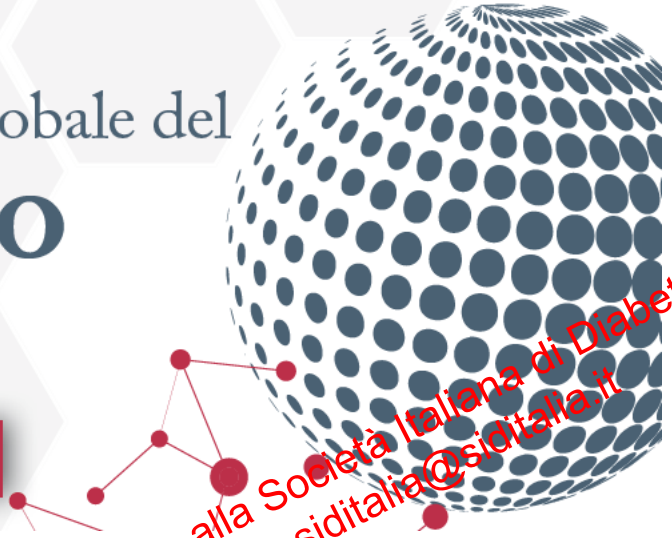
Gestione del rischio globale del

diabetico di tipo 2:

un ruolo per i DPP4?



Quali molecole in popolazioni speciali (anziano)

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ALDO MORO

Disclosures

Nell'arco degli ultimi tre anni dichiaro di aver ricevuto onorari per conferenze, collaborazioni scientifiche, lavori di ricerca clinica e documentale dalle seguenti Aziende:

- ***Novo Nordisk Italia SpA***
- ***Sanofi SpA***
- ***Astra Zeneca SpA***

Annalisa Natalicchio

Background

- Secondo l'*International Diabetes Federation*, la prevalenza del diabete è di circa il 25% nella popolazione di età > 65 anni.
- I farmaci antidiabete sono tra i farmaci più comunemente associati a ricoveri ospedalieri prevenibili, dovuti a eventi avversi o ad un *overtreatment*, specialmente nelle popolazioni più anziane.
- Alcuni studi suggeriscono che uno stretto controllo metabolico potrebbe non essere consigliabile per le persone anziane e fragili, poiché i benefici potrebbero non superare i rischi del trattamento.
- Raggiungere e mantenere gli obiettivi glicemici raccomandati senza causare effetti avversi, come ipoglicemia e aumento di peso, è difficile quando si usano i farmaci ipoglicemizzanti tradizionali. Questo problema è particolarmente rilevante nei pazienti più anziani.

Nat Rev Endocrinol . 2018;14(2):88–98
JAMA. 2003;289(9):1107–16
Diabetes Care. 2012;35(12):2650–64
Acta Diabetol. 2019 Jun;56(6):605-617

Il Paziente Anziano

Il **paziente anziano** affetto da diabete mellito di tipo 2 è un tipo di paziente difficile da trattare in quanto spesso presenta diverse comorbilità e un aumentato rischio di incorrere in ipoglicemie gravi a causa di diverse condizioni legate all'età, tra cui insufficienza renale progressiva, malattia CV, ridotta secrezione di glucagone e ridotta consapevolezza dell'ipoglicemia.

Acta Diabetol. 2019 Jun;56(6):605-617

Secondo le linee guida, il paziente anziano può utilizzare tutte le terapie ipoglicemizzanti disponibili, facendo particolare attenzione a:

- Prevenire le ipoglicemie (le ipoglicemie nell'anziano possono causare cadute, fratture, ricoveri, eventi vascolari, demenza e morte);
- Stato cognitivo del paziente;
- Possibili interazioni con altri farmaci assunti dal paziente;
- Eventuale rischio CV e insufficienza renale.

Doctors Diabetologists Association [AMD]—Italian Society of Diabetology [SID]. Italian standards for the treatment of diabetes.
American Diabetes Association (2017) Standards of medical care in diabetes—2017. Diabetes Care 40(Supplement 1):S1–S135.

Il Paziente Diabetico Anziano

Il paziente anziano è spesso escluso dai trials clinici:
solo l'**1.4%** dei trials recluta pazienti anziani e una percentuale ancora minore recluta pazienti anziani fragili.

Negli anni sono state pubblicate delle linee guida basate soprattutto su **consensus** o **opinioni**, ma nessuna di esse ha stabilito dei **gold standard** di cura.

International Diabetes Federation

New IDF Guideline for managing type 2 diabetes in older people☆

Trisha Dunning, Alan Sinclair, Stephen Colagiuri

Diabet Med. 2018 Jul;35(7):838-845

CONSENSUS REPORT

Diabetes in Older Adults

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Richard E. Pratley, MD[11]
Carrie S. Swift, MS, RD, BC-ADM, CDE[12]

Diabetes Care. 2012 Dec;35(12):2650-64

Diabetes Mellitus in Older People: Position Statement on behalf of the International Association of Gerontology and Geriatrics (IAGG), the European Diabetes Working Party for Older People (EDWPOP), and the International Task Force of Experts in Diabetes

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J Am Med Dir Assoc. 2012 Jul;13(6):497-502

J Am Med Dir Assoc. 2012 Jul;13(6):497-502

SOCIETÀ ITALIANA
DI GERONTOLOGIA
E GERIATRIA

Personalizzazione del trattamento dell'iperglicemia nell'anziano con diabete tipo 2

POSITION STATEMENT

- In caso di utilizzo di farmaci a basso rischio di ipoglicemia (tra cui **DPP4 inibitori**) l'obiettivo di HbA1c è < 7,0 %.
  (Livello della prova VI, forza della raccomandazione B)
- Nei pazienti che presentano controindicazioni o che non tollerano la metformina, è indicato l'impiego in monoterapia di un farmaco che non induce ipoglicemia (tra cui **DPP4 inibitori**).
  (Livello della prova VI, forza della raccomandazione A)
- Per la loro efficacia, l'elevata tollerabilità, la semplicità d'uso, il profilo di sicurezza cardiovascolare e l'ampio numero di studi clinici randomizzati in popolazioni anziane, gli **inibitori della DPP-4** rappresentano una opzione terapeutica da preferire a sulfoniluree e repaglinide nei pazienti anziani non adeguatamente controllati con la sola metformina o con intolleranza o controindicazioni alla metformina.
  (Livello della prova VI, forza della raccomandazione B)

Effectiveness and safety of dipeptidyl peptidase 4 inhibitors in the management of type 2 diabetes in older adults: a systematic review and development of recommendations to reduce inappropriate prescribing

Gisela Schott[1*†], Yolanda V Martinez[2†], R. Erandie Ediriweera de Silva[2,3], Anna Renom-Guiteras[4,5], An David Reeves[2], Ilkka Kunnamo[7], Minna Marttila-Vaara[7] and Andreas Sönnichsen[4]

- In generale, negli anziani con diabete di tipo 2, gli **inibitori della DPP-4** mostrano un profilo di sicurezza simile o migliore rispetto a placebo o ad altri farmaci antidiabetici.
- Tuttavia, i dati sulla sicurezza si basano principalmente su risultati a breve termine (eventi ipoglicemici e eventi avversi acuti). Evidenze di benefici a lungo termine sono più limitate e abbastanza incoerenti.
- La maggior parte degli studi non fornisce alcuna informazione circa il livello di fragilità e lo stato cognitivo dei partecipanti.

BMC Geriatr. 2017 Oct 16;17(Suppl 1):226

Nella prescrizione di un inibitore della DPP-4 in un paziente anziano, cosa vi guida alla scelta?

A. Prevenire il danno cardiovascolare;

B. Prevenire le ipoglicemie;

C. Evitare problemi gastrointestinali;

D. B + C.

Quali molecole in popolazioni speciali (anziano)

- **Saxagliptin**
- **Sitagliptin**
- **Linagliptin**
- **Alogliptin**
- **Vildagliptin**

Efficacy and Safety of Saxagliptin in Older Participants in the SAVOR-TIMI 53 Trial

Diabetes Care 2015;38:1145–1153 | DOI: 10.2337/dc14-2868

*Lawrence A. Leiter,[1] Hwee Teoh,[1,2] Eugene Braunwald,[3] Ofri Mosenzon,[4] Avivit Cahn,[4] K.M. Prasanna Kumar,[5] Alena Smahelova,[6] Boaz Hirshberg,[7] Christina Stahre,[8] Robert Frederich,[9] Francois Bonnici,[10] Benjamin M. Scirica,[3] Deepak L. Bhatt,[3] and Itamar Raz,[4] for the SAVOR-TIMI 53 Steering Committee and Investigators**

P, placebo
S, saxagliptin

Diabetes Care. 2015 Jun;38(6):1145-53

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Table 2—Incidence of primary, secondary, and other prespecified end points

	<65 years (placebo *n* = 3,941; saxagliptin *n* = 3,990)				≥65 years (placebo *n* = 4,271; saxagliptin *n* = 4,290)				
	KM event rate (%)				KM event rate (%)				Interaction
End point	Placebo	Saxagliptin	HR (95% CI)	*P* value	Placebo	Saxagliptin	HR (95% CI)	*P* value	*P* value
Primary* Interaction *P* value 0.06	5.7	6.8	1.15 (0.96, 1.37)	0.128	8.1	7.8	0.92 (0.79, 1.06)	0.243	0.058
Secondary* Interaction *P* value 0.09	10.8	12.3	1.11 (0.98, 1.27)	0.104	13.9	13.3	0.96 (0.85, 1.07)	0.447	0.087
MI	2.7	3.1	1.09 (0.84, 1.41)	0.521	4.0	3.3	0.86 (0.69, 1.07)	0.186	0.179
CV mortality	1.9	2.7	1.33 (0.99, 1.79)	0.056	3.9	3.7	0.92 (0.74, 1.13)	0.420	0.047
Non-CV mortality	1.1	1.5	1.41 (0.91, 2.22)	0.123	1.8	2.3	1.22 (0.92, 1.63)	0.169	0.568
All-cause mortality	2.6	3.7	1.36 (1.06, 1.74)	0.014	5.6	5.9	1.01 (0.86, 1.20)	0.869	0.057
Nonfatal ischemic stroke	1.4	1.7	1.12 (0.78, 1.62)	0.529	1.6	1.8	1.17 (0.85, 1.61)	0.344	0.904
Hospitalization for/due to									
Coronary revascularization	5.7	5.5	0.96 (0.80, 1.16)	0.670	5.5	4.9	0.87 (0.73, 1.05)	0.160	0.492
Heart failure	2.0	2.8	1.32 (0.99, 1.77)	0.062	3.5	4.2	1.25 (1.01, 1.56)	0.042	0.759
Hypoglycemia	0.4	2.4	1.12 (0.57, 2.21)	0.748	0.6	0.8	1.29 (0.78, 2.14)	0.323	0.720
Unstable angina	1.0	1.6	1.50 (1.01, 2.26)	0.043	0.9	0.9	0.89 (0.56, 1.39)	0.594	0.082
Doubling of creatinine level, initiation of dialysis, renal transplantation, or creatinine >6.0 mg/dL (530 mmol/L)	1.6	2.2	1.19 (0.88, 1.60)	0.257	2.3	2.2	0.99 (0.75, 1.31)	0.936	0.368

Mean follow-up duration is 2.0 years. KM, Kaplan-Meier. *Primary end point: CV death, MI, or stroke. Secondary end point: CV death, MI, stroke, hospitalization for unstable angina, heart failure, or coronary revascularization.

	<75 years (placebo *n* = 7,051; saxagliptin *n* = 7,111)				≥75 years (placebo *n* = 1,161; saxagliptin *n* = 1,169)				
	KM event rate (%)		HR	*P*	KM event rate (%)				Interaction
End point	Placebo	Saxagliptin	(95% CI)	value	Placebo	Saxagliptin	HR (95% CI)	*P* value	*P* value
Primary* Interaction *P* value 0.67	6.6	6.9	1.01 (0.89, 1.15)	0.840	11.3	10.0	0.95 (0.75, 1.22)	0.710	0.673
Secondary* Interaction *P* value 0.57	11.9	12.2	1.01 (0.92, 1.11)	0.857	15.7	16.4	1.08 (0.88, 1.32)	0.469	0.573
MI	3.3	3.0	0.9 (0.75, 1.09)	0.289	4.1	4.2	1.17 (0.79, 1.74)	0.437	0.246
CV mortality	2.4	2.8	1.10 (0.90, 1.35)	0.344	6.4	5.5	0.88 (0.63, 1.21)	0.421	0.247
Non-CV mortality	1.1	1.4	1.21 (0.91, 1.61)	0.191	2.2	3.8	1.43 (0.91, 2.29)	0.120	0.531
All-cause mortality	3.4	4.2	1.14 (0.96, 1.34)	0.127	8.5	9.1	1.03 (0.80, 1.34)	0.804	0.563
Nonfatal ischemic stroke	1.5	1.7	1.12 (0.86, 1.45)	0.414	1.5	2.1	1.38 (0.76, 2.57)	0.294	0.53
Hospitalization for/due to									
Coronary revascularization	5.7	5.2	0.90 (0.78, 1.04)	0.167	5.1	5.1	0.98 (0.69, 1.41)	0.924	0.685
Heart failure	2.4	3.0	1.21 (0.99, 1.48)	0.064	4.9	6.8	1.47 (1.05, 2.08)	0.026	0.342
Hypoglycemia	0.5	0.6	1.12 (0.72, 1.77)	0.607	0.7	0.9	1.73 (0.70, 4.65)	0.241	0.415
Unstable angina	1.0	1.3	1.23 (0.90, 1.68)	0.192	0.7	0.7	0.87 (0.31, 2.42)	0.788	0.521
Doubling of creatinine level, initiation of dialysis, renal transplantation, or creatinine >6.0 mg/dL (530 mmol/L)	1.8	2.1	1.13 (0.90, 1.41)	0.288	2.8	2.3	0.87 (0.52, 1.46)	0.610	0.34

Mean follow-up duration is 2.0 years. KM, Kaplan-Meier. *Primary end point: CV death, MI, or stroke. Secondary end point: CV death, MI, stroke, hospitalization for unstable angina, heart failure, or coronary revascularization.

Lo studio **SAVOR-TIMI 53** supporta la sicurezza CV globale di saxagliptin in un numero consistente di pazienti anziani e molto anziani, sebbene **il rischio di ricovero per insufficienza cardiaca sia aumentato, indipendentemente dalla categoria di età.**

Diabetes Care. 2015 Jun;38(6):1145-53
N Engl J Med. 2013 Oct 3;369(14):1317-26

Efficacy and Safety of Saxagliptin in Older Participants in the SAVOR-TIMI 53 Trial

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Table 3—Adverse events

	<65 years			≥65 years			<75 years			≥75 years		
	P (*n* = 3,941)	S (*n* = 3,990)	*P* value*	P (*n* = 4,271)	S (*n* = 4,290)	*P* value*	P (*n* = 7,051)	S (*n* = 7,111)	*P* value*	P (*n* = 1,161)	S (*n* = 1,169)	*P* value*
% AEs (including hypoglycemia)												
≥1 AE	71.4	70.6	0.446	75.7	76.5	0.368	73.2	73.1	0.971	76.4	76.9	0.774
≥1 treatment-related AE	8.6	9.3	0.259	10.6	12.2	0.018	9.6	10.5	0.054	10.0	12.7	0.042
Death due to AE	0.8	1.2	0.129	2.0	2.4	0.251	1.2	1.5	0.212	2.8	3.8	0.171
≥1 SAE	21.4	22.4	0.287	29.4	29.2	0.885	24.2	24.5	0.675	33.9	34.9	0.624
≥1 treatment-related SAE	0.3	0.8	0.007	0.6	0.6	0.987	0.6	0.7	0.259	0.1	0.7	0.020
Discontinued due to SAE(s)	1.2	1.2	0.951	2.6	1.9	0.026	1.8	1.4	0.043	2.8	2.7	0.878
Discontinued due to AE(s)	3.9	3.9	0.903	5.0	5.3	0.676	4.7	4.5	0.554	6.6	7.3	0.544
% AEs (excluding hypoglycemia) reported by ≥5% of patients												
Hypertension	3.8	4.8	0.032	4.5	4.3	0.641	4.0	4.6	0.103	5.1	4.3	0.358
Nausea	2.4	2.3	0.703	2.0	2.6	0.066	2.3	2.3	0.883	1.9	3.4	0.022
Peripheral edema	3.4	3.2	0.632	5.2	5.1	0.962	4.3	4.0	0.321	4.4	5.6	0.166
Renal impairment	1.4	1.8	0.144	2.4	2.3	0.861	1.7	2.0	0.191	3.1	2.5	0.364
Urinary tract infection	3.9	4.3	0.772	5.3	4.8	0.349	3.7	3.8	0.835	8.4	5.9	0.021
% Hyperglycemia	4.4	3.7	0.110	3.7	2.7	0.008	4.1	3.3	0.011	3.6	2.4	0.084
% Hypoglycemia	13.4	14.5	0.006	14.4	16.0	0.043	13.3	15.4	0.001	14.1	14.5	0.774
Major	1.2	1.5	0.319	2.1	2.7	0.073	1.6	1.9	0.306	2.2	3.9	0.017
Only minor	11.2	13.1	0.011	12.4	13.4	0.161	11.8	13.7	0.001	12.0	10.9	0.376
% Pancreatitis												
Acute	0.2	0.4	0.078	0.2	0.2	0.479	0.2	0.3	0.405	0.1	0.1	1.000
Chronic	0.1	0.1	0.450	0.0	0.0	0.499	0.1	0.0	0.451	0.1	0.0	0.498
% Neoplasms												
All cancers	3.3	2.4	0.012	5.4	5.4	0.999	4.2	3.4	0.020	5.7	7.0	0.188
Pancreatic cancer	0.1	0.1	0.405	0.2	0.1	0.130	0.2	0.0	0.012	0.1	0.3	0.320

P, placebo; S, saxagliptin; SAE, serious adverse event. *χ^2 test.

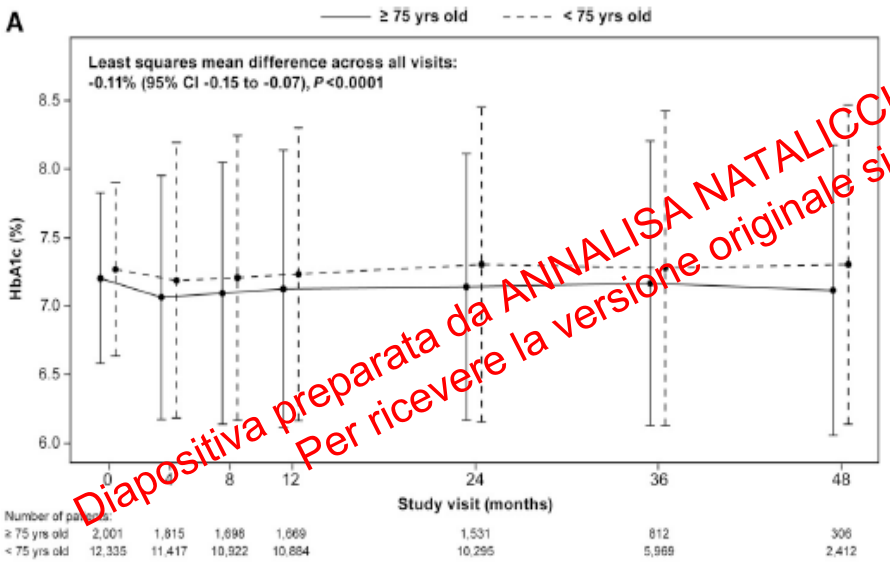
Quali molecole in popolazioni speciali (anziano)

- **Saxagliptin**
- **Sitagliptin**
- **Linagliptin**
- **Alogliptin**
- **Vildagliptin**

Assessing the Safety of Sitagliptin in Older Participants in the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS)

M. Angelyn Bethel,[1] Samuel S. Engel,[2] Jennifer B. Green,[3] Zhen Huang,[3] Robert G. Josse,[4] Keith D. Kaufman,[2] Eberhard Standl,[5] Shailaja Suryawanshi,[2] Frans Van de Werf,[6] Darren K. McGuire,[7] Eric D. Peterson,[3] and Rury R. Holman,[1] for the TECOS Study Group

Diabetes Care 2017;40:494–501 | DOI: 10.2337/dc16-1135



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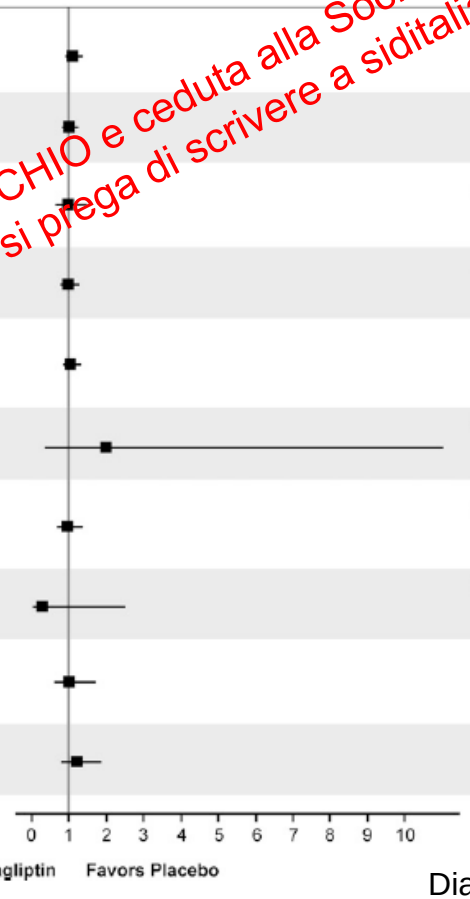
Primary and key secondary outcomes	Number of patients with events: Sitagliptin (n = 970)	Placebo (n = 1,034)	Hazard Ratio (95% CI)	P-value
Primary CV composite (4-point MACE)	170	168	1.10 (0.89–1.36)	0.39
Rate per 100 person-yr	6.75	6.19		
Secondary CV composite (3-point MACE)	152	162	1.01 (0.81–1.26)	0.94
Rate per 100 person-yr	5.97	5.96		
Hospitalization for HF	43	49	0.99 (0.65–1.49)	0.94
Rate per 100 person-yr	1.60	1.70		
Hospitalization for HF or death	113	124	1.00 (0.77–1.29)	0.99
Rate per 100 person-yr	4.41	4.46		
All-cause mortality	141	148	1.05 (0.83–1.32)	0.71
Rate per 100 person-yr	5.10	5.00		
Acute pancreatitis	4	2	2.01 (0.36–11.04)	0.42
Rate per 100 person-yr	0.15	0.07		
Charter defined malignancy	60	64	0.95 (0.67–1.36)	0.78
Rate per 100 person-yr	2.30	2.28		
Pancreatic cancer	1	4	0.28 (0.03–2.50)	0.25
Rate per 100 person-yr	0.04	0.14		
Severe hypoglycemia	29	31	1.03 (0.62–1.71)	0.92
Rate per 100 person-yr	1.14	1.14		
Bone fracture	44	40	1.21 (0.78–1.85)	0.40
Rate per 100 person-yr	1.76	1.49		



Diabetes Care. 2017 Apr;40(4):494-501

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Table 2—Treatment-emergent SAEs by system organ class in the older cohort, by treatment group

	Age ≥ 75 years old		
System organ class preferred term patients with one or more:	Sitagliptin (*n* = 956)	Placebo (*n* = 1,023)	Difference (95% CI)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	80 (8.4%)	94 (9.2%)	−0.82 (−3.33 to 1.70)
Basal cell carcinoma	11 (1.2%)	24 (2.3%)	−1.20 (−2.44 to −0.04)
Squamous cell carcinoma	5 (0.5%)	17 (1.7%)	−1.14 (−2.18 to −0.24)
Squamous cell carcinoma of skin	3 (0.3%)	14 (1.4%)	−1.05 (−2.01 to −0.28)
Injury, poisoning, and procedural complications	36 (3.8%)	27 (2.6%)	1.13 (−0.43 to 2.76)
Gastrointestinal disorders	25 (2.6%)	21 (2.1%)	0.56 (−0.79 to 1.98)
Gastroesophageal reflux disease	4 (0.4%)	0 (0.0%)	0.42 (0.04 to 1.07)
Musculoskeletal and connective tissue disorders	18 (1.9%)	11 (1.1%)	0.81 (−0.27 to 1.99)
Osteoarthritis	13 (1.4%)	3 (0.3%)	1.07 (0.31 to 2.05)
Respiratory, thoracic, and mediastinal disorders	15 (1.6%)	12 (1.2%)	0.40 (−0.66 to 1.52)
Metabolism and nutrition disorders	1 (0.1%)	13 (1.3%)	−1.17 (−2.07 to −0.52)
Hyponatremia	1 (0.1%)	7 (0.7%)	−0.58 (−1.31 to −0.03)
Dehydration	0 (0.0%)	5 (0.5%)	−0.49 (−1.14 to −0.09)

Analysis cohort is all older patients as treated. This table includes *1*) sytem organ classes exceeding 1% or where the 95% CI excludes 0; *2*) within the system organ classes that exceed 1%, any preferred term that exceeds 1%; and *3*) any individual preferred term where the 95% CI excludes 0.

Assessing the Safety of Sitagliptin in Older Participants in the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS)

M. Angelyn Bethel,[1] Samuel S. Engel,[2] Jennifer B. Green,[3] Zhen Huang,[3] Robert G. Josse,[4] Keith D. Kaufman,[2] Eberhard Standl,[5] Shailaja Suryawanshi,[2] Frans Van de Werf,[6] Darren K. McGuire,[7] Eric D. Peterson,[3] and Rury R. Holman,[1] for the TECOS Study Group

Diabetes Care 2017;40:494–501 | DOI: 10.2337/dc16-1135

Lo studio **TECOS** suggerisce che tra i **pazienti più anziani** con diabete di tipo 2 ben controllato**, sitagliptin** ha pari efficacia rispetto ai pazienti più giovani, effetti neutri sul rischio cardiovascolare, senza problemi significativi di sicurezza.

Diabetes Care. 2017 Apr;40(4):494-501
N Engl J Med. 2015 Jul 16;373(3):232-42

Quali molecole in popolazioni speciali (anziano)

- **Saxagliptin**
- **Sitagliptin**
- **Linagliptin**
- **Alogliptin**
- **Vildagliptin**

Safety and efficacy of the dipeptidyl peptidase-4 inhibitor linagliptin in elderly patients with type 2 diabetes: a comprehensive analysis of data from 1331 individuals aged ≥ 65 years

G. Schernthaner[1], A. H. Barnett[2], S. Patel[3], U. Hehnke[4], M. von Eynatten[5] & H.-J. Woerle[4]

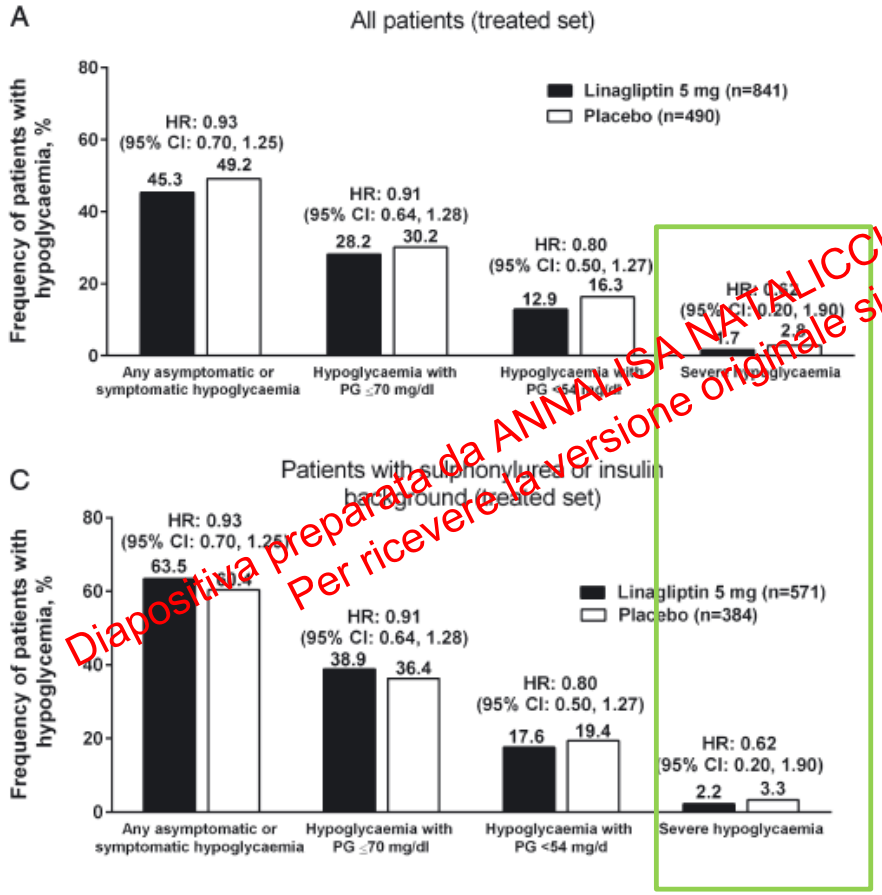
	Linagliptin group	Placebo group
Patients, *n*	841	490
Any AE, %	71.3	73.3
Drug-related AEs, %	18.1	19.8
Significant AEs of interest, %	1.5	2.0
Adjudicated cardiovascular events*	0.7	1.0
GI disorders	14.1	15.5
Pancreatitis	0.0	0.2
Hypersensitivity reactions	0.1	0.4
Increased liver enzymes based on investigator reporting, %		
Alanine aminotransferase increased	0.1	0.0
Aspartate aminotransferase increased	0.2	0.0
Hepatic enzyme increased	0.1	0.0
Renal AEs†	5.6	4.3
AEs leading to discontinuation of trial medication, %	3.7	3.7
Serious AEs, %	7.5	12.9
Immediately life-threatening	0.2	0.0
Disability/incapacitation	0.1	0.2
Requiring hospitalization	7.4	11.4
Prolonged hospitalization	0.7	1.4
Congenital anomaly	0.0	0.0
Other	0.1	1.4

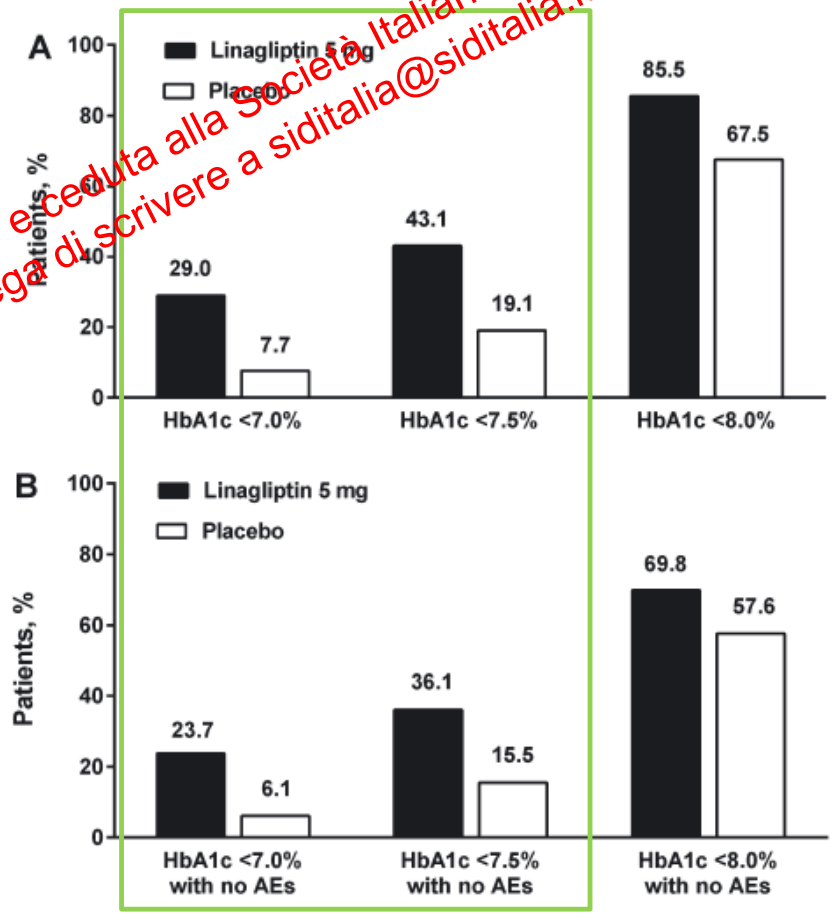
AE, adverse event; GI, gastrointestinal.
*Patients with cardiovascular death, myocardial infarction, stroke or unstable angina.
†Included bladder spasm, calculus ureteric, chromaturia, cystitis glandularis, cystitis non-infective, diabetic nephropathy, dysuria, enuresis, haematuria, hydronephrosis, ketonuria, leukocyturia, microalbuminuria, micturition urgency, nephrolithiasis, nephropathy, nocturia, pollakiuria, proteinuria, pyuria, renal colic, renal failure, renal failure acute, renal failure chronic, renal impairment, renal mass, renal pain, urinary bladder polyp, urinary incontinence and urinary retention.

Diabetes Obes Metab. 2014 Nov;16(11):1078-86

Safety and efficacy of the dipeptidyl peptidase-4 inhibitor linagliptin in elderly patients with type 2 diabetes: a comprehensive analysis of data from 1331 individuals aged ≥ 65 years

G. Schernthaner[1], A. H. Barnett[2], S. Patel[3], U. Hehnke[4], M. von Eynatten[5] & H.-J. Woerle[4]





Diabetes Obes Metab. 2014 Nov;16(11):1078-86

CAROLINA:
evaluating the long-term CV safety profile of linagliptin versus glimepiride in patients with relatively early T2D at increased CV risk

CARMELINA:
a unique trial investigating the long-term CV and kidney safety profile of linagliptin versus placebo

Quali molecole in popolazioni speciali (anziano)

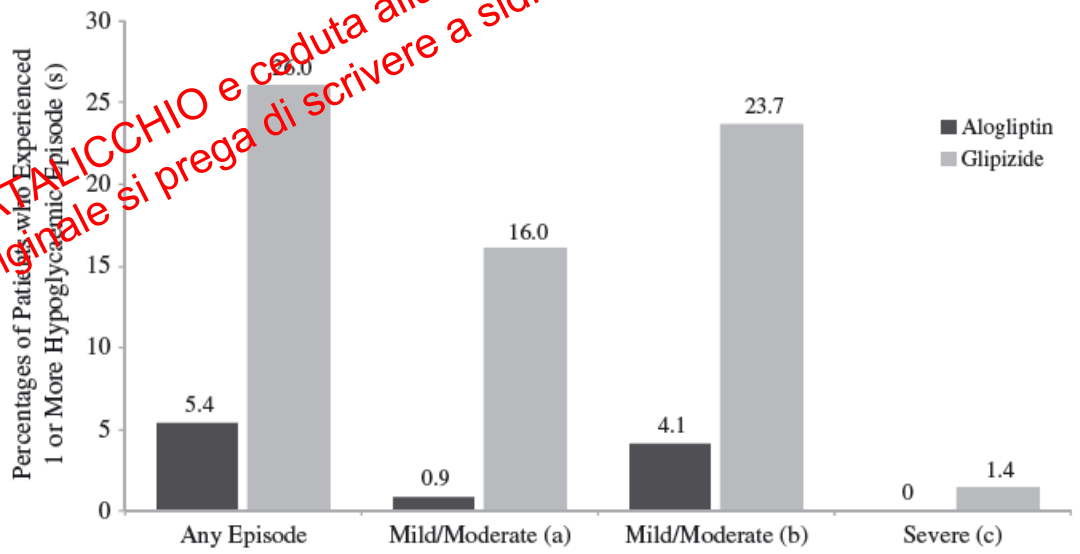
- **Saxagliptin**
- **Sitagliptin**
- **Linagliptin**
- **Alogliptin**
- **Vildagliptin**

Alogliptin versus glipizide monotherapy in elderly type 2 diabetes mellitus patients with mild hyperglycaemia: a prospective, double-blind, randomized, 1-year study†

J. Rosenstock[1], C. Wilson[2] & P. Fleck[2]

Statistics	Analysis set: Alogliptin	Analysis set: Glipizide
PPS	N = 180	N = 162
PPS (LOCF)	n = 180	n = 162
Baseline HbA1c, mean (s.d.)	7.54 (0.698)	7.46 (0.649)
Week 52 CFB in HbA1c, LS mean (s.e.)	−0.14 (0.063)	−0.09 (0.067)
LS mean difference (one-sided 97.5% CI)*		−0.05 (−∞, 0.13)
PPS (completers)	n = 125	n = 117
Baseline HbA1c, mean (s.d.)	7.33 (0.622)	7.28 (0.565)
Week 52 CFB in HbA1c, LS mean (s.e.)	−0.42 (0.055)	−0.33 (0.057)
LS mean difference (one-sided 97.5% CI)*		−0.09 (−∞, 0.07)
FAS	*N* = 222	*N* = 219
FAS (LOCF)	n = 215	n = 214
Baseline HbA1c, mean (s.d.)	7.50 (0.703)	7.43 (0.634)
Week 52 CFB in HbA1c, LS mean (s.e.)	−0.13 (0.055)	−0.11 (0.065)
LS mean difference (one-sided 97.5% CI)*		−0.02 (−∞, 0.13)
FAS (completers)	n = 129	n = 125
Baseline HbA1c, mean (s.d.)	7.33 (0.624)	7.30 (0.589)
Week 52 CFB in HbA1c, LS mean (s.e.)	−0.42 (0.053)	−0.33 (0.055)
LS mean difference (one-sided 97.5% CI)*		−0.09 (−∞, 0.06)

The LS means, s.e. and one-sided 97.5% CIs are from an ANCOVA model with treatment, study schedule and geographic region as class variables, and baseline HbA1c as a covariate. ANCOVA, analysis of covariance; CFB, change from baseline; CI, confidence interval; FAS, full analysis set; HbA1c, glycosylated haemoglobin; LOCF, last observation carried forward; LS, least squares; PPS, per-protocol set; s.d., standard deviation; s.e., standard error.
*The LS mean differences and corresponding 97.5% one-sided upper CIs are for the non-inferiority and superiority comparisons of the average response of the alogliptin group to that of the glipizide group.



Diabetes Obes Metab. 2013 Oct;15(10):906-14

	Alogliptin, N = 222	Glipizide, N = 219
Number of AEs	556	554
Patients with at least one AE, n (%)	163 (73.4)	151 (68.9)
Most common AEs (≥5% of patients in either group), n (%)		
Urinary tract infection	26 (11.7)	23 (10.5)
Dizziness	13 (5.9)	19 (8.7)
Headache	16 (7.2)	15 (6.8)
Diarrhoea	9 (4.1)	14 (6.4)
Nasopharyngitis	13 (5.9)	10 (4.6)
Arthralgia	10 (4.5)	12 (5.5)
Hypertension	12 (5.4)	10 (4.6)
Back pain	9 (4.1)	11 (5.0)
Upper respiratory tract infection	12 (5.4)	5 (2.3)
Severe AEs, n (%)	5 (2.3)	10 (4.6)
Related AEs, n (%)*	36 (16.2)	47 (21.5)
AEs leading to discontinuation, n (%)†	19 (8.6)	27 (12.3)
SAEs, n (%)	16 (7.2)	13 (5.9)
Related SAEs, n (%)*	4 (1.8)	1 (0.5)
Deaths	0	0

A treatment-emergent AE was defined as any AE that started on or after the first dose date and within 14 days of the last dose of double-blind study drug. A patient was counted once if the patient reported one or more events. Percentages were based on the number of safety set patients in each treatment group. AE, adverse event; SAE, serious adverse event.

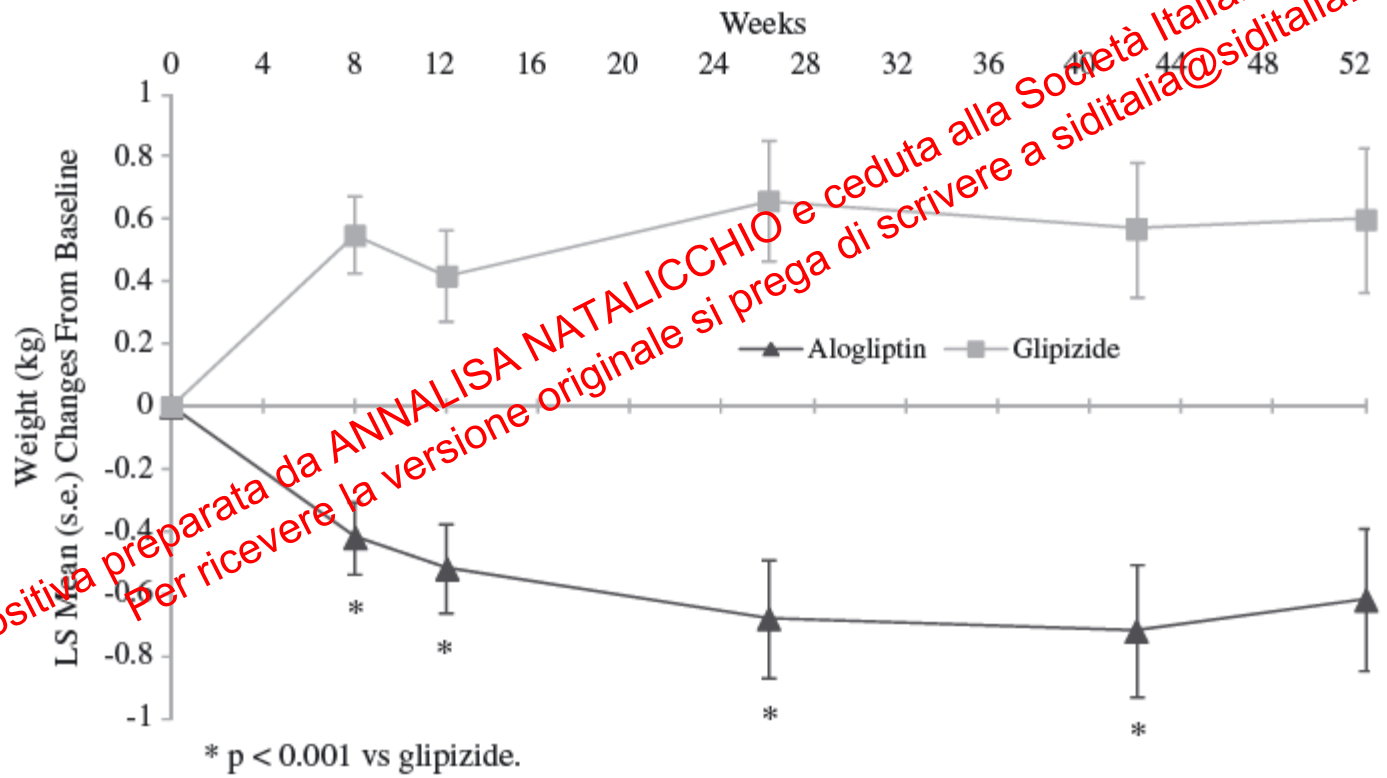
*Considered by the investigator to be possibly, probably or definitely related to study drug.

†The number of subjects who discontinued because of an AE differ between disposition data and safety data, because the disposition data show subjects who permanently discontinued from study drug (i.e. withdrew from the study), whereas the safety data include all subjects who temporarily and permanently discontinued study drug.

Diabetes Obes Metab. 2013 Oct;15(10):906-14

Alogliptin versus glipizide monotherapy in elderly type 2 diabetes mellitus patients with mild hyperglycaemia: a prospective, double-blind, randomized, 1-year study†

J. Rosenstock[1], C. Wilson[2] & P. Fleck[2]



Diabetes Obes Metab. 2013 Oct;15(10):906-14

Quali molecole in popolazioni speciali (anziano)

- **Saxagliptin**
- **Sitagliptin**
- **Linagliptin**
- **Alogliptin**
- **Vildagliptin**

Individualised treatment targets for elderly patients with type 2 diabetes using vildagliptin add-on or lone therapy (INTERVAL): a 24 week, randomised, double-blind, placebo-controlled study

W David Strain, Valentina Lukashevich, Wolfgang Kothny, Marie-José Hoellinger, Päivi Maria Paldánius

	Vildagliptin (n=137)	Placebo (n=137)
Age (years)		
<75	33/67 (49·3%)	22/86 (25·6%)
≥75	39/70 (55·7%)	15/51 (29·4%)
HbA_{1c} levels		
≤8%	46/83 (55·4%)	27/86 (31·4%)
>8%	26/54 (48·1%)	10/51 (19·6%)
≤9%	65/125 (52·0%)	34/128 (26·6%)
>9%	7/12 (58·3%)	3/9 (33·3%)
Frailty status		
Frail	5/12 (41·7%)	6/14 (42·9%)
Non-frail	67/124 (54·0%)	30/121 (24·8%)

Data are number (%). HbA_{1c}=glycosylated haemoglobin A_{1c}.

Table 2: **Proportion of patients achieving individualised HbA_{1c} targets, according to baseline characteristics**

	Vildagliptin (n=139)	Placebo (n=139)
Overall*	66 (47·5%)	63 (45·3%)
SAEs†	8 (5·8%)	5 (3·6%)
Discontinuations due to AEs	6 (4·3%)	3 (2·2%)
Deaths	1 (0·7%)	1 (0·7%)
AEs (of any severity) in ≥5% participants in any treatment group		
Dizziness	11 (7·9%)	3 (2·2%)
Headache	8 (5·8%)	4 (2·9%)
Nasopharyngitis	7 (5·0%)	7 (5·0%)
Any predefined risk‡	21 (15·1%)	24 (17·3%)
Hepatic-related AEs	0	0
Infection-related AEs	18 (12·9%)	24 (17·3%)
Pancreatitis-related AEs	0	0
Muscle-related AEs	1 (0·7%)	0
Neuropsychiatric-related AEs	1 (0·7%)	0
Lactic-acidosis-related AEs	0	0
Skin or vascular-related AEs	1 (0·7%)	0
Cardiovascular or cerebrovascular AEs	5 (3·6%)	3 (2·2%)

Data are number (%). AE=adverse event. *A patient with several occurrences of an AE on one treatment is counted only once in the AE category. †A detailed listing of the SAEs is available in the appendix. ‡Acute pancreatitis-related AEs, hepatic-related AEs, infection-related AEs, lactic-acidosis-related AEs, muscle-related AEs, neuropsychiatric-related AEs, and skin or vascular-related AEs were defined as events of predefined risk.

Table 3: **Treatment-emergent AEs in the safety analysis population**

L'incidenza di eventi ipoglicemici è stata complessivamente bassa: **3 (2.2%)** su 139 pazienti nel gruppo **vildagliptin** e **1 (0.7%)** su 139 pazienti nel gruppo **placebo**. Tutti gli eventi ipoglicemici si sono verificati in pazienti che assumevano sulfaniluree concomitanti. **Non sono stati segnalati eventi ipoglicemici gravi in entrambi i gruppi.**

Lancet. 2013 Aug 3;382(9890):409-416

Un problema dell'anziano è che multi-trattato. Pensate che gli inibitori della DPP-4 siano in grado di interagire con molto farmaci?

- SÌ
- NO
- NON SO

Ten years of experience with DPP-4 inhibitors for the treatment of type 2 diabetes mellitus

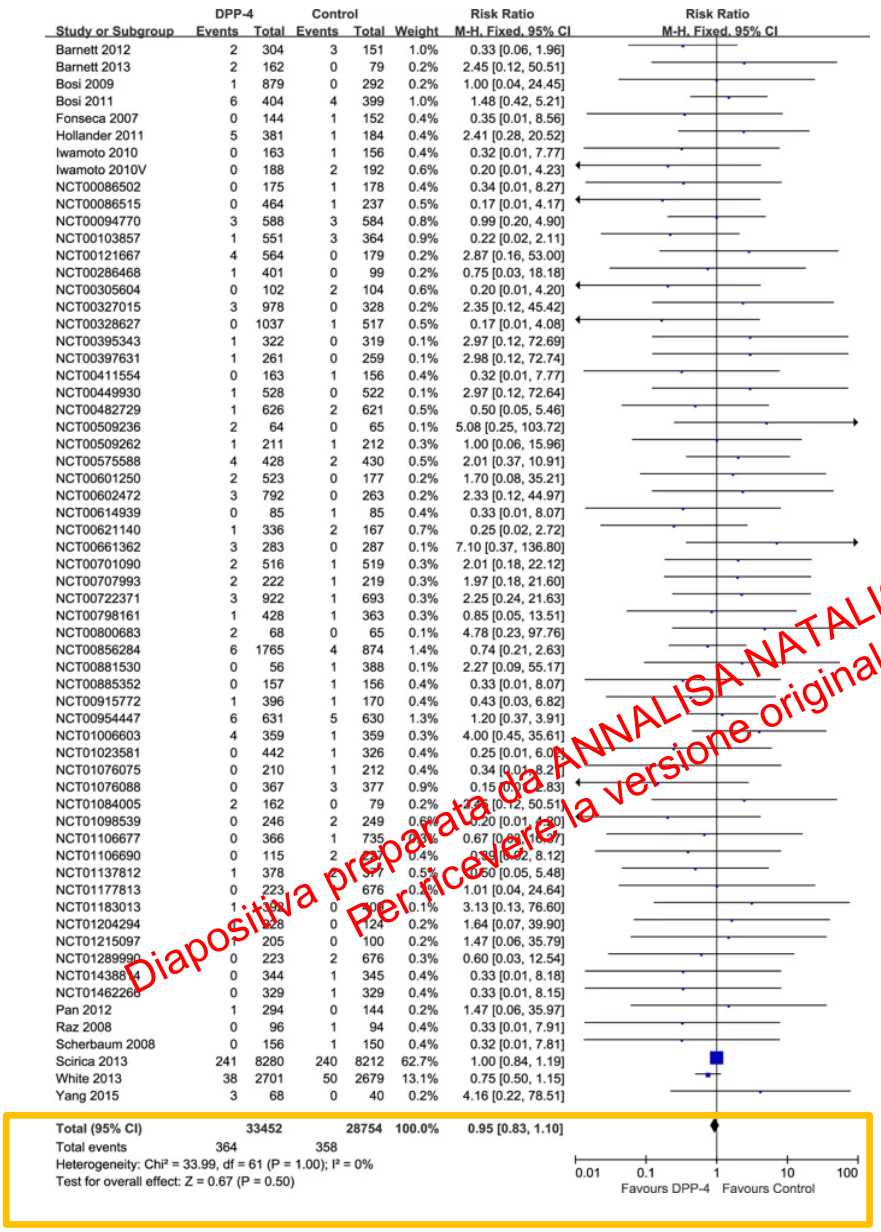
Giorgio Sesti[1] · Angelo Avogaro[2] · Sara Belcastro[3] · Benedetta Maria Bonora[2] · Marina Croci[4] · Giuseppe Daniele[5] · Marco Dauriz[6] · Francesco Dotta[7] · Caterina Formichi[7] · Simona Frontoni[8] · Cecilia Invitti[4] · Emanuela Orsi[9] · Fabiana Picconi[8] · Veronica Resi[9,10] · Enzo Bonora[6] · Francesco Purrello[11]

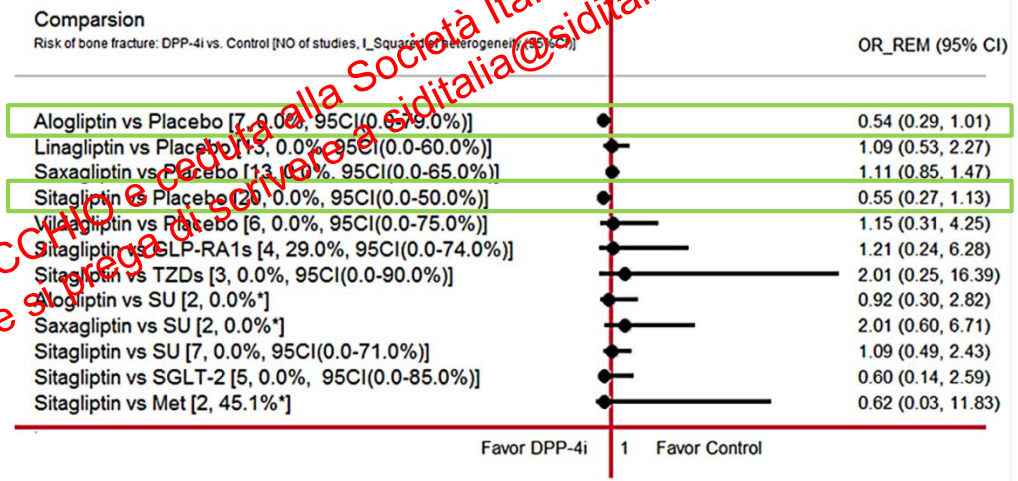
Table 1 Main characteristics of DPP-4 inhibitors currently licensed by the European Medicines Agency [11–15]

DPP-4 inhibitor	Posology and administration	Drug-drug interactions	Renal impairment	Hepatic impairment	Further precautions
Alogliptin	25 mg, once daily When used in combination with SU or insulin, consider a lower dose of SU or insulin Oral, with or without a meal		Mild impairment[a]: no dose adjustment Moderate impairment: 12.5 mg, once daily Severe impairment or ESRD: 6.25 mg, once daily Renal function tests recommended before and during treatment	Mild-moderate impairment: no dose adjustment Severe impairment: not recommended	Obtain liver function tests promptly in pts with symptoms of liver injury
Linagliptin	5 mg, once daily When used in combination with SU or insulin, consider a lower dose of SU or insulin Oral, with or without a meal		No dose adjustment required	No dose adjustment required	Discontinue if bullous pemphigoid is suspected
Saxagliptin	5 mg, once daily When used in combination with SU or insulin, consider a lower dose of SU or insulin Oral, with or without a meal	If used with potent CYP3A4/5 inducers, glycemic control should be assessed	Mild impairment: no dose adjustment Moderate–severe impairment: 2.5 mg, once daily ESRD: not recommended Renal function tests recommended before and during treatment	Mild impairment: no dose adjustment Moderate impairment: use with caution Severe impairment: not recommended	Discontinue if hypersensitivity reactions are suspected Monitoring for skin disorders recommended Caution warranted in pts with known risk factors for hospitalization for HF
Sitagliptin	100 mg, once daily When used in combination with SU or insulin, consider a lower dose of SU or insulin Oral, with or without a meal		Mild impairment[c]: no dose adjustment if GFR ≥ 45 to < 60 ml/min; 50 mg, once daily, if GFR ≥ 30 to < 45 ml/min Severe impairment or ESRD: 25 mg, once daily Renal function tests recommended before and during treatment	Mild-moderate impairment: no dose adjustment Severe impairment: use with caution	Discontinue if hypersensitivity reactions or bullous pemphigoid are suspected
Vildagliptin	50 mg, twice daily 50 mg, once daily, when used in combination with SU; or reduce the SU dose Oral, with or without a meal		Mild impairment[a]: no dose adjustment Moderate–severe impairment: 50 mg, once daily ESRD: use with caution	Should not be used[b]	Not recommended in pts with NYHA functional class IV

Acta Diabetol. 2019 Jun;56(6):605-617

Inibitori della DPP-4 e Rischio di Fratture





Sci Rep. 2016 Jul 7;6:29104

PLoS One. 2017 Dec 5;12(12):e0187537

Personalizzazione del trattamento dell'iperglicemia nell'anziano con diabete tipo 2

POSITION STATEMENT

Conclusioni

- Gli **inibitori della DPP-4** sono ugualmente efficaci nei pazienti giovani e anziani, sono caratterizzati da un basso rischio di ipoglicemia o aumento di peso, sono ben tollerati e non hanno effetti collaterali gastrointestinali.
- Gli inibitori di **DPP-4** possono essere utilizzati in pazienti con insufficienza renale anche grave con un adeguamento della dose per tutte le molecole tranne **linagliptin**.
- Nello studio **SAVOR-TIMI53**, il trattamento con **saxagliptin** è risultato associato ad un aumento modesto, ma statisticamente significativo, dell'incidenza di ricovero per scompenso cardiaco, senza differenze nella mortalità specifica. Un analogo trend, seppure non significativo, è stato osservato nello studio **EXAMINE** con **alogliptin**.
- Per la loro efficacia, l'elevata tollerabilità, la semplicità d'uso e il profilo di sicurezza cardiovascolare, gli **inibitori della DPP-4** rappresentano un'opzione terapeutica da preferire a sulfoniluree e repaglinide nei pazienti anziani inadeguatamente controllati con la sola metformina o con intolleranza o controindicazioni alla metformina. Possono anche essere utilmente associati alla terapia con insulina basale.

STUDI NON INSERITI

FARMACO	CONCLUSIONI	REFERENZA
Sitagliptin	• The efficacy and safety of sitagliptin was confirmed in elderly T2DM patients (≥ 75 years) with improved HbA1c levels and no increased risk of ypoglycemia.	• BMC Endocr Disord. 2015 Jul 3;15:34
Linagliptin	• Linagliptin improved glycaemia and had a safety profile similar to placebo in elderly T2DM patients with inadequate glycemic control despite receiving other glucose-lowering drugs. • Linagliptin was also efficacious in reducing HbA1c and well tolerated, and appears to reduce the risk of hypoglycemia when added to basal insulin.	• Lancet. 2013 Oct 26;382(9902):1413-23 • Diabetes Obes Metab. 2015 Sep;17(9):868-77
Alogliptin	• Well tolerated in elderly T2DM patients (aged ≥ 65 years) with similar HbA1c improvements to younger patients (aged < 65 years) and no increased risk of hypoglycemia, weight gain, or other adverse event.	• J Am Geriatr Soc. 2009 Nov;57(11):2011-9
Vildagliptin	• Treatment with vildagliptin and metformin achieved individualized glycemic target levels with significantly improved compliance and persistence to treatment and lower rates of hypoglycemic events.	• Drug Des Devel Ther. 2014 Jun 18;8:811-8

Clinical experience with vildagliptin in the management of type 2 diabetes in a patient population ≥75 years: a pooled analysis from a database of clinical trials

A. Schweizer[1], S. Dejager[2], I. E. Foley[3], O. Shao[3] & W. Kothny[3]

	Monotherapy				Add-on therapy to metformin			
	Age ≥75 years		Age <75 years		Age ≥75 years		Age <75 years	
	BL	Mean Δ	BL	Mean Δ	BL	Mean Δ	BL	Mean Δ
Main efficacy analyses								
n	62		2303		25		910	
HbA1c (%)	8.26 ± 0.11	−0.87 ± 0.16*	8.67 ± 0.02	−1.16 ± 0.03*	8.47 ± 0.20	−0.08 ± 0.26	8.44 ± 0.03	0.90 ± 0.03*
n	62		2305		25		911	
FPG (mmol/L)	9.69 ± 0.31	−1.09 ± 0.34*	10.45 ± 0.06	−1.23 ± 0.06*	10.35 ± 0.44	−1.24 ± 0.47*	10.71 ± 0.09	−1.36 ± 0.09*
n	62		2299		25		914	
Body weight (kg)	74.88 ± 1.47	−0.86 ± 0.38*	86.08 ± 0.39	−0.35 ± 0.07*	83.71 ± 3.04	−0.24 ± 0.50	89.04 ± 0.59	−0.03 ± 0.09
Responder analyses	n (%)†		n (%)†		n (%)†		n (%)†	
Achieving HbA1c ≤ 7.0%	32 (51.6)		983 (43.2)		12 (50.0)		298 (34.0)	
Subgroup analyses								
BL HbA1c ≤ 8.0%	7.58 (n = 32)	−0.50 ± 0.25	7.62 (n = 787)	−0.68 ± 0.03*	7.67 (n = 10)	−0.43 ± 0.39	7.55 (n = 377)	−0.60 ± 0.04*
BL HbA1c > 8.0%	8.98 (n = 30)	−1.26 ± 0.19*	9.22 (n = 1516)	−1.41 ± 0.04*	9.01 (n = 15)	−1.51 ± 0.31*	9.06 (n = 533)	−1.10 ± 0.05*
Fasting lipids (mmol/l)								
Triglycerides	1.99 ± 0.12	−0.24 ± 0.11*	2.31 ± 0.03	−0.16 ± 0.03*	2.10 ± 0.24	−0.26 ± 0.20	2.33 ± 0.05	−0.19 ± 0.04*
Total cholesterol	5.37 ± 0.13	−0.26 ± 0.10*	5.36 ± 0.02	−0.17 ± 0.02*	4.91 ± 0.23	−0.24 ± 0.11*	5.08 ± 0.04	−0.15 ± 0.03*
LDL	3.14 ± 0.11	−0.19 ± 0.07*	3.22 ± 0.02	−0.13 ± 0.02*	2.88 ± 0.21	−0.08 ± 0.09	2.85 ± 0.03	−0.08 ± 0.02*
HDL	1.34 ± 0.04	0.00 ± 0.02	1.15 ± 0.01	0.02 ± 0.00*	1.20 ± 0.05	−0.06 ± 0.03	1.22 ± 0.01	0.01 ± 0.01
Non-HDL	4.03 ± 0.12	−0.27 ± 0.10*	4.21 ± 0.02	−0.19 ± 0.02*	3.81 ± 0.24	−0.21 ± 0.11	3.83 ± 0.04	−0.15 ± 0.03*
VLDL	0.90 ± 0.05	−0.09 ± 0.04*	0.94 ± 0.01	−0.06 ± 0.01*	0.87 ± 0.08	−0.08 ± 0.07	0.92 ± 0.01	−0.06 ± 0.01*
Hypoglycaemia‡	n (%)		n (%)		n (%)		n (%)	
Any events	0 (0.0)		8 (0.3)		0 (0.0)		23 (0.8)	
Severe events	0 (0.0)		0 (0.0)		0 (0.0)		0 (0.0)	

Data are mean ± standard error or n (%).

BL, baseline; mean Δ, mean change from baseline; HbA1c, haemoglobin A1c; FPG, fasting plasma glucose; LDL, low density lipoprotein; HDL, high density lipoprotein; VLDL, very low density lipoprotein;

*$p < 0.05$ vs. baseline (within group).

†Denominator includes only patients with baseline HbA1c > 7.0% and an endpoint value.

‡Up to 24-week monotherapy (excluding open-label) safety population [n = 71 (≥75 years) and n = 2553 (<75 years)] and up to 24-week add-on therapy to metformin (excluding open-label) safety population [n = 31 (≥75 years) and n = 2990 (<75 years)].

Diabetes Obes Metab. 2011 Jan;13(1):55-64

		Age ≥ 75 years		Age < 75 years	
		Vilda 50 mg bid	Comparators	Vilda 50 mg bid	Comparators
		n = 132	n = 169	n = 5984	n = 6041
Mean exposure (weeks)		55.0	37.4	62.6	55.2
AEs	n (%)	86 (65.2)	114 (67.5)	4139 (69.2)	4174 (69.1)
	SYE-adj	133.9	200.6	147.9	177.3
Drug-related AEs	n (%)	18 (13.6)	24 (14.2)	943 (15.8)	1325 (21.9)
	SYE-adj	14.5	21.8	14.9	26.0
SAEs	n (%)	12 (9.1)	19 (11.2)	533 (8.9)	538 (8.9)
	SYE-adj	8.8	16.5	7.8	8.9
Discontinuation of study drug due to AEs	n (%)	10 (7.6)	9 (5.3)	337 (5.6)	396 (6.5)
	SYE-adj	7.2	7.5	4.7	6.1
Deaths	n (%)	0 (0.0)	2 (1.2)	24 (0.4)	22 (0.3)
	SYE-adj	0.0	1.7	0.3	0.3
AEs in SOCs					
Cardiac disorders	n (%)	9 (6.8)	16 (9.5)	366 (6.1)	359 (5.9)
	SYE-adj	6.8	14.0	5.3	5.9
Gastrointestinal disorders	n (%)	27 (20.5)	33 (19.5)	1413 (23.6)	1360 (22.5)
	SYE-adj	23.3	31.5	24.4	26.2
Infections and infestations	n (%)	44 (33.3)	49 (29.0)	2118 (35.4)	1965 (32.5)
	SYE-adj	42.0	51.9	41.8	42.6
Musculoskeletal and connective tissue disorders	n (%)	22 (16.7)	35 (20.7)	1352 (22.6)	1278 (21.2)
	SYE-adj	18.1	32.7	23.3	24.6
Neoplasms benign, malignant and unspecified	n (%)	3 (2.3)	4 (2.4)	146 (2.4)	140 (2.3)
	SYE-adj	2.2	3.4	2.1	2.2
Nervous system disorders	n (%)	32 (24.2)	28 (16.6)	1288 (21.5)	1446 (23.9)
	SYE-adj	28.4	25.7	21.9	29.6
Skin and subcutaneous tissue disorders	n (%)	13 (9.8)	20 (11.8)	756 (12.6)	873 (14.5)
	SYE-adj	10.1	18.2	11.7	16.0
Hepatic safety					
Any hepatic AE	n (%)	1 (0.8)	2 (1.2)	84 (1.4)	91 (1.5)
	SYE-adj	0.7	1.7	1.2	1.4
ALT or AST ≥ 3× ULN[a]		n = 133	n = 187	n = 6026	n = 6895
	n (%)	0 (0.0)	1 (0.6)	51 (0.9)	40 (0.6)
	SYE-adj	0.0	0.8	0.7	0.6
AEs in mild renal impairment[†]		n = 82	n = 98	n = 1720	n = 1820
	n (%)	51 (62.2)	67 (68.4)	1216 (70.7)	1278 (70.2)
	SYE-adj	120.1	211.3	138.0	178.0

n, number of patients with an AE; a patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment. Only AEs that caused study drug to be permanently discontinued are summarized in that category.
SOCs, system organ classes; ULN, upper limit of normal; Vilda, vildagliptin; SYE-adj, subject year exposure-adjusted = incidence per 100 SYE; comparators, placebo plus active comparators; AEs, adverse events; SAEs, serious adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase.
[a] All studies (including open-label) safety population.
[†] GFR (MDRD) ≥50, ≤80 (ml/min) per (1.73 m^2).

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