Quali Limiti nell'utilizzo di SGLT2-i e GLP1 RA

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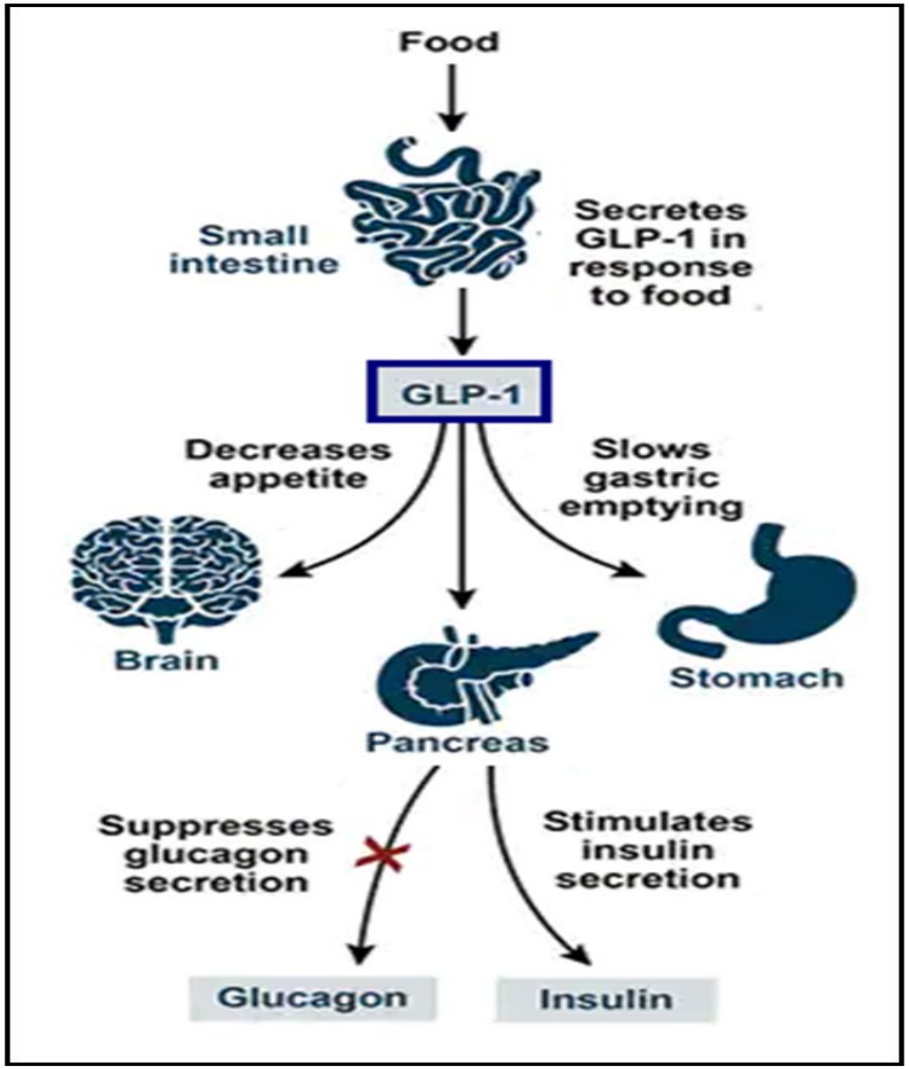
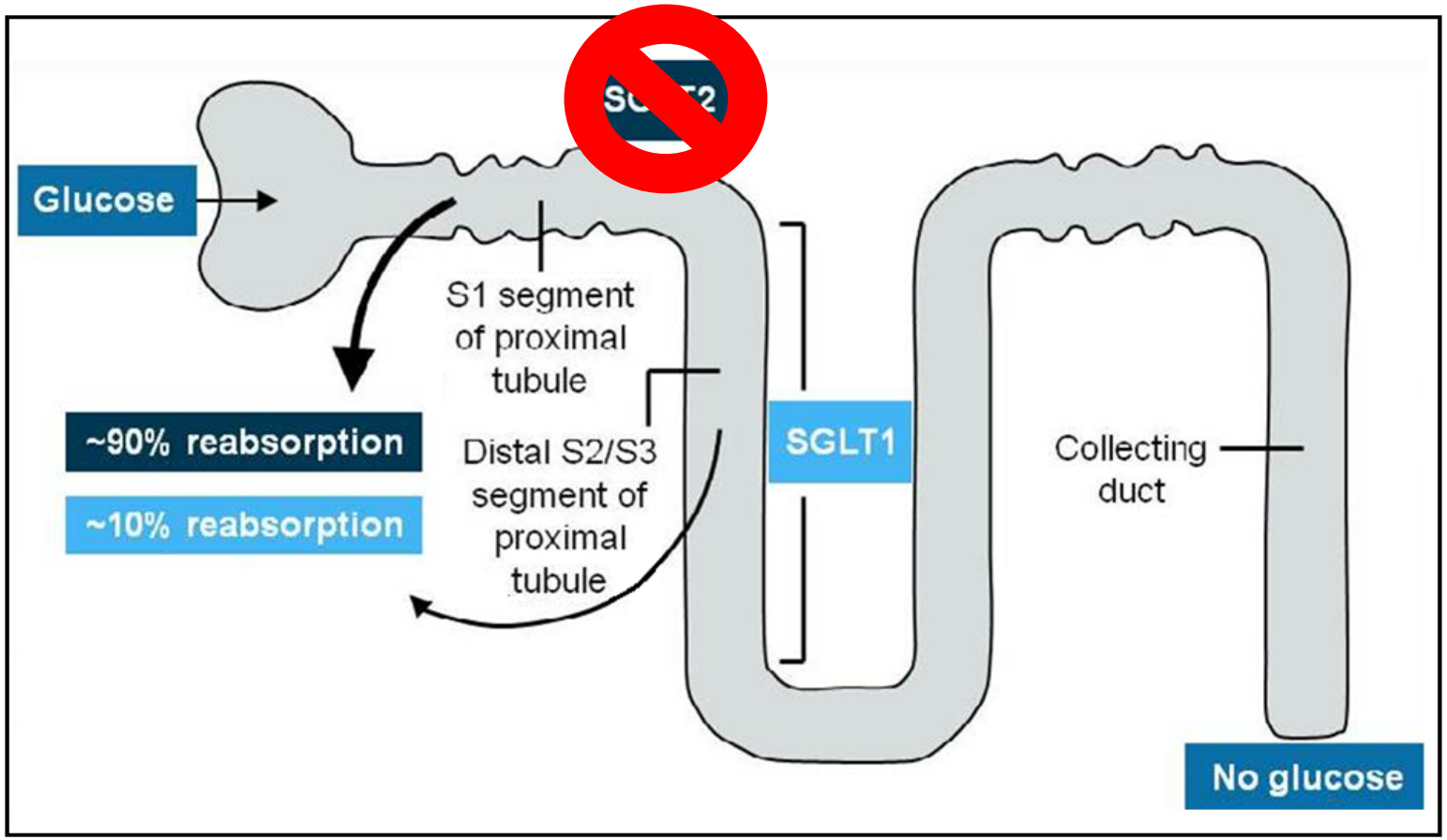
AGONISTI DEL RECETTORE DEL GLP-1

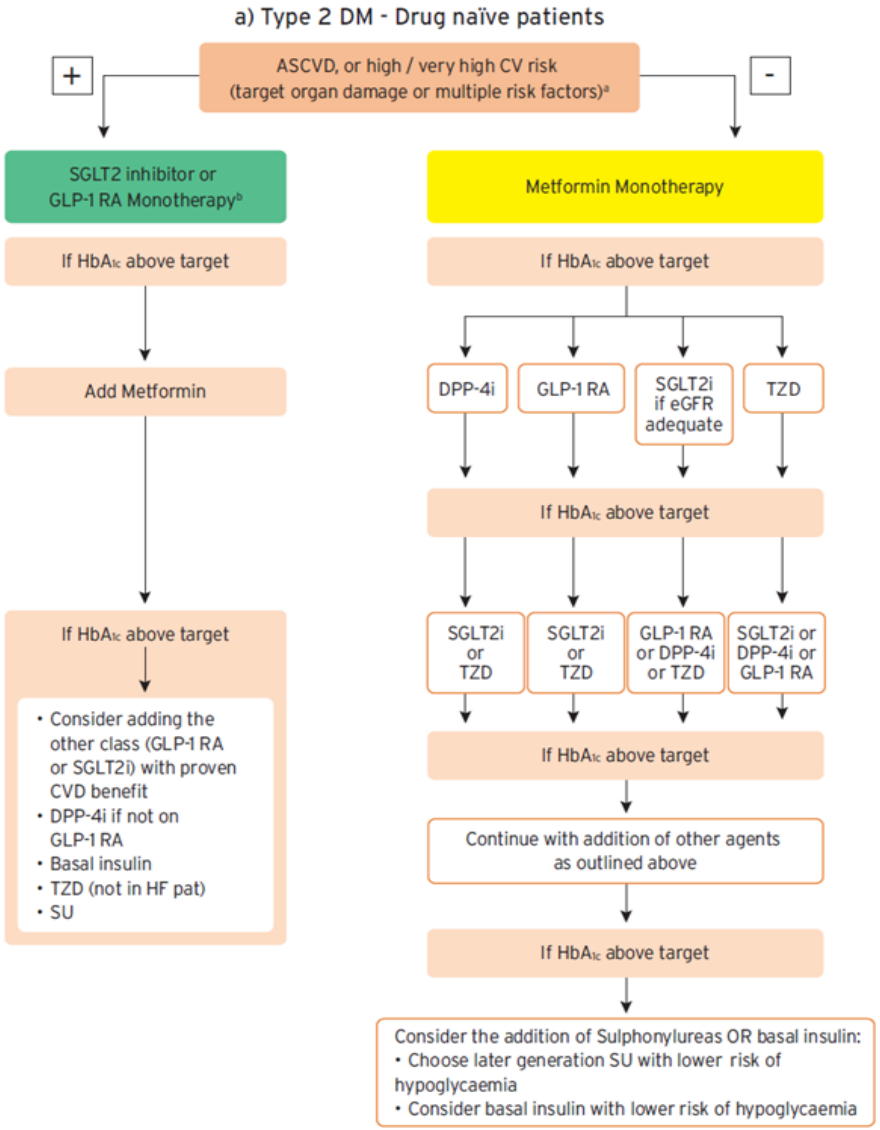


Meier JJ. *Nat Rev Endocrinol*. 2012;8:728-742.

INIBITORI DEL COTRASPORTATORE SGLT2

Meccanismo d'azione





ESC
European Society of Cardiology

Treatment algorithm in patients with T2DM and ASCVD or high/very high CV risk - drug naïve

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Potenziali rischi dei farmaci per il trattamento del diabete mellito tipo 2

	Acarbosio	DPP4i	GLP1-RA	Insulina umana/analoghi dell' insulina	Metformina	Pioglitazone	SGLT2i	SU/repaglinide
Interazione con altri farmaci	-	-	-	-	-	+	-	++
Ipoglicemie	-	-	-	++	-	-	-	+++
Aumento di peso	-	-	-	++	-	++	-	+
Disturbi gastrointestinali	+++	-	++	-	++	-	-	-
Pancreatiti acute	-	+	+/-	-	-	-	-	-
Fratture ossee	-	-	-	-	-	+++	+/-[a]	-
Deplezione di volume/disidratazione	-	-	+/-	-	-	-	+	-
Ritenzione idrica/edemi	-	-	-	-	-	++	-	-
Scompenso cardiaco	-	+/-[b]	-	-	-	++	-	+
Infezioni genito-urinarie	-	-	-	-	-	-	+	-
Chetoacidosi	-	-	-	-	-	-	+	-
Retinopatia diabetica	-	-	+/-[c]	-	-	+	-	-
Amputazioni arti inferiori	-	-	-	-	-	-	+/-[a]	-
Fascite necrotizzante del perineo	-	-	-	-	-	-	+	-

ga del Farmaco

Clinical Recommendations to Manage Gastrointestinal Adverse Events in Patients Treated with Glp-1 Receptor Agonists: A Multidisciplinary Expert Consensus

GLP-1 RA	Program	Refs	Patient Profile	Dose	Method of Administration	Nausea	Vomiting	Diarrhoea	Constipation
Semaglutide	SUSTAIN	9	T2D	1 mg	s.c. once weekly	15–24	7–15	7–19	4–7
Semaglutide	STEP	10	Obesity *	2.4 mg	s.c. once weekly	14–58	22–27	10–36	12–37
Semaglutide	PIONEER	11	T2D	14 mg	p.o. SID	8–23	6–12	5–15	7–12
Liraglutide	LEAD	12	T2D	1.8 mg	s.c. SID	10–40	4–17	8–19	11
Liraglutide	SCALE	13	Obesity *	3 mg	s.c. SID	27–48	7–23	16–26	12–30
Dulaglutide	AWARD	14	T2D	1.5 mg	s.c. once weekly	15–29	7–17	11–17	n.r.
Exenatide	DURATION	15	T2D	2 mg	s.c. once weekly	5–14	<1–6	5–11	1–8
Exenatide	—	16	T2D	10 µg	s.c. BID	35–59	9–14	4–9	5
Lixisenatide	GETGOAL	17	T2D	20 µg	s.c. SID	16–40	7–18	4–12	5†

Table. Frequency of GI AEs in clinical trials with GLP-1 RA in people with obesity or T2D

Juan J Gorgojo-Martínez et al., J Clin Med. - 2022 Dec 24;12(1):145.

Minimizing occurrence/severity of GI AEs: patients general guidelines

1. **Abitudini alimentari**
2. **Tipologia e composizione del cibo**
3. **Stile di vita**

Juan J Gorgojo-Martínez et al., J Clin Med. - 2022 Dec 24;12(1):145.

Additional specific guidelines for each separate GI AE

Juan J Gorgojo-Martínez et al., J Clin Med. - 2022 Dec 24;12(1):145.

1. Before

Save time to speak with the patient

- Transmit realistic expectations regarding treatment results
- Inform about GI AEs, pointing out that they will soon pass
- Highlight the importance of following the available guidelines

2. Dose-escalation

For this purpose, choose one/several among these:

- Extend current phase for 2-4 more weeks before moving forward to next dose
- Suspend treatment temporarily
- If GI AEs appear just after escalation, go back to prior dose for a few days, then increase dose gradually
- If problem persists, consider setting up as maintenance therapy a dose lower than the maximum one

If GI AEs occur, **slow down** the planned dose increments to reach success

3. Dose-escalation or maintenance phase

Consider one/several of these:

- Start a differential diagnosis procedure to rule out underlying conditions that may be responsible
- Check patient understands/complies with diet/lifestyle guidelines
- Start measures specifically focused on the troublesome symptoms
  - Additional patient guidelines (see Figure 2)
  - Pharmacological support (at short term)

If GI AEs persist beyond normal in time/severity, **implement additional** measures

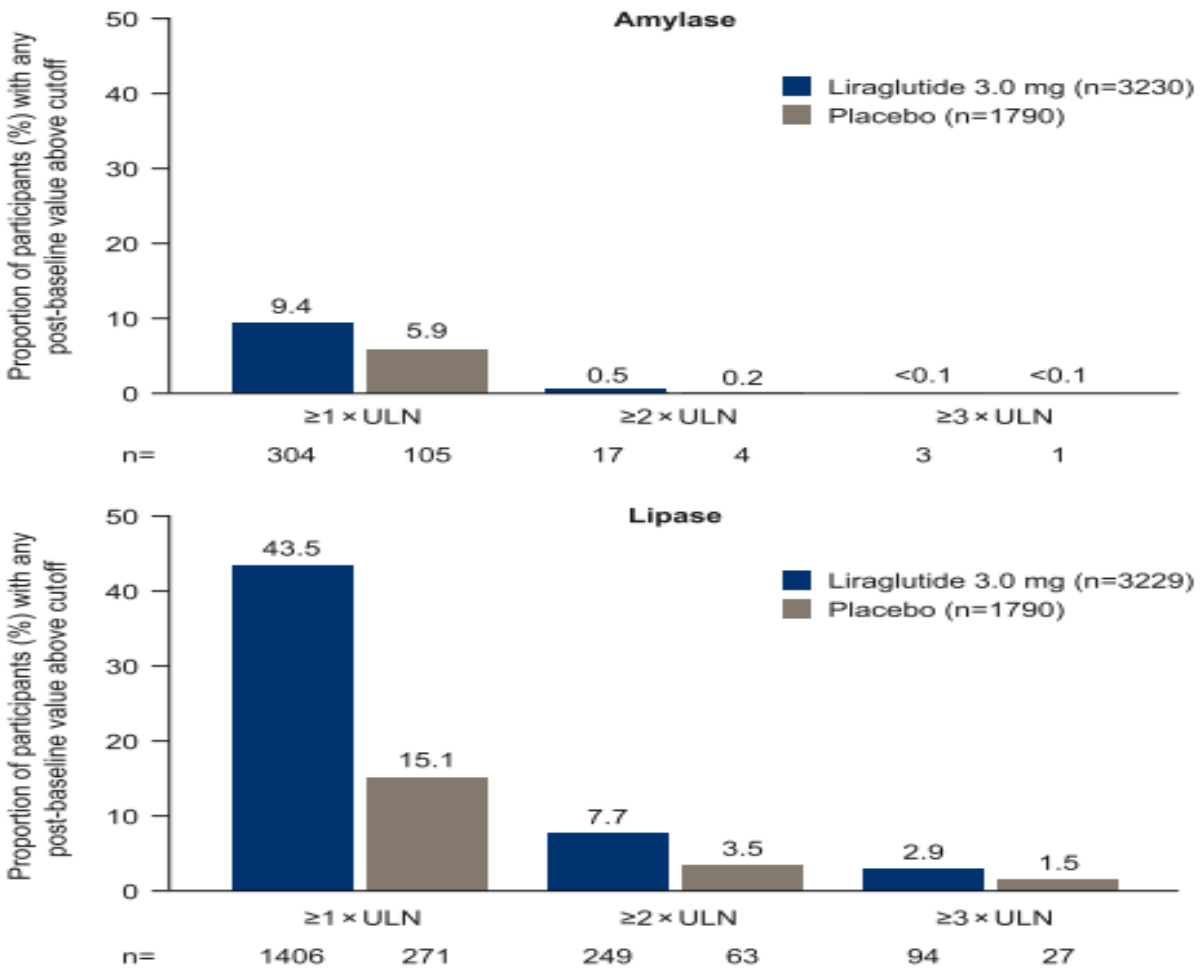
nausea	vomiting	diarrhoea	constipation
•Anti-emetics •Prokinetics (domperidone)	•Anti-emetics •Prokinetics (domperidone) •Standard procedures for severe cases (do not rule out i.v. rehydration)	•Probiotics •Antidiarrhoeals (loperamide) •Consider metformin dose reduction when needed	•Stool softeners •Consider reducing GLP-1 RA dose

- Switch to another GLP-1 RA (start at lowest escalation dose)

Minimizing occurrence/severity of GI AEs: the role of HCPs

Juan J Gorgojo-Martínez et al.,
J Clin Med. - 2022 Dec 24;12(1):145.

Impact of Liraglutide on Amylase, Lipase, and Acute Pancreatitis in Participants With Overweight/Obesity and Normoglycemia, Prediabetes, or Type 2 Diabetes: Secondary Analyses of Pooled Data From the SCALE Clinical Development Program



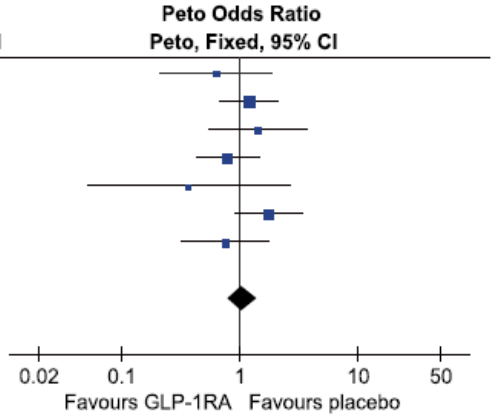
Amylase and lipase elevations at any time during treatment (pooled data from Trials 1–4)

GLP-1 receptor agonists and pancreatic safety concerns in type 2 diabetic patients: data from cardiovascular outcome trials

Fig. 2 Forest plot of GLP-1RA vs. placebo on the risk of acute pancreatitis. CI confidence interval, GLP-1RA GLP-1 receptor agonist

Study or Subgroup	GLP-1RA Events	GLP-1RA Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
ELIXA	5	3031	8	3032	7.2%	0.63 [0.21, 1.87]
EXSCEL	26	7344	22	7372	26.7%	1.19 [0.67, 2.09]
Harmony Outomes	10	4717	7	4715	9.5%	1.42 [0.55, 3.69]
LEADER	18	4668	23	4672	22.8%	0.78 [0.42, 1.45]
PIONEER 6	1	1591	3	1592	2.2%	0.37 [0.05, 2.61]
REWIND	23	4949	13	4952	20.0%	1.75 [0.91, 3.36]
SUSTAIN-6	9	1648	12	1649	11.6%	0.75 [0.32, 1.77]
Total (95% CI)		**27948**		**27984**	**100.0%**	**1.05 [0.78, 1.40]**
Total events	92		88			

Heterogeneity: Chi² = 6.31, df = 6 (P = 0.39); I² = 5%
Test for overall effect: Z = 0.31 (P = 0.76)



Study or Subgroup	GLP-1RA Events	GLP-1RA Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
ELIXA	3	3031	9	3032	11.1%	0.37 [0.12, 1.14]
EXSCEL	15	7344	16	7372	28.7%	0.94 [0.47, 1.90]
Harmony Outomes	6	4717	5	4715	10.2%	1.20 [0.37, 3.91]
LEADER	13	4668	5	4672	16.7%	2.44 [0.97, 6.15]
REWIND	19	4949	12	4952	28.7%	1.57 [0.78, 3.19]
SUSTAIN-6	1	1648	4	1649	4.6%	0.30 [0.05, 1.74]
Total (95% CI)		**26357**		**26392**	**100.0%**	**1.12 [0.77, 1.63]**
Total events	57		51			

Heterogeneity: Chi² = 9.74, df = 5 (P = 0.08); I² = 49%
Test for overall effect: Z = 0.59 (P = 0.56)

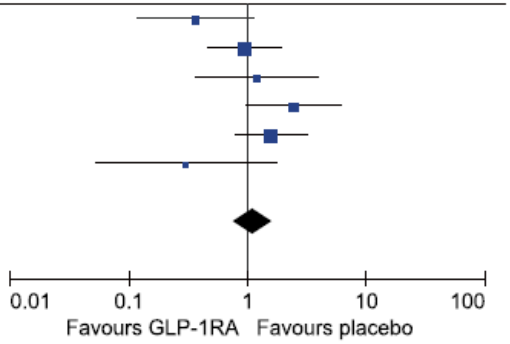


Fig. 3 Forest plot of GLP-1RA vs. placebo on the risk of pancreatic cancer. CI confidence interval, GLP-1RA GLP-1 receptor agonist

Chuqing Cao et al., Endocrine. 2020 Jun;68(3):518-525. doi: 10.1007/s12020-020-02223-6

GLP-1 Receptor Agonists and the Risk of Thyroid Cancer

The use of GLP-1 receptor agonists is associated with an increased risk of thyroid cancer

GLP-1 receptor agonists and the risk of thyroid cancer

Bezin J., Gouverneur A., Pénichon M., Mathieu C., Garrel R., Hillaire-Buys D., Pariente A., Faillie J-L.

Nationwide population-based study on French SNDS database

3,746,672 individuals with type 2 diabetes treated with second-line antidiabetes drugs between 2006-2018

2,562 cases of thyroid cancers

45,184 matched control subjects

	Case subjects *n* = 2,572	Control subjects *n* = 45,184	Adjusted hazard ratio (95%CI)*
GLP-1 receptor agonists			
No use	2,255 (88.0)	40,836 (90.4)	Reference
Cumulative use ≤1 year	117 (4.6)	1,767 (3.9)	1.22 (0.99 to 1.50)
Cumulative use 1-3 years	112 (4.4)	1,419 (3.1)	1.58 (1.27 to 1.95)
Cumulative use >3 years	78 (3.0)	1,162 (2.6)	1.36 (1.05 to 1.74)
DPP-4 inhibitors			
No use	1,522 (59.4)	27,406 (60.7)	Reference
Cumulative use ≤1 year	333 (13.0)	5,209 (11.5)	1.12 (0.99 to 1.28)
Cumulative use 1-3 years	310 (12.1)	5,918 (13.1)	0.96 (0.84 to 1.10)
Cumulative use >3 years	397 (15.5)	6,651 (14.7)	1.19 (1.04 to 1.35)

*Adjusted for social deprivation index, goiter, hypo- and hyperthyroidism in the last year, and use of other antidiabetes drugs in the last 6 years considered in therapeutic class.

Diabetes Care

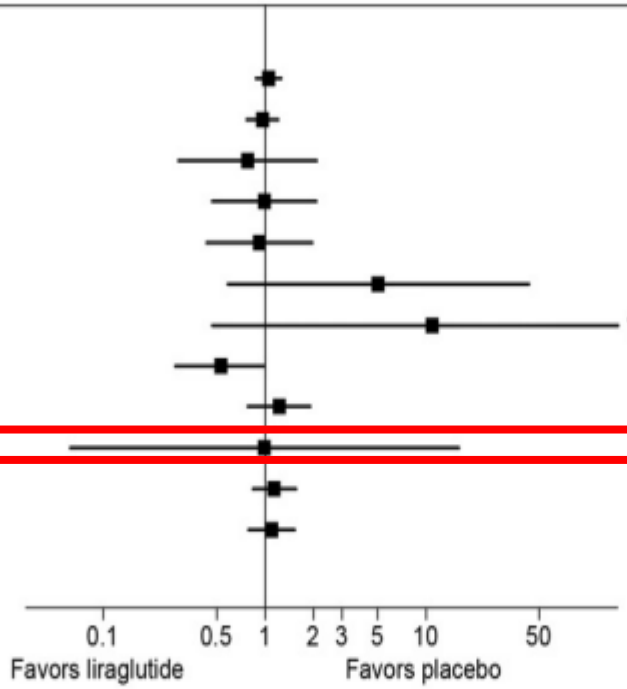
This study is part of the DRUGS-SAFER research program, funded by the French Medicines Agency. This publication represents the views of the authors and does not necessarily represent the opinion of the French Medicines Agency.

American Diabetes Association. Connected for Life

Bezin J et al, Diabetes Care. 2022;46(2):384-390. doi:10.2337/dc22-1148

Neoplasms Reported With Liraglutide or Placebo in People With Type 2 Diabetes: Results From the LEADER Randomized Trial

Diabetes Care 2018;41:1663–1671 | https://doi.org/10.2337/dc17-1825



	Hazard ratio (95% CI)	Liraglutide *n*	(%)	Placebo *n*	(%)
FAS		4505		4479	
All neoplasms	1.05 (0.88;1.26)	245	(5.4)	231	(5.2)
All malignant neoplasms	0.96 (0.77;1.20)	149	(3.3)	154	(3.4)
Breast – female only	0.78 (0.29;2.09)	7	(0.4)	9	(0.6)
Colon/rectum	0.99 (0.47;2.07)	14	(0.3)	14	(0.3)
Lung/bronchus	0.92 (0.43;1.96)	13	(0.3)	14	(0.3)
Melanoma of the skin	4.97 (0.58;42.54)	5	(0.1)	1	(0.0)
Pancreatic	10.90 (0.46;260.03)	5	(0.1)	0	(0.0)
Prostate – male only	0.53 (0.28;1.02)	14	(0.5)	26	(0.9)
Skin (non-melanoma)	1.22 (0.78;1.90)	43	(1.0)	35	(0.8)
Thyroid	0.99 (0.06;15.80)	1	(0.0)	1	(0.0)
All benign neoplasms	1.14 (0.83;1.55)	86	(1.9)	75	(1.7)
Colon/rectum	1.09 (0.78;1.53)	73	(1.6)	66	(1.5)

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes (SUSTAIN-6)

* Hazard ratios and P values were estimated with the use of a Cox proportional-hazards model with the study treatments as fixed factors and stratified according to all combinations of stratification factors used in the randomization.

† The primary composite outcome was the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke

‡ The expanded composite outcome included death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, revascularization (coronary or peripheral), and hospitalization for unstable angina or heart failure.

§ Retinopathy complications include vitreous hemorrhage, onset of diabetes-related blindness, and the need for treatment with an intravitreal agent or retinal photocoagulation

¶ New or worsening nephropathy includes persistent macroalbuminuria, persistent doubling of the serum creatinine level and a creatinine clearance of less than 45 ml per minute per 1.73 m2 of body-surface area (according to the Modification of Diet in Renal Disease criteria), or the need for continuous renal-replacement therapy.

Table . Primary and Secondary Cardiovascular and Microvascular Outcomes.

Outcome	Semaglutide (N=1648)		Placebo (N=1649)		Hazard Ratio (95% CI)*	P Value
	no. (%)	*no./100 person-yr*	*no. (%)*	*no./100 person-yr*		
Primary composite outcome†	108 (6.6)	3.24	146 (8.9)	4.44	0.74 (0.58–0.95)	<0.001 for noninferiority; 0.02 for superiority
Expanded composite outcome‡	199 (12.1)	6.17	264 (16.0)	8.36	0.74 (0.62–0.89)	0.002
All-cause death, nonfatal myocardial infarction, or nonfatal stroke	122 (7.4)	3.66	158 (9.6)	4.81	0.77 (0.61–0.97)	0.03
Death						
From any cause	62 (3.8)	1.82	60 (3.6)	1.76	1.05 (0.74–1.50)	0.79
From cardiovascular cause	44 (2.7)	1.29	46 (2.8)	1.35	0.98 (0.65–1.48)	0.92
Nonfatal myocardial infarction	47 (2.9)	1.40	64 (3.9)	1.92	0.74 (0.51–1.08)	0.12
Nonfatal stroke	27 (1.6)	0.80	44 (2.7)	1.31	0.61 (0.38–0.99)	0.04
Hospitalization for unstable angina pectoris	22 (1.3)	0.65	27 (1.6)	0.80	0.82 (0.47–1.44)	0.49
Revascularization	83 (5.0)	2.50	126 (7.6)	3.85	0.65 (0.50–0.86)	0.003
Hospitalization for heart failure	59 (3.6)	1.76	54 (3.3)	1.61	1.11 (0.77–1.61)	0.57
Retinopathy complications§	50 (3.0)	1.49	29 (1.8)	0.86	1.76 (1.11–2.78)	0.02
New or worsening nephropathy¶	62 (3.8)	1.86	100 (6.1)	3.06	0.64 (0.46–0.88)	0.005

Steven P. Marso et al., N Engl J Med 2016; 375:1834-1844. DOI: 10.1056/NEJMoa1607141

Semaglutide and Diabetic Retinopathy Risk in Patients with Type 2 Diabetes Mellitus: A Meta-Analysis of Randomized Controlled Trials

Study or Subgroup	Semaglutide Events	Semaglutide Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 New Subgroup						
Ahrén 2016 (SUSTAIN2)	1	818	3	407	1.3%	0.17 [0.02, 1.59]
Aroda 2017 (SUSTAIN4)	1	722	1	360	0.4%	0.50 [0.03, 7.95]
Aroda 2019 (PIONEER1)	9	525	3	178	1.5%	1.02 [0.28, 3.72]
Capehorn 2020 (SUSTAIN10)	3	290	4	287	1.3%	0.74 [0.17, 3.29]
Davies 2021 (STEP2)	27	807	11	403	4.8%	1.23 [0.61, 2.45]
Husain 2019 (PIONEER6)	113	1591	101	1592	33.3%	1.12 [0.86, 1.45]
Ji 2021 (SUSTAIN China)	33	578	10	290	4.4%	1.66 [0.83, 3.31]
Kaku 2018	27	480	6	120	3.2%	1.13 [0.48, 2.66]
Lingvay 2018	2	319	3	386	0.9%	0.81 [0.14, 4.80]
Lingvay 2019 (SUSTAIN8)	9	392	15	394	4.9%	0.60 [0.27, 1.36]
Marso 2016 (SUSTAIN6)	50	1648	29	1649	9.6%	1.73 [1.10, 2.71]
Mosenzon 2019 (PIONEER5)	5	163	2	161	0.7%	2.47 [0.49, 12.54]
Pieber 2019 (PIONEER7)	6	253	6	251	2.0%	0.99 [0.32, 3.03]
Pratley 2018 (SUSTAIN7)	4	601	5	598	1.7%	0.80 [0.21, 2.95]
Pratley 2019 (PIONEER4)	8	285	6	426	1.6%	1.99 [0.70, 5.68]
Rodbard 2018 (SUSTAIN5)	5	263	0	133	0.2%	5.58 [0.31, 100.22]
Rodbard 2019 (PIONEER2)	14	411	5	410	1.7%	2.79 [1.02, 7.68]
Rosenstock 2019 (PIONEER3)	69	1396	29	467	14.3%	0.80 [0.52, 1.21]
Seino 2018	6	205	4	103	1.8%	0.75 [0.22, 2.61]
Yabe 2020 (PIONEER10)	28	393	3	65	1.7%	1.54 [0.48, 4.93]
Yamada 2019 (PIONEER9)	2	146	2	97	0.8%	0.66 [0.10, 4.64]
Zinman 2019 (PIONEER8)	38	547	11	184	5.4%	1.16 [0.61, 2.23]
Zinman 2019 (SUSTAIN9)	3	151	8	151	2.6%	0.38 [0.10, 1.39]
Subtotal (95% CI)		**12984**		**9112**	**100.0%**	**1.14 [0.98, 1.33]**
Total events	463		267			
Heterogeneity: $Chi^2 = 23.43$, df = 22 (P = 0.38); $I^2 = 6\%$						
Test for overall effect: Z = 1.73 (P = 0.08)						
Total (95% CI)		**12984**		**9112**	**100.0%**	**1.14 [0.98, 1.33]**
Total events	463		267			
Heterogeneity: $Chi^2 = 23.43$, df = 22 (P = 0.38); $I^2 = 6\%$						
Test for overall effect: Z = 1.73 (P = 0.08)						
Test for subgroup differences: Not applicable						

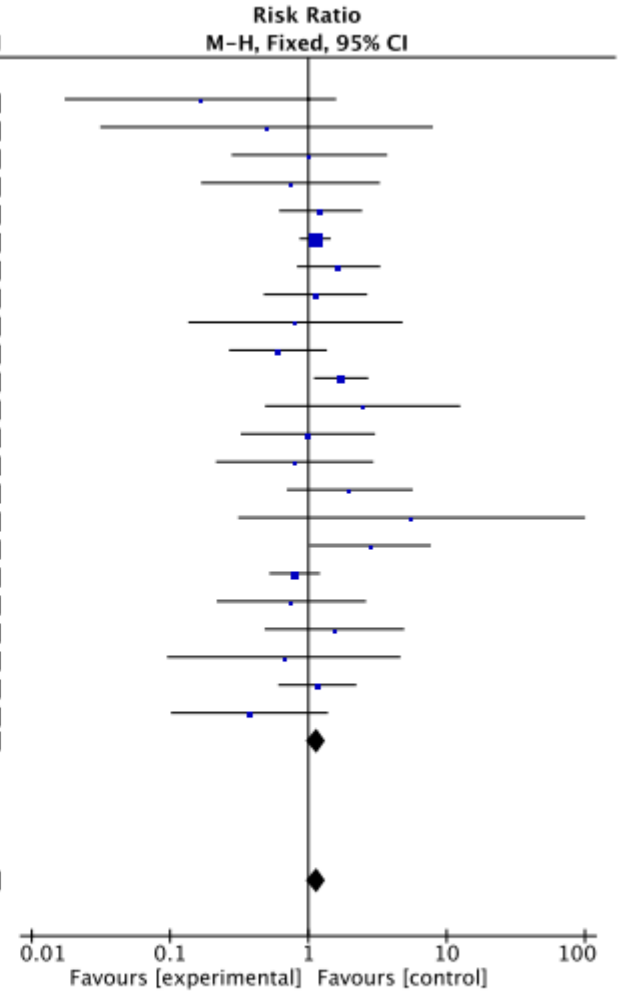


Fig. 3 Forest plot of semaglutide versus controlled drugs on risk of retinopathy. *CI* confidence interval, *M–H* Mantel–Haenszel, *df* degrees of freedom

Wang F. et al., Clin Drug Invest. 2022 Jan;42(1):17-28. doi: 10.1007/s40261-021-01110-w.

Subgroup analysis of effects of semaglutide on risk of retinopathy in patients with T2DM

Subgroup analyses	No. of trials	Semaglutide No. of events/patients	Control No. of events/patients	RR (95% CI)	I^2 (%)	*p* value
Subgroup by form of semaglutide						
Subcutaneous semaglutide	13	171/7274	99/5281	1.16 (0.91–1.50)	20	0.23
Oral semaglutide	10	292/5710	168/3831	1.13 (0.93–1.36)	0	0.21
Subgroup by type of control						
Placebo	10	260/6125	173/4974	1.24 (1.03–1.50)	0	0.03
Other antidiabetic drugs	14	205/7003	96/4235	0.98 (0.77–1.26)	0	0.90
Subgroup by mode of therapy						
Monotherapy	3	17/876	9/378	0.83 (0.37–1.88)	6	0.66
Add-on therapy	20	446/12,108	258/8734	1.15 (0.99–1.35)	16	0.07
Subgroup by race						
White	17	364/10,892	238/8150	1.13 (0.96–1.32)	24	0.15
Asian	6	99/2092	29/962	1.24 (0.81–1.89)	0	0.31
Subgroup by mean age, years						
< 60	20	295/9582	135/5710	1.04 (0.85–1.28)	0	0.70
≥ 60	3	168/3402	132/3402	1.27 (1.02–1.59)	40	0.03
Subgroup by BMI						
< 30	5	96/1802	25/675	1.30 (0.84–2.01)	0	0.25
≥ 30	18	367/11182	242/8437	1.12 (0.95–1.32)	6	0.16
Subgroup by diabetes duration, years						
< 10	18	252/8772	121/5393	1.03 (0.83–1.28)	0	0.80
≥ 10	5	211/4212	143/3719	1.28 (1.04–1.58)	9	0.02
Subgroup by HbA1c, %						
< 8.3	19	311/9284	206/6798	1.13 (0.94–1.36)	0	0.24
≥ 8.3	4	152/3700	61/2314	1.24 (0.91–1.69)	59	0.17
Subgroup by dosage						
0.5 mg qw subcutaneous	7	42/1834	26/1712	1.37 (0.85–2.20)	0	0.20
1 mg qw subcutaneous	11	61/3069	65/2947	0.83 (0.59–1.18)	0	0.31
3 mg qd oral	5	50/1005	45/991	1.05 (0.70–1.56)	0	0.83
7 mg qd oral	5	57/1003	45/991	1.18 (0.80–1.74)	0	0.4
14 mg qd oral	9	180/3449	159/3580	1.14 (0.92–1.40)	27	0.22
Subgroup by trial duration, weeks						
< 52	11	184/5408	141/4239	1.12 (0.90–1.39)	0	0.32
≥ 52	12	279/7576	126/4873	1.17 (0.95–1.44)	31	0.15

Wang F. et al., Clin Drug Invest. 2022 Jan;42(1):17-28. doi: 10.1007/s40261-021-01110-w.

UTILIZZO GLP1-RA e FUNZIONALITA' RENALE

VFG fino a (mL/min*1.73 m²)	90	80	70	60	50	40	30	20	15	dialisi
GLP1-RA										
Dulaglutide										
Exenatide										
Exenatide LAR										
Liraglutide										
Lixisenatide										
Semaglutide s.c.										
Semaglutide orale										

Potenziali rischi dei farmaci per il trattamento del diabete mellito tipo 2

	Acarbosio	DPP4i	GLP1-RA	Insulina umana/analoghi dell' insulina	Metformina	Pioglitazone	SGLT2i	SU/repaglinide
Interazione con altri farmaci	-	-	-	-	-	+	-	++
Ipoglicemie	-	-	-	++	-	-	-	+++
Aumento di peso	-	-	-	++	-	++	-	+
Disturbi gastrointestinali	+++	-	++	-	++	-	-	-
Pancreatiti acute	-	+	+/-	-	-	-	-	-
Fratture ossee	-	-	-	-	-	+++	+/-[a]	-
Deplezione di volume/disidratazione	-	-	+/-	-	-	-	+	-
Ritenzione idrica/edemi	-	-	-	-	-	++	-	-
Scompenso cardiaco	-	+/-[b]	-	-	-	++	-	+
Infezioni genito-urinarie	-	-	-	-	-	-	+	-
Chetoacidosi	-	-	-	-	-	-	+	-
Retinopatia diabetica	-	-	+/-[c]	-	-	+	-	-
Amputazioni arti inferiori	-	-	-	-	-	-	+/-[a]	-
Fascite necrotizzante del perineo	-	-	-	-	-	-	+	-

Rivista del Farmaco

SGLT2 Inhibitor–associated Diabetic Ketoacidosis: Clinical Review and Recommendations for Prevention and Diagnosis

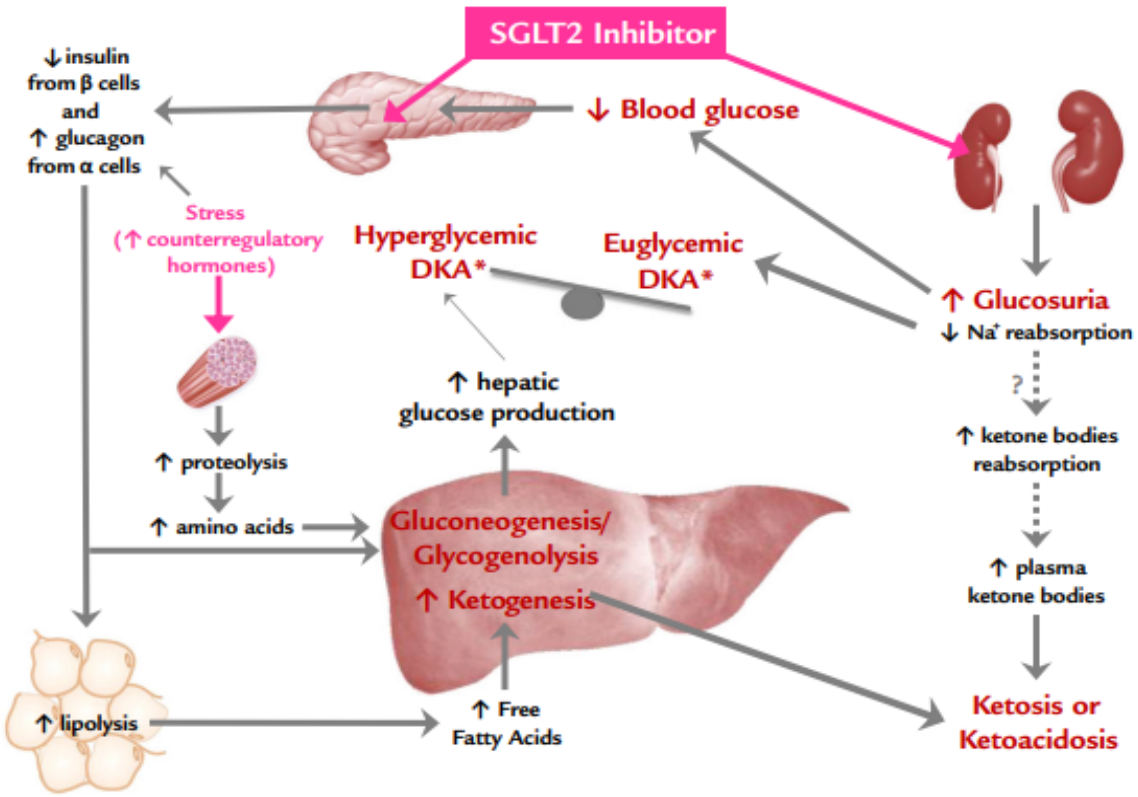


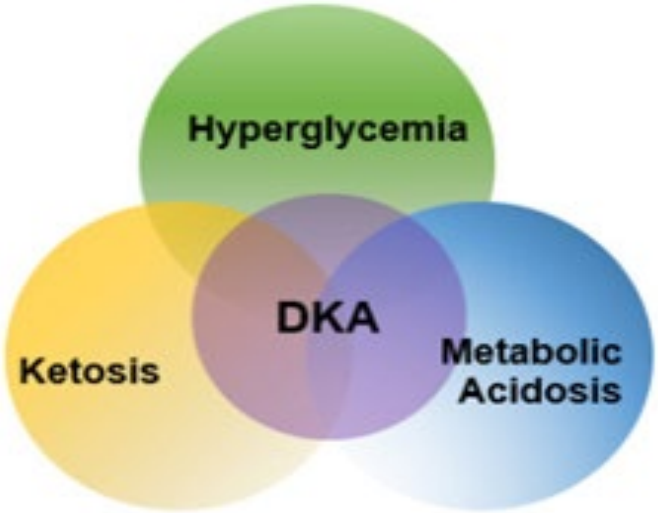
Figure 1. Mechanism of sodium-glucose cotransporter 2 (SGLT2) inhibitor–associated diabetic ketoacidosis. *The balance between hepatic glucose production and glucosuria determines euglycemic or hyperglycemic diabetic ketoacidosis (DKA). Adapted from Singh.[7]

Ronald M Goldenberg et al., Clin Ther. 2016 Dec;38(12):2654-2664.e1.

Chetoacidosi

- Meccanismo non completamente noto

- Rischio maggiore nei soggetti con deficit insulinico



Prima di iniziare il trattamento con SGLT2i, considerare tutti i possibili fattori precipitanti:

- bassa riserva di beta-cellule (ad es. pazienti con DMT2 e C-peptide basso)
- LADA
- pazienti con una storia di pancreatite
- condizioni che portano ad una limitata assunzione di cibo o grave disidratazione
- repentina riduzione di insulina
- incremento del fabbisogno insulinico a causa di malattia acuta
- intervento chirurgico
- abuso di alcol

Ronald M Goldenberg et al., Clin Ther. 2016 Dec;38(12):2654-2664.e1

Effect of Dapagliflozin on Genital Infections

Incidence, n/N (%)	Placebo	DAPA 10 mg
Studies in patients with T2D		
Phase 2b/3 glycemic control 13-study pool[1,a] (N=4655)	14/2295 (0.6)	130/2360 (5.5)
DECLARE-TIMI 58[2,b] (N=17,143)	9/8569 (0.1)	76/8574 (0.9)
Studies in patients with and without T2D		
DAPA-HF[3] (N=4736)		
Serious AE	1/2368 (0.0)	0/2368
Leading to treatment discontinuation	0/2368	7/2368 (0.3)
DAPA-CKD[4] (N=4298)		
Serious AE	0/2149	3/2149 (0.14)
Leading to treatment discontinuation	0/2149	3/2149 (0.14)

[a]Includes the overall incidence of genital infections in the 13-study pool; [b]Includes reports of genital infections which led to study treatment discontinuation or were considered SAEs.
AE= adverse event; DAPA = dapagliflozin; SAE = serious adverse events; T2D = type 2 diabetes.

1. Jabbour S et al. *Diabetes Obes Metab*. 2018;20:620-628. 2. Wiviott SD et al. *N Engl J Med.* 2019; 380:347-357. 3. Inzucchi SE. Presented at: European Association for the Study of Diabetes Congress. September 16-20, 2019; Barcelona, Spain. 4. Wheeler DC et al. [supplementary appendix]. *Lancet Diabetes Endocrinol.* 2021;9:22–31.

Sodium–Glucose Cotransporter 2 Inhibitor Use Associated With Fournier's Gangrene: A Review of Case Reports and Spontaneous Post-Marketing Cases

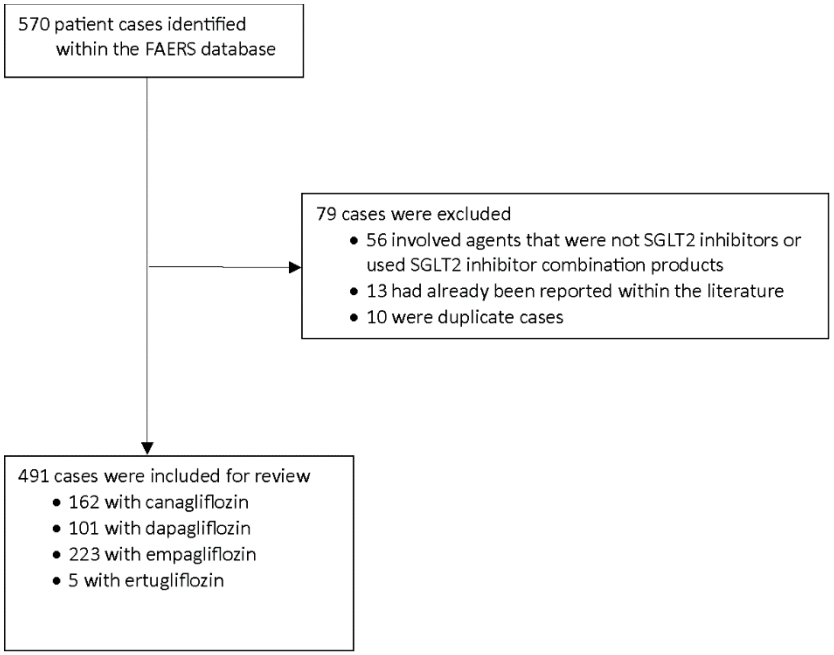


Figure Legend: Cases from FAERS database meeting inclusion criteria for review

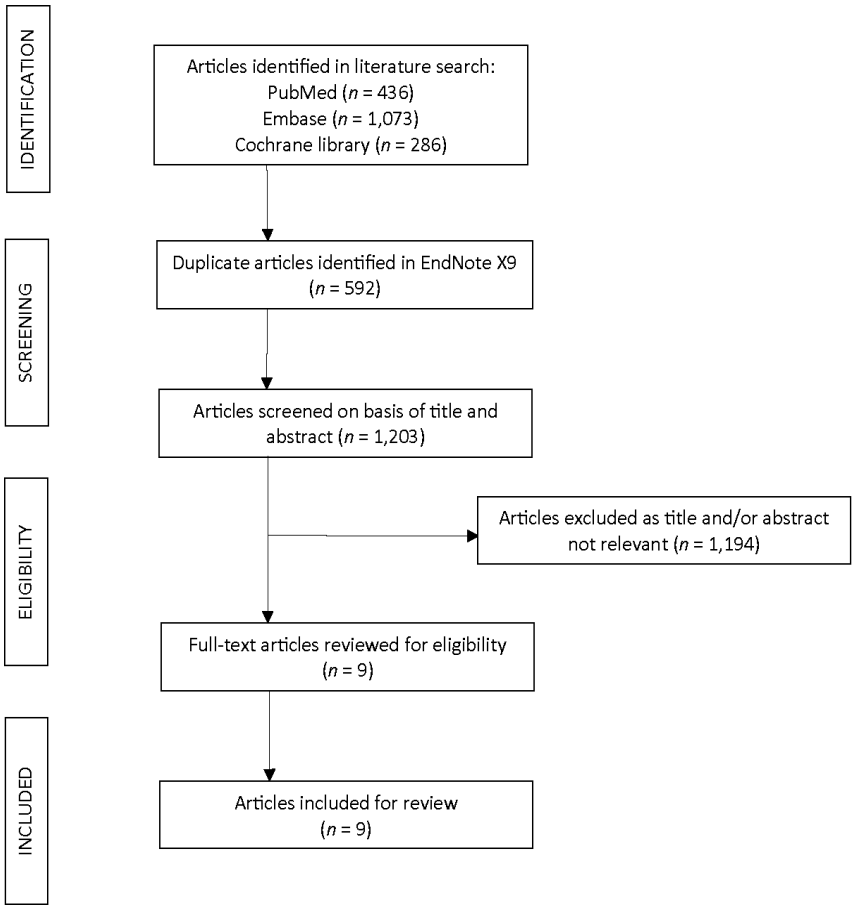


Figure Legend: Case reports from literature search meeting inclusion criteria for review

American Diabetes Association®

Clin Diabetes. 2022;40(1):78-86. doi:10.2337/cd21-0015

CANVAS PROGRAM

RESULTS:
adverse reactions were consistent with the previously reported risks associated with canagliflozin except for an increased risk of amputation (6.3 vs. 3.4 participants per 1000 patient-years; hazard ratio, 1.97; 95% CI, 1.41 to 2.75); amputations were primarily at the level of the toe or metatarsal.

Event	Canagliflozin	Placebo	P Value†
	event rate per 1000 patient-yr		
All serious adverse events	104.3	120.0	0.04
Adverse events leading to discontinuation	35.5	32.8	0.07
Serious and nonserious adverse events of interest recorded in the CANVAS Program			
Acute pancreatitis (adjudicated)	0.5	0.4	0.63
Cancer			
Renal cell	0.6	0.2	0.17
Bladder	1.0	1.1	0.74
Breast	3.1	2.6	0.65
Photosensitivity	1.0	0.3	0.07
Diabetic ketoacidosis (adjudicated)	0.6	0.3	0.14
Amputation	6.3	3.4	<0.001
Fracture (adjudicated)‡			
All	15.4	11.9	0.02
Low-trauma	11.6	9.2	0.06
Venous thromboembolic events	1.7	1.7	0.63
Infection of male genitalia§	34.9	10.8	<0.001
Serious and nonserious adverse events of interest collected in CANVAS alone¶			
Osmotic diuresis	34.5	13.3	<0.001
Volume depletion	26.0	18.5	0.009
Hypoglycemia	50.0	46.4	0.20
Acute kidney injury	3.0	4.1	0.33
Hyperkalemia	6.9	4.4	0.10
Urinary tract infection	40.0	37.0	0.38
Mycotic genital infection in women	68.8	17.5	<0.001
Severe hypersensitivity or cutaneous reaction	8.5	6.1	0.17
Hepatic injury	7.4	9.1	0.35
Renal-related (including acute kidney injury)	19.7	17.4	0.32

CREDENCE TRIAL

RISULTATI:
no significant differences in rates of amputation or fracture

Table 2. Efficacy and Safety.*

Variable	Canagliflozin	Placebo	Canagliflozin	Placebo	Hazard Ratio (95% CI)	P Value
	no./total no.		events/1000 patient-yr			
Efficacy						
Primary composite outcome	245/2202	340/2199	43.2	61.2	0.70 (0.59–0.82)	0.00001
Doubling of serum creatinine level	118/2202	188/2199	20.7	33.8	0.60 (0.48–0.76)	<0.001
End-stage kidney disease	116/2202	165/2199	20.4	29.4	0.68 (0.54–0.86)	0.002
Estimated GFR<15 ml/min/1.73 m^2	78/2202	125/2199	13.6	22.2	0.60 (0.45–0.80)	NA
Dialysis initiated or kidney transplantation	76/2202	100/2199	13.3	17.7	0.74 (0.55–1.00)	NA
Renal death	2/2202	5/2199	0.3	0.9	NA	NA
Cardiovascular death	110/2202	140/2199	19.0	24.4	0.78 (0.61–1.00)	0.05
Secondary outcomes						
Cardiovascular death or hospitalization for heart failure	179/2202	253/2199	31.5	45.4	0.69 (0.57–0.83)	<0.001
Cardiovascular death, myocardial infarction, or stroke	217/2202	269/2199	38.7	48.7	0.80 (0.67–0.95)	0.01
Hospitalization for heart failure	89/2202	141/2199	15.7	25.3	0.61 (0.47–0.80)	<0.001
End-stage kidney disease, doubling of serum creatinine level, or renal death	153/2202	224/2199	27.0	40.4	0.66 (0.53–0.81)	<0.001
Death from any cause	168/2202	201/2199	29.0	35.0	0.83 (0.68–1.02)	NA
Cardiovascular death, myocardial infarction, stroke, or hospitalization for heart failure or unstable angina	273/2202	361/2199	49.4	66.9	0.74 (0.63–0.86)	NA
End-stage kidney disease, renal death, or cardiovascular death†	214/2202	287/2199	37.6	51.2	0.73 (0.61–0.87)	NA
Dialysis, kidney transplantation, or renal death†	78/2202	105/2199	13.6	18.6	0.72 (0.54–0.97)	NA
Safety‡						NA
Any adverse event	1784/2200	1860/2197	351.4	379.3	0.87 (0.82–0.93)	NA
Any serious adverse event	737/2200	806/2197	145.2	164.4	0.87 (0.79–0.97)	NA
Serious adverse event related to trial drug	62/2200	42/2197	12.2	8.6	1.45 (0.98–2.14)	NA
Amputation	70/2200	63/2197	12.3	11.2	1.11 (0.79–1.56)	NA
Fracture	67/2200	68/2197	11.8	12.1	0.98 (0.70–1.37)	NA
Cancer						
Renal-cell carcinoma	1/2200	5/2197	0.2	0.9	NA	NA
Breast cancer§	8/761	3/731	4.1	1.6	2.59 (0.69–9.76)	NA
Bladder cancer	10/2200	9/2197	1.7	1.6	1.10 (0.45–2.72)	NA
Acute pancreatitis	5/2200	2/2197	1.0	0.4	NA	NA
Hyperkalemia¶	151/2200	181/2197	29.7	36.9	0.80 (0.65–1.00)	NA
Acute kidney injury	86/2200	98/2197	16.9	20.0	0.85 (0.64–1.13)	NA
Diabetic ketoacidosis‖	11/2200	1/2197	2.2	0.2	10.80 (1.39–83.65)	NA

V. Perkovic et al., N Engl J Med 2019;380:2295-306.

Cardiovascular and renal outcomes with canagliflozin in patients with peripheral arterial disease: Data from the CANVAS Program and CREDENCE trial

CONCLUSIONS:
Patients with T2D and PAD
derived similar relative cardiorenal benefits
from canagliflozin treatment but
higher absolute benefits compared with those without PAD,
with no increase in extended MALE

Barraclough JY, Yu J, et al. Diabetes Obes Metab. 2022;24:1072–1083. DOI: 10.1111/dom.14671

CANVAS PROGRAM

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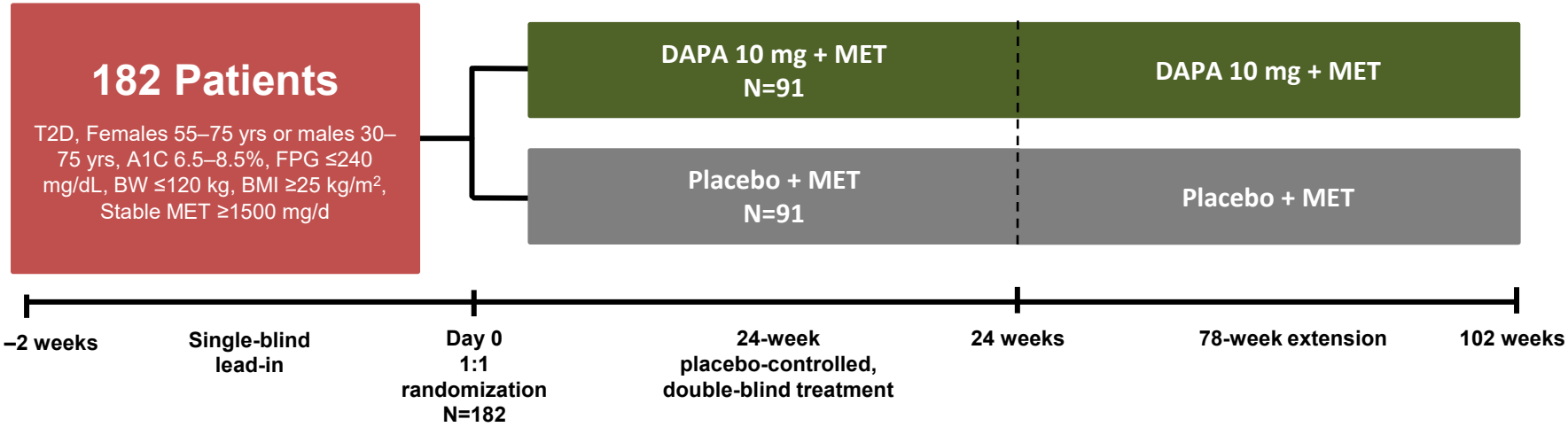
Effect on Body Composition and Bone Safety, DXA Study

Phase 3 Study over 102 Weeks



Primary End Point[1]
- Change in total BW from BL to week 24

Safety End Points[2]
- Bone mineral density
- Markers of bone formation
- Adverse events of bone fracture

- Primary outcome: Adjusted mean change in total body weight was greater with the DAPA group
  - Week 24: DAPA 10 mg plus MET (-2.96 kg) vs PBO plus MET (-0.88 kg)[1]
  - Week 102: DAPA 10 mg plus MET (-4.54 kg) vs PBO plus MET (-2.12 kg)[2]

BW = body weight; DAPA = dapagliflozin; DXA = dual-energy X-ray absorptiometry; MET = metformin; PBO = placebo; T2D = type 2 diabetes.

1. Bolinder J, et al. *J Clin Endocrinol Metab.* 2012;97:1020–1031. 2. Bolinder J et al. *Diabetes Obes Metab*. 2014;16:159-169.

Bone Mineral Density and Markers of Bone Formation and Resorption at Week 102, DXA Study

	Mean Change from Baseline		Difference Dapa vs. PBO (95% CI)	p-value
	DAPA 10 mg n = 91	PBO n = 91		
Bone Mineral Density[a], g/cm²				
Lumbar Spine (L1-4)	0.69	0.47	0.22 (-0.89, 1.34)	0.7013
Femoral Neck	-0.85	0.09	-0.94 (-2.21, 0.35)	0.1521
Total Hip	-0.82	-0.37	-0.45 (-1.32, 0.43)	0.3105
Bone Biomarkers				
P1NP (bone formation), µg/L	1.66	0.50	1.16 (-2.16, 4.48)	0.4906
CTX (bone resorption), ng/mL	0.02	0.02	0.01 (-0.02, 0.04)	0.6918

Note: There were no meaningful gender differences between treatment groups

[a]DAPA 10 mg N=68, PBO N=71

CTX = C-terminal cross-linking telopeptides of type I collagen; DAPA = dapagliflozin; DXA= dual-energy X-ray absorptiometry; P1NP = procollagen type 1 N-terminal propeptide; PBO = placebo.

Ptaszynska A, et al. Presented at: ADA 2014; June 13-17, 2014; San Francisco, CA.

Sodium Glucose Co-Transporter 2 (SGLT2) inhibitors and Fracture Risk in Patients with Type 2 Diabetes Mellitus: A Meta-Analysis

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Bailey et al. 2010	1	409	0	137	2.1%	1.01 [0.04, 24.64]
Roden et al. 2013	1	447	0	229	2.1%	1.54 [0.06, 37.66]
NCT01106690. 2013	1	227	0	115	2.1%	1.53 [0.06, 37.18]
Lavelle-Gonzalex et al. 2013	1	735	0	183	2.1%	0.75 [0.03, 18.34]
NCT01064414. 2013	0	179	2	90	2.4%	0.10 [0.00, 2.08]
NCT01042977. 2013	0	482	3	482	2.5%	0.14 [0.01, 2.76]
Kohan et al. 2013	13	168	0	84	2.8%	13.58 [0.82, 225.70]
Haring et al. 2013	2	431	0	206	2.4%	2.40 [0.12, 49.68]
NCT01106625. 2013	0	313	1	156	2.1%	0.17 [0.01, 4.07]
NCT01011868. 2014	1	324	1	170	2.8%	0.52 [0.03, 8.34]
Jabbour et al. 2014	0	225	1	226	2.1%	0.33 [0.01, 8.18]
NCT1106651. 2014	2	477	2	237	5.7%	0.50 [0.07, 3.51]
Rosenstock et al. 2014	0	375	1	188	2.1%	0.17 [0.01, 4.09]
Neal et al. 2014	26	1382	11	533	44.6%	0.91 [0.45, 1.83]
Wilding et al. 2014	3	610	1	197	4.3%	0.97 [0.10, 9.26]
Barnett et al. 2014	3	419	3	319	8.6%	0.76 [0.15, 3.75]
Stenlof et al. 2014	0	392	1	192	2.1%	0.16 [0.01, 4.00]
Inagaki et al. 2014	0	179	2	93	2.4%	0.10 [0.01, 2.15]
Rosenstock et al. (2) 2015	0	179	1	176	2.1%	0.33 [0.01, 7.99]
Kovac et al. 2015	0	333	3	165	2.5%	0.07 [0.00, 1.37]
Total (95% CI)		**8286**		**4178**	**100.0%**	**0.67 [0.42, 1.07]**
Total events	54		33			

Heterogeneity: Tau² = 0.00; Chi² = 15.55, df = 19 (P = 0.69); I² = 0%
Test for overall effect: Z = 1.70 (P = 0.09)

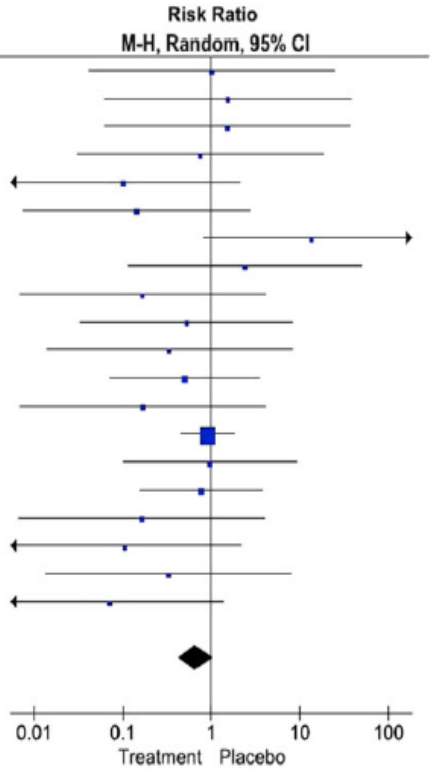


FIGURE 1 Forest plot of MH-OR (95% confidence interval [CI]) for all included studies for fracture risk in type 2 diabetes who treated with all Food and Drug Administration–approved sodium-glucose cotransporter 2 inhibitors and those with placebo; square data markers represent risk ratios; horizontal lines, the 95% CIs with marker size reflecting the statistical weight of the study using random-effect meta-analysis. A diamond data marker represents the overall risk ratio and 95% CI for the outcome of interest

Ruanpeng D et al., Diabetes Metab Res Rev. 2017 Apr 25. doi: 10.1002/dmrr.2903.

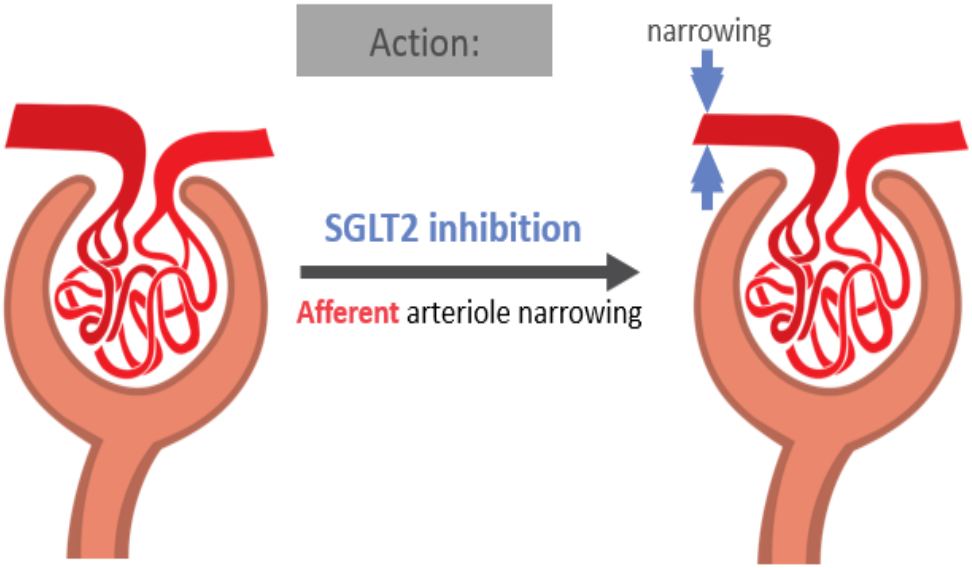
Sodium Glucose Co-Transporter 2 (SGLT2) inhibitors and Fracture Risk in Patients with Type 2 Diabetes Mellitus: A Meta-Analysis

Conclusions:
Increased risk of bone fracture among patients with type 2 diabetes mellitus treated with SGLT2 inhibitors compared with placebo was not observed in this meta-analysis.
However, the results were limited by short duration of treatment/follow-up and low incidence of the event of interest.

Ruanpeng D et al., Diabetes Metab Res Rev. 2017 Apr 25. doi: 10.1002/dmrr.2903.

SGLT2-I exert a hemodynamic effect within the kidney

- By restoring the Tubulo-Glomerular Feedback (TGF), empagliflozin increases the afferent arteriole tone, thereby lowering glomerular hypertension

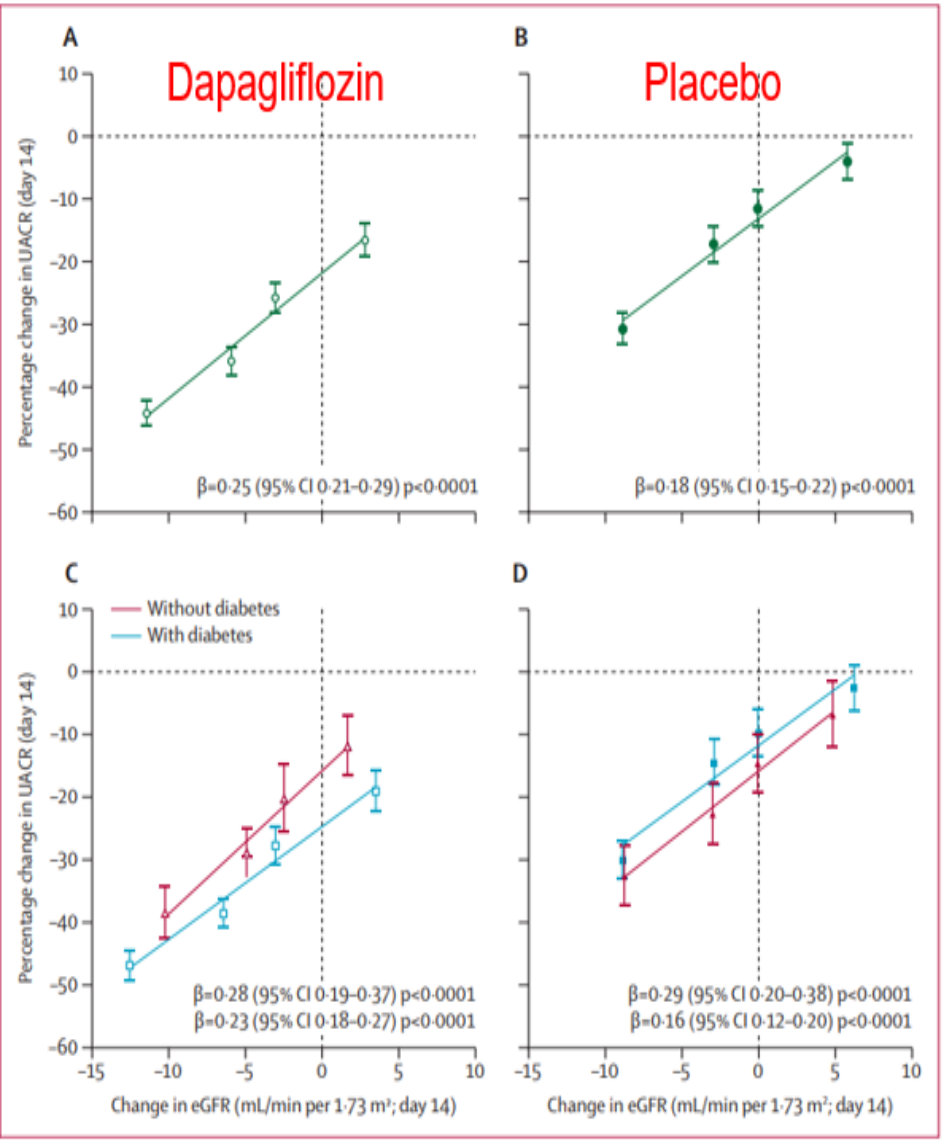


Clinical implications:

- Glomerular pressure decreases
- Early clinical marker:
  - Initial dip in GFR
  - Reduction of albuminuria

SGLT, sodium glucose cotransporter; GFR, glomerular filtration rate.
Adapted from: Cherney D *et al. Circulation* 2014;129:587
Skrtic M *et al. Diabetologia* 2014;57:2599

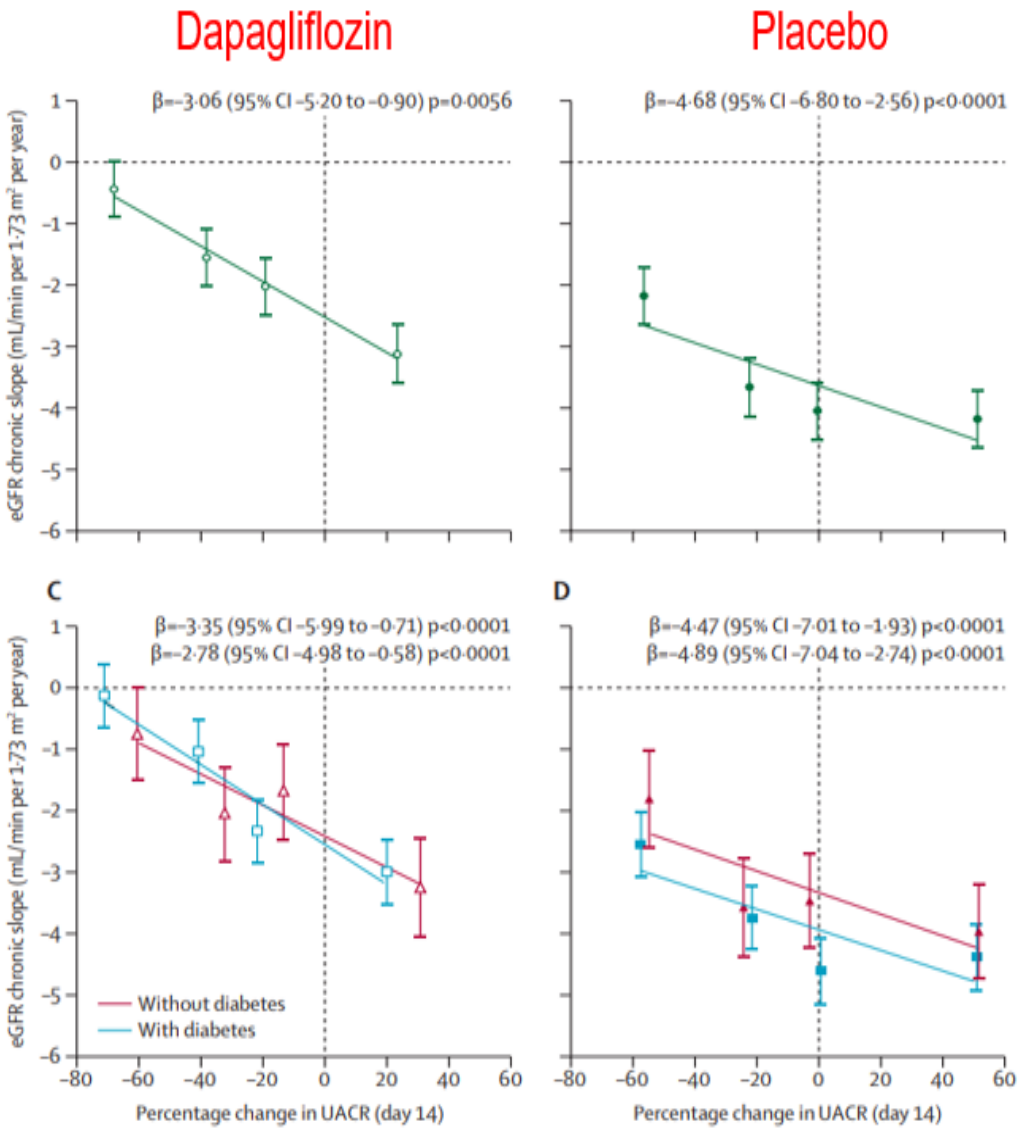
Association between changes in UACR and eGFR



Larger acute declines in eGFR 2 weeks after random assignment were significantly associated with a larger reduction in UACR at day 14

N Engl J Med. 2020 Oct 8;383(15):1436-1446

Associations between changes from baseline to day 14 in geometric mean UACR with eGFR slope from day 14 through to the end-of-treatment



Larger reductions in UACR at week 2 were associated with less steep declines in eGFR over time

N Engl J Med. 2020 Oct 8;383(15):1436-1446

SGLT2i e **funzionalità renale**

Tabella 1. Raccomandazioni relative all'aggiustamento della dose[a]

Indicazione	eGFR [ml/min/1,73 m²] o CrCl [ml/min]	Dose giornaliera totale
Diabete mellito di tipo 2	≥60	Iniziare con 10 mg di empagliflozin. Nei pazienti che tollerano 10 mg di empagliflozin e che necessitano di un controllo glicemico aggiuntivo, la dose può essere aumentata a 25 mg di empagliflozin.
	da 45 a <60	Iniziare con 10 mg di empagliflozin.[b] Continuare con 10 mg di empagliflozin nei pazienti che stanno già assumendo Jardiance.
	da 30 a <45[b]	Iniziare con 10 mg di empagliflozin. Continuare con 10 mg di empagliflozin nei pazienti che stanno già assumendo Jardiance.
	<30	Empagliflozin non è raccomandato.
Insufficienza cardiaca (con o senza diabete mellito di tipo 2)	≥20	La dose giornaliera raccomandata è di 10 mg di empagliflozin.
	<20	Empagliflozin non è raccomandato.

[a] Vedere paragrafi 4.4, 4.8, 5.1 e 5.2

[b] pazienti con diabete mellito di tipo 2 e malattia cardiovascolare accertata

EMPAGLIFLOZIN

Vi è esperienza con empagliflozin per il trattamento del diabete in pazienti con malattia renale cronica (eGFR ≥30 mL/min/1,73 m2) con o senza albuminuria.
I pazienti con albuminuria possono trarre maggiore beneficio dal trattamento con empagliflozin.

Per l'indicazione di diabete mellito di tipo 2, nei pazienti con eGFR inferiore a 60 ml/min/1,73 m2 o con CrCl.
Per l'indicazione di insufficienza cardiaca, Jardiance non è raccomandato nei pazienti con eGFR < 20 ml/min/1.73 m2

*Documento reso disponibile da AIFA il 29/03/2022

DAPAGLIFLOZIN

Compromissione renale
Non è richiesto alcun adeguamento della dose sulla base della funzionalità renale.

In pazienti con GFR < 25 mL/min, a causa dell'esperienza limitata, non è raccomandato iniziare il trattamento con dapagliflozin.

L'efficacia ipoglicemizzante di dapagliflozin dipende dalla funzione renale, ed è ridotta in pazienti con GFR < 45 mL/min ed è praticamente assente in pazienti con una compromissione renale severa (vedere paragrafi 4.2, 5.1 e 5.2).

In uno studio condotto in pazienti con diabete mellito di tipo 2 con compromissione renale moderata (GFR < 60 mL/min), una maggiore proporzione di pazienti trattati con dapagliflozin ha avuto reazioni avverse quali aumento di creatinina, fosforo, ormone paratiroideo (PTH) e ipotensione, rispetto al placebo.

*Documento reso disponibile da AIFA il 15/03/2022

SGLT2i e **funzionalità renale**

CANAGLIFLOZIN

Documento reso disponibile da AIFA il 15/12/2021

Tabella 1: Raccomandazioni relative all'aggiustamento della dose[a]

eGFR (mL/min/1,73 m^2) o CrCl (mL/min)	Dose totale giornaliera di canagliflozin
≥ 60	Iniziare con 100 mg. Nei pazienti che tollerano 100 mg e richiedono un controllo glicemico addizionale, la dose può essere aumentata a 300 mg.
Da 30 a < 60[b]	Usare 100 mg.
< 30[b, c]	Continuare con 100 mg nei pazienti che stavano già assumendo Invokana[d]. Invokana non deve essere iniziato.

[a] Vedere paragrafi 4.4, 4.8, 5.1 e 5.2.
[b] Se è necessario un controllo glicemico addizionale, si deve considerare l'aggiunta di altri agenti anti-iperglicemizzanti.
[c] Con rapporto albumina/creatinina nell'urinaalbuminuria > 300 mg/dieg
[d] Continuare la somministrazione fino alla dialisi o al trapianto renale.

ERTUGLIFLOZIN

L'inizio della terapia con questo medicinale non è raccomandato in pazienti con velocità di filtrazione glomerulare stimata (eGFR) inferiore a 45 mL/min/1,73 m^2 o clearance della creatinina (CrCl) inferiore a 45 mL/min (vedere paragrafo 4.4).

Nei pazienti con una eGFR da ≥ 45 a < 60 mL/min/1,73 m^2, la terapia con Steglatro deve essere iniziata con 5 mg con titolazione fino a 15 mg, se necessario per il controllo glicemico.

La terapia con Steglatro deve essere interrotta in caso di eGFR costantemente inferiore a 30 mL/min/1,73 m^2 o CrCl costantemente inferiore a 30 mL/min.

Steglatro non deve essere usato in pazienti con compromissione renale severa, con malattia renale allo stadio terminale (ESRD, *End Stage Renal Disease*) o dializzati, poiché non sono disponibili dati clinici a supporto dell'efficacia in questi pazienti.

*Documento reso disponibile da AIFA il 16/12/2022

Utilizzo di SGLT2i e GLP1-RA nell'anziano ….

Target glicemici nell'anziano

Linee guida ADA (American Diabetes Association)

1. Anziani "sani" ("Fit"): HbA1c < 7.5 % (eAG ≈ 160 – 170 mg/dl)
2. Anziani "complessi": HbA1c < 8 % (eAG ≈ 180 mg/dl)
3. Anziani "molto complessi": HbA1c < 8.5 % (eAG ≈ 195 – 200 mg/dl)

Linee guida AGS (American Geriatrics Society)

1. Anziani in generale: HbA1c 7.5 – 8 % (eAG ≈ 170 – 185 mg/dl)
2. Anziani con poche comorbilità e buon sato funzionale: HbA1c 7 – 7.5 % (eAG ≈ 155 - 170 mg/dl)
3. Anziani molto compromessi e con ridotta aspettativa di vita: HbA1c 8 – 9 % (eAG ≈ 185 – 210 mg/dl)

Evitare ipoglicemie

GLP1-RA:

- ef
- ag
  co

…

Variable	Median	Range values
Blood glucose level (mmol/l)	−27	146
HbA1c (%)	−0.80	4.60
BMI (Kg/m^2)	−0.78	4.11
Waist circumference (cm)	−2	114
Body weight (g)	−2000	11400
Total tissue (g)	−2328	10825
Fat mass (%) on total tissue	−0.70	11
Free fat mass (%) on total tissue	0.70	11
Fat mass (g)	−1498	8585
Free fat mass (g)	9	5072
Arm free fat mass (g)	13	2344
Leg free fat mass (g)	172	4103
SMI (kg/m^2)	0.03	2.14
Android fat (A) (%)	−0.90	15.70
Gynoid fat (G) (%)	−1.30	11.10
A/G ratio (units)	0	0.37
PASE score (point)	−11.60	44

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nia….

Table 3

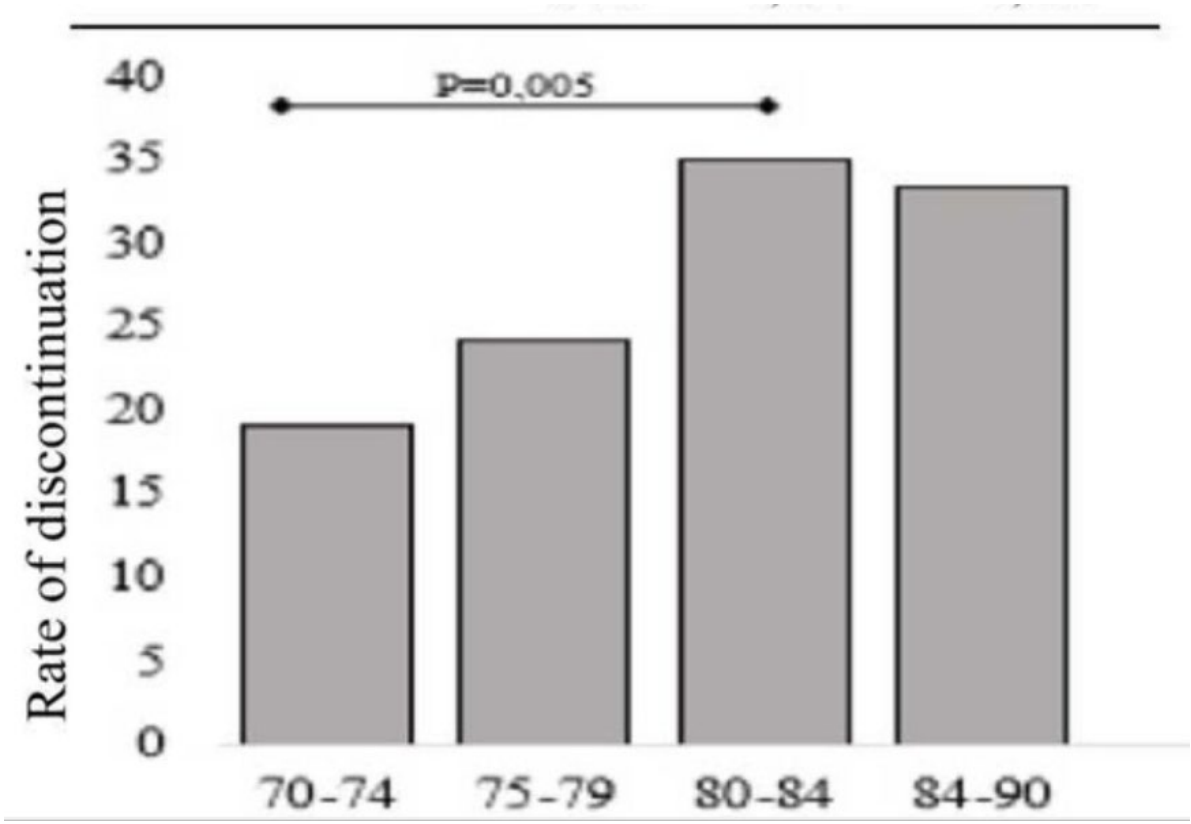
eks with liraglutide

Patient									Changes from baseline (g) ($t_1 - t_0$)
1								2	1048
2								8	−1193
3								3	−830
4								8	2119
5								7	−2953
6								9	−1789
7								9	9
8	65	F	6.42	7.66	1.24	38,166	39,282		1176
9	66	F	6.09	6.02	−0.07	35,166	36,300		1134

Aging Clin Exp Res. 2016 Dec;28(6):1251-1257. doi: 10.1007/s40520-015-0525-y

SGLT2-inhibitors are effective and safe in the elderly: The SOLD study

Discontinuation rate during the follow-up period was different across age groups, being urinary tract infections and worsening of renal function the most common cause.



Pharmacol Res. 2022 Sep;183:106396

Consigli……

- Benefici cardio-vascolari e renali
- Semplicità della somministrazione
- Valutare la funzionalità renale
- Considerare Possibili infezioni delle vie urinarie e dell’apparato genitale (in paziente fragile)
- Rischio di deplezione volemica (modulare la terapia diuretica, sospendere in caso di vomito, monitorare ematocrito)
- Evitare SGLT2-i durante la fase di scompenso glicemico acuto
- Eseguire una buona anamnesi (storia familiare, presenza di calcolosi delle colecisti)
- Attento monitoraggio clinico