

L'anziano con diabete, fragilità cumulativa!

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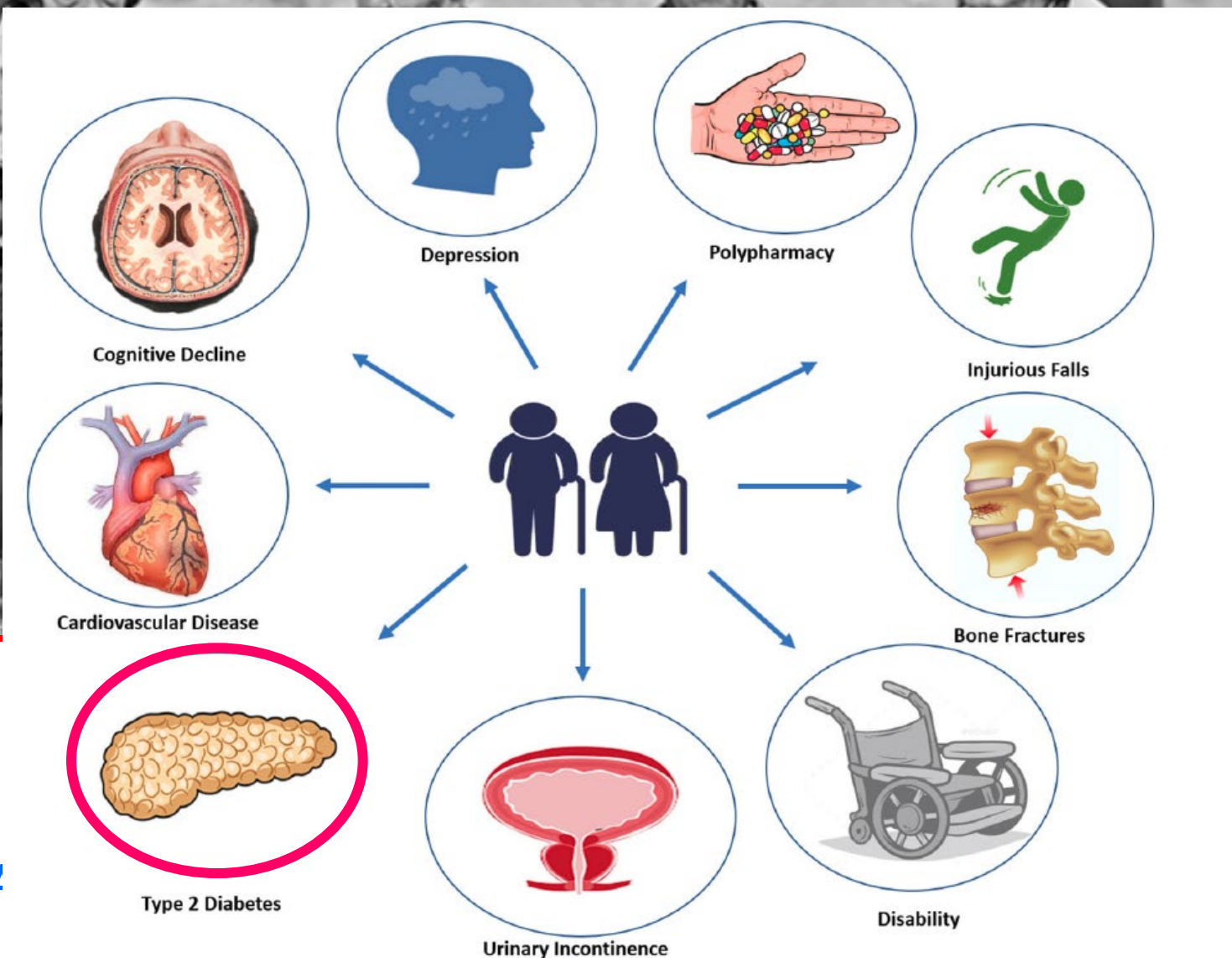
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A

Grafico 3
Prevalenza del diabete in funzione del sesso e dell'età²

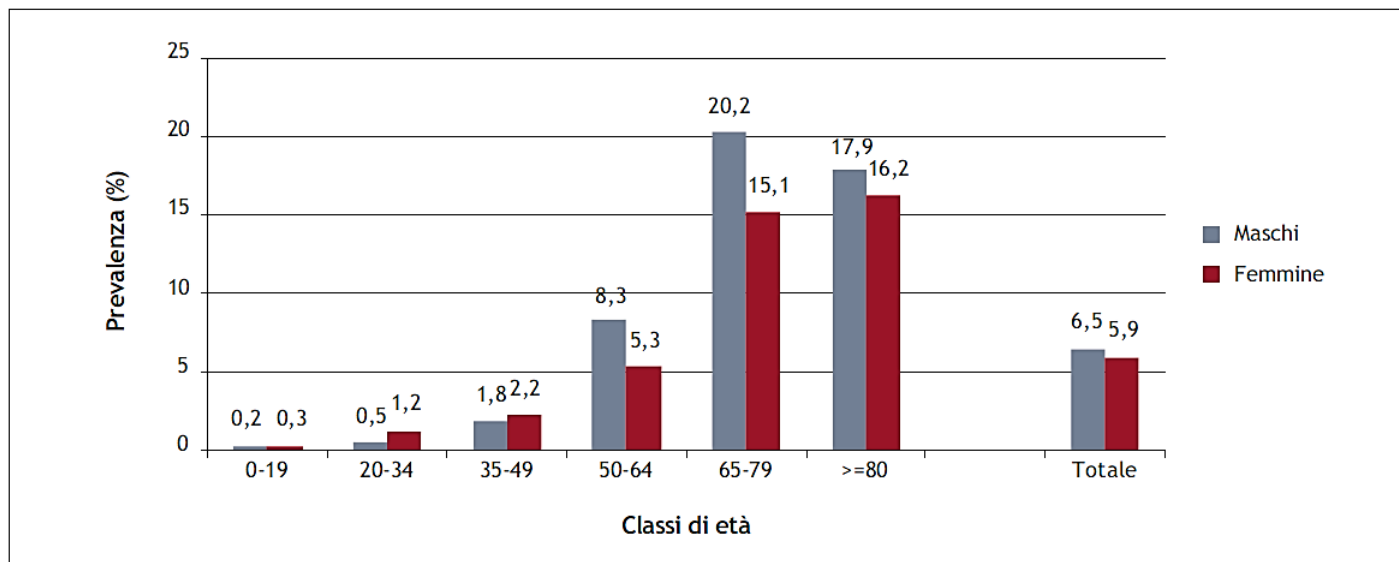
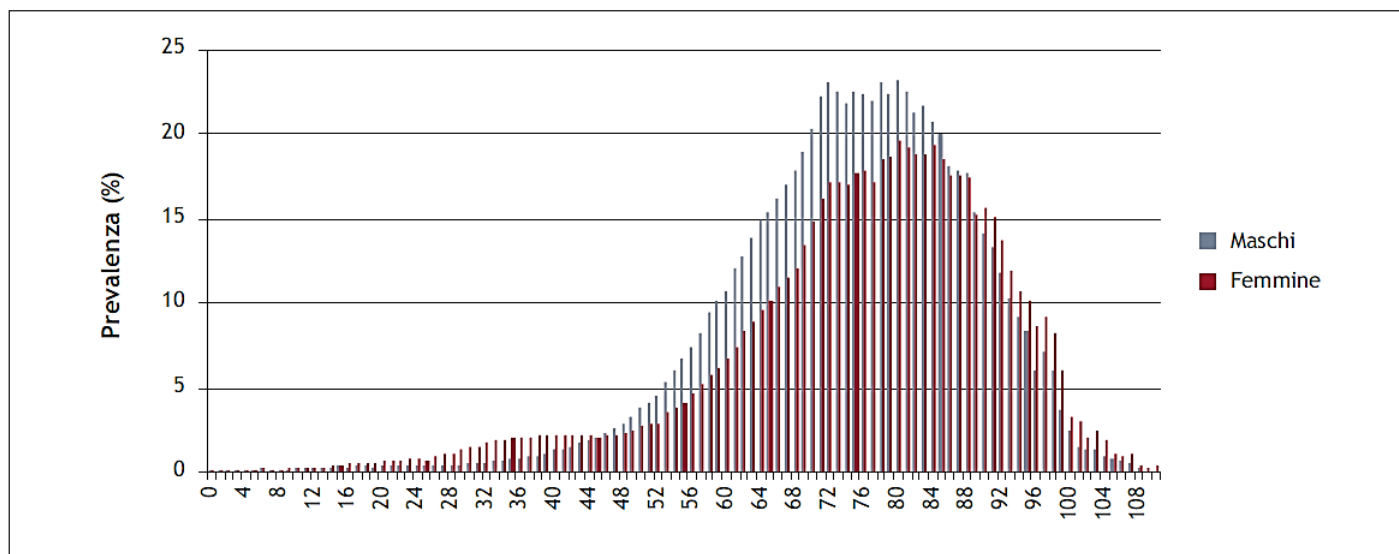


Grafico 3a
Prevalenza del diabete in funzione del sesso e dell'età



L'invecchiamento favorisce la comparsa e la progressione del DM2

- ❖ **Cambiamento composizione corporea con riduzione della massa magra e aumento del grasso viscerale**
- ❖ **Sarcopenia**
- ❖ **Infiammazione cronica subclinica**
- ❖ **Apoptosi beta cellulare**
- ❖ **Riduzione del GH e prolungata risposta allo stress con inappropriata attivazione dell'asse ACTH-cortisolo**
- ❖ **Insulino resistenza e ridotta risposta alle incretine**

Fattori che possono influenzare l'approccio alla gestione degli anziani affetti da diabete

- **Comorbilità** significative (almeno 4 nel 40% casi) in grado di limitare le capacità di riconoscere ed

- **Maggiori alterazioni**

- **Maggiori**

- **Assunzione di**

- **Fragilità** e limitata aspettativa di vita

La Fragilità è per sua natura multidimensionale e multifattoriale: non si identifica con la multimorbilità anche se la comprende, ma include determinanti di natura funzionale e motoria (fragilità fisica), mentale (fragilità cognitiva), psicoemotiva (labilità reattiva), biologica (malnutrizione), ma anche sociale (solitudine, mancanza di reti di solidarietà) ed economica (povertà). Tutto ciò predispone a >vulnerabilità ad insulti esterni> rischio di declino funzionale, cadute, istituzionalizzazione e morte.

Association Between Hypoglycemia and Fall-Related Events in Type 2 Diabetes Mellitus: Analysis of a U.S. Commercial Database

Kachroo S et al. J of Managed Care & Specialty Pharmacy 2015

Hypoglycemic Episodes and Risk of Dementia in Older Patients with Type 2 Diabetes Mellitus

Hypoglycemia and risk of incident dementia in 16,667 older T2DM patients followed up for 27 yrs (mean age 65 yrs)

No. of Hypoglycemic Episodes ^b	No. of Dementia Cases	Hazard Ratio (95% Confidence Interval)		
		Adjusted for Age (As Time Scale), BMI, Race/Ethnicity, Education, Sex, and Duration of Diabetes	Additionally Adjusted for Comorbidities ^c	Additionally Adjusted for 7-Year Mean HbA _{1c} Level, Diabetes Treatment, and Years of Insulin Use
1 or more	250	1.68 (1.47-1.93)	1.48 (1.29-1.70)	1.44 (1.25-1.66)
1	150	1.45 (1.23-1.72)	1.29 (1.10-1.53)	1.26 (1.10-1.49)
2	57	2.15 (1.64-2.81)	1.86 (1.42-2.43)	1.80 (1.37-2.36)
3 or more	43	2.60 (1.78-3.79)	2.10 (1.48-2.73)	1.94 (1.42-2.64)

Accesso al PS

Whitmer RA et al. JAMA 2009

Trattamento del diabete tipo 2 nell'anziano: quali nuovi farmaci?

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.

di Diab

POSITION STATEMENT

- ❖ Evitare complicanze acute
- ❖ Evitare lo sviluppo e la progressione delle complicanze nei pazienti con più lunga aspettativa di vita
- ❖ Garantire una buona qualità di vita nei pazienti con breve aspettativa di vita

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

Current antidiabetes drugs

DPP-4 inhibitors

Improve glucose-dependent insulin secretion from pancreatic β -cells, suppress glucagon secretion from α -cells

GLP-1 analogues

Improve glucose-dependent insulin secretion from pancreatic β -cells, suppress glucagon secretion from α -cells, slow gastric emptying, induce weight loss

Sulfonylureas and Meglitinides

Increase insulin secretion from pancreatic β -cells

Thiazolidinediones

Increase glucose uptake in skeletal muscle and enhance FFA clearance by SC adipose tissue

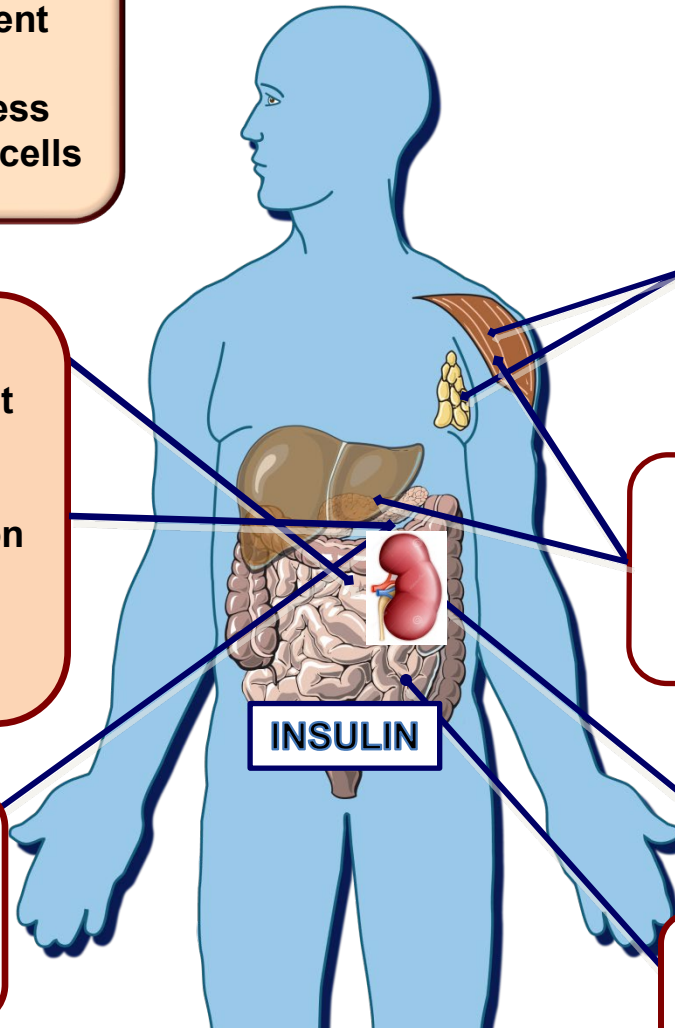
Metformin

Decreases hepatic glucose production and increases glucose uptake

SGLT2-inhibitors

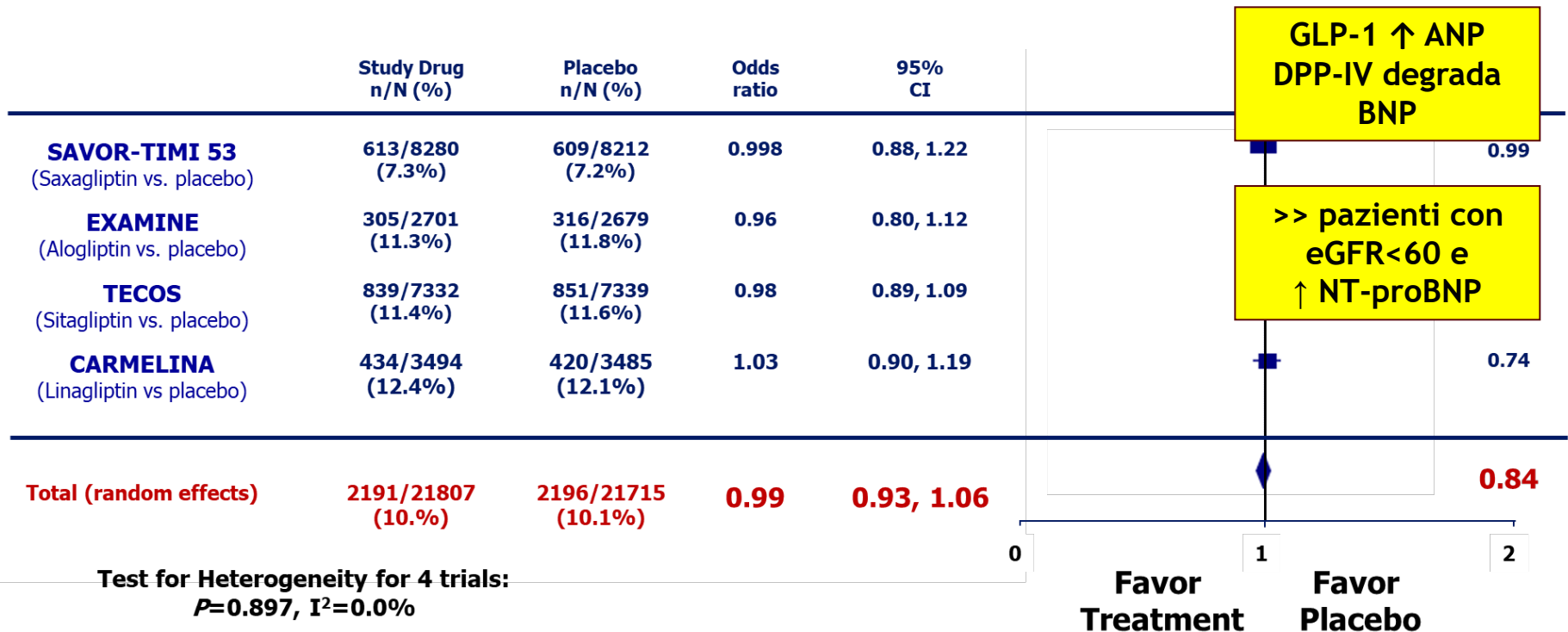
Increase renal excretion of glucose

α -Glucosidase inhibitors
Inhibit intestinal carbohydrate absorption



Cardiovascular safety trials of DPP-4 inhibitors

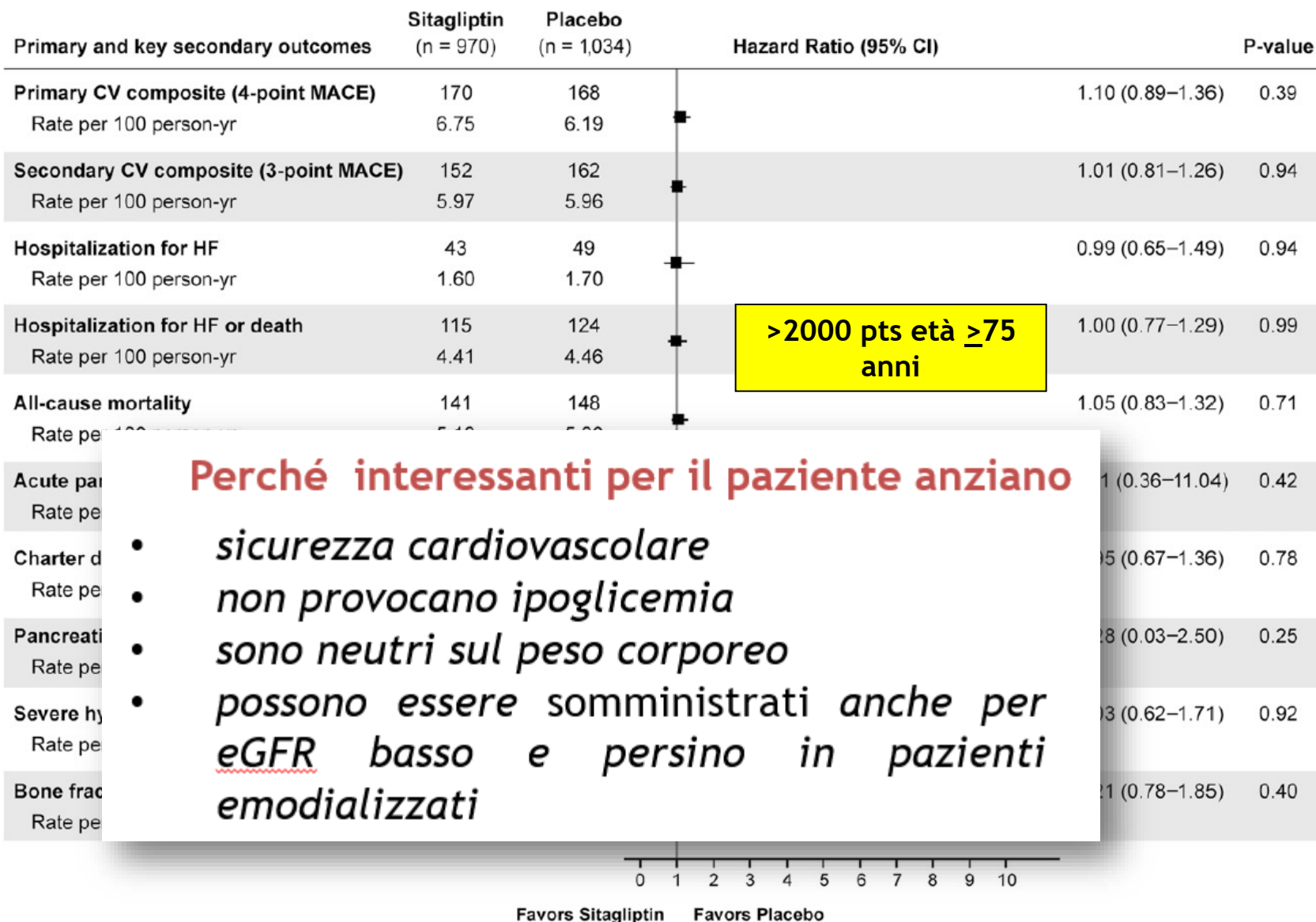
Maggiore sicurezza sulle ipoglicemie e non aumento del rischio di frattura (tendenza alla riduzione con SITA e ALO)



Lo Studio SAVOR-TIMI53, TECOS, EXAMINE e CARMELINA hanno dimostrato non aumentare rischio di sviluppare un evento CV rispetto al placebo. Aumento del 27% RR hHF con saxa

Assessing the Safety of Sitagliptin

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Primary and key secondary outcomes in the older cohort by treatment group. CV, cardiovascular; HF, heart failure

Effects of glucagon-like peptide 1 receptor agonists on comorbidities in older patients with diabetes mellitus

- Elderly patients with diabetes are at high risk of polypharmacy because of multiple coexisting diseases and syndromes.
- Polypharmacy increases the risk of drug-drug and drug-disease interactions in these patients, who may already have age-related sensory and cognitive deficits.
- GLP-1 RAs are diabetes medications potentially impacting on polypharmacy reduction in older diabetes patients because of their multiple pleiotropic effects on comorbidities (e.g. hyperlipidemia, hypertension, and fatty liver) and syndromes (e.g. osteoporosis and sleep apnea) that commonly co-occur with diabetes.
- Using GLP-1 RAs to address multiple conditions may help reduce costs, medication burden, adverse drug events, and medication nonadherence.

Proportion of non-elderly and elderly subjects achieving HbA_{1c} <7% without severe or BG-confirmed hypoglycaemia and no weight gain in the SUSTAIN 1–5 trials

**SUSTAIN 1:
semaglutide
vs placebo**

**SUSTAIN 2:
semaglutide vs
sitagliptin**

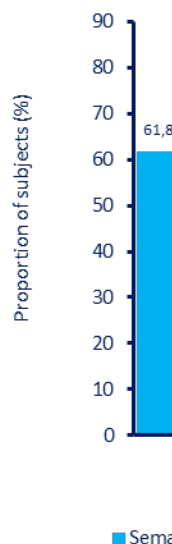
**SUSTAIN 3:
semaglutide vs
exenatide ER**

**SUSTAIN 4:
semaglutide vs
IGlar**

**SUSTAIN 5:
semaglutide add-on to
insulin vs placebo**

Treatment duration:

No. of subjects:



Subjects reporting any AE, pooled across SUSTAIN 1–5 trials, were comparable between the two age groups

- Severity of AEs was also comparable between age groups; most AEs were mild to moderate
- **More elderly subjects treated with semaglutide reported serious AEs than non-elderly subjects**
- **More elderly subjects treated with semaglutide discontinued treatment prematurely due to AEs, compared with non-elderly subjects**

A greater proportion of elderly subjects treated with semaglutide reported gastrointestinal AEs, compared with non-elderly subjects

Mean reductions in renal function, measured by the change from baseline in eGFR at week 30, were 4.8, 5.4 and 3.4 mL/min/1.73 m² in non-elderly subjects receiving semaglutide 0.5 mg, 1.0 mg and comparators, respectively, and were 3.2, 2.2 and 2.5 mL/min/1.73 m² in elderly subjects

Figure 4. Non-elderly, <65 years old; E BG, blood glucose; exenatide ER, exen

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Diabetes

Table 1—Baseline demogra

Characteristic
Age (years)
Age ≥75 years, n (%)
Male, n (%)
White, n (%)
BMI (kg/m ²)
Body weight (kg)
eGFR, n (%)
≥30 to <60 mL/min/1.73 m ²
≥60 mL/min/1.73 m ²
FPG (mmol/L)
HbA _{1c} at week -1 (%)
HbA _{1c} at week -1 (mmol/mol)

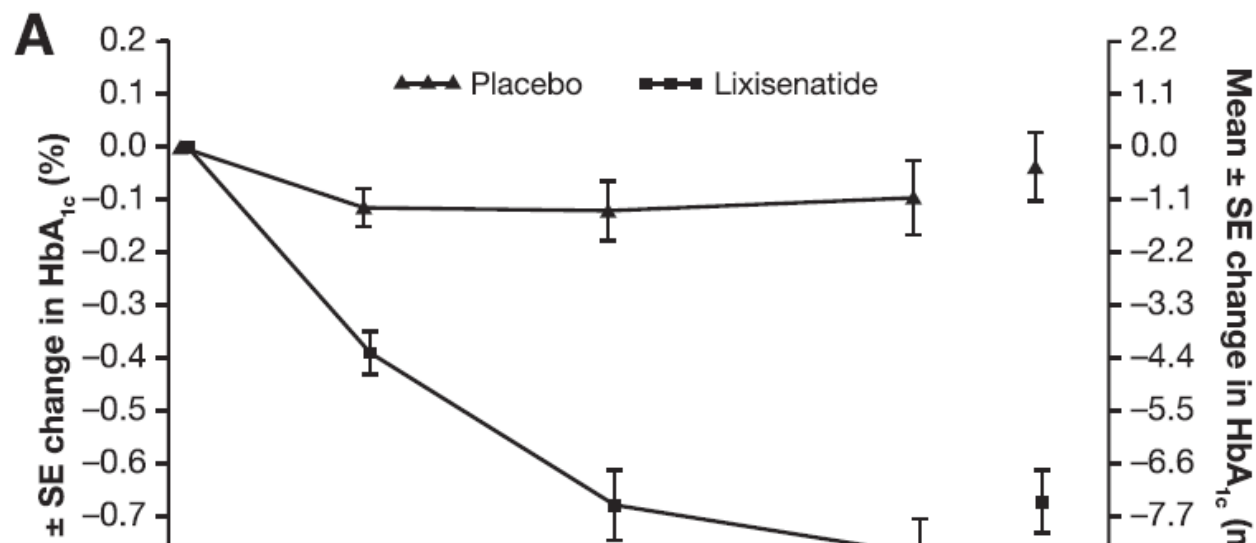


Table 3—Symptomatic hypoglycemia by background therapy during the on-treatment period (safety population)

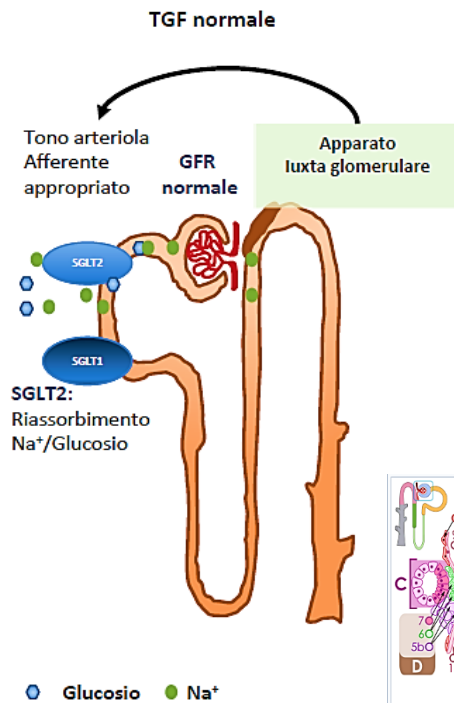
	Basal insulin + OADs		Met + OADs (except SU)		SU + Met + other OADs	
	Placebo (n = 55)	Lixi (n = 54)	Placebo (n = 57)	Lixi (n = 52)	Placebo (n = 51)	Lixi (n = 59)
Symptomatic hypoglycemia						
Patients with events	7 (12.7)	3 (5.6)	1 (1.8)	1 (1.9)	2 (3.9)	7 (11.9)
Patients with events per 100 patient-years*	29.3	12.2	3.7	4.5	8.8	26.7
Events	9	7	1	1	2	18
Events per 100 patient-years†	37.7	28.6	3.7	4.5	8.8	68.7
Documented symptomatic hypoglycemia <3.3 mmol/L‡						
Patients with events	7 (12.7)	3 (5.6)	1 (1.8)	1 (1.9)	2 (3.9)	6 (10.2)
Patients with events per 100 patient-years*	29.3	12.2	3.7	4.5	8.8	22.9
Events	9	7	1	1	2	15
Events per 100 patient-years†	37.7	28.6	3.7	4.5	8.8	57.2

Data are n or n (%). Lixi, lixisenatide; Met, metformin; SU, sulfonylurea. *Calculated as number of patients with events × 100/total exposure + 3 days in patient-years. †Calculated as number of events × 100/total exposure + 3 days in patient-years. ‡Three patients receiving lixisenatide and SU + Met + other OADs had no blood glucose reported.

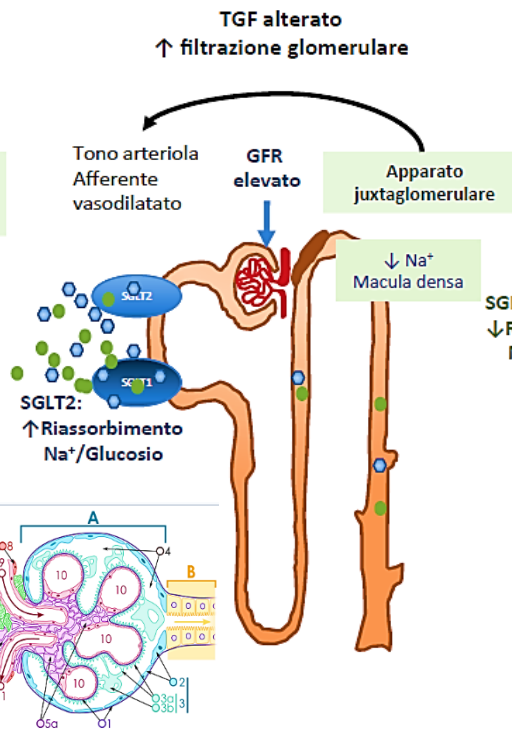
Data are mean (SD) unless otherwise indicated. Met, metformin; SU, sulfonylurea. *Protocol deviation.

SGLT-2 INIBITORI

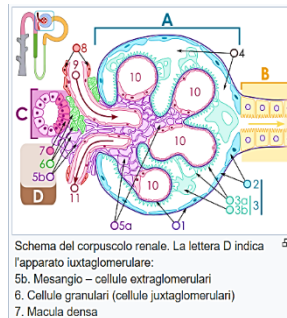
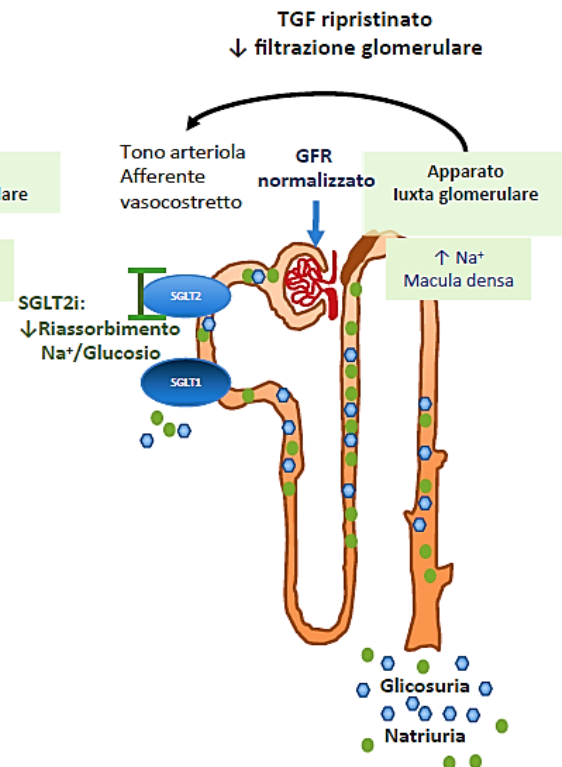
A Paziente normale



B Paziente diabetico

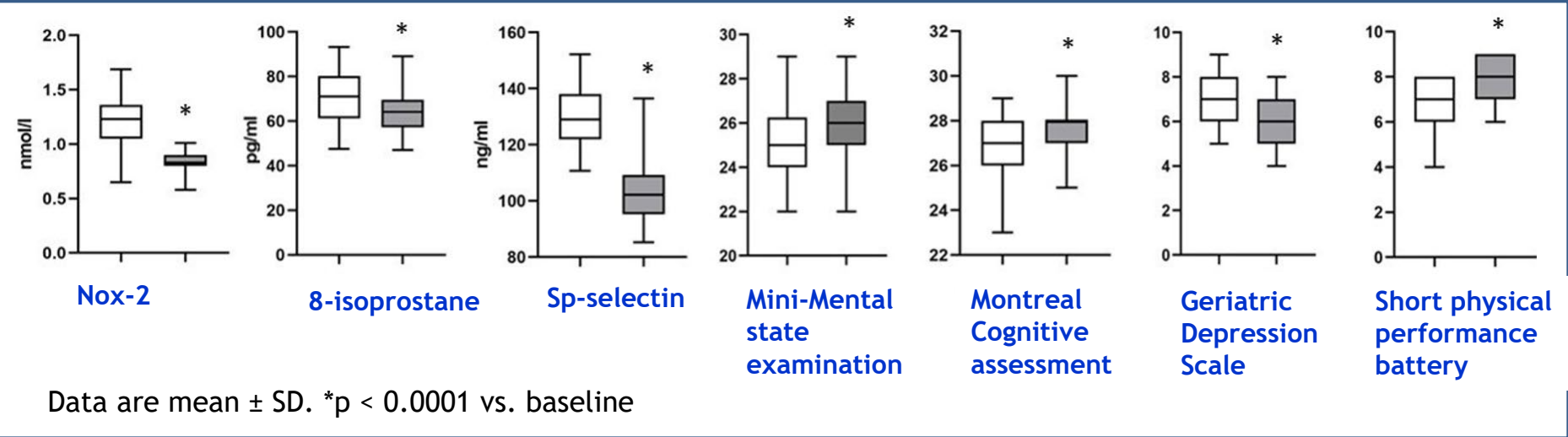


C Paziente diabetico + SGLT2i



Association of SGLT2-inhibitors with changes in Comprehensive Geriatric Assessment in Elderly Diabetic Patients with Heart Failure - data from MAGIC-HF (NCT03015344)

Total population (n. 134)	Baseline (134)	Follow-up (134)	p*
MMSE, pt	25.3±1.8	25.9±1.5	<0.0001
MoCA, pt	26.5±1.4	27.3±1.4	<0.0001
GDS, pt	7.0±0.9	6.0±0.9	<0.0001
SPPB, pt	6.4±1.1	7.7±1.0	<0.0001
BMI, Kg/m ²	29.9±4.2	29.3±4.0	<0.0001
SBP, mmHg	116.3±11.7	115.9±9.7	0.666
DBP, mmHg	68.9±6.7	68.1±6.8	<0.0001
PPV, %	17.1±11.9	17.8±18.1	0.579



NGF-1, ng/ml	107.5±31.0	116.7±30.2	<0.0001
8-Isoprostane, pg/ml	60.7±11.4	54.5±9.5	<0.0001
Nox-2, nmol/l	1.4±0.2	1.0±0.08	<0.0001
Sp-Selectina, ng/ml	140.3±10.4	114.3±12.2	<0.0001

Table 1. Clinical, anthropometric, and laboratoristic characteristic of the study population at baseline.

	All Population (n. 514)	Without SGLT2i (n. 228)	With SGLT2i (n. 286)	<i>p</i>
Age, years	76.3 ± 7.1	76.4 ± 6.8	76.2 ± 7.2	0.702

Elderly
tus, and

Table 2. Comorbidities and therapies of the study population at baseline.

		All Population (n. 514)	Without SGLT2i (n. 228)	With SGLT2i (n. 286)	<i>p</i>
BMI, Kg/m ²					
SBP, mmHg					
DBP, mmHg					
HR, bpm	IHD, <i>n</i> (%)	320 (62.3)	138 (60.5)	182 (63.6)	0.469
RR, afm	Atrial Fibrillation, <i>n</i> (%)	156 (30.4)	68 (29.8)	88 (30.8)	0.816
eGFR, mL/min/1.73	HFrEF, <i>n</i> (%)	182 (35.4)	90 (39.5)	92 (32.2)	0.085
Uric acid, mg/dL	HFmrEF-HFpEF, <i>n</i> (%)	332 (64.6)	138 (60.5)	194 (67.8)	0.085
Hb, g/dL	Arterial Hypertension, <i>n</i> (%)	360 (70)	154 (67.5)	206 (72.0)	0.270
HTC, %					
Na ⁺ , mmmol/L					
K ⁺ , mmol/L	COPD, <i>n</i> (%)	136 (26.5)	58 (25.4)	78 (27.3)	0.639
NTpro-BNP, pg/mL	Dislipidemia, <i>n</i> (%)	294 (57.2)	124 (54.3)	170 (59.4)	0.249
HOMA-IR, pt	CKD, <i>n</i> (%)	166 (32.3)	72 (31.6)	94 (32.9)	0.756
HbA1c, %	ICD-CRTd, <i>n</i> (%)	312 (60.7)	144 (63.1)	168 (58.7)	0.308
hs-CRP, mg/L	ACEi/ARBs, <i>n</i> (%)	204 (39.7)	80 (35.0)	124 (43.4)	0.056
• To evaluate the effect of SGLT2i on the clinical outcomes in patients with HF and CKD. • In patients with HF and CKD, the clinical outcomes were significantly improved in the SGLT2i group compared with the control group.	Sacubitril-Valsartan, <i>n</i> (%)	182 (35.4)	90 (39.5)	92 (32.2)	0.085
	Loop-Diuretics, <i>n</i> (%)	450 (87.5)	192 (84.2)	258 (90.2)	0.040
	MRAs, <i>n</i> (%)	260 (50.6)	116 (50.1)	144 (50.3)	0.905
	β-blockers, <i>n</i> (%)	352 (68.5)	166 (72.8)	186 (65.0)	0.059
	OAC, <i>n</i> (%)	156 (30.4)	68 (29.8)	88 (30.8)	0.816
	Antiplatelet, <i>n</i> (%)	316 (61.5)	148 (64.9)	168 (58.7)	0.153
	Statins, <i>n</i> (%)	342 (66.5)	164 (71.9)	178 (62.2)	0.020

- To evaluate the impact of polypharmacy and medication management on the central pattern and 202 by a predominantly obstructive pattern.
- A simple logistic regression model was built using 50% reduction in AHI as the dependent variable and other variables as covariates.

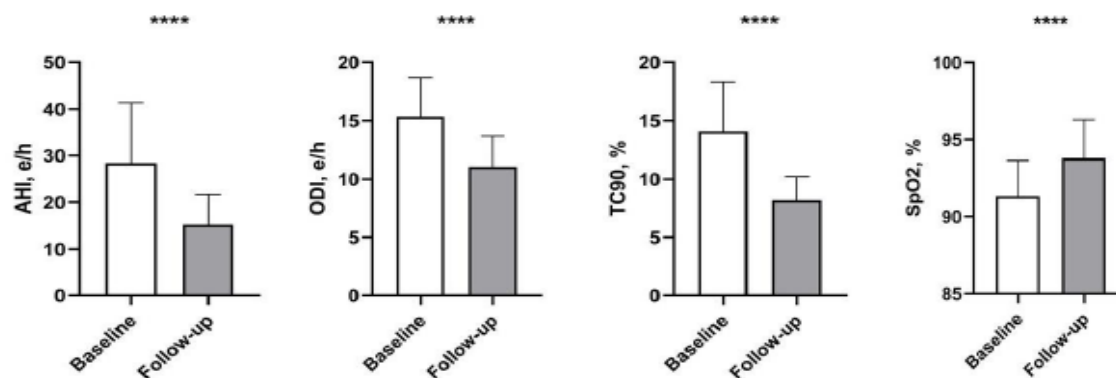


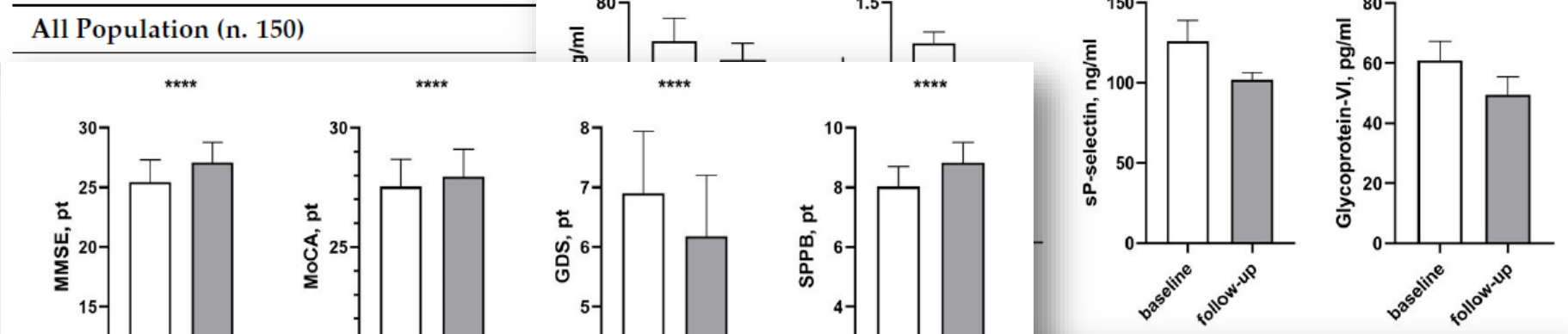
Figure 1. Baseline to follow-up change in polygraphic parameters in patients treated with SGLT2i. Data are mean $\pm$ SD. **** $p < 0.0001$ vs. baseline.

Table 5. Multivariate stepwise logistic regression model focused on the 50% reduction in the AHI value.

	OR	CI 95%	<i>p</i>
SGLT2i, yes/no	1.60	1.08–2.35	0.004
BMI, 1 kg/m ²	1.05	1.01–1.09	0.022
IHD, yes/no	0.44	0.29–0.67	<0.0001
Female gender, yes/no	0.51	0.34–0.78	0.002
Age, 10 years	0.61	0.32–0.85	0.023
HOMA-IR, 1 pt	0.90	0.83–0.98	0.020
IVC, 1 mm	0.91	0.84–0.98	0.019

Effects of SGLT2-Inhibitors on Comprehensive Geriatric Assessment, Biomarkers of Oxidative Stress, and Platelet Activation in Elderly Diabetic Patients with Heart Failure with Preserved Ejection Fraction

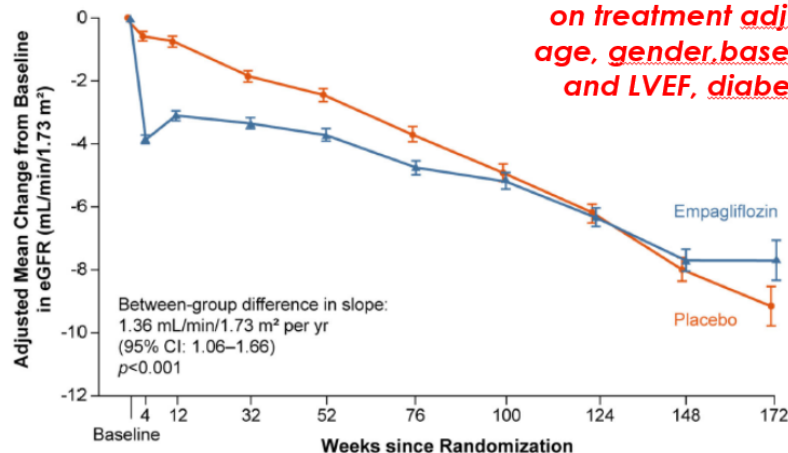
Table 2. Cont.



Changes in eGFR during double-blind therapy - EMPEROR-Preserved

Anker SD et al. *N Engl J Med* 2021

on treatment adjusted for age, gender, baseline eGFR and LVEF, diabetes, etc



No. with Data at Visit

Placebo	2911	2887	2759	2488	2333	1996	1443	1014	637	209
Empagliflozin	2925	2893	2785	2521	2343	1970	1431	1039	620	212

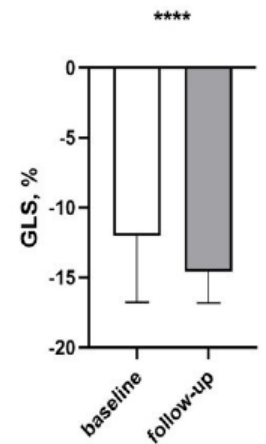
The rate of eGFR decline in patients treated with empagliflozin was half that of patients treated with placebo

Empagliflozin Placebo

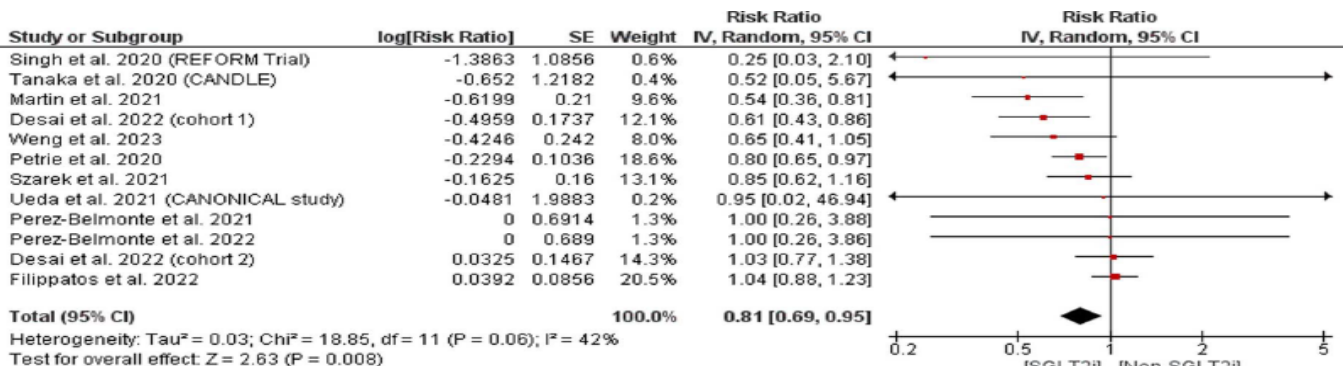
-1.25
(±0.11)

-2.62
(±0.11)

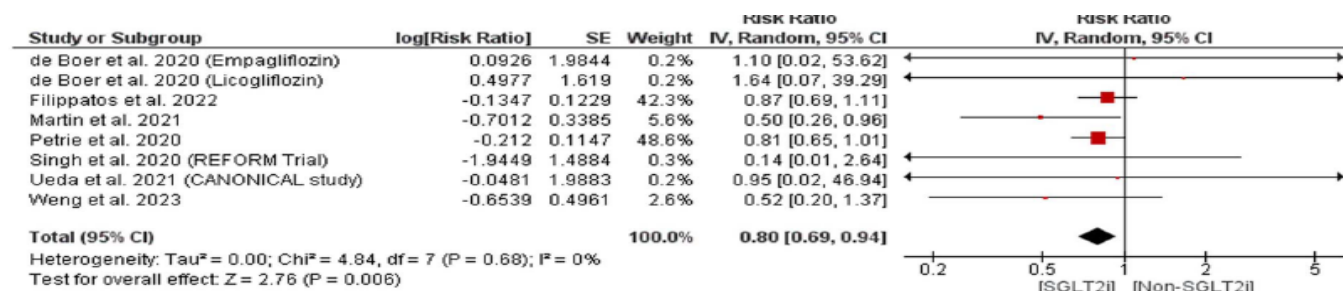
mean (±SE)
mL/min/1.73 m²/year



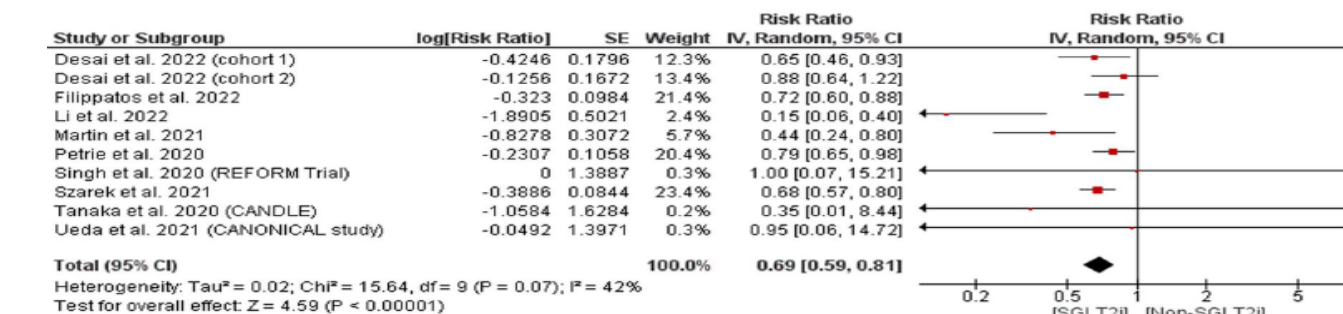
SYSTEMATIC REVIEW



All cause mortality



Cardiac death



hHF

were identified in 2392 (50.4%), 1,606 (33.9%) and 744 (15.7%)) 6254
 pts prefrail-frail, all patients

Potential Safety Issues with Use of Sodium-Glucose Cotransporter 2 Inhibitors, Particularly in People with Type 2 Diabetes and Chronic Kidney Disease

Table 4 Strategies to reduce the risk of SGLT2 inhibitor-associated DKA

Careful prescription of an SGLT2 inhibitor in light of a patient's risk factors for DKA (see Table 1)

Reducing a patient's insulin dose cautiously when commencing an SGLT2 inhibitor, as excessive insulin dose reduction or cessation of insulin therapy can contribute to the risk of DKA

Informing patients about the risk of SGLT2 inhibitor-associated DKA, including when to withhold an SGLT2 inhibitor, including acute illness with reduced oral intake (part of a sick day management plan), symptoms of DKA (nausea, vomiting, abdominal pain, tiredness, rapid breathing), and the need to seek medical attention if symptoms occur (provision of written information is recommended)

Cessation of an SGLT2 inhibitor ≥ 3 days prior to an operation and only recommencing therapy when a patient is eating and drinking normally

Table 3 Risk factors for SGLT2 inhibitor-associated DKA

Type 1 diabetes including latent autoimmune diabetes in adults (patients with presumed type 2 diabetes where there is clinical suspicion of type 1 diabetes should have autoantibodies tested)

Type 2 diabetes with insulin deficiency

Excessive reduction in exogenous insulin dose or insulin cessation

Diabetes due to pancreatic disease

Fasting, including during the perioperative state

Very low carbohydrate diet

Hypovolaemia

Excessive alcohol consumption (daily consumption and/or binge drinking)

Metabolic stress including acute infection, surgery, myocardial infarction, pancreatitis, and intensive exercise

Diuretics, SGLT2 inhibitors and falls in older heart failure patients: to prescribe or to deprescribe? A clinical review

Methods We comprehensively searched and summarized published literature and international guidelines on the efficacy, fall-related safety issues, and deprescribing of the commonly prescribed diuretics and SGLT2 inhibitors in older adults.

Results Both diuretics and SGLT2 inhibitors potentially cause various fall-related adverse effects. Their fall-related side effect profiles partly overlap (e.g., tendency to cause hypotension), but there are also important differences; based on the currently available evidence of this relatively new drug class, SGLT2 inhibitors seem to have a favorable fall-related adverse effect profile compared to diuretics (e.g., low/absent tendency to cause hyperglycemia or electrolyte abnormalities, low risk of worsening chronic kidney disease). In addition, SGLT2 inhibitors have potential beneficial effects (e.g., disease-modifying

Efficacy and safety profile of SGLT2 inhibitors in the elderly: How is the benefit/risk balance?

atric Medicine 2023

The aims of this comprehensive review were to analyze the benefit-risk ratio of SGLT2i therapy in older patients with T2DM by collecting data from (i) large prospective placebo-controlled cardiovascular outcome trials (including those dedicated to heart failure), using both original publications and dedicated post-hoc analyses across different age groups and (ii) observational cohort studies, describing the effects of SGLT2is versus other glucose-lowering agents on cardiovascular outcomes and hHF in elderly patients or these effects in different age groups. **Overall, consistent results showed a similar relative risk reduction in cardiovascular mortality and hHF with SGLT2is independently of age. The absolute risk reduction may be greater in elderly because of a higher background risk in older versus younger patients. Similarly, the safety profile of SGLT2is appeared comparable in older versus younger patients. In conclusion, the benefit/risk balance favors the use of SGLT2is in older patients at risk of cardiovascular disease and/or heart failure. Caution may be required in very old frail patients, especially those exposed to an increased risk of volume depletion.**

André J Scheen et al. Diabetes Metab 2023

13. Older Adults: *Standards of Care in Diabetes—2024*

Diabetes Care 2024;47(Suppl. 1):S244–S257 | <https://doi.org/10.2337>

Recommendations

13.1 Consider the assessment of medical, psychological, functional (e.g., management abilities), and social domains in older adults with diabetes to provide a framework to determine goals and therapeutic approaches for diabetes management. **B**

13.2 Screen for geriatric syndromes (e.g., cognitive impairment, depression, urinary incontinence, falls, persistent pain, and frailty) and polypharmacy in older adults with diabetes, as they may affect diabetes self-management and diminish quality of life. **B**

NEUROCOGNITIVE FUNCTION

Recommendation

13.3 Screening for early detection of mild cognitive impairment or dementia should be performed for adults 65 years of age or older at the initial visit, annually, and as appropriate. **B**

HYPOGLYCEMIA

Recommendations

13.4 Because older adults with diabetes have a greater risk of hypoglycemia, especially when treated with hypoglycemic agents (e.g., sulfonylureas, meglitinides, and insulin), than younger adults, episodes of hypoglycemia should be ascertained and addressed at routine visits. **B**

13.5 For older adults with type 1 diabetes, continuous glucose monitoring is recommended to reduce hypoglycemia. **A**

13.6 For older adults with type 2 diabetes on insulin therapy, continuous glucose monitoring should be considered to improve glycemic outcomes and reduce hypoglycemia. **B**

13.7 For older adults with type 1 diabetes, consider the use of automated insulin delivery (AID) systems **A** and other advanced insulin delivery devices such as connected pens **E** to reduce risk of hypoglycemia, based on individual ability and support system.

Table 13.1—Framework for considering treatment goals for glycemia, blood pressure, and dyslipidemia in older adults with diabetes

Characteristics and health status of person with diabetes	Rationale	Reasonable A1C goal*	Fasting or preprandial glucose	Bedtime glucose	Blood pressure	Lipids
Healthy (few coexisting chronic illnesses, intact cognitive and functional status)	Longer remaining life expectancy	<7.0–7.5% (<53–58 mmol/mol)	80–130 mg/dL (4.4–7.2 mmol/L)	80–180 mg/dL (4.4–10.0 mmol/L)	<130/80 mmHg	Statin, unless contraindicated or not tolerated
Complex/intermediate (multiple coexisting chronic illnesses† or two or more instrumental ADL impairments or mild to moderate cognitive impairment)	Variable life expectancy. Individualize goals, considering: • Severity of comorbidities • Cognitive and functional limitations • Frailty • Risk-to-benefit ratio of diabetes medications • Individual preference	<8.0% (<64 mmol/mol)	90–150 mg/dL (5.0–8.3 mmol/L)	100–180 mg/dL (5.6–10.0 mmol/L)	<130/80 mmHg	Statin, unless contraindicated or not tolerated
Very complex/poor health (LTC or end-stage chronic illnesses‡ or moderate to severe cognitive impairment or two or more ADL impairments)	Limited remaining life expectancy makes benefit minimal	Avoid reliance on A1C; glucose control decisions should be based on avoiding hypoglycemia and symptomatic hyperglycemia	100–180 mg/dL (5.6–10.0 mmol/L)	110–200 mg/dL (6.1–11.1 mmol/L)	<140/90 mmHg	Consider likelihood of benefit with statin

13.16c Simplification of complex treatment plans (especially insulin) is recommended to reduce the risk of hypoglycemia and polypharmacy and decrease the treatment burden if it can be achieved using the individualized glycemic goals. **B**

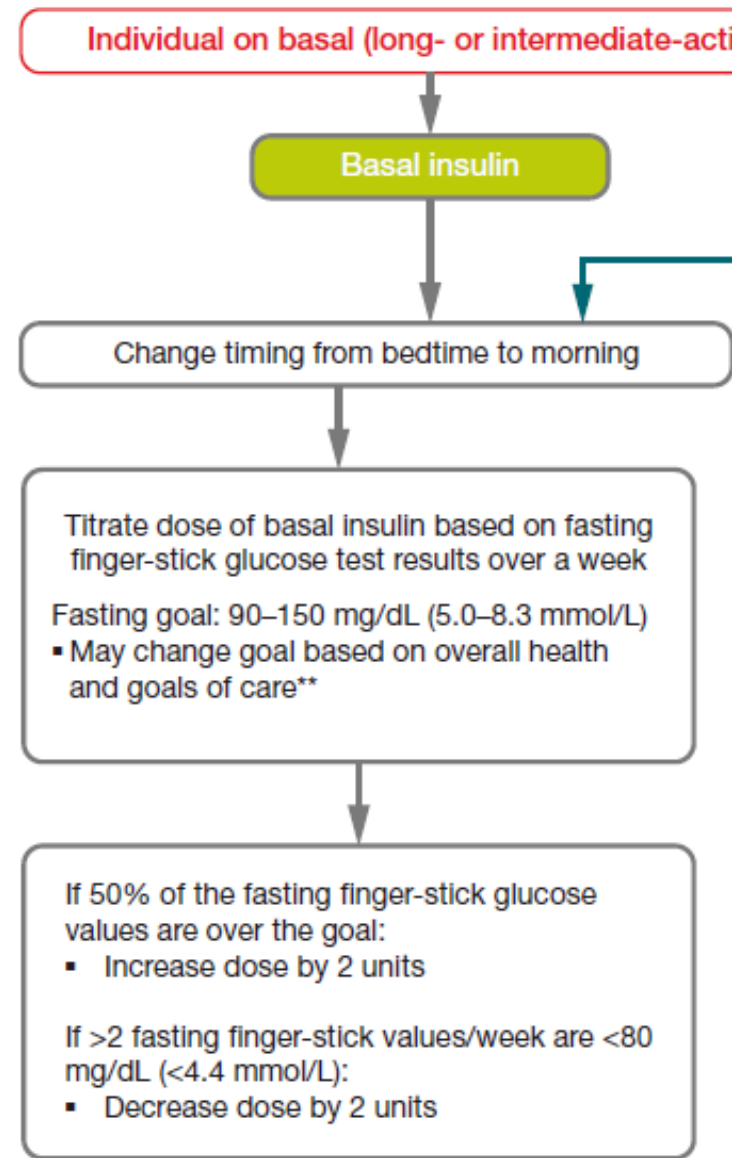
Terapia insulinica

Raccomandazioni

- In alcuni pazienti anziani, soprattutto con lunga storia di diabete endogena, anche stimolata da secretagoghi, rende indispensabile insulinica.
(Livello di prova I, forza della raccomandazione A)
- La prima insulina da prescrivere è un analogo basale.
(Livello di prova I, forza della raccomandazione A)
La scelta fra i diversi analoghi basali deve essere adattata alle specifiche sociali del singolo paziente.
(Livello di prova VI, forza della raccomandazione C)
- L'inizio di una terapia insulinica deve essere accompagnata da concomitante terapia non insulinica per il diabete, possibilmente con glicinidi.
(Livello di prova II, forza della raccomandazione B)

Tabella 1 Azioni terapeutiche preliminari alla prescrizione di una terapia insulinica

1. Verifica (almeno annuale) delle capacità di apprendimento, memoria, motorie e visive del paziente
2. Eventuale verifica (almeno annuale) dell'apprendimento e della continuità assistenziale dei care-givers (parenti, badanti, altro)
3. Educazione al corretto utilizzo del sistema iniettivo
4. Educazione al corretto utilizzo del sistema di monitoraggio della glicemia
5. Educazione per la prevenzione dell'ipoglicemia
6. Prescrizione nutrizionale personalizzata (con eventuale counting carboidrati)
7. Eventuale educazione all'autotitolazione



"Take home message"

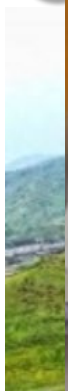
➤ Decide

➤ Stabilize

➤ Valuta

*Start low and go
slow...*

a)



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