Percorsi in diabetologia: dai target ai benefici per la persona con diabete

Percorsi terapeutici della U.O.C. Medicina Interna ad indirizzo Diabetologico DACP - AUSL Modena



Terapie ipoglicemizzanti innovative e personalizzazione della terapia ipoglicemizzante: SGLT2 inibitori, GLP1 RA, metformina e fenotipi clinici

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Dichiarazione dei conflitti d'interesse

Ai sensi dell'art. 3.3 sul conflitto di interessi, pag 17 del Regolamento Applicativo Stato-Regioni del 5/11/2009, dichiaro che negli ultimi 2 anni ho avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

- Advisory Board Membership and Consultancy: Boehringer Ingelheim, Eli-Lilly, Mundipharma Pharmaceutica, Novo Nordisk, Astra-Zeneca, Sanofi-Aventis, Roche Diabetes Care.
- Lectures: Astra Zeneca, Boehringer Ingelheim, Eli-Lilly, Novo Nordisk, Sanofi-Aventis, Mundipharma Pharmaceutica, Abbott, MSD, Neopharmed Gentili, Menarini, Essex Italia, Ascensia Diabetes.

STADIAZIONE del DIABETE

1.Durata (neodiagnosi?)

2.Modalità di <u>esordio</u> (diagnosi fatta in corso di OGTT in paziente asintomatico? Esordio con iperglicemia importante?)

- 3.Compenso glicemico (Hba1c)
- 4. Riserva pancreatica
- 5.<u>Complicanze</u> micro e macrovascolari associate

6.Tipo di <u>trattamento</u> <u>ipoglicemizzante</u> (Monoterapia o multiterapia? ipoglicemizzante orale o insulina?

STADIAZIONE CLINICA del PAZIENTE

1. Obesità associata (diabesità)?

2.Altre patologie associate?

-Ipertensione arteriosa

- -Dislipidemia
- -Cardiopatia ischemica
- -Malattie cerebrovascolari
- -Insufficienza renale
- -Neoplasie
- 3.Compliance
- 4. Aspettativa di vita
- 5. Terapia farmacologica (interazioni farmacologiche?

L'approccio internistico-metabolico deve integrare tutti i diversi aspetti del paziente e individuare un trattamento personalizzato cha abbia come obiettivo la cura della malattia diabetica nella sua complessità piuttosto che la glicemia





Personalized Management of Hyperglycemia in Type 2 Diabetes

Reflections from a Diabetes Care Editors' Expert Forum



Itamar Raz, md¹ Matthew C. Riddle, md² Julio Rosenstock, md³ John B. Buse, md, phd⁴ Silvio E. Inzucchi, md⁵ Philip D. Home, dm, dphil⁶ Stefano Del Prato, md⁷ ELE FERRANNINI, MD⁸ JULIANA C.N. CHAN, MD⁹ LAWRENCE A. LEITER, MD¹⁰ DEREK LEROITH, MD, PHD¹¹ RALPH DEFRONZO, MD¹² WILLIAM T. CEFALU, MD¹³



SISTEMA NAZIONALE LINEE GUIDA DELL'ISTITUTO SUPERIORE DI SANITÀ





Linea guida pubblicata nel Sistema Nazionale Linee Guida

Roma, 26 luglio 2021

1.1 Si raccomanda un target di HbA1c tra 49 mmol/mol (6.6%) e 58 mmol/mol (7.5%) in pazienti con diabete di tipo 2 trattati con farmaci associati ad ipoglicemia.

1.2.1. Si raccomanda un target di HbA1c inferiore 53 mmol/mol (7%) in pazienti con diabete di tipo 2 trattati con farmaci non associati ad ipoglicemia.

Forza della raccomandazione: forte. Qualità delle prove: bassa.

1.2.2. Si suggerisce un target di HbA1c inferiore o uguale a 48 mmol/mol (6.5%) in pazienti con diabete di tipo 2 trattati con farmaci non associati ad ipoglicemia.

Forza della raccomandazione: debole. Qualità delle prove: molto bassa.

Considerazioni su sottogruppi di pazienti

- Non sono disponibili dati di efficacia e sicurezza nei soggetti ultrasettantacinquenni con diabete.
- I benefici osservati con l'intensificazione del controllo glicemico si iniziano ad evidenziare dopo 2 anni di trattamento.
- Tali considerazioni porterebbero a raccomandare valori di HbA1c più elevati in soggetti di età avanzata e/o con aspettativa di vita limitata.

Individualized Glycemic Goals for Older Adults Are a Moving Target

Scott J. Pilla,^{1,2,3} Zhinous Shahidzadeh Yazdi,⁴ and Simeon I. Taylor⁴

Diabetes Care 2022;45:1029–1031 | https://doi.org/10.2337/dci22-0004

- So long as it can be achieved safely, a therapeutic target HbA1c <7.0% will provide the best protection from complications of diabetes.
- Patients with life expectancy of less than 3–5 years are unlikely to benefit from tight glycemic control, although prognosis may be difficult to determine. Deintensification of drugs with high risk of hypoglycemia (i.e., insulins and insulin secretagogues) should be strongly considered in patients with limited life expectancy.
- Insulins should be reserved for patients with late-stage T2D with insulin-dependent physiology due to advanced b-cell failure. When insulin is prescribed, it may be appropriate to relax HbA1c targets (e.g., HbA1c <8.0% rather than <7.0%).

	GLP-1 receptor agonist, n/N (%)	Placebo, n/N (%)		Hazard ratio (95% CI)	NNT (95% CI)	p value
Three-point MACE	-14%					
ELIXA	400/3034 (13%)	392/3034 (13%)	-	1.02 (0.89–1.17)		0.78
LEADER	608/4668 (13%)	694/4672 (15%)		0.87 (0.78-0.97)		0.01
SUSTAIN-6	108/1648 (7%)	146/1649 (9%)	_	0.74 (0.58-0.95)		0.016
EXSCEL	839/7356 (11%)	905/7396 (12%)	-	0.91 (0.83-1.00)		0.061
Harmony Outcomes	338/4731 (7%)	428/4732 (9%)		0.78 (0.68–0.90)		0.0006
REWIND	594/4949 (12%)	663/4952 (13%)		0.88 (0.79-0.99)		0.026
PIONEER 6	61/1591 (4%)	76/1592 (5%)		0.79 (0.57-1.11)		0.17
AMPLITUDE-0	189/2717 (7%)	125/1359 (9%)	_	0.73 (0.58-0.92)		0.0069
Subtotal (1²=44.5%, p=0	.082)			0.86 (0.80-0.93)	65 (45-130)	<0.0001
Cardiovascular death	-13%		Ŭ	(
ELIXA	156/3034 (5%)	158/3034 (5%)	_ _	0.98 (0.78–1.22)		0.85
LEADER	219/4668 (5%)	278/4672 (6%)		0.78 (0.66–0.93)		0.007
SUSTAIN-6	44/1648 (3%)	46/1649 (3%)		0.98 (0.65–1.48)		0.92
EXSCEL	340/7356 (5%)	383/7396 (5%)		0.88 (0.76-1.02)		0.096
Harmony Outcomes	122/4731 (3%)	130/4732 (3%)	_	0.93 (0.73-1.19)		0.58
REWIND	317/4949 (6%)	346/4952 (7%)	-	0.91 (0.78-1.06)		0.21
PIONEER 6	15/1591 (1%)	30/1592 (2%)	•	0.49 (0.27-0.92)		0.021
AMPLITUDE-0	75/2717 (3%)	50/1359 (4%)		0.72 (0.50-1.03)		0.07
Subtotal (<i>l</i> ²=13·4%, p=0	.33)		\bigcirc	0.87 (0.80-0.94)	163 (103-353)	0.0010
Fatal or non-fatal myoca	rdial infarction	0%	Ŭ			
ELIXA	270/3034 (9%)	261/3034 (9%)		1.03 (0.87–1.22)		0.71
LEADER	292/4668 (6%)	339/4672 (7%)		0.86 (0.73-1.00)		0.046
SUSTAIN-6	54/1648 (3%)	67/1649 (4%)		0.81 (0.57–1.16)		0.26
EXSCEL	483/7356 (7%)	493/7396 (7%)		0.97 (0.85–1.10)		0.62
Harmony Outcomes	181/4731 (4%)	240/4732 (5%)	_ —	0.75 (0.61-0.90)		0.003
REWIND	223/4949 (5%)	231/4952 (5%)		0.96 (0.79–1.15)		0.63
PIONEER 6	37/1591 (2%)	35/1592 (2%)		1.04 (0.66–1.66)		0.49
AMPLITUDE-0	91/2717 (3%)	58/1359 (4%)		0.75 (0.54–1.05)		0.09
Subtotal (<i>I</i> ²=26·9%, p=0	·21)			0.90 (0.83-0.98)	175 (103-878)	0.020
Fatal or non-fatal stroke	7 -27%					
ELIXA	67/3034 (2%)	60/3034 (2%)		1.12 (0.79–1.58)		0.54
LEADER	173/4668 (4%)	199/4672 (4%)		0.86 (0.71–1.06)		0.16
SUSTAIN-6	30/1648 (2%)	46/1649 (3%)		0.65 (0.41–1.03)		0.066
EXSCEL	187/7356 (3%)	218/7396 (3%)		0.85 (0.70-1.03)		0.095
Harmony Outcomes	94/4731 (2%)	108/4732 (2%)		0.86 (0.66–1.14)		0.30
REWIND	158/4949 (3%)	205/4952 (4%)		0.76 (0.62–0.94)		0.010
PIONEER 6	13/1591 (1%)	17/1592 (1%)		0.76 (0.37–1.56)		0.43
AMPLITUDE-0	47/2717 (2%)	31/1359 (2%)		0.74 (0.47–1.17)		0.19
Subtotal (<i>I</i> ² =0·0%, p=0·6	54)			0.83 (0.76-0.92)	198 (140-421)	0.0002
		Favours (I P-1 receptor agonists Eavours placebo			

Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials

Naveed Sattar*, Matthew M Y Lee*, Søren L Kristensen*, Kelley R H Branch, Stefano Del Prato, Nardev S Khurmi, Carolyn S P Lam, Renato D Lopes, John J V McMurray, Richard E Pratley, Julio Rosenstock, Hertzel C Gerstein

Lancet Diabetes Endocrinol 2021 9: 653-62



		GLP-1 receptor agonist, n/N (%)	Placebo, n/N (%)		Hazard ratio (95% CI)	NNT (95% CI)	p value					
All-causee ELIXA LEADER SUSTAIN EXSCEL Harmony REWIND PIONEER AMPLITU SUbtotal Hospital ELIXA	-6 Outcomes 6 DE-0 (l ² =10·1%, p=0·3 admission for he	-12% 211/3034 (7%) 381/4668 (8%) 62/1648 (4%) 507/7356 (7%) 196/4731 (4%) 536/4949 (11%) 23/1591 (1%) 111/2717 (4%) 35) eart failure 122/3034 (4%)	223/3034 (7%) 447/4672 (10%) 60/1649 (4%) 584/7396 (8%) 205/4732 (4%) 592/4952 (12%) 45/1592 (3%) 69/1359 (5%)		0.94 (0.78 to 1.13) 0.85 (0.74 to 0.97) 1.05 (0.74 to 1.50) 0.86 (0.77 to 0.97) 0.95 (0.79 to 1.16) 0.90 (0.80 to 1.01) 0.51 (0.31 to 0.84) 0.78 (0.58 to 1.06) 0.88 (0.82 to 0.94)	114 (76 to 228)	0.50 0.02 0.79 0.016* 0.64 0.067 0.008 0.11 0.0001 0.75	Cardio recept a syste Naveed Sattar John J V McMu Lance	ovascular, mortality, and cor agonists in patients ematic review and meta *, Matthew M Y Lee*, Søren L Kristensen*, Kelley R H Brr rray, Richard E Pratley, Julio Rosenstock, Hertzel C Gerst et Diabetes Endocrinol	d kidney outcomes w with type 2 diabetes a-analysis of random unch, Stefano Del Prato, Nardev S Khurmi, Caroly ein 2021 9: 653–62	vith GLP-1 : ised trials n S P Lam, Renato D Lope:	CrossMark
LEADER SUSTAIN	Compo	site kidney	outcome including mad	roalbun	0.87 (0.73 to 1.05)	21%	0.14	_			0.007	
Harmon	ELIXA		1/2/264/ (6%) 2	03/2639 (8%)				0.84 (0.68 to 1.02)		0.083	
REWIND	LEADER	R	268/4668 (6%) 3	3//46/2(/%)				0.78 (0.67 to 0.92)		0.003	
PIONEE	SUSTAI	N-6	62/1648 (4%) 1	00/1649 (6%)			•	0.64 (0.46 to 0.88)		0.005	
Subtota	EXSCEL		366/6256 (6%) 4	.07/6222 (7%)			•	0.88 (0.76 to 1.01)		0.065	
Compos	REWIND)	848/4949 (179	%) 9	70/4952 (20%)				0·85 (0·77 to 0·93)		0.0004	
ELIXA	AMPLIT	UDE-O	353/2717 (13%) 2	50/1359 (18%)			•	0.68 (0.57 to 0.79)		<0.0001	
LEADER	Subtota	al (1²=47·5%	5, p=0·090)					\bigcirc	0·79 (0·73 to 0·87)	47 (37 to 77)	<0.0001	
SUSTAIN	Worsen	ning of kidn	ey function -149	6								
REWIND	ELIXA		41/3031 (1%)	-	35/3032 (1%)			•	— 1·16 (0·74 to 1·83)		0.513	
AMPLIT	LEADER	R	87/4668 (2%)	97/4672 (2%)				0·89 (0·67 to 1·19)		0.43	
Subtota	SUSTAI	N-6	18/1648 (1%)	14/1649 (1%)				1.28 (0.64 to 2.58)		0.48	
Worsen	EXSCEL		246/6456 (4%) 2	73/6458 (4%)				0.88 (0.74 to 1.05)		0.16	
LEADER	RFWING)	169/4949 (3%) 2	37/4952 (5%)				0·70 (0·57 to 0·85)		0.0004	
SUSTAI	AMPLIT	- TUDF-0	7/2717 (<1%)	7/1359 (1%) –				0·35 (0·10 to 1·27)		0.11	
EXSCEL	Subtota	al (1²=43.0%	(, n=0.12)						0.86 (0.72 to 1.02)	241 (120 to –1694)†	0.089	
REWIND AMPLIT	500000	un (, – + 5 ° ,	o, p=0 12)									
Subtota						(0·5	1	1.5			
					Favo	urs GLP-1 re	ceptor aq	onists Favo	urs placebo			
L			Favours GLP-1 receptor ago	nists Favours	placebo		. 5		-			

Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials

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Lancet Diabetes Endocrinol 2021 9: 653-62

	GLP-1 receptor agonist, n/N (%)	Placebo, n/N (%)		Hazard ratio (95% CI)	p _{interaction}
MACE incidence rate in place	oo group*				
Higher	927/10482 (9%)	945/9125 (10%)	•	0.84 (0.68–1.04)	0.94
Intermediate	947/9004 (11%)	1051/9045 (12%)		0.85 (0.70–1.03)	
Lower	1263/11208 (11%)	1433/11216 (13%)		0.87 (0.81–0.94)	
Subtotal (l ² =0·0%, p=0·94)			$\langle \rangle$	0.86 (0.81–0.92)	
Established cardiovascular dis	sease				
Yes	2608/23673 (11%)	2877/22432 (13%)	•	0.85 (0.78–0.92)	0.18
No	492/6725 (7%)	521/6684 (8%)		0.94 (0.83–1.06)	
Subtotal (l ² =44·1%, p=0·181)		$\langle \rangle$	0.88 (0.80–0.97)	
Baseline HbA _{1c} †					
High	1777/16361 (11%)	1955/15237 (13%)	•	0.83 (0.77–0.90)	0.14
Low	1357/14270 (10%)	1477/14081 (10%)		0.90 (0.84–0.97)	
Subtotal (12=55·3%, p=0·14)	_		$\langle \rangle$	0.87 (0.80–0.94)	
Median duration of follow-up	p ‡			_	
<3 years	1096/13721 (8%)	1167/12366 (9%)		0.82 (0.71–0.95)	0.30
≥3 years	2041/16973 (12%)	2262/17020 (13%)		0.89 (0.84–0.94)	
Subtotal (l²=5·5%, p=0·30)			\diamond	0.88 (0.83–0.93)	
Drug dosing					
Daily	1069/9293 (12%)	1162/9298 (12%)		0.92 (0.80–1.05)	0.26
Weekly	2068/21401 (10%)	2267/20088 (11%)	•	0.84 (0.77–0.91)	
Subtotal (l²=19·9%, p=0·26)			<>	0.86 (0.80–0.94)	
Human GLP-1 homology					
Yes	1/09/1/58/(10%)	200//1/59/(11%)	•	0.84 (0.79-0.90)	0.39
No	1428/1310/ (11%)	1422/11/89(12%)		0.90 (0.78-1.04)	
Subtotal (1 ² =0.0%, p=0.392)				0.85 (0.80–0.90)	
BIMI, Kg/m ²	1711/17076 (1001)	1476/17606 (1701)			0.52
<30	1341/130/0(10%)	14/0/12000 (12%)		0.83(0.73-0.95)	0.53
≥30 Subtatel //2 0.00/ 0.52	1/01/1/500 (10%)	1944/10008 (12%)		0.87 (0.81 - 0.92)	
Subtotal (1°=0.0%, p=0.53)			<>	0.86 (0.81–0.91)	
Age, years	1000/10 476 (00/)	1402/14621 (100/)			0.79
<05	1335/154/0(9%)	1403/14021 (10%)		0.86 (0.90 0.00)	U•∕ŏ
≥05 Subtatel (1 ² 0.0% n.0.70)	1000/15/218 (12%)	2033/14/05(14%)		0.86 (0.80 - 0.92)	
SUBTOTAL ($I^{-}=0.0\%$, $p=0.78$)	72 m²		$\langle \rangle$	0.90-0.91)	
-60	850/6204 (14%)	000/5856 (16%)		0 88 (0 77 1 01)	0.52
<00 <60	1686/10 507 (00/)	18EV/18E21 (10%)		0.00(0.77-1.01)	0.22
 ∠UU Subtotal (12-0.0% p=0.519) 	1000/13207 (3%)	1024/10231 (10%)		0.03 (0.74-0.93)	
500101ar (1 = 0.0%, p = 0.518)		_		0.02 (0.70-0.93)	
		0.5	1	1.5	
		F	vours GLP-1 receptor agonists Favo	→ urs placebo	
				e e proveee e	

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Association of SGLT2 Inhibitors With Cardiovascular and Kidney Outcomes in Patients With Type 2 Diabetes A Meta-analysis

A Overall MACEs

	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
EMPA-REG OUTCOME	490/4687	37.4	282/2333	43.9	0.86 (0.74-0.99)
CANVAS program	NA/5795	26.9	NA/4347	31.5	0.86 (0.75-0.97)
DECLARE-TIMI 58	756/8582	22.6	803/8578	24.2	0.93 (0.84-1.03)
CREDENCE	217/2202	38.7	269/2199	48.7	0.80 (0.67-0.95)
VERTIS CV	735/5499	40.0	368/2747	40.3	0.99 (0.88-1.12)
Fixed-effects model (O :	= 5 22 · df = 4 · P = 3	$27 \cdot l^2 = 23.4\%$			0 90 (0 85-0 95)



A Overall CV death

	Treatment		Placebo				
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)	Favors Favors treatment placebo	Weight, %
EMPA-REG OUTCOME	172/4687	12.4	137/2333	20.2	0.62 (0.49-0.77)	⊢-●	15.61
CANVAS program	NA/5795	11.6	NA/4347	12.8	0.87 (0.72-1.06)	⊢●	21.32
DECLARE-TIMI 58	245/8582	7.0	249/8578	7.1	0.98 (0.82-1.17)	⊢ •−1	25.24
CREDENCE	110/2202	19.0	140/2199	24.4	0.78 (0.61-1.00)	⊢ ●	13.05
VERTIS CV	341/5499	17.6	184/2747	19.0	0.92 (0.77-1.10)		24.77
Fixed-effects model (Q=	= 11.22; df = 4; P =	.02; <i>I</i> ² =64.3%)			0.85 (0.78-0.93)	\diamond	
					().2 1	1 2

HR (95% CI)

B MACEs by ASCVD status

	Treatment		Placebo					
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)	Favors treatment	Favors placebo	Weight, %
Patients with ASCVD						-		
EMPA-REG OUTCOME	490/4687	37.4	282/2333	43.9	0.86 (0.74-0.99)		-	19.19
CANVAS program	NA/3756	34.1	NA/2900	41.3	0.82 (0.72-0.95)			21.16
DECLARE-TIMI 58	483/3474	36.8	537/3500	41.0	0.90 (0.79-1.02)		+	24.90
CREDENCE	155/1113	55.6	178/1107	65.0	0.85 (0.69-1.06)		-1	8.82
VERTIS CV	735/5499	40.0	368/2747	40.3	0.99 (0.88-1.12)	_	H	25.93
Fixed-effects model (Q	= 4.53; df = 4; P	=.34; / ² =11.8%)			0.89 (0.84-0.95)	♦		
Patients without ASCVD								
CANVAS program	NA/2039	15.8	NA/1447	15.5	0.98 (0.74-1.30)			21.70
DECLARE-TIMI 58	273/5108	13.4	266/5078	13.3	1.01 (0.86-1.20)		•	62.07
CREDENCE	62/1089	22.0	91/1092	32.7	0.68 (0.49-0.94)			16.23
Fixed-effects model (Q	= 4.59; df = 2; P	=.10; / ² =56.5%)			0.94 (0.83-1.07)	- (<		
						0.2	1	י 2
						HR (95% CI)		

B CV death by ASCVD status

	Treatment	Treatment		Placebo				
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)	Favors treatment	Favors placebo	Weight, %
Patients with ASCVD								
EMPA-REG OUTCOME	172/4687	12.4	137/2333	20.2	0.62 (0.49-0.77)	⊢-●		18.61
CANVAS program	NA/3756	14.8	NA/2900	16.8	0.86 (0.70-1.06)	⊢●-	Н	22.08
DECLARE-TIMI 58	153/3474	10.9	163/3500	11.6	0.94 (0.76-1.18)	⊢•	-	19.64
CREDENCE	75/1113	25.7	93/1107	32.4	0.79 (0.58-1.07)	⊢ ●	Н	10.14
VERTIS CV	341/5499	17.6	184/2747	19.0	0.92 (0.77-1.10)		Н	29.52
Fixed-effects model (Q	= 9.10; df = 4; P =	=.06; <i>I</i> ² = 56.1%)			0.83 (0.76-0.92)	\diamond		
Patients without ASCVD						\smile		
CANVAS program	NA/2039	6.5	NA/1447	6.2	0.93 (0.60-1.43)	⊢ —●		24.02
DECLARE-TIMI 58	92/5108	4.4	86/5078	4.1	1.06 (0.79-1.42)	⊢	•	52.70
CREDENCE	35/1089	12.2	47/1092	16.4	0.75 (0.48-1.16)		-	23.27
Fixed-effects model (Q	= 1.65; df = 2; P =	=.44; <i>I</i> ² =0.0%)			0.95 (0.77-1.17)		2	1
						0.2 1	L I	2

HR (95% CI)

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JAMA Cardiology | Original Investigation

Association of SGLT2 Inhibitors With Cardiovascular and Kidney Outcomes in Patients With Type 2 Diabetes A Meta-analysis

A Overall HHF

	Treatment		Placebo			
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)	
EMPA-REG OUTCOME	126/4687	9.4	95/2333	14.5	0.65 (0.50-0.85)	
CANVAS program	NA/5795	5.5	NA/4347	8.7	0.67 (0.52-0.87)	
DECLARE-TIMI 58	212/8582	6.2	286/8578	8.5	0.73 (0.61-0.88)	
CREDENCE	89/2202	15.7	141/2199	25.3	0.61 (0.47-0.80)	
VERTIS CV	139/5499	7.3	99/2747	10.5	0.70 (0.54-0.90)	
Fixed-effects model (Q=	1.39; df = 4; P = .8	85; 1 ² = 0.0%)			0.68 (0.61-0.76)	
						-
						0.2



Weight, %

19.62 17.13 29.66 12.74 20.84

16.38 55.07 28.56

2

A Overall kidney outcomes

	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
EMPA-REG OUTCOME	81/4645	6.3	71/2323	11.5	0.54 (0.40-0.75)
CANVAS program	NA/5795	5.5	NA/4347	9.0	0.60 (0.47-0.77)
DECLARE-TIMI 58	127/8582	3.7	238/8578	7.0	0.53 (0.43-0.66)
CREDENCE	153/2202	27.0	224/2199	40.4	0.66 (0.53-0.81)
VERTIS CV	175/5499	9.3	108/2747	11.5	0.81 (0.64-1.03)
Fixed-effects model (0 =	$7.96 \cdot df = 4 \cdot P = 0$	$(9: 1^2 = 49.7\%)$			0.62 (0.56-0.70)



B HHF by ASCVD status

	Treatment		Placebo				
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)	Favors treatment	Favors placebo
Patients with ASCVD							
EMPA-REG OUTCOME	126/4687	9.4	95/2333	14.5	0.65 (0.50-0.85)	⊢ ●−−	
CANVAS program	NA/3756	7.3	NA/2900	11.3	0.68 (0.51-0.90)	⊢_●	
DECLARE-TIMI 58	151/3474	11.1	192/3500	14.1	0.78 (0.63-0.97)		ł
CREDENCE	59/1113	20.6	92/1107	33.2	0.61 (0.44-0.85)	⊢ ●──	
VERTIS CV	139/5499	7.3	99/2747	10.5	0.70 (0.54-0.90)		
Fixed-effects model (Q	= 1.97; df = 4; P	=.74; <i>I</i> ² = 0.0%)			0.70 (0.62-0.78)		
Patients without ASCVD							
CANVAS program	NA/2039	2.6	NA/1447	4.2	0.64 (0.35-1.15)	•	-
DECLARE-TIMI 58	61/5108	3.0	94/5078	4.6	0.64 (0.46-0.88)		
CREDENCE	30/1089	10.6	49/1092	17.5	0.61 (0.39-0.96)		
Fixed-effects model (Q	=0.03; df = 2; P	=.99; <i>I</i> ² = 0.0%)			0.63 (0.50-0.80)		
						0.2	1

HR (95% CI)

B Kidney outcomes by ASCVD status

	Treatment	Treatment						
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)	Favors treatment	Favors placebo	Weight, %
Patients with ASCVD								
EMPA-REG OUTCOME	81/4645	6.3	71/2323	11.5	0.54 (0.40-0.75)			16.67
CANVAS program	NA/3756	6.4	NA/2900	10.5	0.59 (0.44-0.79)	⊢ ●−−		19.23
DECLARE-TIMI 58	65/3474	4.7	118/3500	8.6	0.55 (0.41-0.75)	⊢_●		18.06
CREDENCE	69/1113	24.1	102/1107	36.5	0.64 (0.47-0.87)			17.37
VERTIS CV	175/5499	9.3	108/2747	11.5	0.81 (0.64-1.03)		4	28.66
Fixed-effects model (Q	= 6.09; df = 4; P =	=.19; / ² = 34.4%)			0.64 (0.56-0.72)			
Patients without ASCVD								
CANVAS program	NA/2039	4.1	NA/1447	6.6	0.63 (0.39-1.02)	•	1	15.72
DECLARE-TIMI 58	62/5108	3.0	120/5078	5.9	0.51 (0.37-0.69)			37.41
CREDENCE	84/1089	29.9	122/1092	44.3	0.68 (0.51-0.89)			46.87
Fixed-effects model (Q	= 1.86; df = 2; P =	=.40; <i>I</i> ² =0.0%)			0.60 (0.50-0.73)			

0.2

HR (95% CI)

2

JAMA Cardiol. 2021;6(2):148-158.

0.2



SISTEMA NAZIONALE LINEE GUIDA DELL'ISTITUTO SUPERIORE DI SANITÀ

Linea Guida SID – AMD 2021 La terapia del diabete mellito di tipo 2

Pazienti con diabete di tipo 2 senza pregressi eventi cardiovascolari

Pazienti con diabete di tipo 2 con pregressi eventi cardiovascolari



Pazienti con diabete di tipo 2 con scompenso cardiaco



9. Pharmacologic Approaches to Glycemic Treatment: *Standards of Medical Care in Diabetes—2022 Diabetes Care 2022;45(Suppl. 1):5125-5143 | https://doi.org/10.2337/dc22-5009*

PHARMACOLOGIC TREATMENT OF HYPERGLYCEMIA IN ADULTS WITH TYPE 2 DIABETES

FIRST-LINE THERAPY depends on comorbidities, patient-centered treatment factors, including cost and access considerations, and management needs and generally includes metformin and comprehensive lifestyle modification[^]



ASCVD/INDICATORS OF HIGH RISK, HF, CKD†



Diabetes Care 2022;45(Suppl. 1):S125-S143 | https://doi.org/10.2337/dc22-S009



PHARMACOLOGIC TREATMENT OF HYPERGLYCEMIA IN ADULTS WITH TYPE 2 DIABETES

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Diabetes Care 2022;45(Suppl. 1):S125-S143 | https://doi.org/10.2337/dc22-S00

Terapia non insulinica nel DM tipo 2 Anziano



L'approccio clinico assistenziale al paziente anziano con diabete mellito tipo 2



10 maggio 201

BOX 4. Metformina e/o DPP4 inibitori sono i farmaci da considerare di prima linea (salvo

controindicazioni) nel trattamento del paziente diabetico anziano.

VANTAGGI DEI DPP4-Inibitori

- Sono tutti farmaci somministrabili per os
- Non provocano ipoglicemia
- Sono neutri sul peso corporeo
- Somministrati, con opportune riduzioni di dosaggio e senza effetti avversi, nell'IRC, e persino in pazienti emodializzati
- Sono farmaci che possono vantare il maggior numero di studi di intervento effettuati specificamente su pazienti diabetici di età ≥ 65 e perfino 75 anni
- Sicuri quando usati in pazienti ad elevato rischio CV

Efficacy and Safety of Dapagliflozin According to Frailty in Heart **Failure With Reduced Ejection Fraction**

A Post Hoc Analysis of the DAPA-HF Trial

Butt JH et Al. Ann Intern Med 175, 820-830 (2022).

Dapagliflozin substantially reduced the risk for worsening HF events, cardiovascular death, and all-cause death, and improved symptoms, physical function, and quality of life, regardless of frailty class.

The absolute reductions in clinical events and improvements in health status were generally larger in the most frail patients.

Figure 2. Mean change in individual physical and social activity items from baseline to 8 months with dapagliflozin versus placebo according to FI.



Across all time points empagliflozin reduced the risk of HF rehospitalization or death outcomes versus placebo



Frequency of HF re-hospitalization (second events), separate or combined with CV death or any death by time window following admission date of first HHF. A total of n=221 patients with index HHF were evaluated (126 receiving either dose of empagliflozin, and 95 receiving placebo). CV, cardiovascular; HF, heart failure; HHF, hospitalization for heart failure.

Predictors of response to glucagon-like peptide-1 receptor agonists: a meta-analysis and systematic review of randomized controlled trials



Effect of GLP-1 RA on HbA1c at 24 weeks

Monami M. et Al. Acta Diabetol 54, 1101-1114 (2017).

GLP-1 receptor agonists and SGLT2 inhibitors for older people with type 2 diabetes: A systematic review and meta-analysis



	Outcome (n events/N analysed)	Number of studies	P-interaction	Random Effects Model (Hazard Ratio)	Hazard ratio [95% CI]
MACE	Three-component MACE <65 years (1839/19584) >65 years (2855/20889)	6 6	0.73		0.89 [0.76; 1.03] 0.86 [0.80; 0.92]
Morte CV	Cardiovascular death <65 years (167/4200) >65 years (420/8437)	2 2	0.95		0.80 [0.42; 1.51] 0.81 [0.67; 0.99]
Stroke	Stroke <65 years (273/9437) >65 years (497/13101)	3 3	0.70		0.77 [0.61; 0.98] 0.82 [0.68; 0.98]
IMA	Myocardial infarction <65 years (207/4200) >65 years (502/8437)	2 2	0.75		0.81 [0.58; 1.13] 0.86 [0.72; 1.02]
HF	Heart failure hospitalisatio <65 years (152/4200) >65 years (427/8427)	n 2 2	0.25		1.14 [0.73; 1.77] 0.86 [0.71; 1.04]
			Fav	0.5 1 2 ors GLP-1 RAs Favors placebo)

Karagiannis T et Al. Diabetes Res Clin Pract 174, 108737 (2021)



Diabetes Ther 12, 1227-1247 (2021).

Individualized Glycemic Goals for Older Adults Are a Moving Target

Scott J. Pilla,^{1,2,3} Zhinous Shahidzadeh Yazdi,⁴ and Simeon I. Taylor⁴

Diabetes Care 2022;45:1029–1031 | https://doi.org/10.2337/dci22-0004

Some coexisting medical conditions (e.g., major adverse cardiovascular disease, congestive heart failure, or diabetic kidney disease) represent indications for using an SGLT2 inhibitor or a GLP-1 receptor agonist, regardless of HbA1c

NOTA 100

Nel paziente senza malattia renale cronica, senza malattia cardiovascolare e non ad alto rischio per malattia cardiovascolare, non sono attualmente disponibili evidenze sufficienti a raccomandare l'utilizzo di una specifica classe di farmaci rispetto alle altre oggetto della Nota. In tali pazienti la scelta terapeutica deve tenere conto di diversi fattori quali le caratteristiche individuali del soggetto, il profilo di tollerabilità del farmaco, l'entità di riduzione di HbA1c che si intende raggiungere o l'effetto sul peso corporeo.

REVIEW

Comparative Effectiveness of Glucose-Lowering Drugs for Type 2 Diabetes

A Systematic Review and Network Meta-analysis

Ann Intern Med. 2020;173:278-286

Change in Hemoglobin A1c Level in Patients Receiving Metformin-Based Background Therapy MD (95% Cl)

Subcutaneous semaglutide		–1.33 (–1.50 to –1.16)						
Oral semaglutide		–0.89 (–1.09 to –0.70)						
Premixed insulin		–0.89 (–1.08 to –0.71)						
Dulaglutide		–0.89 (–1.05 to –0.73)						
Basal–bolus insulin		–0.89 (–1.17 to –0.60)						
Extended-release exenatide	e	–0.80 (–0.99 to –0.62)						
Liraglutide	-	–0.80 (–0.89 to –0.70)						
Basal insulin	-	–0.71 (–0.82 to –0.60)						
Prandial insulin		–0.67 (–0.86 to –0.47)						
Meglitinides		–0.64 (–0.85 to –0.43)						
Canagliflozin		–0.63 (–0.78 to –0.47)						
Pioglitazone	-	–0.60 (–0.71 to –0.50)						
Exenatide		–0.60 (–0.73 to –0.47)						
Ertugliflozin		–0.58 (–0.79 to –0.36)						
Sulphonylureas	-	–0.57 (–0.66 to –0.48)						
Empagliflozin		–0.57 (–0.71 to –0.42)						
DPP-4 inhibitors	+	–0.53 (–0.58 to –0.47)						
Dapagliflozin	-	–0.51 (–0.63 to –0.40)						
a-Glucosidase inhibitors		–0.50 (–0.67 to –0.34)						
Lixisenatide		–0.43 (–0.57 to –0.29)						
	-1.5 -1 -0.5 0	0.5 1 1.5						
Four we have shown and a Four side side a								

Favors treatment Favors placebo

Annals of Internal Medicine

REVIEW

Annals of Internal Medicine

Comparative Effectiveness of Glucose-Lowering Drugs for Type 2 Diabetes

A Systematic Review and Network Meta-analysis

Ann Intern Med. 2020;173:278-286



Tsapas A et al., Comparative efficacy of glucose-lowering medications on body weight and blood pressure in patients with type 2 diabetes: A systematic review and network meta-analysis; Diabetes Obes Metab 2021; 1-9.

Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy

Dovepress

Open Access Full Text Article

ORIGINAL RESEARCH

open access to scientific and medical research

Gender difference in response predictors after I-year exenatide therapy twice daily in type 2 diabetic patients: a real world experience



Proportion of participants achieving different categories of weight loss at week 68 by sex



More semaglutide-treated females achieved weight loss of ≥5%, ≥10%, ≥15% and ≥20% than males Similar proportions of females and males receiving placebo achieved each weight loss category

Batterham RL et al. presented at the America College of Obstetrician and Gynecologist Annual Meeting- April 30-May 2, 2021

Relative change in body composition (%-points) from baseline to week 68 by sex (DEXA subgroup)

Changes relative to total body mass



*Visceral fat mass was calculated in the L4 region (males or females), android region (males only), or in the gynoid region (females only), depending on the methodology of the scanner available at participating study sites. Treatment policy estimand data. CI, confidence interval; DEXA, dual energy X-ray absorptiometry; ETD, estimated treatment difference

Batterham RL et al. presented at the America College of Obstetrician and Gynecologist Annual Meeting- April 30-May 2,2021

Gender difference in cardiovascular outcomes with SGLT-2 inhibitors and GLP-1 receptor agonist in type 2 diabetes: A systematic review and meta-analysis of cardio-vascular outcome trials

Awadhesh Kumar Singh^{*}, Ritu Singh

Diabetes & Metabolic Syndrome: Clinical Research & Reviews 14 (2020) 181–187





MACE outcome in Female on GLP-1RA: A Meta-analysis of CVOTs

Check for updates Gender difference in cardiovascular outcomes with SGLT-2 inhibitors and GLP-1 receptor agonist in type 2 diabetes: A systematic review and meta-analysis of cardio-vascular outcome trials

Awadhesh Kumar Singh^{*}, Ritu Singh

Diabetes & Metabolic Syndrome: Clinical Research & Reviews 14 (2020) 181-187

Check for updates

MACE outcome in Female on SGLT-2I: A Meta-analysis of CVOTs Study name Statistics for each study Hazard ratio and 95% CI Hazard Lower Upper Relative p-Value limit weight limit ratio 0.210 20.30 EMPA-REG 0.830 0.620 1.111 CANVAS 0.663 1.065 0.149 30.67 0.840 1.122 0.448 49.03 DECLARE TIMI 0.930 0.771 0.773 1.004 0.058 Random model 0.881 0.5 2 Heterogeneity: Tau² = 0.0; Q value = 0.64; df = 2 (P = 0.73); l² = 0.0%

Test for overall effect: Z = 1.90; P = 0.058

Favours SGLT-21 Favours PBO

MACE outcome in Male on SGLT-2I: A Meta-analysis of CVOTs

Study name	Statistics for each study			tudy	Hazard ratio and 95%	CI
	Hazard ratio	Lower limit	Upper limit	p-Value		Relative weight
EMPA-REG	0.870	0.741	1.021	0.089		25.01
CANVAS	0.860	0.740	1.000	0.050		28.41
DECLARE TIMI	0.930	0.827	1.046	0.226	-0-	46.59
Random model	0.895	0.826	0.969	0.006		
					0.5 1	2
Heterogeneity: Ta	$u^2 = 0.0; Q^2$	value = 0.8	80; df = 2 ($P = 0.67$; $I^2 = 0$.0%	
Test for overall eff	ect: Z = 2.7	2; P = 0.00	06		Favours SGLT-21 Favour	s PBO

Gender difference in cardiovascular outcomes with SGLT-2 inhibitors and GLP-1 receptor agonist in type 2 diabetes: A systematic review and meta-analysis of cardio-vascular outcome trials

Check for updates

Awadhesh Kumar Singh^{*}, Ritu Singh

Diabetes & Metabolic Syndrome: Clinical Research & Reviews 14 (2020) 181–187

Conclusions:

- GLP-1RAs confers a similar reduction in MACE, irrespective of the gender.
- Whether these results are related to inadequate statistical power (underrepresentation of women) in CVOT, or it reflects a true gender difference, still remains to be established.
- Whether this could be related to a relative larger weight loss due to the reduced fat mass with GLP- 1RAs compared to SGLT-2Is, remains to be established.

Sex Differences in Cardiovascular Effectiveness of Newer Glucose-Lowering Drugs Added to Metformin in Type 2 Diabetes Mellitus

Valeria Raparelli, MD, PhD; Malik Elharram, MD; Cristiano S. Moura, PhD; Michal Abrahamowicz, PhD; Sasha Bernatsky, MD, PhD; Hassan Behlouli, PhD; Louise Pilote MD, MPH, PhD J Am Heart Assoc. 2020;9:e012940



Sex Differences in Cardiovascular Effectiveness of Newer Glucose-Lowering Drugs Added to Metformin in Type 2 Diabetes Mellitus

Valeria Raparelli, MD, PhD; Malik Elharram, MD; Cristiano S. Moura, PhD; Michal Abrahamowicz, PhD; Sasha Bernatsky, MD, PhD; Hassan Behlouli, PhD; Louise Pilote MD, MPH, PhD J Am Heart Assoc. 2020;9:e012940

- Our findings are certainly **hypothesis-generating** and, at the moment, we can **only speculate on the reasons** underlying the greater effect of GLP-1RA in women.
- A study reported that the function of the receptor for glucagon-like peptide can be modified by sex hormones, while some authors proposed the hypothesis that GLP-1 receptor stimulation may have the potential to reduce platelet aggregation, resulting in the lower cardiovascular risk especially in women who have higher baseline platelet activation than men.

Comparing medication persistence among patients with type 2 diabetes using sodium-glucose cotransporter 2 inhibitors or glucagon-like peptide-1 receptor agonists in real-world setting



Federico Rea^{a,b,1}, Stefano Ciardullo^{c,d,1}, Laura Savaré^{a,b,*}, Gianluca Perseghin^{c,d,2}, Giovanni Corrao^{a,b,2}

Diab Res Clin Pract 180 (2021) 109035



NUOVO PARADIGMA NELLA CURA DEL DIABETE



ADA 2022 Standard of Medical Care: il treat to care e l'importanza di trattare subito

