Congresso congiunto
AMD - SID Piemonte - V. d'Aosta.

"Happy Birthday:"
Forever young

Innovazione farmacologica e tecnologica:
Il futuro della Diabetologia

Centro Congressi
The Place TORINO

11-12 ottobre 2024

I sessione: **PASSATO...**
"Il passato mi ha rivelato la struttura del futuro"
Pierre Teilhard de Chardin
Moderatori: Giuseppe Bargero, Paolo Cavallo Perin

14.20 - 14.40 **Insulina... dal passato al futuro**
Francesco Tassone

14.40 - 15.00 **Dalla glicosuria ai sensori...**
Agostino Consoli

15.00 - 15.20 **Dalla ipogligemia alla normoglicemia farmacologica**
Laura Gianotti

15.20 - 15.50 **Discussione sui temi trattati**

Dalla ipoglicemia alla normoglicemia farmacologica

Laura Gianotti
SC Endocrinologia e Diabetologia territoriale
Azienda Sanitaria Locale Cuneo 1

A.S.L. CN1
Azienda Sanitaria Locale
di Cuneo, Mondovì e Savigliano

Il trattamento e la gestione del diabete mellito rappresentano un "**impegno**" **che parte da molto lontano**...

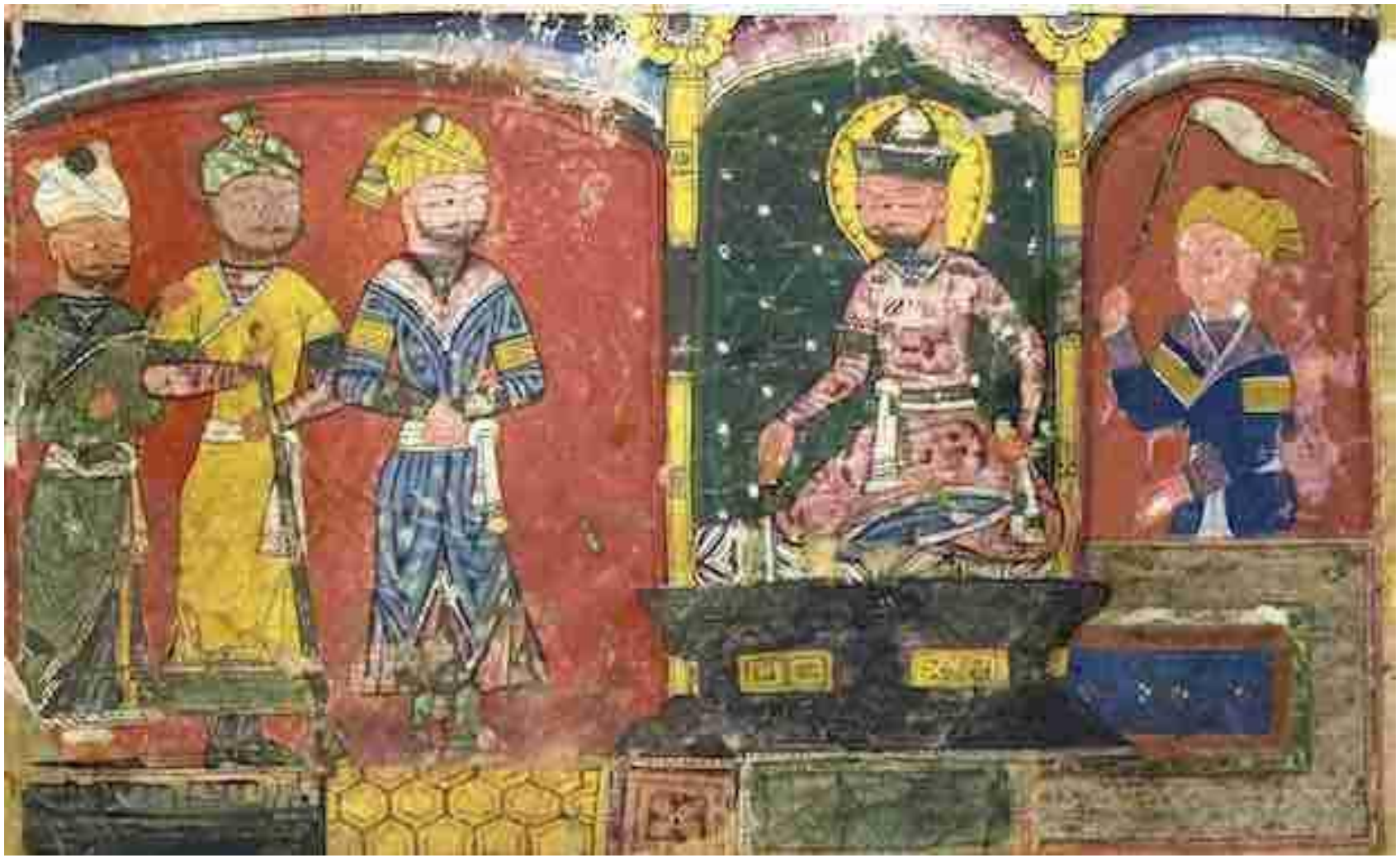
dalla modifica dello stile di vita alla ***scoperta dell'insulina***,

dal dosaggio della glicosuria al ***monitoraggio glicemico*** *capillare e al monitoraggio in continuo del glucosio interstiziale, ai* ***sensori***

dalle siringhe, alle penne e ai microinfusori.

dai farmaci ipoglicemizzanti a quelli normoglicemizzanti ..

serendipità s. f. [dall'ingl. *serendipity*, coniato (1754) dallo scrittore ingl. Horace Walpole che lo trasse dal titolo della fiaba *The three princes of Serendip*: era questo l'antico nome dell'isola di Ceylon, l'odierno Srī Lanka] – La capacità o fortuna di **fare per caso inattese e felici scoperte,** specialmente in campo scientifico, **mentre si sta cercando altro.**



Seconda Guerra mondiale

1942

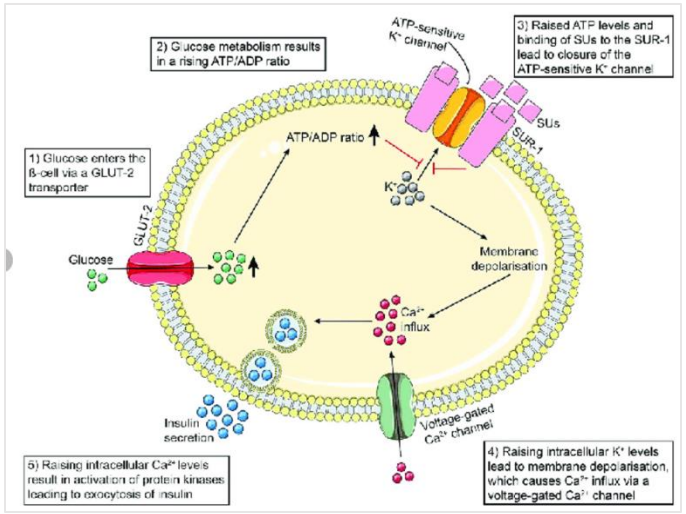
In 1942, a new sulfonamide compound (2254RP) was tested in the infectious diseases department of Pr M. Janbon on cases of typhoid fever, leading to several deaths rapidly related to hypoglycaemia.

The physiologist Auguste Loubatières (1912-1977) rapidly demonstrated that this **hypoglycaemic effect** required the presence of pancreas and was explained **by stimulation of insulin secretion**.
He contributed to the description of a hypoglycaemic effect of several other sulphonamide compounds.

This is a good example of **a medical discovery combining a favourable local environment, serendipity and perfect experimental approach**

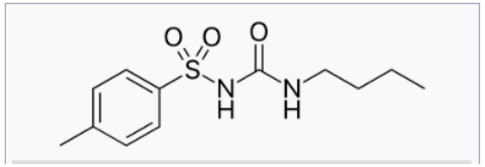
Le Professeur Marcel Janbon (1898-1996) entouré de son équipe, devant la Clinique Pasteur où se trouvait le service des maladies infectieuses au sein de **l'hôpital Saint-Eloi, Montpellier.** *Photographie datant de 1962*.

L'ERA DEI FARMACI IPOGLICEMIZZANTI

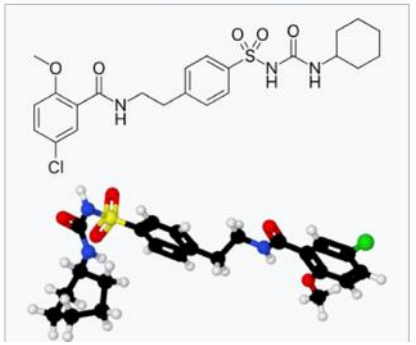


Rastinon
Diabemide

Tolbutamide

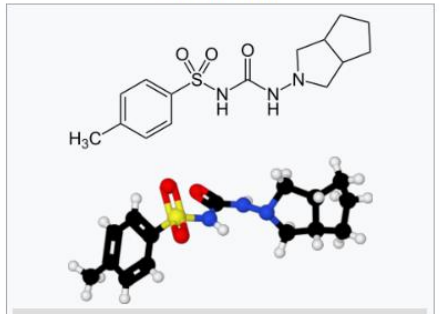


Glibenclamide

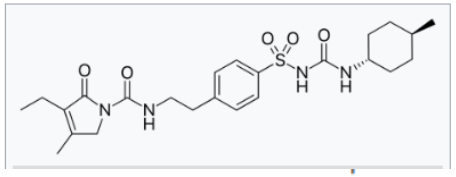


	Duration of action		
era-	Short	Intermediate	Long
First-generation sulfonylureas			
Tolbutamide			
Chlorpropamide			
Second-generation sulfonylureas			
Glipizide	+		
Gliquidone	+		
Glibenclamide (Glyburide)	+		+
Gliclazide		+	
Third-generation sulfonylureas			
Glimepiride		+	
Gliclazide-modified release (MR)		+	
Glipizide MR/extended release (XL)		+	+

Gliclazide



Glimepiride



Diabetes Ther (2024) 15:1687–1716
https://doi.org/10.1007/s13300-024-01612-8

1942

SULFONILUREE

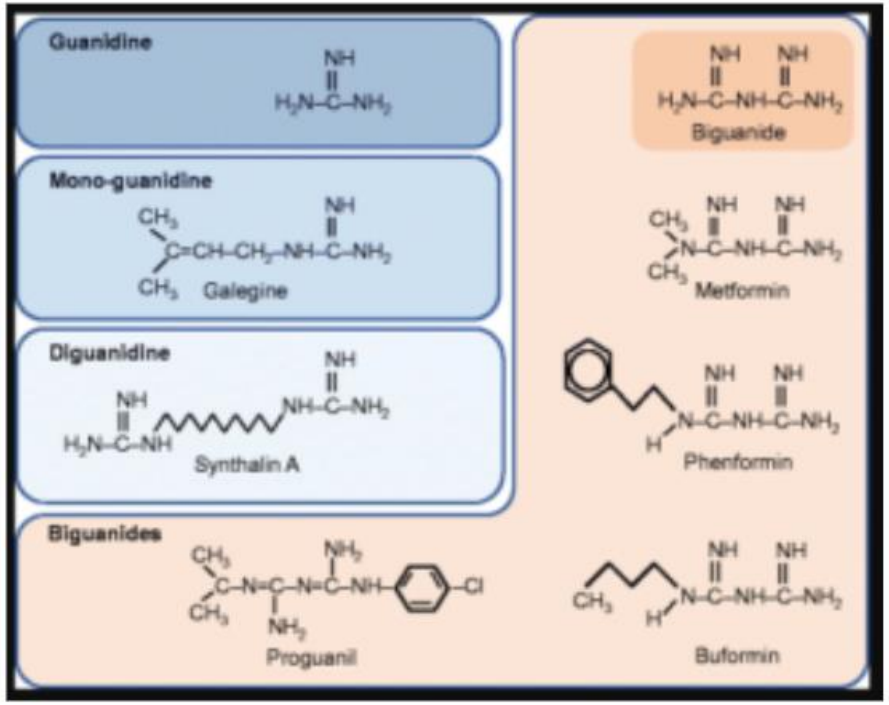
Scoperta casuale da parte del francese dr. Marcel Janbon che alcuni sulfamidici, usati per curare le infezioni, abbassavano la glicemia. E' la premessa allo sviluppo, a cura di August Loubatieres, e poi all'uso clinico delle sulfoniluree che entrano in commercio nel 1955 e che ancora oggi sono largamente utilizzate per la terapia orale del diabete tipo 2 (non-insulino-dipendente).

1961

METFORMINA

Immissione in commercio della metformina, il farmaco che ancora oggi è indicato dalle linee guida internazionali come il primo antidiabetico da impiegare per la terapia orale del diabete tipo 2 (non-insulino-dipendente).

La **galega** o ***Galega officinalis*** è una pianta appartenente alla famiglia delle *Fabaceae* nota per le sue proprietà particolarmente utili nel trattamento delle affezioni al fegato.



Struttura chimica della guanidina e relativi composti.

Negli anni cinquanta, il dott. **Jean Sterne**, un medico dell'*Ospedale Laennec* di Parigi, **selezionò per uso clinico la metformina**
Nel **1957** il dott. Sterne pubblicò il suo **primo studio sulla metformina, che chiamò '*Glucophage*' (mangiatore di zucchero)**.

Nel 1968 venne pubblicato in Gran Bretagna il primo grande studio comparativo prospettico sulla metformina. Successivamente, tra il **1977 ed il 1980** vennero **ritirati dal mercato** la f**enformina e la buformina a** causa dei rischi prodotti di **acidosi lattica**.

Nel **2011 la metformina è stata inclusa dall'Organizzazione Mondiale della Sanità nella lista dei 'farmaci essenziali'**.

The New England
Journal of Medicine

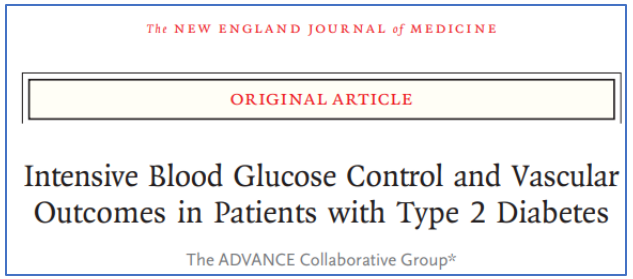
Volume 329 SEPTEMBER 30, 1993 Number 14

THE EFFECT OF INTENSIVE TREATMENT OF DIABETES ON THE DEVELOPMENT AND PROGRESSION OF LONG-TERM COMPLICATIONS IN INSULIN-DEPENDENT DIABETES MELLITUS

THE DIABETES CONTROL AND COMPLICATIONS TRIAL RESEARCH GROUP*

Conclusions. Intensive therapy effectively delays the onset and slows the progression of diabetic retinopathy, nephropathy, and neuropathy in patients with IDDM.

Intensive glucose control in DM2 and hypoglycemic risk


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

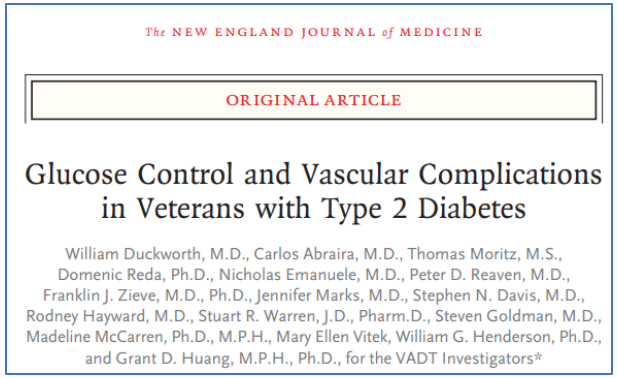
Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes

The ADVANCE Collaborative Group*

2008

A strategy of intensive glucose control, involving gliclazide (MR) and other drugs, that **lowered the glycated hemoglobin value to 6.5% yielded a 10% relative reduction in the combined outcome of major macrovascular and microvascular events**, primarily as a consequence of a 21% relative reduction in nephropathy

Severe hypoglycemia, although uncommon, was more common in the intensive-control group (2.7%, vs. 1.5% in the standard-control group;


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

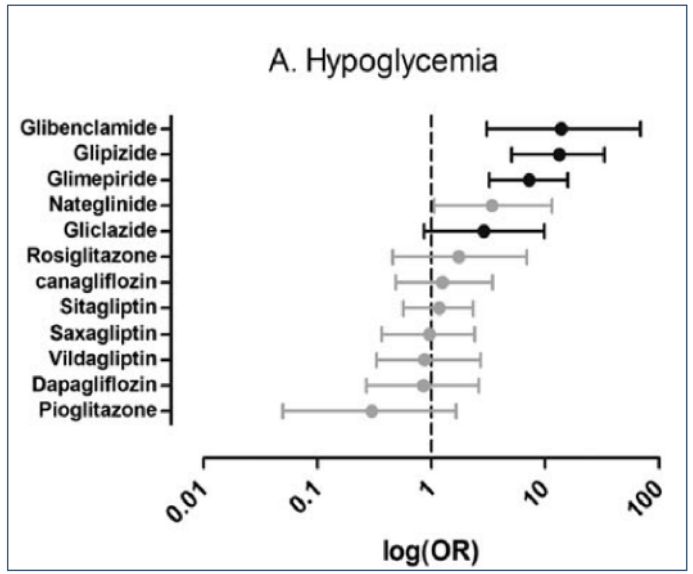
Glucose Control and Vascular Complications in Veterans with Type 2 Diabetes

William Duckworth, M.D., Carlos Abraira, M.D., Thomas Moritz, M.S., Domenic Reda, Ph.D., Nicholas Emanuele, M.D., Peter D. Reaven, M.D., Franklin J. Zieve, M.D., Ph.D., Jennifer Marks, M.D., Stephen N. Davis, M.D., Rodney Hayward, M.D., Stuart R. Warren, J.D., Pharm.D., Steven Goldman, M.D., Madeline McCarren, Ph.D., M.P.H., Mary Ellen Vitek, William G. Henderson, Ph.D., and Grant D. Huang, M.P.H., Ph.D., for the VADT Investigators*

2009

Intensive glucose control in patients with poorly controlled type 2 diabetes had no significant effect on the rates of major cardiovascular events, death, or microvascular complications, with the exception of progression of albuminuria (P=0.01).

The rates of adverse events, predominantly **hypoglycemia, were 17.6% in the standard-therapy group and 24.1% in the intensive-therapy group**



Network meta-analysis of RCTs lasting 12–52 weeks and evaluating SUs added to inadequate metformin monotherapy (≥1000 mg/day) in type 2 diabetes

Andersen SE et al. Br J Clin Pharmacol 2016

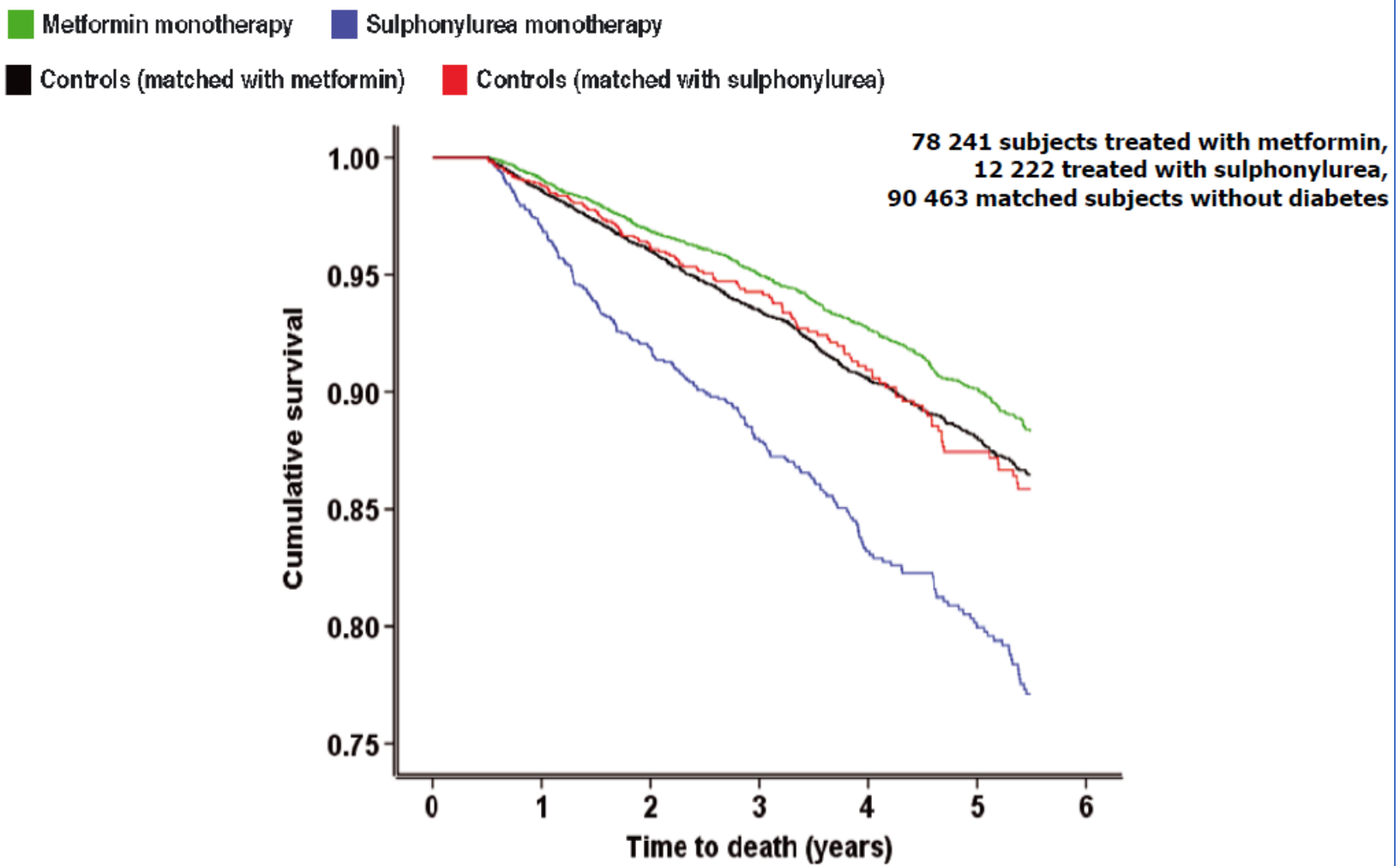
Frequency of hypoglycemic episodes by dementia status

	No. (%)		Age-adjusted incidence rates per 10,000 person-years (95% CI)	Excess attributable risk per year, % (95% CI)[a]
	Dementia (n=1822)	Nondementia (n=14,845)		
Any hypoglycemia				
No	1572 (10.34)	13,630 (89.66)	327.60 (311.02-343.18)	
Yes	250 (16.95)	1215 (83.05)[b]	566.82 (496.52-637.48)	2.39 (1.72-3.01)
No. of hypoglycemic episodes				
0	1572 (10.34)	13,630 (89.66)	327.60 (311.02-343.18)	
1	150 (14.84	852 (85.16)	491.73 (412.60-570.80)	1.64 (0.91-2.36)
2	57 (22.26)	201 (77.74)	761.75 (561.24-962.27)	4.34 (2.36-6.32)
3 or more	43 (20.40)	162 (79.60)[b]	755.46 (526.46-984.46)	4.28 (2.10-6.44)

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

Rachel A. Whitmer[1], Andrew J. Karter[1], Kristine Yaffe[2], Charles P. Quesenberry Jr.[1], and Joseph V. Selby[1]

Kaplan–Meier curves comparing metformin or sulphonylurea monotherapy with their matched non-diabetic control group in patients aged 71–75 years at baseline from the UK Clinical Practice Research Datalink (CPRD)



Bannister CA et al Diabetes Obes Metab16: 1165–1173, 2014

Diabetes Ther (2021) 12:2115–2132
https://doi.org/10.1007/s13300-021-01059-1

GUIDELINES

Sulfonylureas in the Current Practice of Type 2 Diabetes Management: Are They All the Same? Consensus from the Gulf Cooperation Council (GCC) Countries Advisory Board on Sulfonylureas

Non tutte le SULFONILUREEE sono uguali

Table 1 Cardiac and renal benefits of SU-based therapies, as observed in the ADVANCE trials

Study	T2D participants	Cardiac outcomes	Renal outcomes
ADVANCE Patel et al. [35]	*N* = 11,140 adults ≥ 55 years with known major macrovascular or microvascular disease or ≥ 1 other risk factor for vascular disease, allocated to either standard therapy (other SUs) or intensive therapy using gliclazide MR for 5 years (*N* = 5571 intensive control: 42.6% females, 32.2% history of major macrovascular disease, 27% history of microalbuminuria, 90.5% on gliclazide MR at end of follow-up; *N* = 5569 standard control: 42.3% females, 32.3% history of major macrovascular disease, 26.7% history of microalbuminuria, 1.6% on gliclazide MR at end of follow-up)	No difference between groups in the frequency of macrovascular events during intervention [HR 0.94, 95% CI 0.84–1.06; *p* = 0.32]	14% decrease in major microvascular events [HR 0.86, 95% CI 0.77–0.97; *p* = 0.01] and 21% relative reduction in worsening nephropathy [HR 0.79, 95% CI 0.66–0.93; *p* = 0.0006] with gliclazide MR
ADVANCE ON Zoungas et al. [37]	*N* = 8494 participants with post-trial follow-up of 5.9 years (*N* = 4283 intensive control: 43.6% females, 29.7% major macrovascular disease, 9% major microvascular disease; *N* = 4211 standard control: 42.3% females, 30.9% major macrovascular disease, 9.9% major microvascular disease)	No differences after follow-up in major macrovascular events [HR 1.0, 95% CI 0.92–1.08; *p* = 0.93]	Cumulative benefit regarding end-stage renal disease (ESRD)* [HR 0.54, 95% CI 0.34–0.85; *p* = 0.007]
erkovic et al. [38]	*N* = 11,140 (*N* = 5571 intensive control: 42.6% females, 27% history of microalbuminuria, no CKD 54.8%; *N* = 5569 standard control: 42.3% females, 26.7% history of microalbuminuria, no CKD 55%)		Risk of ESRD was 65% lower (HR 0.35, 95% CI 0.15–0.83; *p* = 0.02) with gliclazide MR Risk of albuminuria reduced by 9% (95% CI 2–15%; *p* = 0.01) with intensive treatment

Monogenic Diabetes

Hepatocyte nuclear factor 1alpha (HNF-1A) and *HNF4A* gene mutations are common causes of maturity-onset diabetes of the young (MODY) and patients with HNF-MODY diabetes show **greater response to SUs, particularly to gliclazide**

1942

SULFONILUREE

Scoperta casuale da parte del francese dr. Marcel Janbon che alcuni sulfamidici, usati per curare le infezioni, abbassavano la glicemia. E' la premessa allo sviluppo, a cura di August Loubatieres, e poi all'uso clinico delle sulfoniluree che entrano in commercio nel 1955 e che ancora oggi sono largamente utilizzate per la terapia orale del diabete tipo 2 (non-insulino-dipendente).

1961

METFORMINA

Immissione in commercio della metformina, il farmaco che ancora oggi è indicato dalle linee guida internazionali come il primo antidiabetico da impiegare per la terapia orale del diabete tipo 2 (non-insulino-dipendente).

1998

REPAGLINIDE

Immissione in commercio della repaglinide , una molecola di derivazione aminoacidica che legandosi ai recettori delle sulfoniluree stimola la secrezione insulinica soprattutto in corrispondenza del pasto.

Lo studio inglese UKPDS dimostra che nel diabete tipo 2 mantenere le glicemie più basse riduce il rischio di complicanze croniche

1999

GLITAZONICI

Immissione in commercio di due molecole (rosiglitazone e pioglitazone) appartenenti alla classe dei tiazoledinendioni, farmaci con attività insulino-sensibilizzante.

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

Rosiglitazone and Cardiovascular Risk

Bruce M. Psaty, M.D., Ph.D., and Curt D. Furberg, M.D., Ph.D.

In this issue of the *Journal*, Nissen and Wolski[1] report the results of a meta-analysis of treatment trials of rosiglitazone, as compared either with other therapies for type 2 diabetes or with placebo. Eligible studies included randomized trials that lasted for at least 24 weeks. The prespecified primary end points of interest were myocardial infarction and death from cardiovascular causes. The authors identified 42 eligible studies, many of which were small or short-term trials, that included a total of 158 myocardial infarctions and 61 deaths from cardiovascular causes. They used the Peto method to combine data from the trials. In this meta-analysis, rosiglitazone was associated with a significant increase in the risk of myocardial infarction (odds ratio, 1.43; 95% confidence interval [CI], 1.03 to 1.98; P=0.03) and a borderline-significant finding for death from cardiovascular causes (odds ratio, 1.64; 95% CI, 0.98 to 2.74; P=0.06).

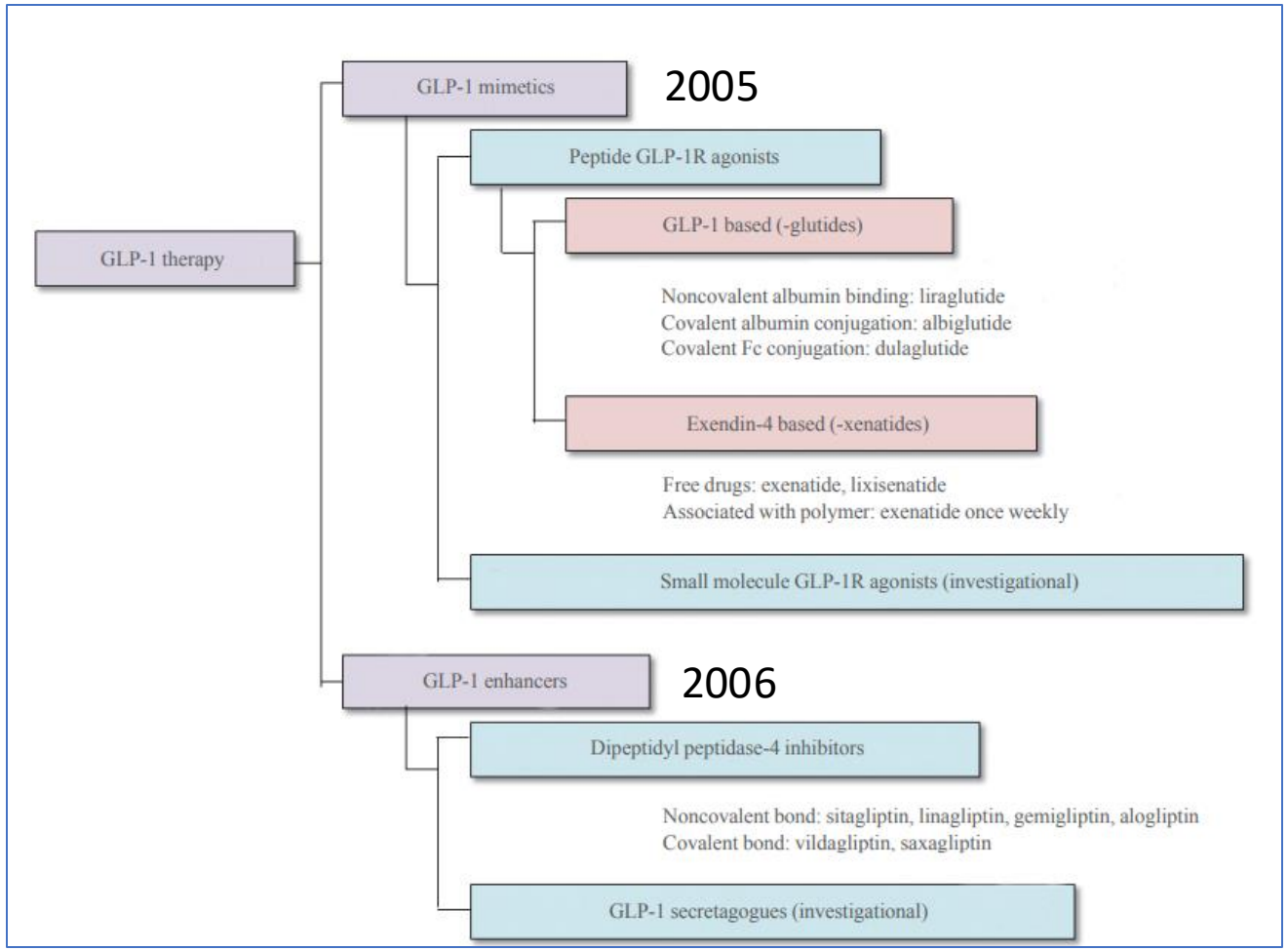
trials included both placebo and active-treatment control groups. Across the trials, there was no standard method for identifying or validating outcomes; events in eligible or ineligible trials may have been missed or misclassified. The total number of events was relatively small, with the result that there was little or no power to detect potential differences among the trials if they were present. Although, in general, these limitations are likely to move estimated odds ratios toward the null, the weaknesses, which are largely related to the quality of the available data, are nonetheless substantial. A few events either way might have changed the findings for myocardial infarction or for death from cardiovascular causes. In this setting, the possibility that the findings were due to chance cannot be excluded. In their discussion, the authors properly emphasize the fragility of their findings.

Rosiglitazone, a thiazolidinedione, is an ago-

2007

A partire dal 2009 FDA pretese che TUTTI i nuovi farmaci per DM2 venissero testati vs placebo per la safety cardiovascolare

OUTCOME: MACE (IMA non fatale, ICTUS non fatale, mortalità CV)



Generazione Z (1997-2012)

L'era delle glifozine

Generazione alpha

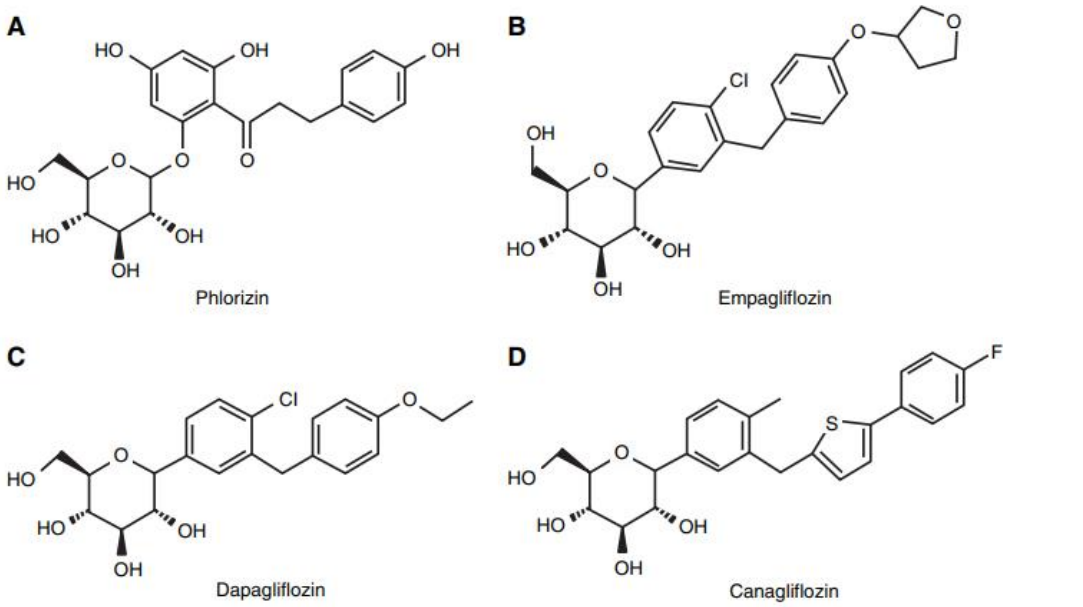


Figure 1. | **The chemical structure of phlorizin, empagliflozin (Jardiance), dapagliflozin (Forxiga), and canagliflozin (Invokana).** Note that phlorizin is an O-glucoside that can be hydrolyzed by the intestinal brush border lactase, whereas the aryl-glucosides are not. The selectivity of these sodium glucose cotransporter (SGLT) inhibitors is given in Table 1. Modified from Wright, 2013 (9).

Table 1
Characteristics of currently approved sodium-glucose cotransporter 2 inhibitors

Name of the Drug	Available Tablet Doses	Indications	Renal Function[b]	Approvals[a]
Canagliflozin	100 mg, 300 mg	T2DM	Initiation contraindicated if eGFR <30	EMA (2013), FDA (2013), Australia (2013)
Dapagliflozin	5 mg, 10 mg	T2DM, HF, CKD (FDA only)	Initiation contraindicated if eGFR <25	EMA (2012), FDA (2014)
Empagliflozin	10 mg, 25 mg	T2DM, HF	In T2DM: not recommended if eGFR <45 (EMA)/30 (FDA) In HF: not recommended if eGFR <20	EMA (2014), FDA (2014)
Ertugliflozin	5 mg, 15 mg	T2DM	EMA: initiation not recommended if eGFR <45 FDA: initiation not recommended if eGFR <30	EMA (2018), FDA (2019)
Sotagliflozin	200 mg	T1DM	EMA: initiation not recommended if eGFR <60	EMA 2019
Ipragliflozin	25 mg, 50 mg	T2DM	Not stated	Japan 2014, Republic of Korea and Thailand 2015, Russia 2019
Luseogliflozin	2.5 mg, 5 mg	T2DM	Not recommended if GFR <60	Japan 2014
Tofogliflozin	20 mg	T2DM	Not stated	Japan 2014
Remogliflozin	100 mg	T2DM, NAFLD	Not stated	India 2019

KIDNEY360 2: 2027–2037, 2021.

L'era delle incretine

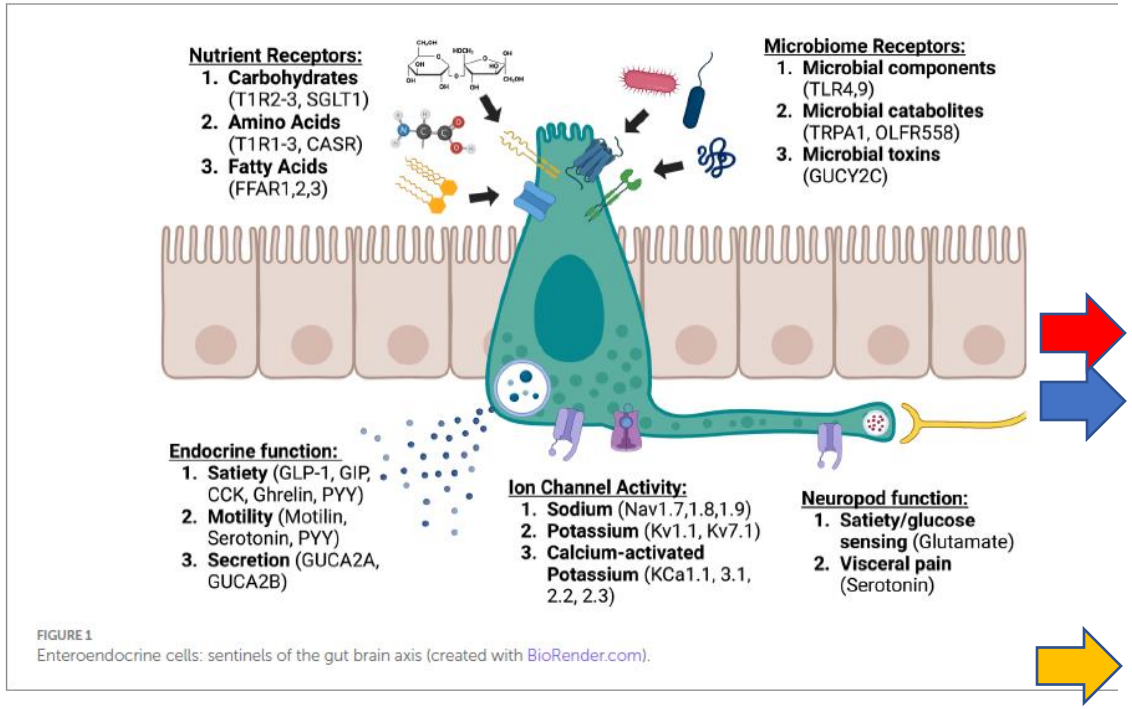


FIGURE 1
Enteroendocrine cells: sentinels of the gut brain axis (created with BioRender.com).

TABLE 1 Enteroendocrine nomenclature.

Cell name	Hormone	Hormone receptor	Receptor expression by circumventricular brain region
D cell	Somatostatin (SST)	SSTR1, SSTR2	Hypothalamus (Breder et al., 1992)
EC (enterochromaffin) cell	Serotonin (5-HT)	5-HT_{1-7}	Hypothalamus (Burnet et al., 1995), area postrema (Glaum et al., 1992)
I cell	Cholecystokinin (CCK)	CCK1 (Alimentary Tract), CCK2 (Brain)	Hypothalamus and area postrema (Moran et al., 1986)
K cell	Glucose-dependent Insulino-Peptide (GIP)	GIPR	Hypothalamus (ARC) (Adriaenssens et al., 2019)
L cell	Glucagon-Like Peptide 1 (GLP1)	GLP-1R	Hypothalamus, NTS, area postrema (Sisley et al., 2014)
	Peptide YY (PYY)	Y1R, Y2R (most selective), Y5R	Hypothalamus (Batterham and Bloom, 2003), area postrema (Deng et al., 2001)
M cell	Motilin	MLN-R	Hypothalamus (Depoortere et al., 1997)
N cell	Neurotensin (NTS)	NTSR1 (neurons), NTSR2 (glia), NTSR3 (intracellular)	Hypothalamus (Tanaka et al., 1990)
S cell	Secretin (SCT)	SCT-R	Hypothalamus (Siu et al., 2006)
X and A cell	Ghrelin (GHRL)	GHRL-R	Hypothalamus, NTS, and area postrema (Zigman et al., 2006)

Enteroendocrine cells (responsible for communicating signals from gut to brain and other organs) : gut interoceptors

Endocrinol Metab 2013;28:262-274

THE MECHANISM OF PANCREATIC SECRETION.

By W. M. BAYLISS AND E. H. STARLING. (Seventeen Figures in Text.)

(*From the Physiological Laboratory of University College, London.*)

CONTENTS.

Journal of Physiology
1902

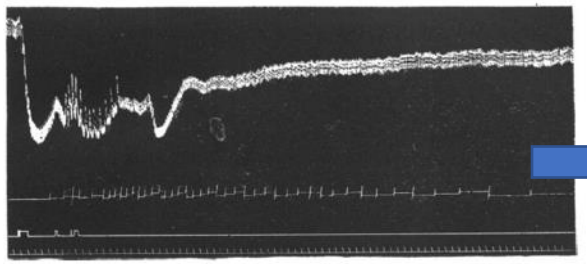


Fig. 2. *Effect of injecting acid extract of jejunal mucous membrane into vein.* Explanation as Fig. 1. The steps on the drop-tracing are due to a gradual accumulation of secretion on the lever of the drop-recorder, which fluid falls off at intervals. Blood-pressure zero = level of drop recorder.

XIII. SUMMARY OF CONCLUSIONS.

1. The secretion of the pancreatic juice is normally evoked by the entrance of acid chyme into the duodenum, and is proportional to the amount of acid entering (Pawlow). This secretion does not depend on a nervous reflex, and occurs when all the nervous connections of the intestine are destroyed.

2. The contact of the acid with the epithelial cells of the duodenum causes in them the production of a body (secretin), which is absorbed from the cells by the blood-current, and is carried to the pancreas, where it acts as a specific stimulus to the pancreatic cells, exciting a secretion of pancreatic juice proportional to the amount of secretin present.

3. This substance, secretin, is produced probably by a process of hydrolysis from a precursor present in the cells, which is insoluble in water and alkalis and is not destroyed by boiling alcohol.

4. Secretin is not a ferment. It withstands boiling in acid, neutral or alkaline solutions, but is easily destroyed by active pancreatic juice or by oxidising agents. It is not precipitated from its watery solution by tannic acid, or alcohol and ether. It is destroyed by most metallic salts. It is slightly diffusible through parchment paper.

5. The pancreatic juice obtained by secretin injection has no action on proteids until "enterokinase" is added. It acts on starch and to some extent on fats, the action on fats being increased by the addition of succus entericus. It is, in fact, normal pancreatic juice.

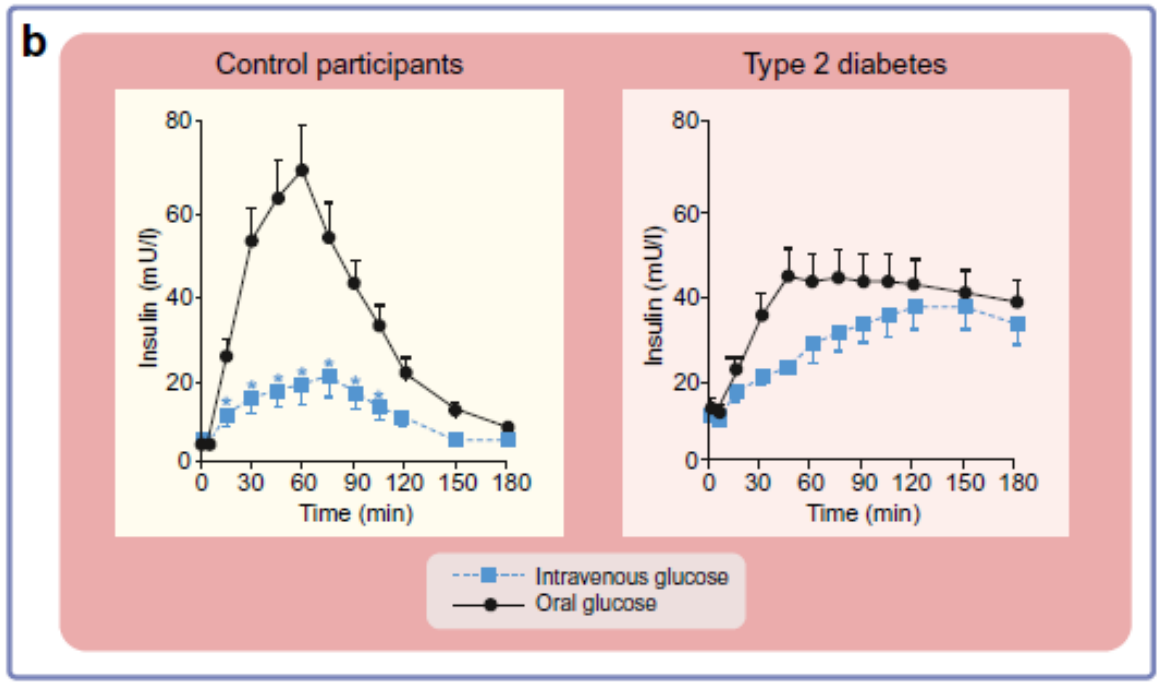
6. Secretin rapidly disappears from the tissues, but cannot be detected in any of the secretions. It is apparently not absorbed from the lumen of the intestine.

7. It is not possible to obtain a body resembling secretin from any tissues of the body other than the mucous membrane of the duodenum and jejunum.

8. Secretin solutions, free from bile-salts, cause some increase in the secretion of bile. They have no action on any other glands.

9. Acid extracts of the mucous membrane normally contain a body which causes a fall of blood-pressure. This body is not secretin, and the latter may be prepared free from the depressor substance by acting on desquamated epithelial cells with acid.

10. There is some evidence of a specific localized action of the vaso-dilator substances which may be extracted from various tissues.



EFFETTO INCRETINICO ATTENUATO IN DM2

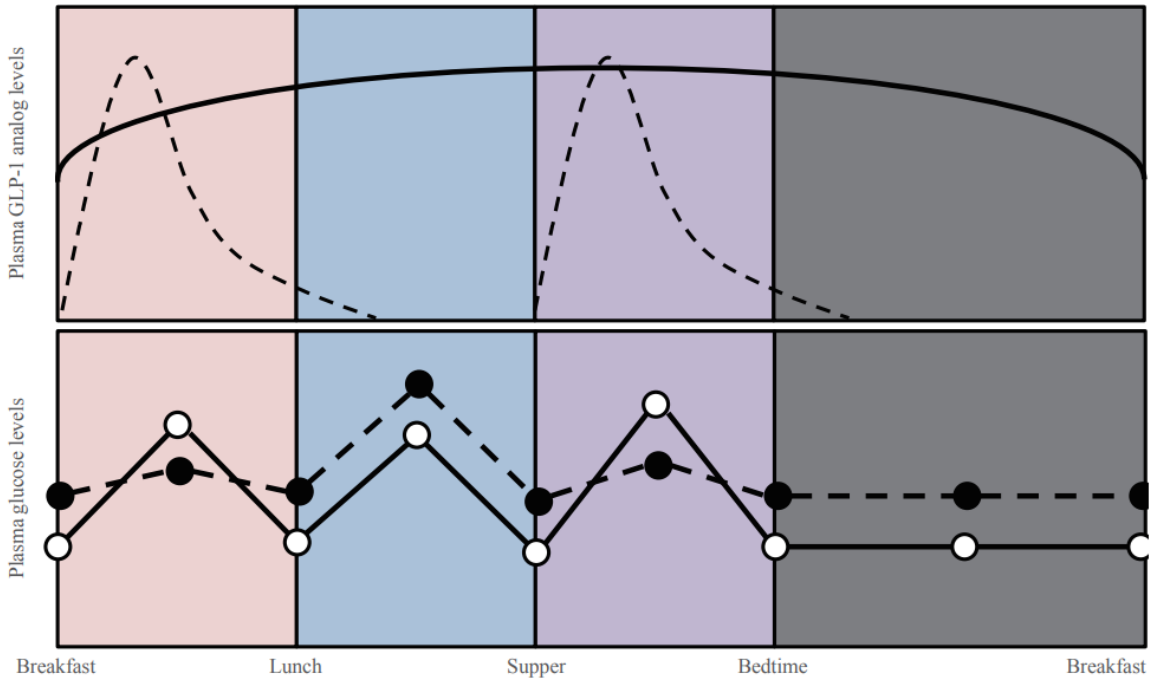


Fig. 2. Schematic of plasma glucagon-like peptide 1 (GLP-1) analog levels and plasma glucose levels with short- versus long (or prolonged)-acting analogs. Plasma levels of representative GLP-1 analogs and corresponding plasma glucose levels are depicted over a 24-hour period. Dashed line and closed circle, short-acting GLP-1 analog; continuous line and open circle, long or prolonged-acting GLP-1 analog.

Diabetologia (2023) 66:1765–1779
https://doi.org/10.1007/s00125-023-05906-7

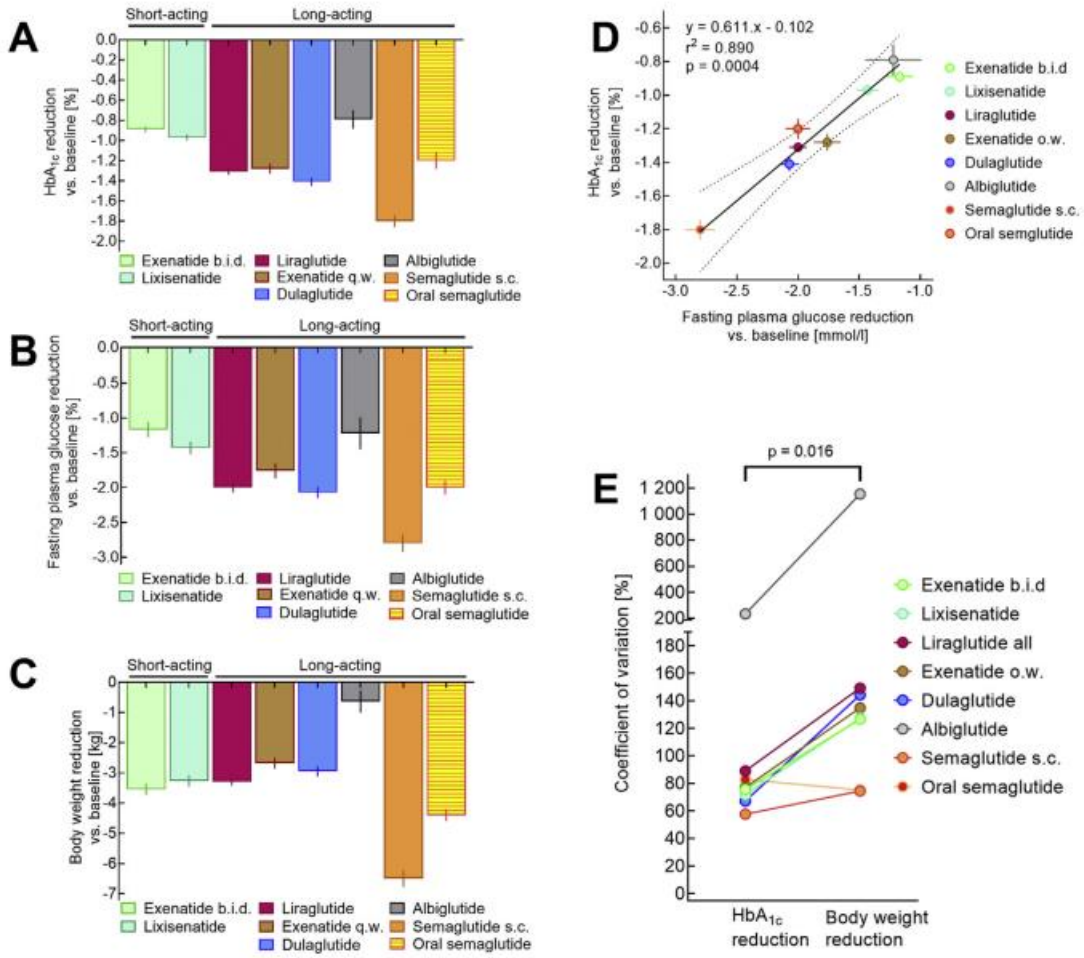
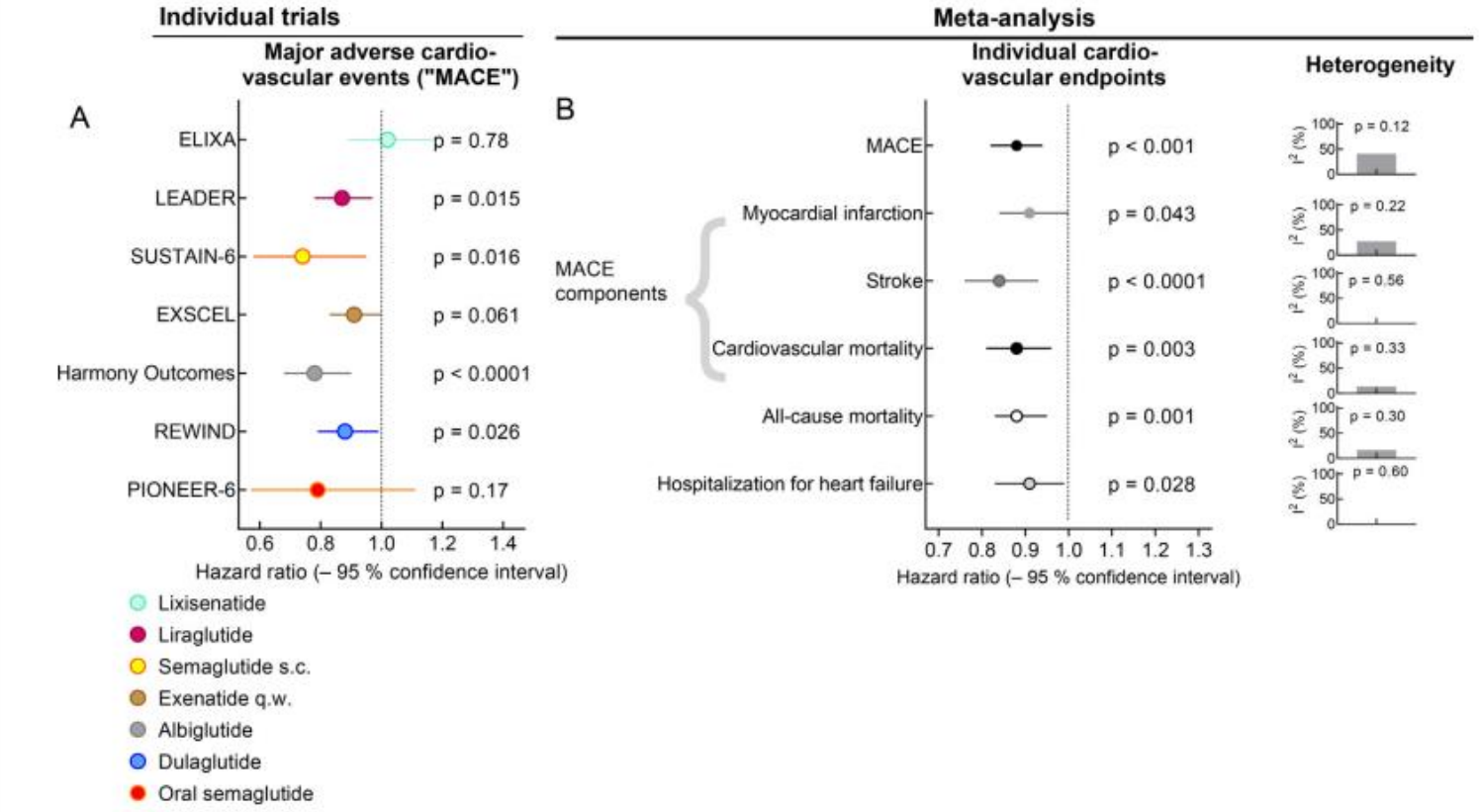


Figure 4: Comparison of approved GLP-1 RAs with respect to their effectiveness in reducing HbA_{1c} (A), fasting plasma glucose (B), and body weight (C). A linear regression analysis relating reductions in fasting plasma glucose to reductions in HbA_{1c} is shown in panel D. A comparison of the reported coefficients of variation for reducing HbA_{1c} and body weight is displayed in panel E. All data are from clinical trials reporting head-to-head comparisons between various GLP-1 RAs (exenatide b.i.d. vs lixisenatide [36], exenatide b.i.d. vs liraglutide [37], lixisenatide vs liraglutide [38], exenatide once-weekly vs liraglutide [39], albiglutide vs liraglutide [40], dulaglutide vs liraglutide [41], subcutaneous semaglutide vs dulaglutide [42], and oral semaglutide vs liraglutide [43]) on a background of oral glucose-lowering agents. Data concerning the same GLP-1 RA were pooled using conventional equations to calculate common means and their standard deviations.

MOLECULAR METABOLISM
46 (2021) 101102

Cardiovascular outcome studies of GLP-1 RAs

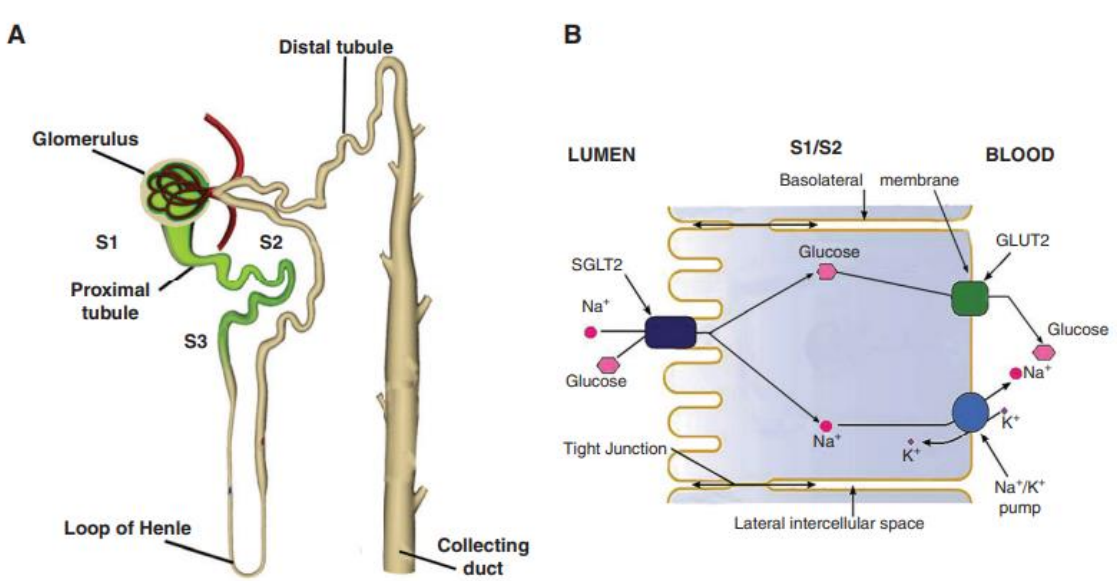


MOLECULAR METABOLISM
46 (2021) 101102

Results of cardiovascular outcome studies comparing GLP-1 RAs with placebo on a background of standard of care.
(A) Reduction in major adverse cardiovascular events (MACE: time to first event) in published individual clinical trials.
(B) Results of a published meta-analysis analyzing various cardiovascular endpoints across all of the clinical trials shown in panel A. MACE (a combination of either cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) was the primary endpoint in all studies.

Table 1. Results of Head to Head Comparisons among Short-, Long-, and Prolonged-Acting Glucagon-Like Peptide 1 Analogs

Study class of drug	LEAD-6 [76]		DURATION-1 [17]		DURATION-6 [19]	
	Short acting	Long acting	Short acting	Prolonged acting	Long acting	Prolonged acting
Drugs used	Exenatide BD	Liraglutide OD	Exenatide BD	Exenatide LAR	Liraglutide OD	Exenatide LAR
Number	231	233	147	148	450	461
Age, yr	57.1±10.8	56.3±9.8	55±10	55±10	57±9.6	57±9.4
Sex, male:female	49:51	55:45	51:49	55:45	54:46	55:45
Duration of diabetes, yr	8.5±6.2	7.9±5.9	6±5	7±6	9±6	8±6
Baseline HbA1c, %	8.2±1.0	8.1±1.0	8.3±1.0	8.3±1.0	8.4±1.0	8.5±1.0
Baseline body weight, kg	93.1±20.1	93.0±19.5	102±21	102±19	91.1±19.1	90.9±19.5
Baseline BMI, kg/m^2	32.9±5.5	32.9±5.7	35±5	35±5	32.3±5.4	32.3±5.6
ΔFG, mmol/L	-0.60[a]	-1.61[a]	-1.4[a]	-2.3[a]	-2.12[a]	-1.76[a]
ΔPG, mmol/L	↓↓a	↓a	-6.9[a]	-5.3[a]	NR	NR
ΔHbA1c, %	-0.79[a]	-1.12[a]	-1.5[a]	-1.9[a]	-1.48[a]	-1.28[a]
ΔBody weight, kg	-2.87[a]	-3.24[a]	-3.6	-3.7	-3.57[a]	-2.68[a]
ΔSBP, mm Hg	-2.0	-2.51	-3.4	-4.7	-3.45	-2.48
ΔDBP, mm Hg	-1.98	-1.05	-1.7	-1.7	-0.51	-0.49
ΔHR, bpm	0.69[a]	3.28[a]	NR	NR	NR	NR
Nausea, %	28.0[b]	25.5[b]	34.5[b]	26.4[b]	21[b]	9[b]
Vomiting, %	9.9[b]	6.0[b]	18.6[b]	10.8[b]	13[b]	6[b]
Diarrhea, %	12.1[b]	12.3[b]	13.1[b]	13.5[b]	11[b]	4[b]
Ab formation, %	61[c]	2.6[c]	48.3[b]	74.3[b]	NR	NR
Injection site reaction, %	6.9[b,d]	3.4[b,d]	1.4[b,e]	17.6[b,e]	1[b,f]	10[b,f]
Pancreatitis	None	1 Case	None	None	None	1 Case
Mild hypoglycemia, %	34%[a]	26%[a]	15.4% with SU, 1.1 % without SU	14.5% with SU, 6% without SU	12% with SU, 3 % without SU	15% with SU, 4% without SU
Severe hypoglycemia	2 Cases	None	None	None	None	None
HbA1c <7%, %[g]	43[a]	54[a]	61[a,h]	77[a,h]	60[a]	53[a]
HbA1c ≤6.5%, %[g]	21[a]	35[a]	42	49	NR	NR
Gastric emptying	NR	NR	↓↓[a]	↓[a]	NR	NR



1. by reduction of chronic hyperglycaemia and attenuation of glucose toxicity, SGLT-2 inhibitors can **improve both insulin secretion by beta cells and peripheral tissue insulin sensitivity**.
2. chronic **glucose loss most probably leads to compensatory mechanisms**. One of them, might involve an **increase in energy intake**, an effect that may limit weight loss in the long run. Another could be an increase in **endogenous glucose production**, most probably driven **by increased glucagon secretion**, which may somewhat **attenuate the glucose lowering effect**.
3. SGLT-2 inhibitors exert clinically relevant glucose-lowering activity while **promoting weight loss**

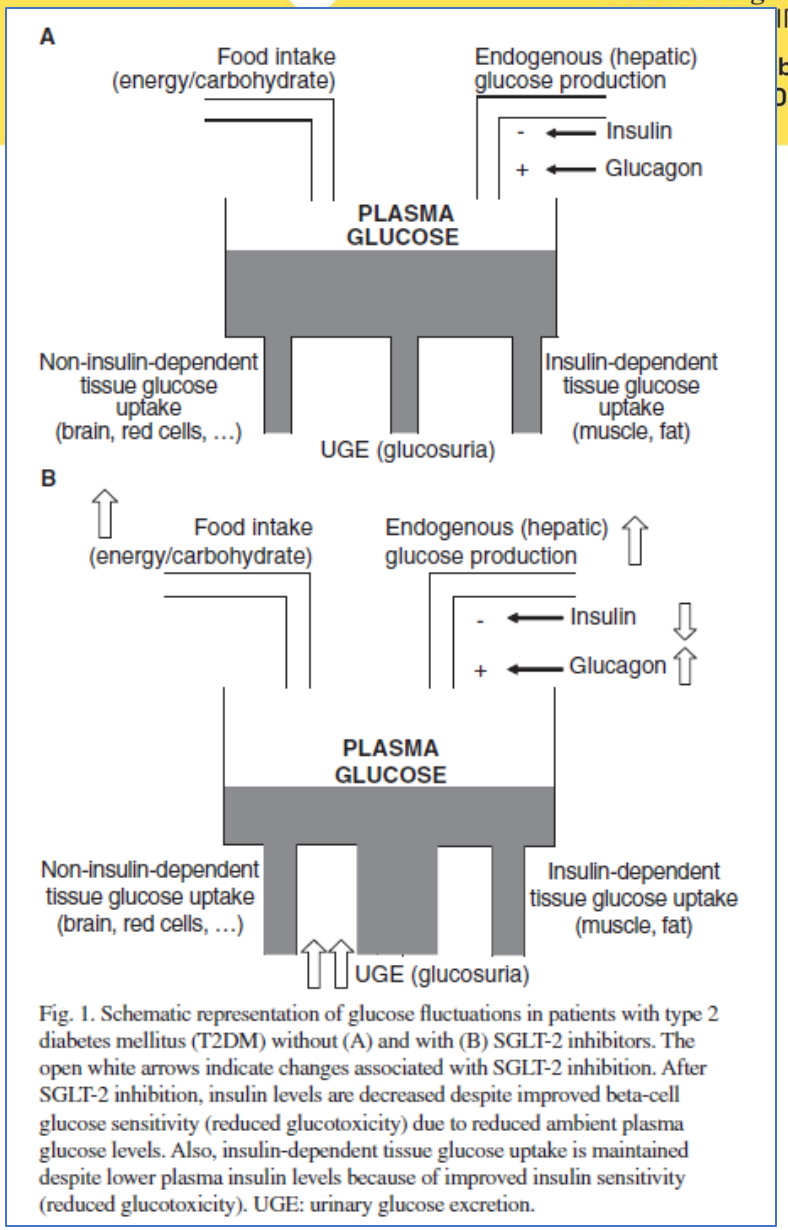
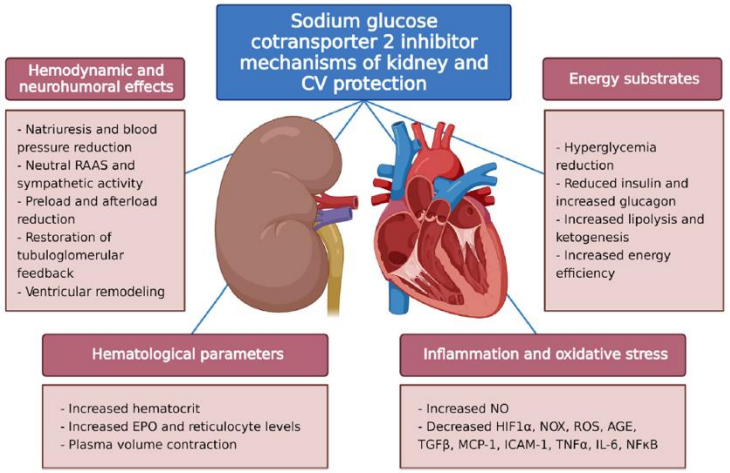


Fig. 1. Schematic representation of glucose fluctuations in patients with type 2 diabetes mellitus (T2DM) without (A) and with (B) SGLT-2 inhibitors. The open white arrows indicate changes associated with SGLT-2 inhibition. After SGLT-2 inhibition, insulin levels are decreased despite improved beta-cell glucose sensitivity (reduced glucotoxicity) due to reduced ambient plasma glucose levels. Also, insulin-dependent tissue glucose uptake is maintained despite lower plasma insulin levels because of improved insulin sensitivity (reduced glucotoxicity). UGE: urinary glucose excretion.

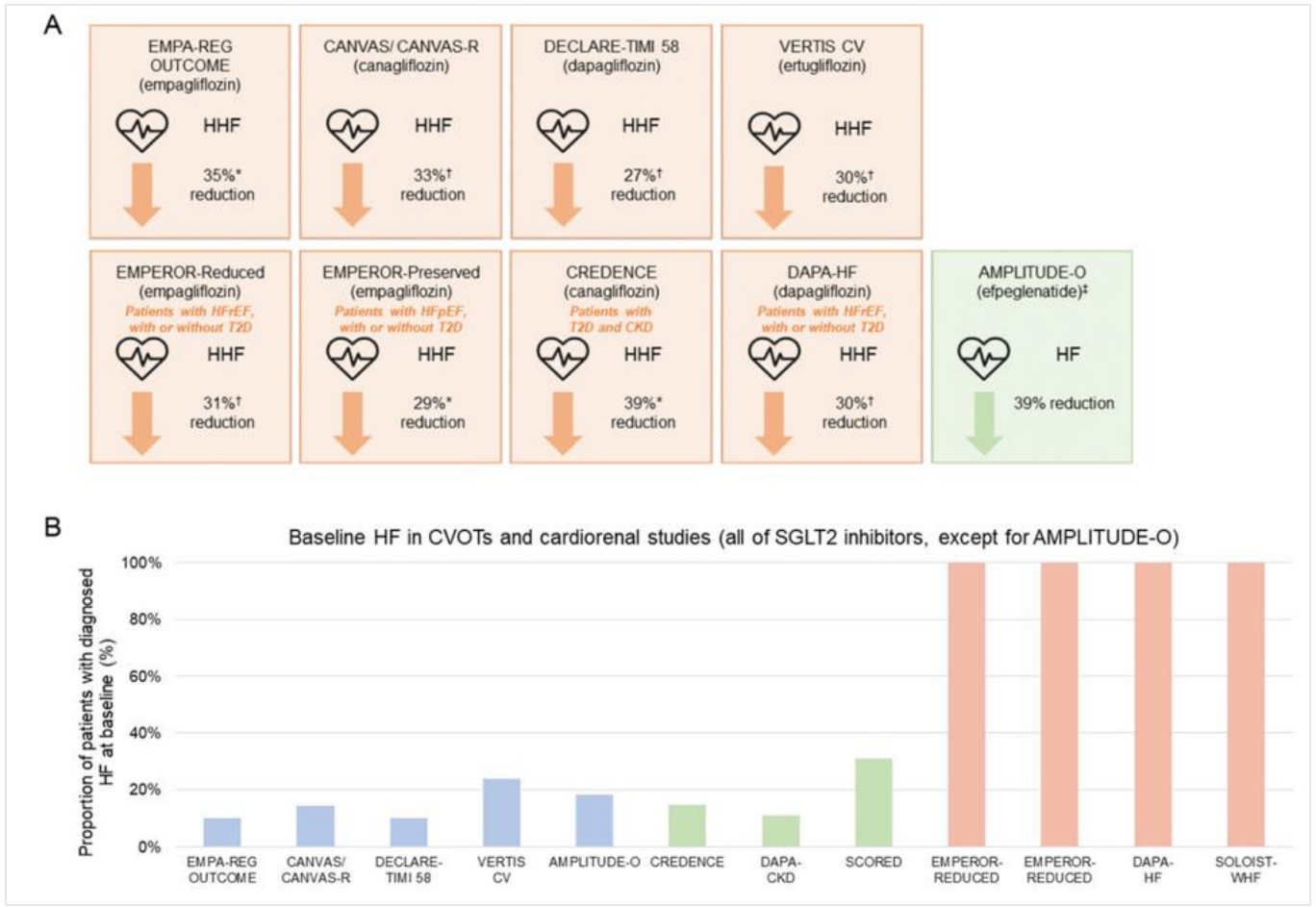


Davies *et al. Cardiovascular Diabetology* (2022) 21:144
https://doi.org/10.1186/s12933-022-01575-9

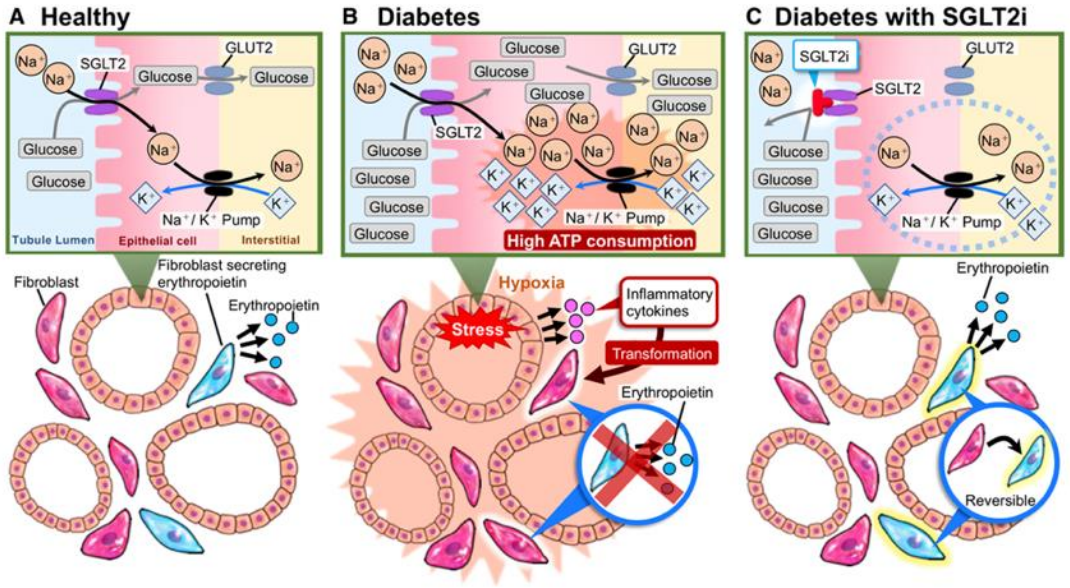
Cardiovascular Diabetology

REVIEW Open Access

Cardiovascular outcomes trials: a paradigm shift in the current management of type 2 diabetes

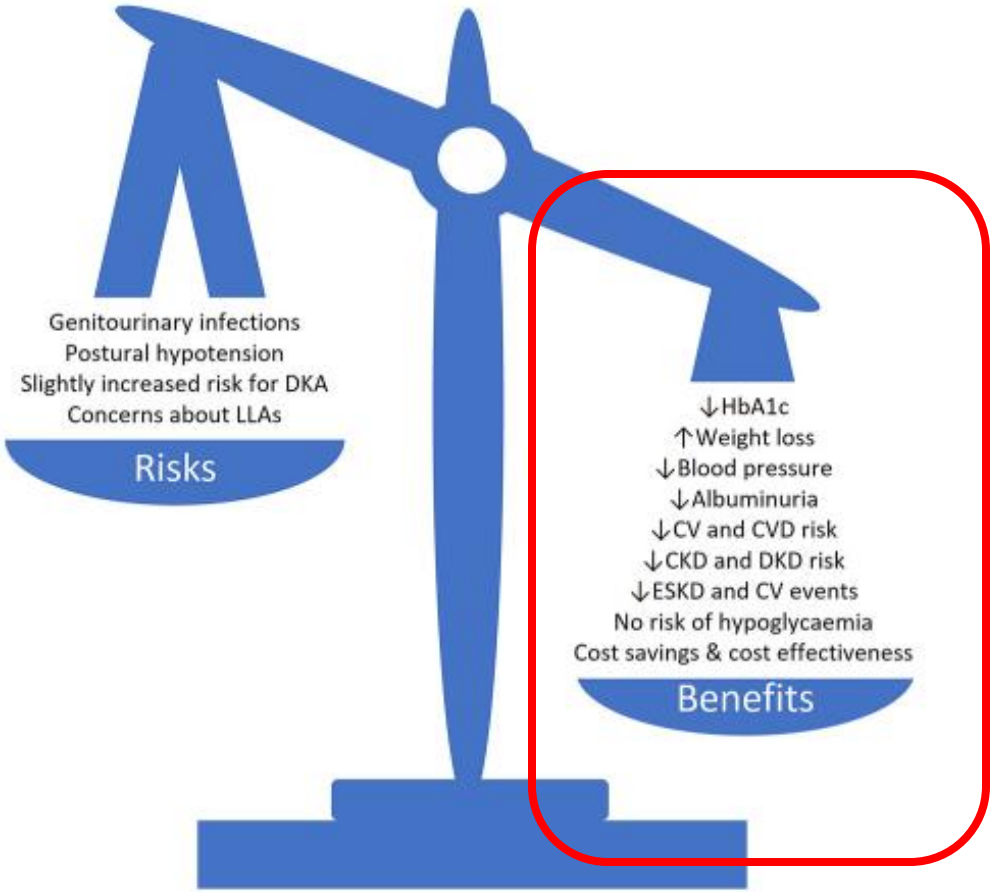


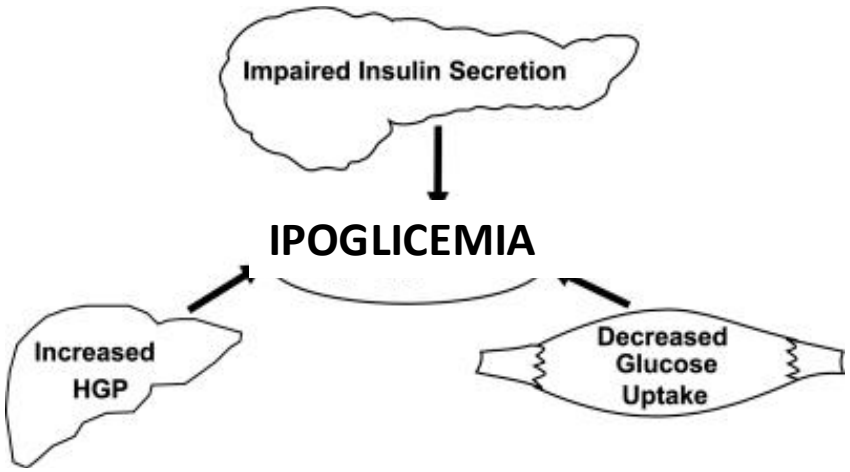
Cardiovascular, **Renal** and Metabolic Protection in Type 2 Diabetes

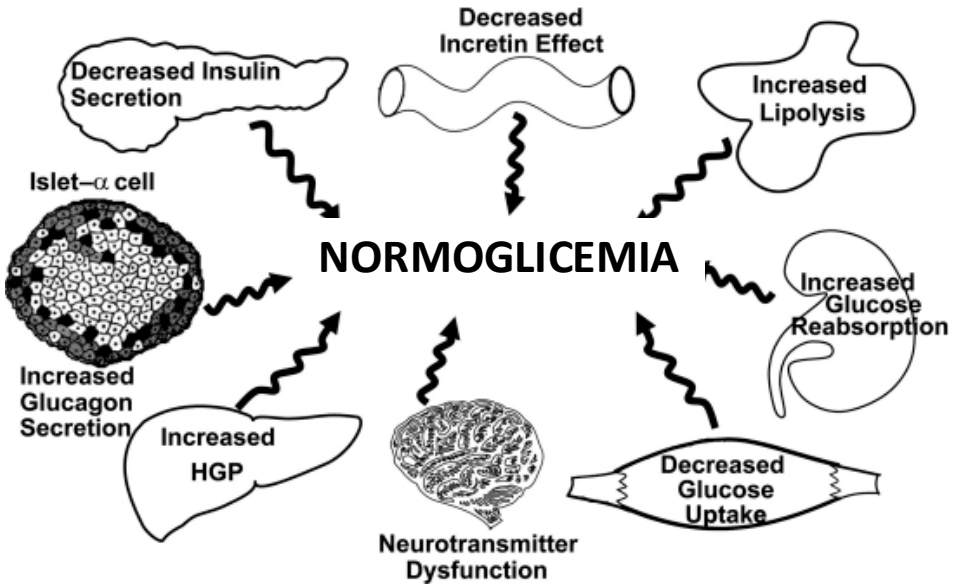


Schema dell'ambiente del tubulo prossimale: adulto sano (**A**), paziente con diabete mellito (**B**) e paziente con diabete mellito in terapia con SGLT2i (**C**). GLUT2: glucotrasportatore-2.

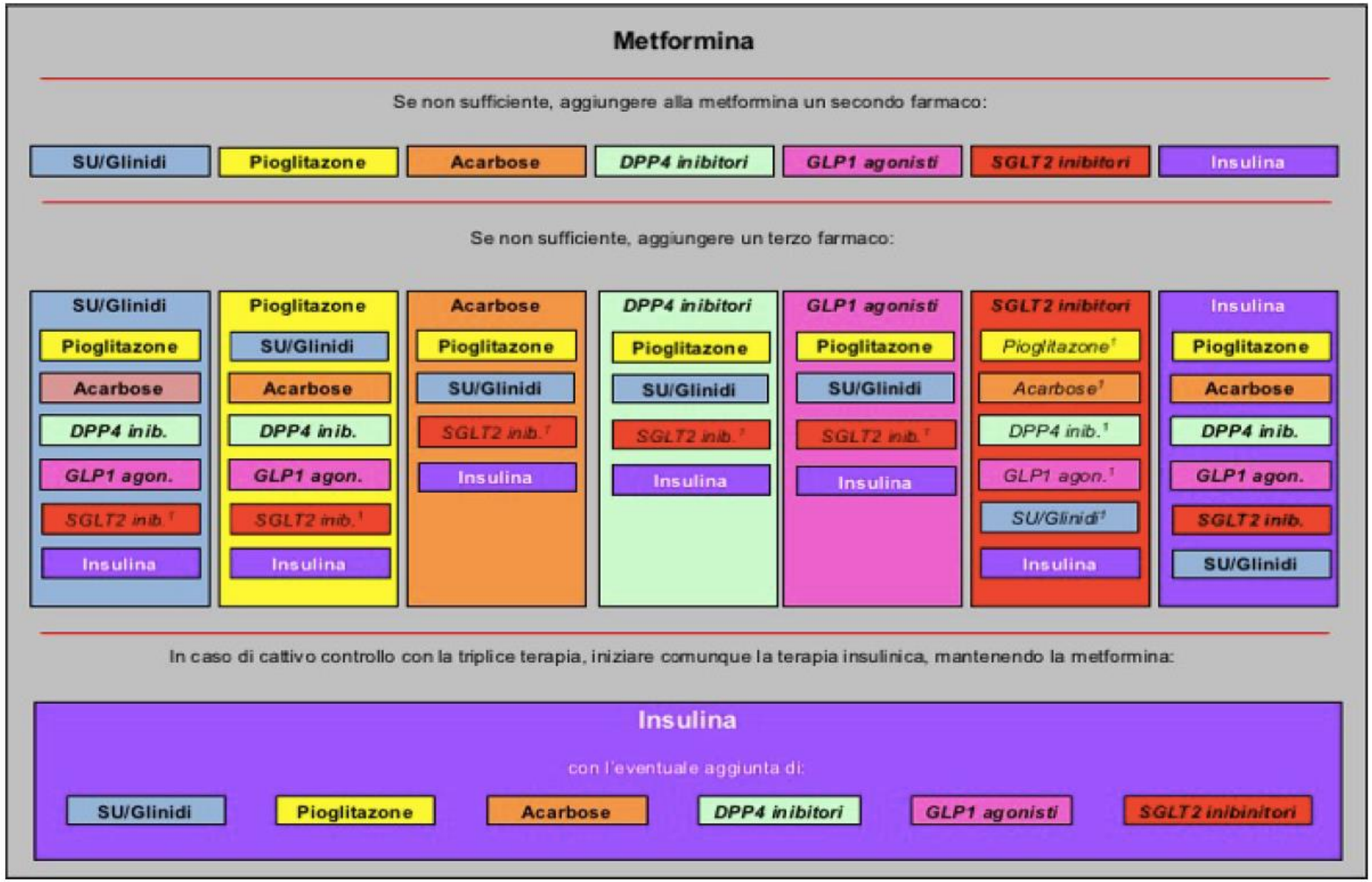
Circulation. 2019 Apr 23;139(17):1985-1987




Impaired Insulin Secretion
IPOGLICEMIA
Increased HGP
Decreased Glucose Uptake


Decreased Insulin Secretion
Decreased Incretin Effect
Increased Lipolysis
Islet–α cell
NORMOGLICEMIA
Increased Glucose Reabsorption
Increased Glucagon Secretion
Increased HGP
Neurotransmitter Dysfunction
Decreased Glucose Uptake

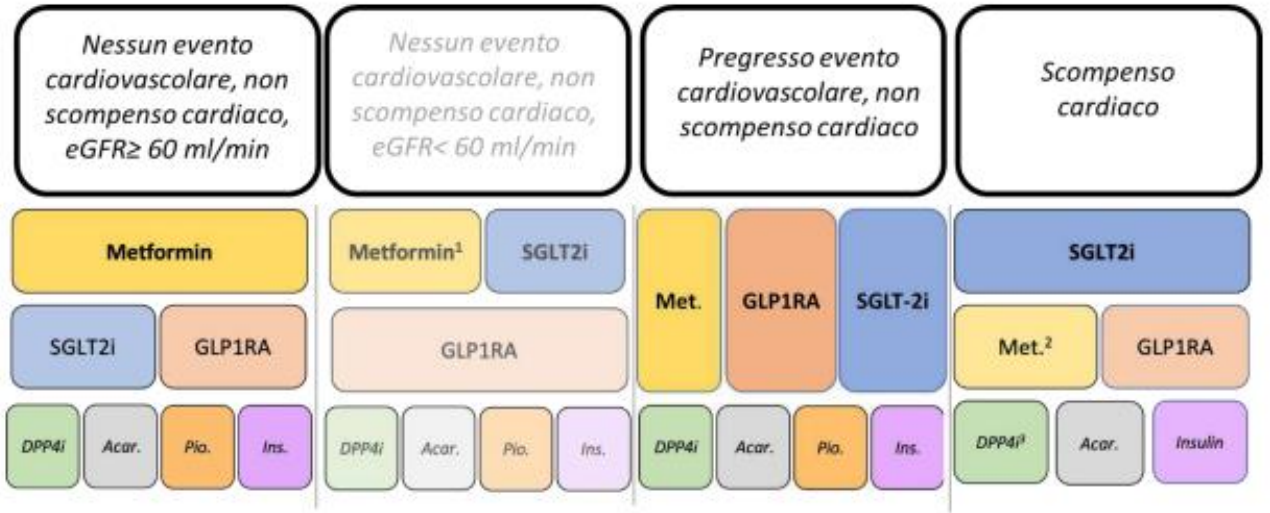
Standard Italiani per la cura del diabete mellito 2016



Linea Guida della Società Italiana di Diabetologia (SID) e dell'Associazione dei Medici Diabetologi (AMD)

La terapia del diabete mellito di tipo 2

Versione aggiornata a dicembre 2022



[1]*Se la metformina non è controindicata per ridotto eGFR.*
[2]*Se la metformina non è controindicata per ridotta funzione cardiaca.*
[3]*Eccetto saxagliptin che non è indicato in caso di scompenso cardiaco.*
La raccomandazione sui pazienti con eGFR< 60ml/min è debole per carenza di studi clinici effettuati su questa popolazione
Si raccomanda la deprescrizione di sulfanilurre e glinidi

Molti studi clinici randomizzati sostengono l'uso di metformina, SGLT-2i o GLP-1 RA come farmaci preferenziali nel trattamento dei pazienti con diabete di tipo 2, per la loro efficacia nella riduzione della HbA1c, il basso rischio di ipoglicemia e la riduzione degli eventi cardiovascolari maggiori e della mortalità. Inoltre, GLP-1 RA e SGLT-2i hanno effetti favorevoli sul peso corporeo. Anche il pioglitazone si associa ad una riduzione del'incidenza di eventi cardiovascolari maggiori, accompagnata però da un aumentato rischio di scompenso cardiaco. Gli insulino-secretagoghi (sulfaniluree e repaglinide) hanno minore efficacia a lungo termine, con rischio di ipoglicemia severa, eventi cardiovascolari maggiori e mortalità maggiori delle altre classi e pertanto non dovrebbero essere più considerati nel trattamento del paziente con diabete di tipo 2.

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

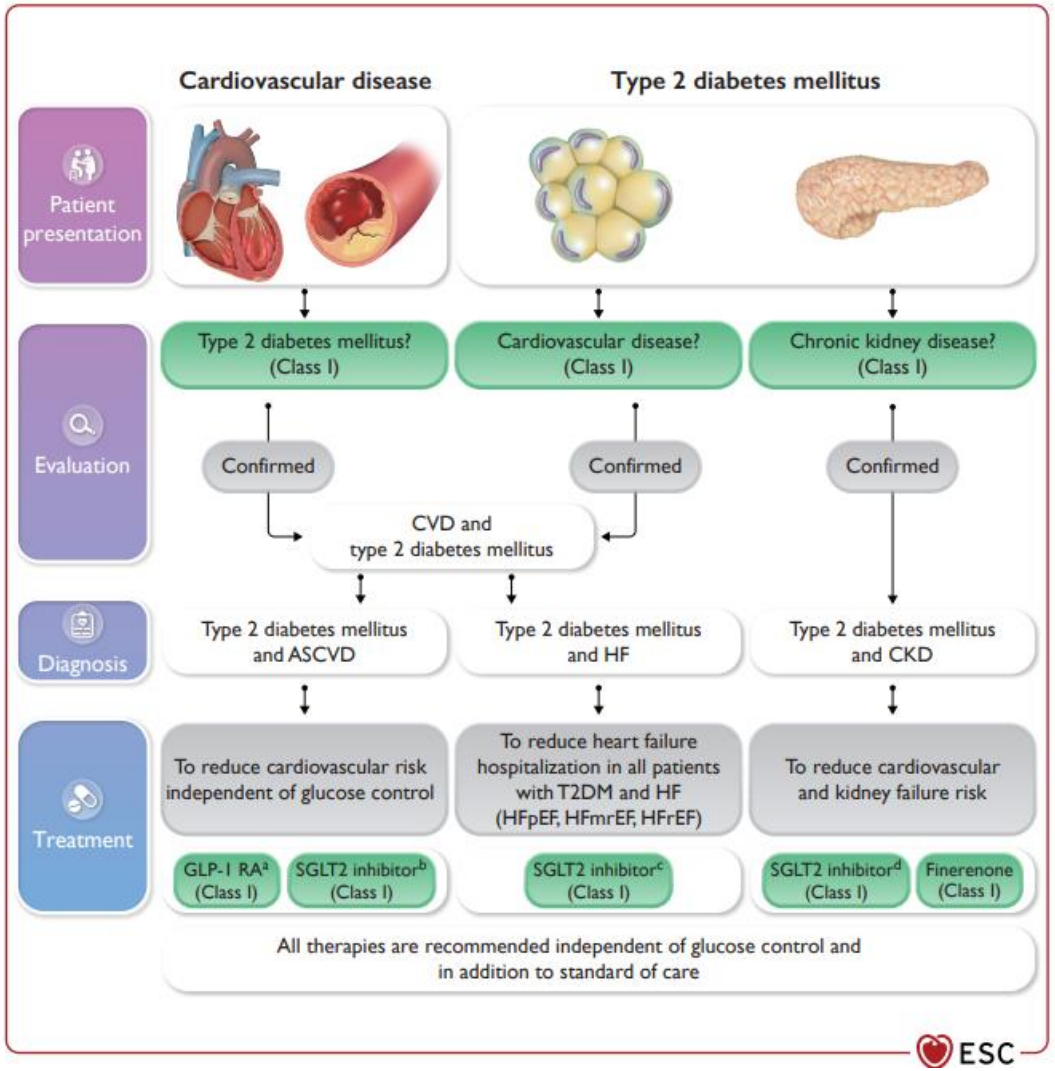
ESC European Society of Cardiology
European Heart Journal (2023) **44**, 4043–4140
https://doi.org/10.1093/eurheartj/ehad192

ESC GUIDELINES

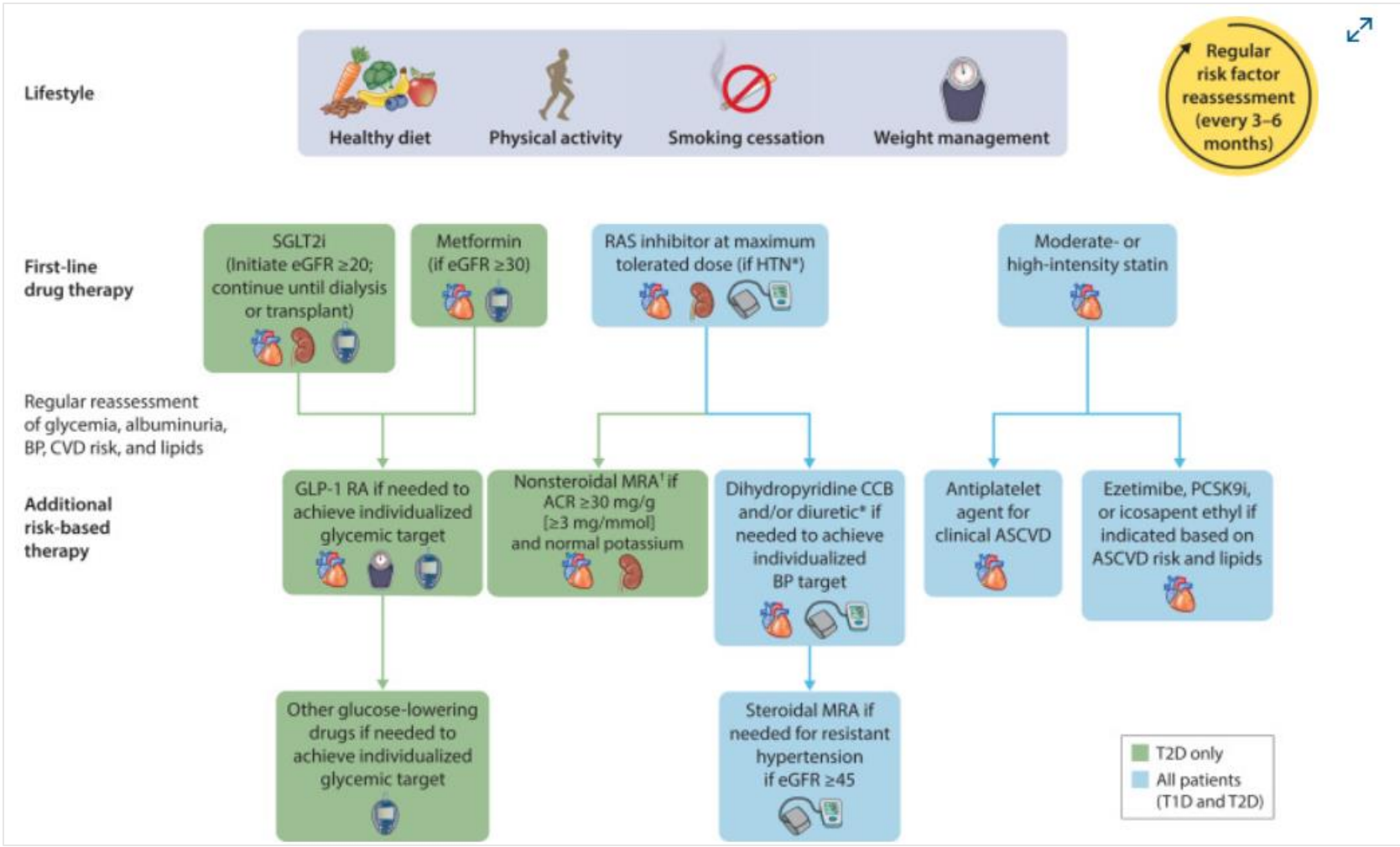
2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes

Recommendation Table 7 — Recommendations for glycaemic targets in patients with diabetes

Recommendations	Class[a]	Level[b]
It is recommended to apply tight glycaemic control (HbA1c <7%) to reduce microvascular complications.[126–128,133]	I	A
It is recommended to avoid hypoglycaemia, particularly in patients with CVD.[134–137,147]	I	B
It is recommended to individualize HbA1c targets according to comorbidities, diabetes duration, and life expectancy.[134,137]	I	C
Tight glycaemic control should be considered for reducing CAD in the long term, preferably using agents with proven CV benefit.[c,129–132]	IIa	B



KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease



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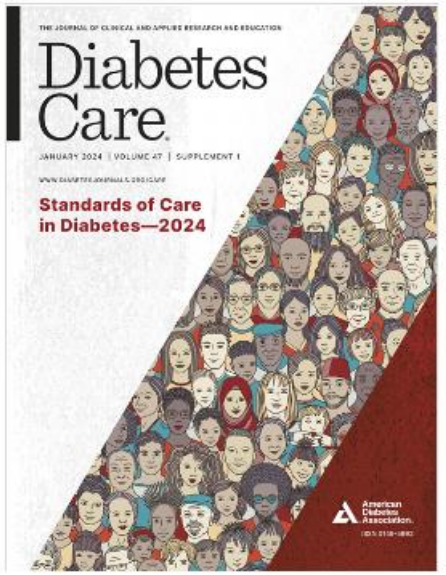

USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES

HEALTHY LIFESTYLE BEHAVIORS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)

TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

Goal: Achievement and Maintenance of Glycemic and Weight Management Goals

Glycemic Management: Choose approaches that provide the efficacy to achieve goals:

Metformin OR Agent(s) including COMBINATION therapy that provide adequate EFFICACY to achieve and maintain treatment goals

Prioritize avoidance of hypoglycemia in high-risk individuals

In general, higher efficacy approaches have greater likelihood of achieving glycemic goals

Efficacy for glucose lowering

Very High:
Dulaglutide (high dose), Semaglutide, Tirzepatide
Insulin
Combination Oral, Combination Injectable (GLP-1 RA/Insulin)

High:
GLP-1 RA (not listed above), Metformin, SGLT2i, Sulfonylurea, TZD

Intermediate:
DPP-4i

Achievement and Maintenance of Weight Management Goals:

Set individualized weight management goals

General lifestyle advice: medical nutrition therapy/eating patterns/ physical activity

Intensive evidence-based structured weight management program

Consider medication for weight loss

Consider metabolic surgery

When choosing glucose-lowering therapies:
Consider regimen with high-to-very-high dual glucose and weight efficacy

Efficacy for weight loss

Very High:
Semaglutide, Tirzepatide

High:
Dulaglutide, Liraglutide

Intermediate:
GLP-1 RA (not listed above), SGLT2i

Neutral:
DPP-4i, Metformin

If A1C above target

Identify barriers to goals:
- Consider DSMES referral to support self-efficacy in achievement of goals
- Consider technology (e.g., diagnostic CGM) to identify therapeutic gaps and tailor therapy
- Identify and address SDOH that impact achievement of goals

* In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin; † A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF, and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and renal endpoints in individuals with T2D with established/high risk of CVD.

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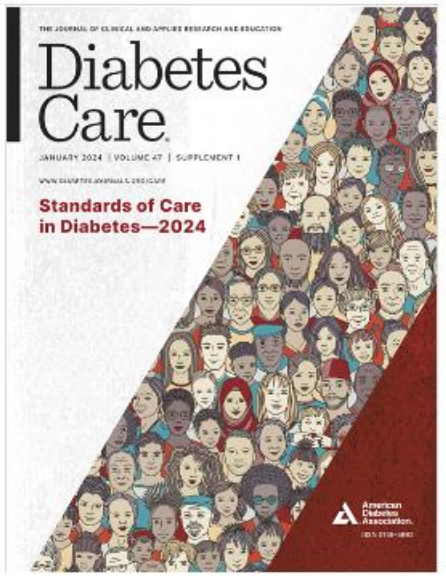
January 2024



USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES

HEALTHY LIFESTYLE BEHAVIORS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)

TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

Goal: Cardiorenal Risk Reduction in High-Risk Individuals with Type 2 Diabetes (in addition to comprehensive CV risk management)*

+ASCVD†
Defined differently across CVOTs but all included individuals with established CVD (e.g., MI, stroke, any revascularization procedure). Variably included: conditions such as transient ischemic attack, unstable angina, amputation, symptomatic or asymptomatic coronary artery disease.

+Indicators of high risk
While definitions vary, most comprise ≥55 years of age with two or more additional risk factors (including obesity, hypertension, smoking, dyslipidemia, or albuminuria)

+ASCVD/Indicators of High Risk
GLP-1 RA# with proven CVD benefit — EITHER/OR — SGLT2i§ with proven CVD benefit
If A1C above target
- For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit or vice versa
- TZD^

+HF
Current or prior symptoms of HF with documented HFrEF or HFpEF

+HF
SGLT2i§ with proven HF benefit in this population

+CKD
eGFR <60 mL/min per 1.73 m² OR albuminuria (ACR ≥3.0 mg/mmol [30 mg/g]). These measurements may vary over time; thus, a repeat measure is required to document CKD.

+CKD (on maximally tolerated dose of ACEi/ARB)
PREFERABLY
SGLT2i§ with primary evidence of reducing CKD progression
Use SGLT2i in people with an eGFR ≥20 mL/min per 1.73 m²; once initiated should be continued until initiation of dialysis or transplantation
OR
GLP-1 RA with proven CVD benefit if SGLT2i not tolerated or contraindicated
If A1C above target, for patients on SGLT2i, consider incorporating a GLP-1 RA or vice versa

If additional cardiorenal risk reduction or glycemic lowering needed

Goal: Achievement and Maintenance of Glycemic and Weight Management Goals

Glycemic Management: Choose approaches that provide the efficacy to achieve goals:
Metformin OR Agent(s) including COMBINATION therapy that provide adequate EFFICACY to achieve and maintain treatment goals
Prioritize avoidance of hypoglycemia in high-risk individuals

In general, higher efficacy approaches have greater likelihood of achieving glycemic goals
Efficacy for glucose lowering
Very High: Dulaglutide (high dose), Semaglutide, Tirzepatide
Insulin
Combination Oral, Combination Injectable (GLP-1 RA/Insulin)
High: GLP-1 RA (not listed above), Metformin, SGLT2i, Sulfonylurea, TZD
Intermediate: DPP-4i

Achievement and Maintenance of Weight Management Goals:
Set individualized weight management goals
General lifestyle advice: medical nutrition therapy/eating patterns/ physical activity
Intensive evidence-based structured weight management program
Consider medication for weight loss
Consider metabolic surgery

When choosing glucose-lowering therapies:
Consider regimen with high-to-very-high dual glucose and weight efficacy

Efficacy for weight loss
Very High: Semaglutide, Tirzepatide
High: Dulaglutide, Liraglutide
Intermediate: GLP-1 RA (not listed above), SGLT2i
Neutral: DPP-4i, Metformin

If A1C above target

Identify barriers to goals:
- Consider DSMES referral to support self-efficacy in achievement of goals
- Consider technology (e.g., diagnostic CGM) to identify therapeutic gaps and tailor therapy
- Identify and address SDOH that impact achievement of goals

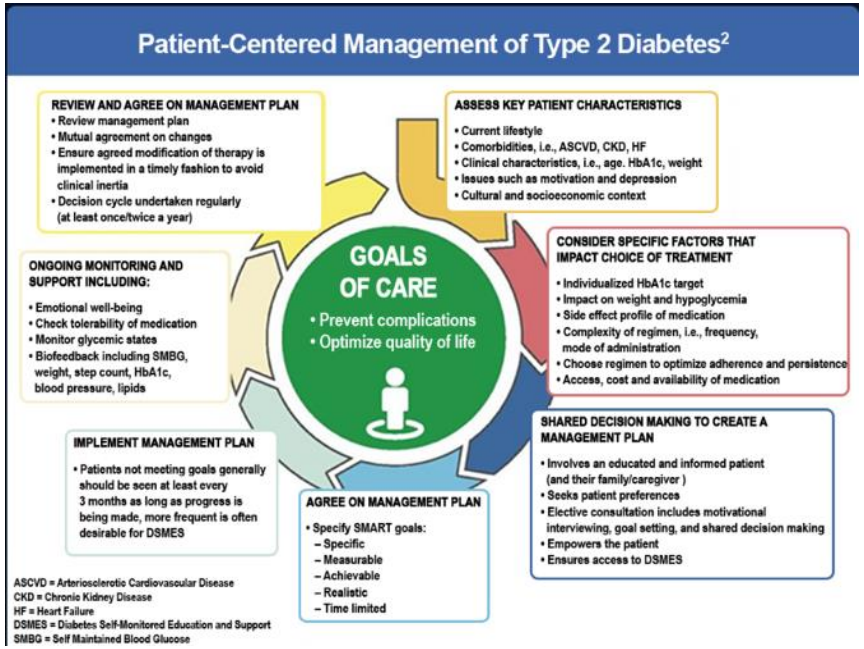
* In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin; † A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF, and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and renal endpoints in individuals with T2D with established/high risk of CVD.

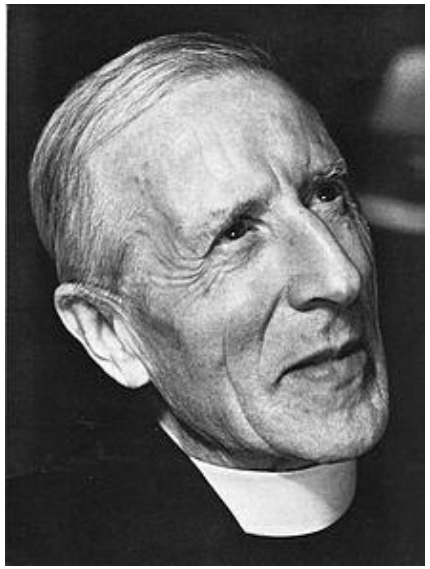
Conclusioni

La ricerca farmacologica , talora avvantaggiata dalla serendipità , ha permesso nel corso dei decenni di ottimizzare la terapia del diabete

Da una terapia focalizzata sul target glicemico (a rischio ipoglicemia) si è giunti ad una terapia patient-centered euglicemizzante

Il futuro: … una terapia *social e patient-centered*





Pierre Teilhard de Chardin
(1881-1955)

"Il **passato** mi ha rivelato la **struttura del futuro**."

"**Noi stessi** siamo il nostro peggior nemico. Nulla può distruggere **l'Umanità** ad eccezione dell'Umanità stessa."

Franco Camanni
(1930-2019)

L'amicizia è il più grande di tutti i sacramenti; dove c'è amicizia, lì c'è Dio. L'azione creatrice di Dio passa sempre attraverso le creature; questo mette in luce la **responsabilità** che abbiamo gli uni verso gli altri, proprio in ordine alla vita, al vivere serenamente, al crescere positivamente. Una psicologia della **fiducia** è necessariamente una psicologia di crescita, una psicologia che incoraggia l'espansione continua delle nostre **potenzialità**.
(Franco Camanni, 2015)

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Forever young

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Un grazie speciale a che mi ha insegnato l'importanza dell'amicizia