeruli e tubulo nell'uomo
  - Infusione GLP1: ↑ diuresi ed escrezione sodio, calcio, fosfato e cloruri (uomo)
  - Effetto antipertensivo
- **DPP4:** substrati diversi oltre a GLP1 e GIP

Makino Y. et al., *Curr Opin Nephrol Hypertens* 2015

effetti renali dei DPP4-i: presupposti

EFF. INCRETINO-DIPENDENTI

- **glicemia**
- **GLP1:** eff. antinfiammatorio
  - ↓RAGE e MCP-1
  - inibiz. angiotensina II glomerulare
- (DPP4i: sufficienti?)

EFF. INCRETINO-INDIPENDENTI

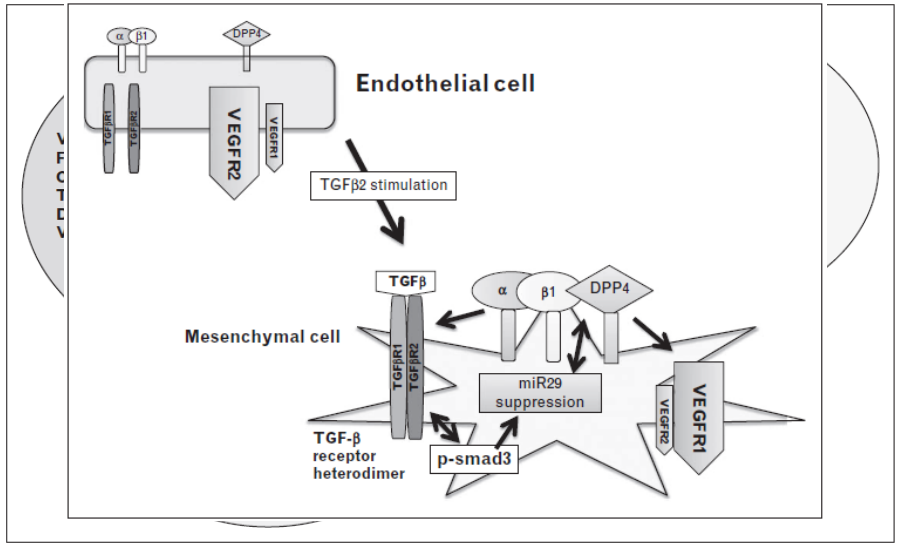
- **regolaz. tono vascolare, flogosi, migrazione e differenziazione cellulare**
  - ✓ **BNP**
  - ✓ **Sostanza P**
  - ✓ **Neuropeptide Y**
  - ✓ **Stromal-derived factor 1α** (SDF-1α)
  - ✓ **High-mobility group protein B1** (HMGB1)
  - ✓ **Transforming Growth Factor β1** (TGF-β1)
- **rimodellamento matrice extracellulare**

Substrates of DPP-4	Consequence of DPP-4 inhibition
GLP-1 [22,27,28,34,35]	Natriuresis ↑, urinary excretion of calcium ↑, inflammation ↓, RAAS activity ↓
BNP/ANP [17]	Natriuresis ↑, inflammation ↓, sympathetic activity ↑, RAAS activity ↓, vasodilation
Substance P [18]	Natriuresis ↑, inflammation ↑, sympathetic activity ↑
NPY [19]	Natriuresis ↑, inflammation ↓, sympathetic activity ↑, RAAS activity ↓, vasoconstriction
SDF-1α [20]	Renal cell protection, repair from injury
HMGB1 [21]	Inflammation ↑, angiogenesis

Makino Y. et al., *Curr Opin Nephrol Hypertens* 2015

Dipeptidyl peptidase-4 inhibition and renoprotection: the role of antifibrotic effects oposti

- DPP-4 is involved in the kidney fibrosis process via either catalytic-dependent or -independent mechanisms.
- DPP-4 and integrin β1 interaction induces profibrotic cellular signaling and EndMT.
- DPP-4 inhibition induces miR-29, the key antifibrotic miR that targets DPP-4, integrin β1, and IFN-γ.
- DPP-4 inhibition may result in the induction of antifibrotic miR crosstalk.



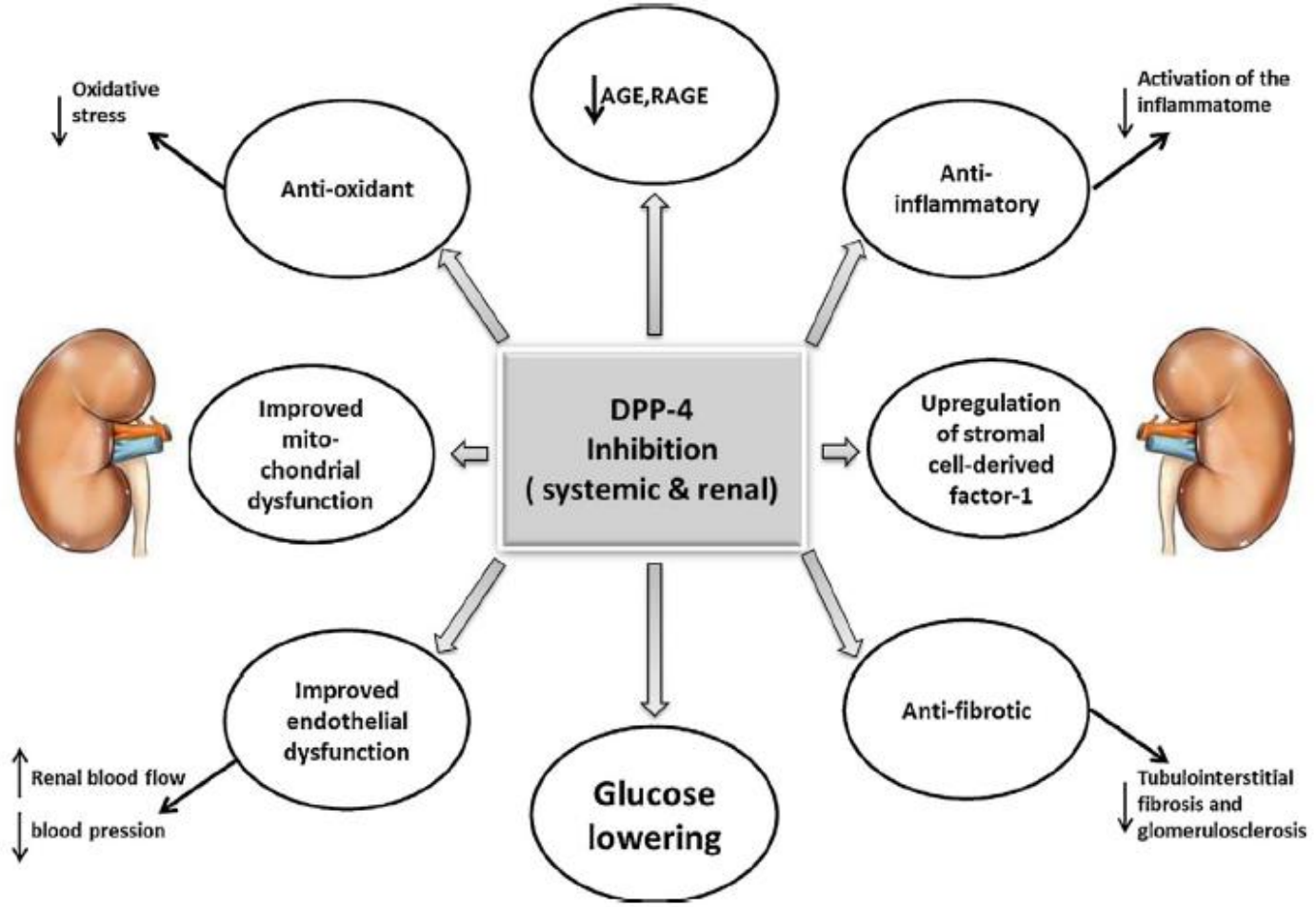
M Gallo

- **DPP4**: coinvolto nella endothelial mesenchimal transition (cellule endoteliali danneggiate → cell mesenchimali producenti matrice → fibrosi renale)
- **DPP4-i**
  - effetto enzimatico antifibrotico (proteasi)
  - effetto non enzimatico: legame con proteine della matrice
  - ↓ fibrosi tubulointerstiziale e glomerulosclerosi

Takagaki AJ et al., *Curr Opin Nephrol Hypertens 2017*

effetti renali dei DPP4-i: presupposti

Mechanisms
Upregulation of GLP-1 and GLP-1 receptors
Inhibition of renal DPP-4 activity
Reduction of inflammation
Attenuation of activation of NLRP3/ASC inflammasome
Reduction of oxidative stress
Reduction of mitochondrial dysfunction and apoptosis
Suppression of connective tissue growth factor
Regulation of preglomerular vascular smooth muscle and mesangial cell proliferation
Restoration of renal myogenic function
Reduction of tubulointerstitial fibrosis and renal sclerosis
Upregulation of stromal cell-derived factor-1
Suppression of advanced glycation end-products
Reduction of blood pressure



Scheen AJ &. Delanaye P, *Diab & Metab* 2017

effetti renali dei DPP4-i: risultati preliminari

- **Studi preclinici**
  - Effetti protettivi in roditori diabetici dimostrati per alo, sita, saxa, lina, vildagliptin
    - az. antinfiammatoria, antiossidante e antiapoptotica
    - riduzione infiltrazione macrofagi e az. NF-kB
    - riduzione sclerosi glomerulare e albuminuria
  - Effetti deleteri?
    - aumento vasocostrizione a. renale indotta da angiotensina II (sita)
- **Studi clinici**
  - **Alogliptin:** riduzione albuminuria e marker di danno ossidativo
  - **Sitagliptin:** riduzione albuminuria (?), PAO, PCR
  - **Saxagliptin** (SAVOR-TIMI 53): miglioramento uACR, riduzione declino funzione renale; CHF??
  - **Linagliptin:** miglioramento uACR
  - (**Vildagliptin:** riduzione albuminuria?)

Makino Y. et al., *Curr Opin Nephrol Hypertens* 2015
Penno G. et al., *Nutr Metab Cardiovasc Diseases* 2016
Scheen AJ &. Delanaye P, *Diab & Metab* 2017

effetti renali dei DPP4-i
negli RCT comprendenti pz con IRC

uACR

DPP-4 inhibitors	Reference	Type of kidney disease patient	Duration (weeks)	Dose (mg/day)	Comparator	Patients (*n*)	Baseline UACR (mg/g ± SD or IQR)	Change UACR (% vs. baseline or placebo)	*P*
Sitagliptin	[71]	No CKD	12	100	Placebo	17 vs. 19	124.4 (54.3–463.8)	−32 vs. placebo (95% CI: −69 to 46)	NS
Sitagliptin	[72]	No CKD	26	50 (Japan)	Other OADs	42 vs. 38	61.4 ± 154.3	−23.3 vs. 0.8	0.0001
Sitagliptin	[73]	Moderate-to-severe CKD	54	50–25	Glipizide	211 vs. 212	107.7 ± 170.0	6.8 vs. 12.4	NS
Linagliptin	[96]	UACR 30–3000 mg/g	24	5	Placebo	162 vs. 55	73.8 (30.1–2534.4)	−32 vs. −6	0.0357
Linagliptin	[96]	UACR 30–3000 mg/g, eGFR ≥ 30 mL/min/1.73 m^2	24	5	Placebo	178 vs. 173	121 ± 153	−6 (95% CI: −15 to 3) vs. placebo	0.1954

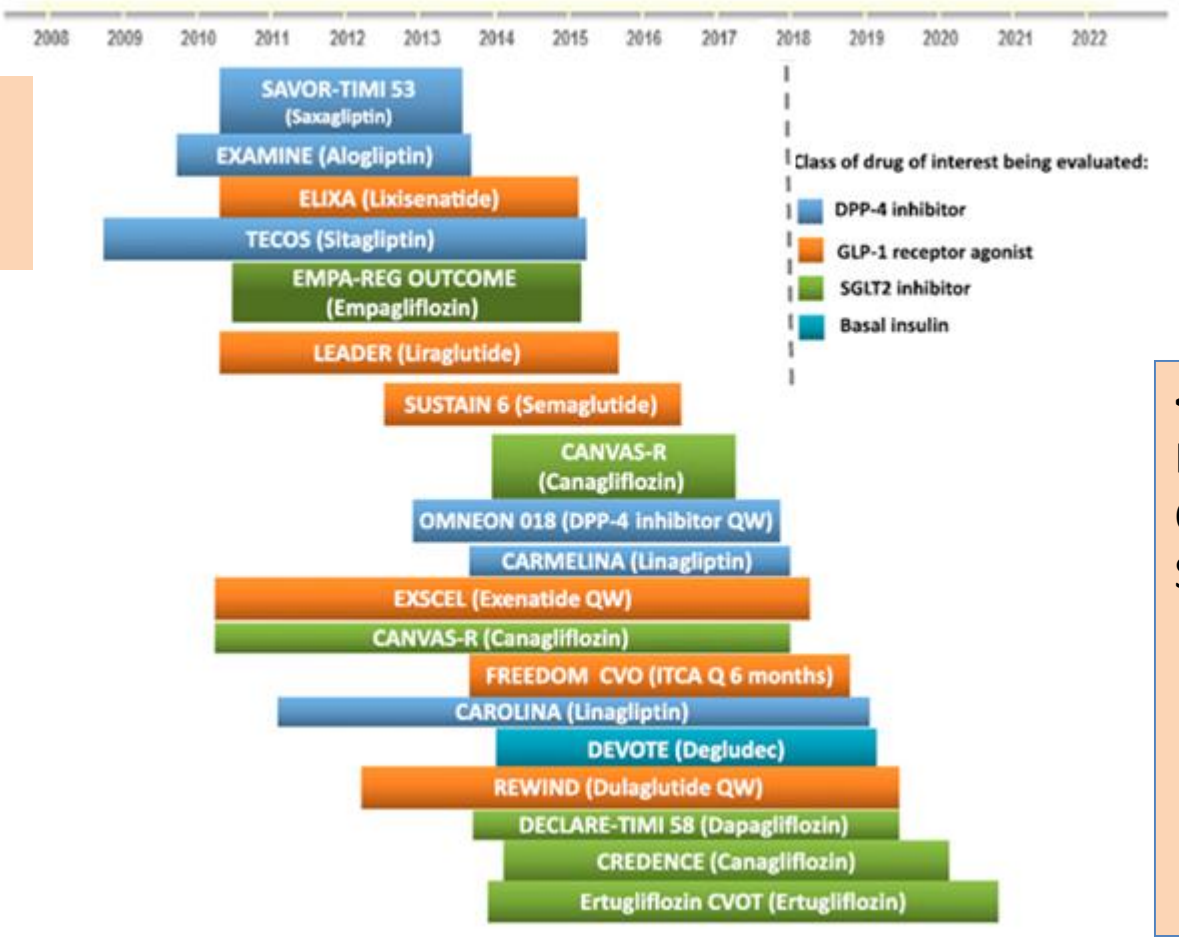
eGFR

DPP-4 inhibitor	Reference	Type of kidney patient	Duration (weeks)	Dose (mg/day)	Comparator	Patients (*n*)	Baseline eGFR (mL/min/1.73m^2)[a]	Change eGFR (mL/min/1.73 m^2, vs. baseline or placebo)	*P*
Sitagliptin	[71]	No CKD	12	100	Placebo	17 vs. 19	83 ± 16	−6.0 (−14 to 3) vs. placebo	NS (0.17)
Sitagliptin	[72]	No CKD	26	50 (Japan)	Other OADs	42 vs. 38	77.1 ± 18.9	−4.7 vs. −3.4	NS
Sitagliptin	[73]	Moderate-to-severe CKD	54	50-25	Glipizide	211 vs. 212	35.6 ± 10.9	−3.9 vs. −3.3	NS
Linagliptin	[99]	No CKD Mild CKD Moderate CKD	24	5	Placebo	870 vs. 342 620 vs. 218 68 vs. 25	107.9 (90.0–266.4) 78.5 (60.1–90.0) 56.4 (34.2–59.5)	Virtually unchanged	NS
Linagliptin	[100]	Severe CKD	52	5	Placebo	68 vs. 65	22.1 ± 6.3	−0.8 vs. −2.2	NS
Vildagliptin	[110]	Moderate CKD	52	50	Placebo	122 vs. 89	39.5 ± 6.0	−1.62 vs. −1.80	NS
		Severe CKD	52	50	Placebo	94 vs. 64	22.3 ± 5.6	−1.98 vs. −2.44	NS

Scheen AJ &. Delanaye P, *Diab & Metab* 2017

cardiovascular safety of all new ADDs

demonstrated through:
- **pooled analyses of phase III studies**
- or **specifically designed trials.**



<2008
Breve termine
Obiettivo: HbA1c
Soggetti "sani"

>2008
Obiettivo: sicurezza CV
Soggetti ad alto rischio
(età avanzata, lunga durata DM, insuff renale)

effetti renali dei DPP4-i negli studi di outcome CV

sicurezza di saxa, sita e alogliptin in popolazione a elevato rischio CV

- generalizzabilità dei risultati?
- outcome renali?

Clinical trial	DPP-4 inhibitor	Primary cardiovascular composite outcome[a]	Myocardial infarction (fatal or nonfatal)	Stroke (fatal or nonfatal)	Cardiovascular mortality	All-cause mortality	Hospitalization for heart failure
SAVOR-TIMI 53 [38]	Saxagliptin	1.00 (0.89 – 1.12)	0.95 (0.80 – 1.12)	1.11 (0.88 – 1.39)	1.03 (0.87 – 1.22)	1.11 (0.96 – 1.27)	1.27 (1.07 – 1.51) P = 0,007
EXAMINE [39]	Alogliptin	0.96 (≤1.16)[b]	1.08 (0.88 – 1.33)	0.95 (≤1.14)[b]	0.85 (0.66 – 1.10)	0.88 (0.71 – 1.09)	1.07 (0.79 – 1.46)
TECOS [40]	Sitagliptin	0.98 (0.89–1.08)	0.95 (0.81 – 1.11)	0.97 (0.79 – 1.19)	1.03 (0.89 – 1.19)	1.01 (0.90 – 1.14)	1.00 (0.83 – 1.20)

Scheen AJ, Exp Rev Clin Pharmacol 2017

effetti renali dei DPP4-i
negli studi di outcome CV

renal outcomes

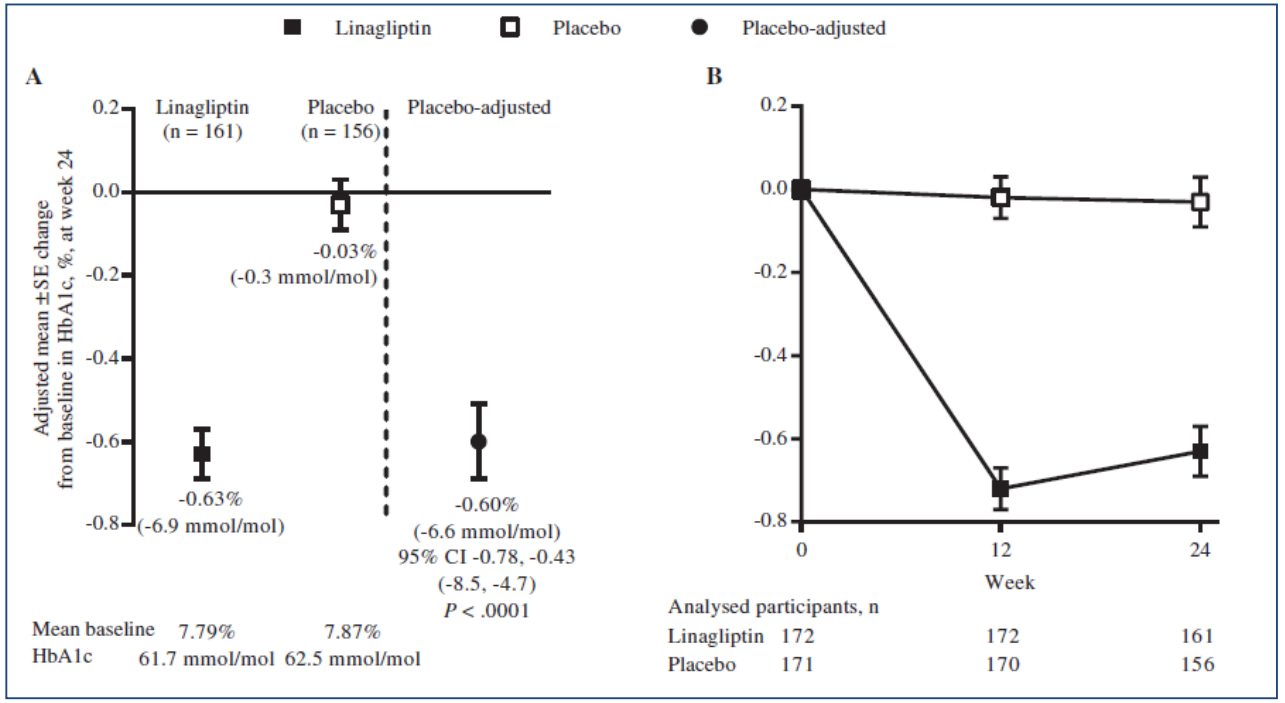
Renal endpoints	TECOS [19] (sitagliptin)	SAVOR–TIMI 53 [17] (saxagliptin)
Baseline UACR (median mg/g)	10.3 (3.5–34.6)	203.6 (79.2–848.4)
UACR (mg/g or %, placebo-subtracted)	−0.18 mg/g (−0.35 to −0.02) $P=0.031$	−34.3[a] mg/g (NA) $P<0.004$
Progression to macroalbuminuria (HR)	NA	NA
Baseline eGFR (mL/min/1.73 m^2)	74.9 ± 21.3	72.5 ± 22.6
Change in eGFR (mL/min/1.73 m^2, placebo-subtracted)	−1.34 (−1.76 to −0.91) $P<0.001$	−0.13 (NA) $P=0.5794$
Doubling of serum creatinine (HR)	NA	1.1 (0.89–1.36) NS
Continuous renal replacement therapy (RRT)	NA	0.90[c] (0.61–1.32) NS
Composite renal outcomes (HR)	0.90 (NA) $P=$NS	1.08[d] (0.88–1.32) $P=0.46$
Definition of composite renal outcomes (variable across trials)	Renal failure[b]	Doubling of SCr, dialysis, renal transplantation or SCr > 6 mg/dL

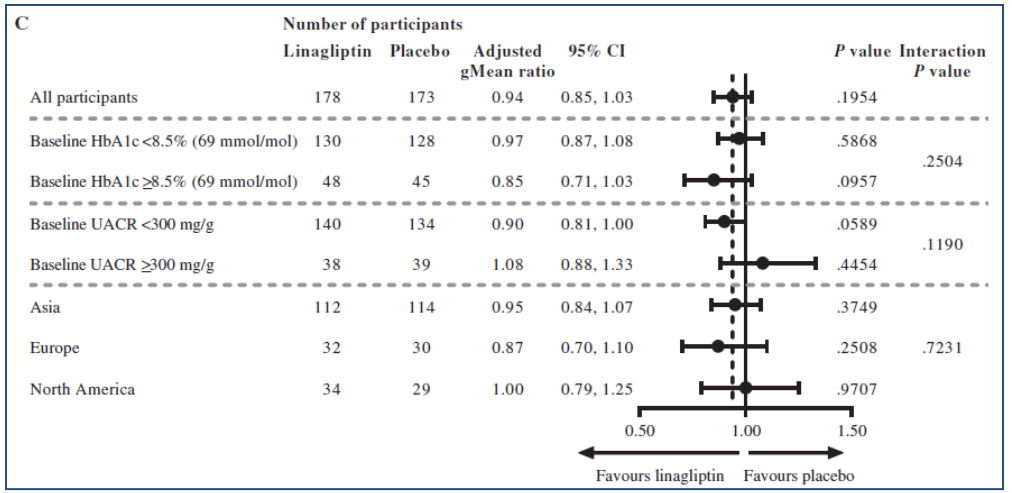
Scheen AJ &. Delanaye P, *Diab & Metab* 2017

Linagliptin and its effects on hyperglycaemia and albuminuria in patients with type 2 diabetes and renal dysfunction: the randomized MARLINA-T2D trial

Conclusions: In individuals at early stages of diabetic kidney disease, linagliptin significantly improved glycaemic control but did not significantly lower albuminuria. There was no significant change in placebo-adjusted eGFR. Detection of clinically relevant renal effects of linagliptin may require longer treatment, as its main experimental effects in animal studies have been to reduce interstitial fibrosis rather than alter glomerular haemodynamics.

360 individuals with T2DM
HbA1c 6.5-10.0%
eGFR ≥30 mL/min/1.73 m^2
and uACR 30-3000 mg/g





Groop PH et al., *Diabetes Obes & Metab* 2017

CARMELINA
A CV and renal outcome study with linagliptin

- CARMELINA (NCT01897532) is evaluating the long-term impact of linagliptin on CV morbidity, mortality and renal function in patients with T2D at high CV risk, and comparing the outcomes against placebo in a setting of standard care
- Thus, CARMELINA is currently exploring whether a renoprotective effect of linagliptin could emerge from chronic intervention in more advanced diabetic CKD

https://clinicaltrials.gov/ct2/show/NCT01897532

CARMELINA
A CV and renal outcome study with linagliptin

- HbA1c 6.5-10.0%
- exclusion criteria: eGFR <15 ml/min/1.73 m2

Estimated Study Completion Date: January 22, 2018

Secondary Outcome Measures:

- Time to the first occurrence of any of the following (composite renal endpoint)
  - renal death
  - sustained end stage renal disease
  - sustained decrease ≥ 40% in eGFR

https://clinicaltrials.gov/ct2/show/NCT01897532

take home messages

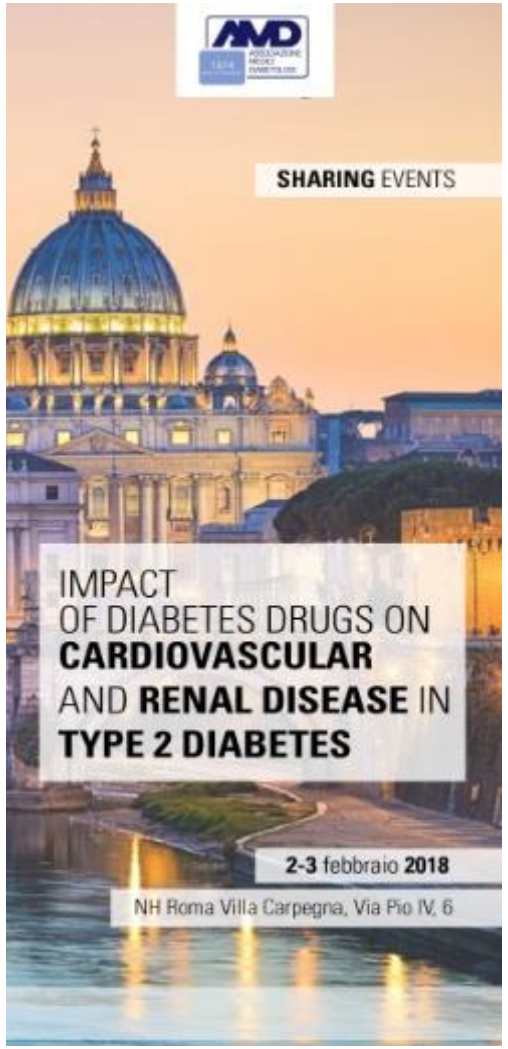
- eccellente profilo tollerabilità e safety, effetto neutro sul peso e basso rischio ipoglicemie
- efficaci e sicuri per tutti gli stadi di insufficienza renale, compresa la dialisi e il post-trapianto
- effetto neutro su endpoint CV
- effetto neutro sul rene (modesta riduzione albuminuria?)
- **NON** 1ª scelta per prevenire/ritardare nefropatia diabetica nel T2DM (liraglutide, canagliflozin, empagliflozin)

DPP4i & endpoint renali

Dipeptidyl peptidase-4 inhibitors (DPP-4is) are increasingly being used in the management of type 2 diabetes (T2D). The present review summarizes the current knowledge of the effects of DPP-4is on renal outcomes by analyzing the experimental preclinical data, the effects of DPP-4is on urinary albumin–creatinine ratios (UACRs) and estimated glomerular filtration rates (eGFRs) from observational studies and clinical trials, and renal events (including kidney failure requiring renal replacement therapy) in recent large prospective cardiovascular outcome trials. Renal protection has been demonstrated in various animal models that have implicated different underlying mechanisms independent of glucose control, whereas prevention of new onset microalbuminuria and/or progression of albuminuria has been reported in some clinical studies, but with no significant effects on eGFR in most of them. The long-term clinical effects of DPP-4is on renal outcomes and the development of end-stage renal disease remain largely unknown and, thus, demand further investigations in prospective trials and long-term observational studies. In conclusion, despite promising results in animal models, data on surrogate biological markers of renal function and clinical renal outcomes remain rather scanty in patients with T2D, and mostly demonstrate the safety rather than true efficacy of DPP-4is.

più sicuri, che efficaci

Scheen AJ &. Delanaye P, *Diab & Metab* 2017



Grazie!

EFFETTO DEI NUOVI FARMACI SUL RENE

Inibitori DPP4

Marco Gallo

SCDU Endocrinologia Oncologica, AOU Città della Salute e della Scienza di Torino - Molinette - COES