Materiale didattico lezioni di Farmacologia per il corso di Medicina & Chirurgia Scuola di Scienze della Salute Umana

Anno accademico 2018-19

Farmaci antidiabetici

CdL Infermieristica a.a. 2019-2010

Prof.ssa Laura Raimondi

- Worldwide, the number of adults with diabetes is expected to reach 366 million by 2030.
- Epidemiological evidence indicates that type 2 diabetes is an independent risk factor for cardiovascular disease and microvascular complications, such as retinopathy.
- The rate of cardiovascular diseases is about twice as high in people with diabetes than without.

Essential glossary

Type 1 diabetes, insulin dependent (IDDM), insulinopenic, iodiopathic or immunomediated

Type 2 , non-insulin dependent (NIDDM), normal or high levels of insulin, based on peripheral insulin resistance

Gestational diabetes

Insulin Resistance : the aetiology of type 2 diabetes mellitus (T2DM) is intricate and multifaceted, but virtually all patients contend with both relative insulin deficiency and insulin resistance to varying degrees.

Glucotoxiciyty (oxidative stress) The resulting hyperglycemia can facilitate β-cell failure in the pancreas and worsen insulin resistance, thus triggering a cycle of impaired metabolism and glucotoxicity.

Pancreatic dysfunction: increased apoptosis of β-cells, diminished β-cell mass and reduced gene transcription, synthesis and secretion of insulin.

Hyperglycemia: Plasma glucose levels over 101 mg/dl, HbA1c levels over 6%

Glycusuria: glucose is present in the urine

Polyuria: excessive urine production/elimination

Polydispsia: excessive thirst

Diabetic Microcomplications: alteration of the basal membrane structure/function of microvessels (retinopathy and/or nepropathy, neuropathy)

Diabetic Macrocomplications: atheriosclerotic disease of large vessels (cardiovascular risk)

Clinical condition of hyperglycemia

- Current guidelines recommend a target glycated haemoglobin level (HbA1c) of 7% or less.

The lesson from UKPDS

(1998 + 2008)

A statistically significant reduction in the rate of microvascular and renal events after intensive glycaemic control was reported in the United Kingdom Prospective Diabetes Study (UKPDS) 33 on intensive blood glucose control with sulfonylureas or insulin

compared with conventional treatment and risk of complications in patients with type 2 diabetes

The results of major randomised clinical trials on the benefits, in respect of diabetes complications, of treatments are, however, controversial.

Meta-Analysis (BMJ 2011)

- The overall results of this meta-analysis show limited benefits of intensive glucose lowering treatment on all cause mortality and deaths from cardiovascular causes.
- We cannot exclude a 9% reduction or a 19% increase in all cause mortality and a 14% reduction or a 43% increase in cardiovascular death.
- The benefit:risk ratio of intensive glucose lowering treatment in the prevention of macrovascular and microvascular events remains uncertain.
- The harm associated with severe hypoglycaemia might counterbalance the potential benefit of intensive glucose lowering treatment.
- More double blind randomised controlled trials are needed to establish the best therapeutic approach in people with type 2 diabetes

Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4·4 million participants

*NCD Risk Factor Collaboration (NCD-RisC)**

Lancet 2016; 387: 1513–30
Published Online
April 6, 2016
http://dx.doi.org/10.1016/S0140-6736(16)00618-8

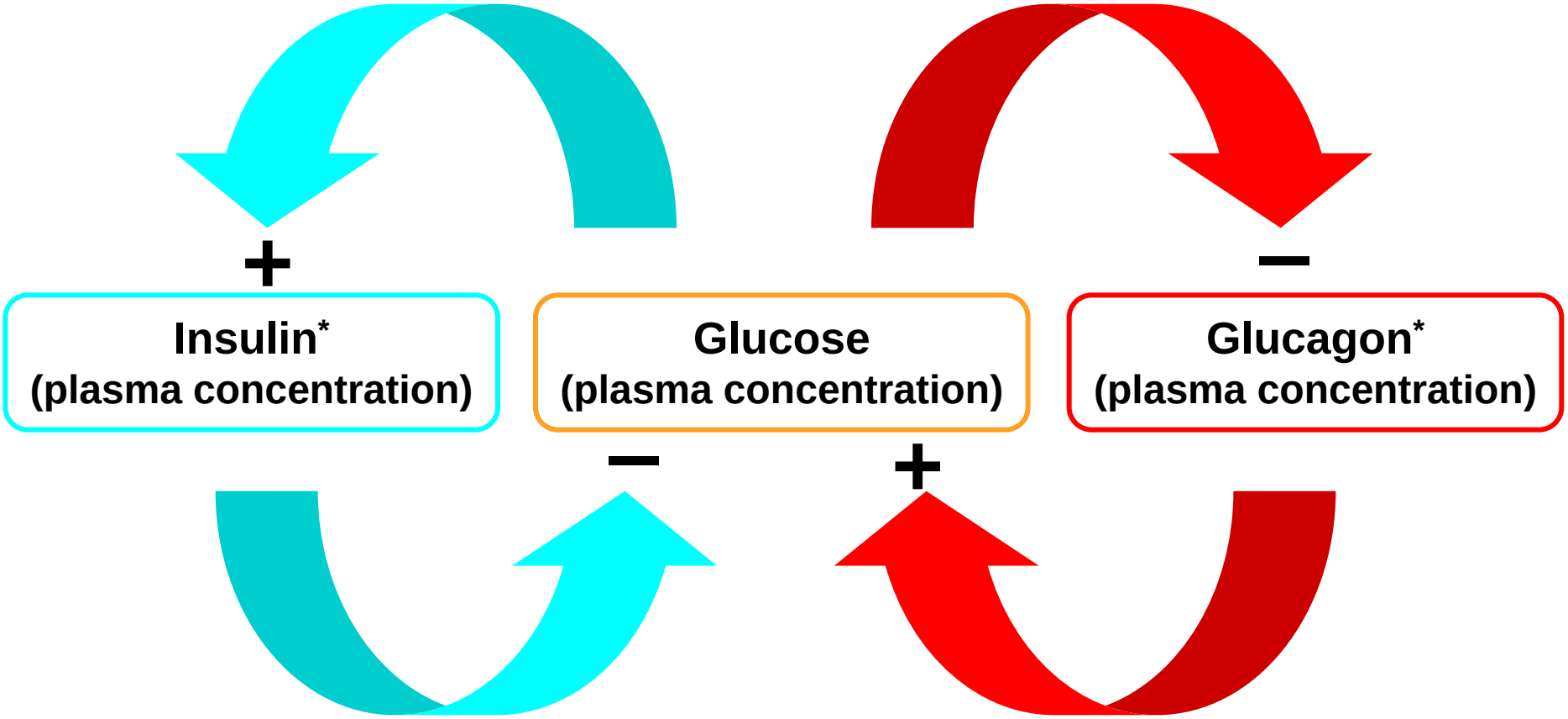
Summary

Background One of the global targets for non-communicable diseases is to halt, by 2025, the rise in the age-standardised adult prevalence of diabetes at its 2010 levels. We aimed to estimate worldwide trends in diabetes, how likely it is for countries to achieve the global target, and how changes in prevalence, together with population growth and ageing, are affecting the number of adults with diabetes.

Interpretation Since 1980, age-standardised diabetes prevalence in adults has increased, or at best remained unchanged, in every country. Together with population growth and ageing, this rise has led to a near quadrupling of the number of adults with diabetes worldwide. The burden of diabetes, both in terms of prevalence and number of adults affected, has increased faster in low-income and middle-income countries than in high-income countries.

Funding Wellcome Trust.

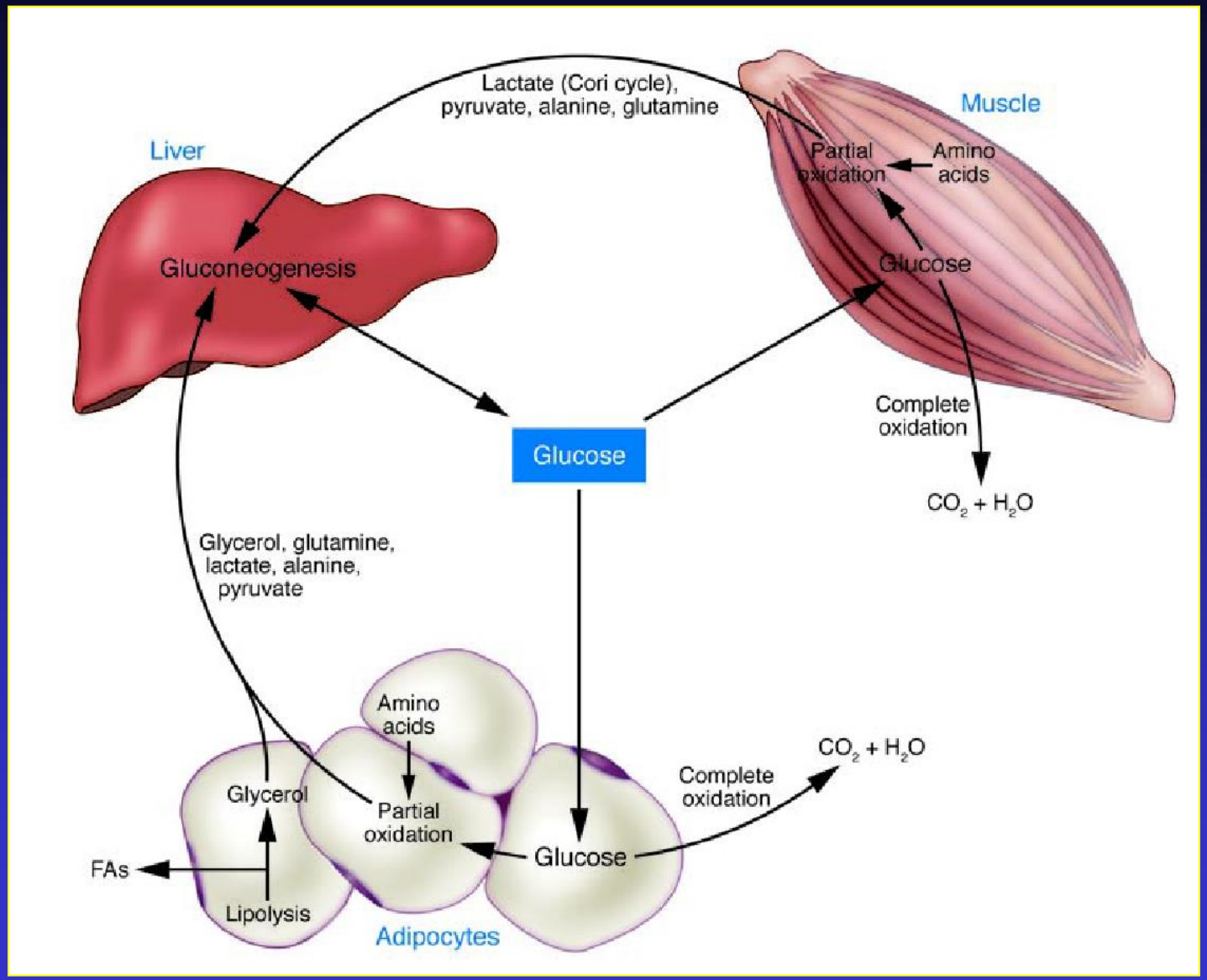
The physiological balance between insulin and glucagon is essential for normal metabolic control



*Insulin and glucagon secretion are also influenced by other nutrients, hormones, and neural input

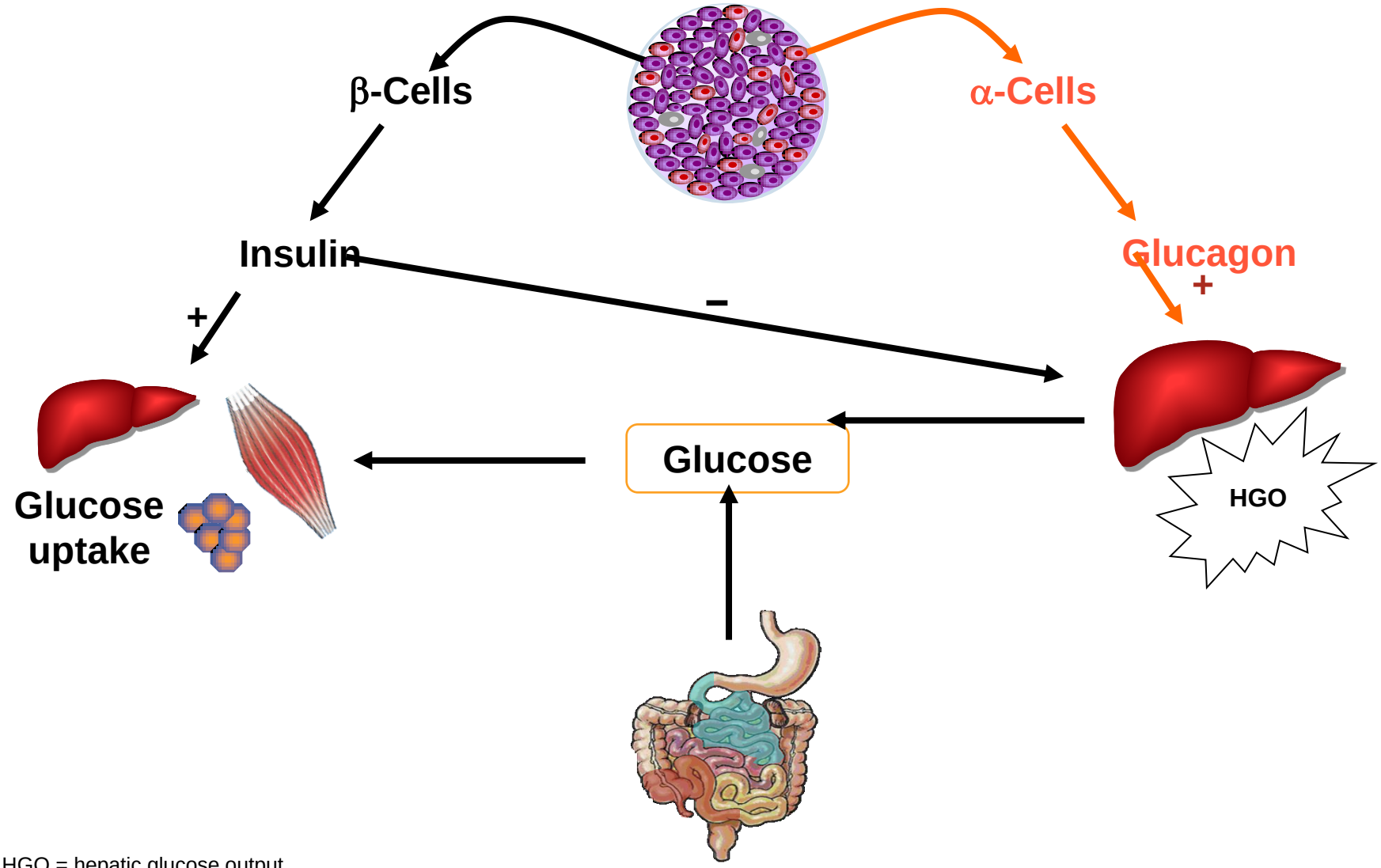
Adapted from Berne RM, Levy MN, eds. *Physiology.* St. Louis, Mo: Mosby, Inc; 1998:822–847.

Substrate cycles as glucose-derived signals



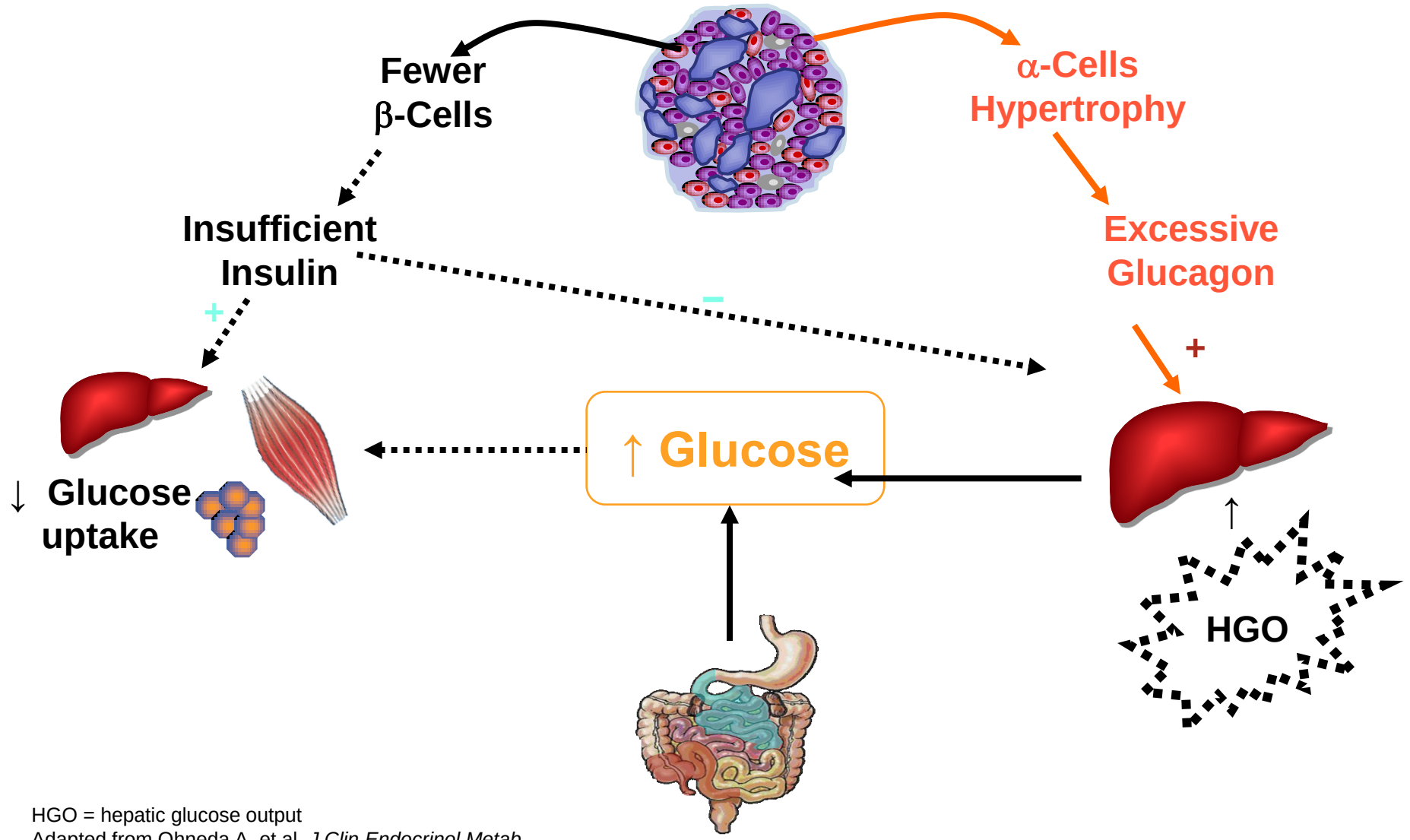
Mark A. Herman and Barbara B. Kahn. J. Clin. Invest. 2006 116:1767-75

Pancreatic Islet Hormones Are Critical for Normal Glucose Tolerance now including also the gut



HGO = hepatic glucose output
Adapted from Unger RH. *Metabolism.* 1974;23:581.

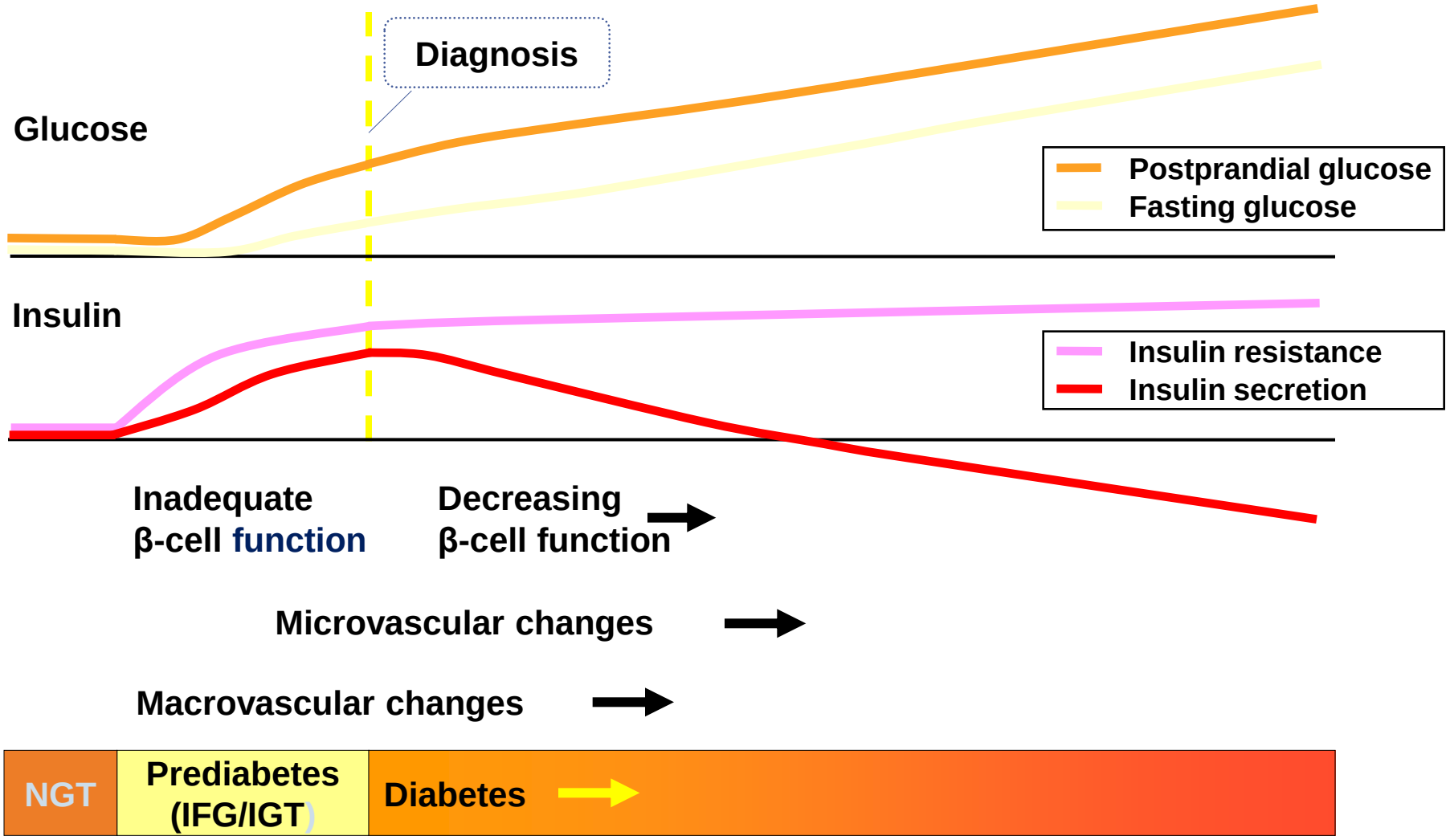
Pancreatic Islet and Gut endocrine Function Dysfunction Leads to Hyperglycemia in T2DM



HGO = hepatic glucose output

Adapted from Ohneda A, et al. *J Clin Endocrinol Metab.* 1978;46:504–510; Gomis R, et al. *Diabetes Res Clin Pract*. 1989;6:191–198.

Pancreatic Islet Function Deteriorates Over Time, Causing Disease Progression

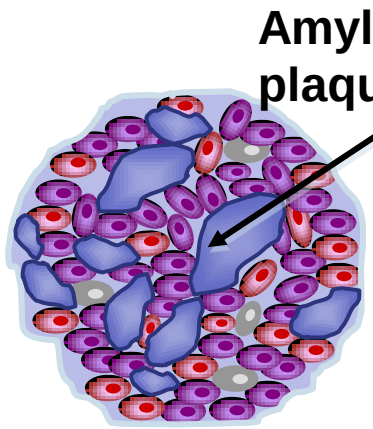


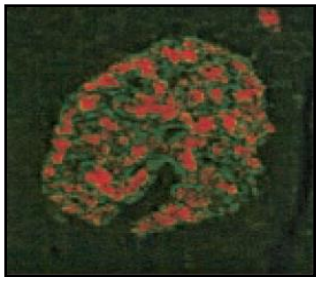
IFG = impaired fasting glucose; IGT = impaired glucose tolerance; NGT = normal glucose tolerance

Adapted from Rickheim P, et al. *Type 2 Diabetes BASICS*. 2nd ed. Minneapolis, Minn: International Diabetes Center; 2000.

Structural and functional changes in pancreatic islets in T2DM

- Disorganized and misshapen
- Marked reduction in β-cell number (apoptosis)
- and volume
- α cells hypertophy
- Amyloid plaques





- Functional changes:
- α/β
- reduced α cells sensitivity to glucose
- reduction of insulin secretion
- increased hepatic glucose ouput

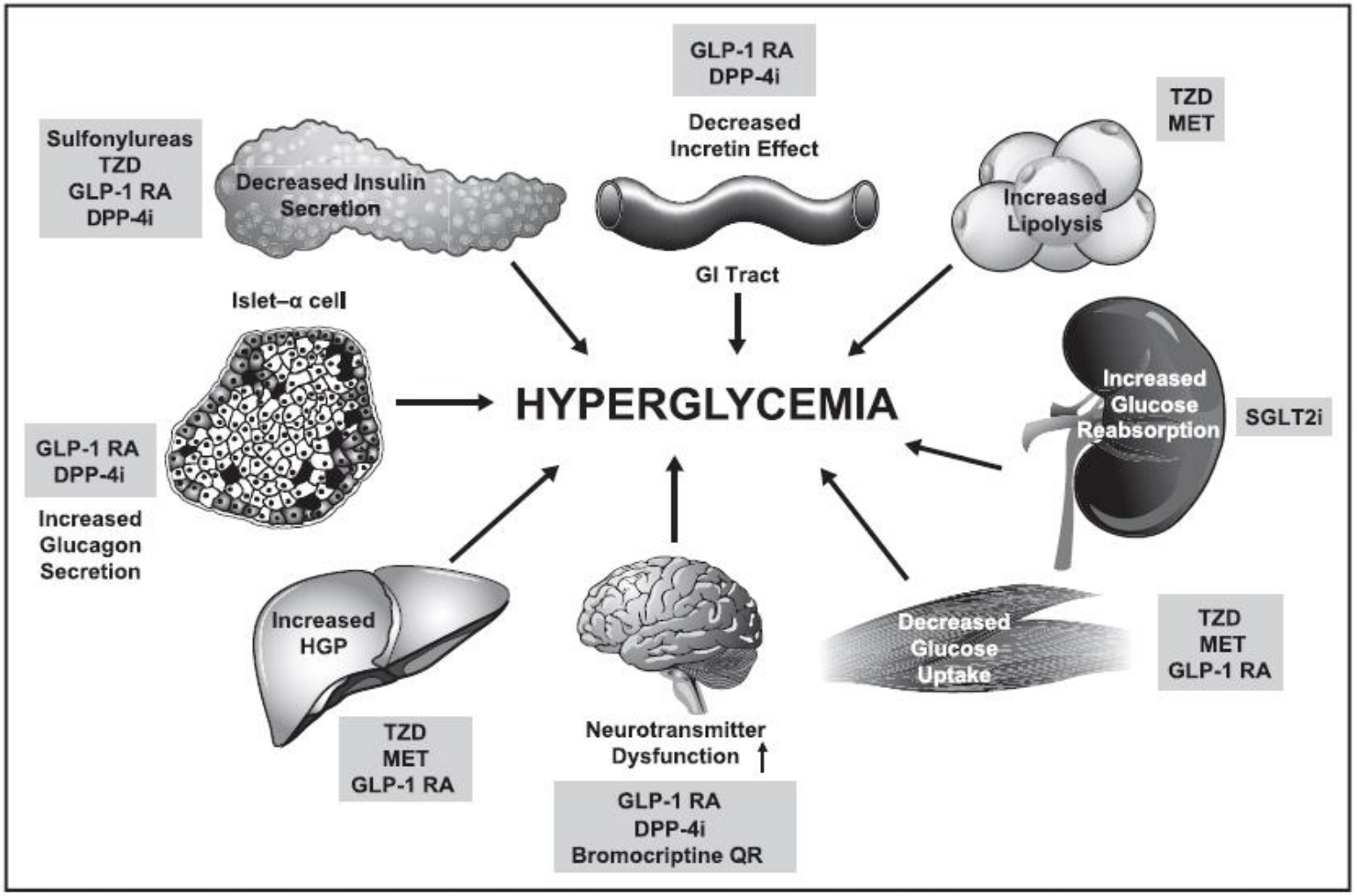


Figure 1. The ominous octet showing the mechanism and site of action of glucose-lowering medications based on pathophysiologic disturbances present in T2DM.[1–3] DPP-4i = dipeptidyl peptidase-4 inhibitor; GI = gastrointestinal; GLP-1 RA = glucagon-like peptide-1 receptor agonist; HGP = hepatic glucose production; MET = metformin; QR = quick release; SGLT2i = sodium glucose cotransporter 2 inhibitor; T2DM = type 2 diabetes mellitus; TZD = thiazolidinedione. Adapted from DeFronzo RA, Eldor R, Abdul-Ghani M. Pathophysiologic approach to therapy in patients with newly diagnosed type 2 diabetes. American Diabetes Association. 2013 Copyright and all rights reserved. Material from this publication has been used with the permission of American Diabetes Association. Available at: http://care.diabetesjournals.org/content/36/Supplement_2/S127.

La terapia farmacologica del diabete

Ipoglicemizzanti

parenterali

- formulazioni di insulina e di analoghi dell'insulina, per il trattamento del paziente tipo 1, diabete gravidico e tipo 2,
- analoghi del GLP-1 o agonisti del recettore per il GLP-1 (GLP-1R), diabete tipo 2

orali

- sulfaniluree e derivati acido benzoico ad esclusiva indicazione per il diabete tipo 2;

Terapia farmacologica del diabete

- **anti-iperglicemizzanti** orali: metformina e inibitori della dipeptidil-dipeptidasi- IV (DPPIV; esclusiva indicazione per il diabete tipo2);
- ***(insulino-sensibilizzanti**: tiazolidindioni, esclusiva indicazione per il diabete tipo2)*
- **inibitori dell' assorbimento** del glucosio a livello intestinale: acarbosio
- **Farmaci che inducono glucosuria:** inibitori della riassorbimento del glucosio a livello renale
- **farmaci della terapia di fondo delle complicanze**

Curr Cardiol Rep (2013) 15:327
DOI 10.1007/s11886-012-0327-1

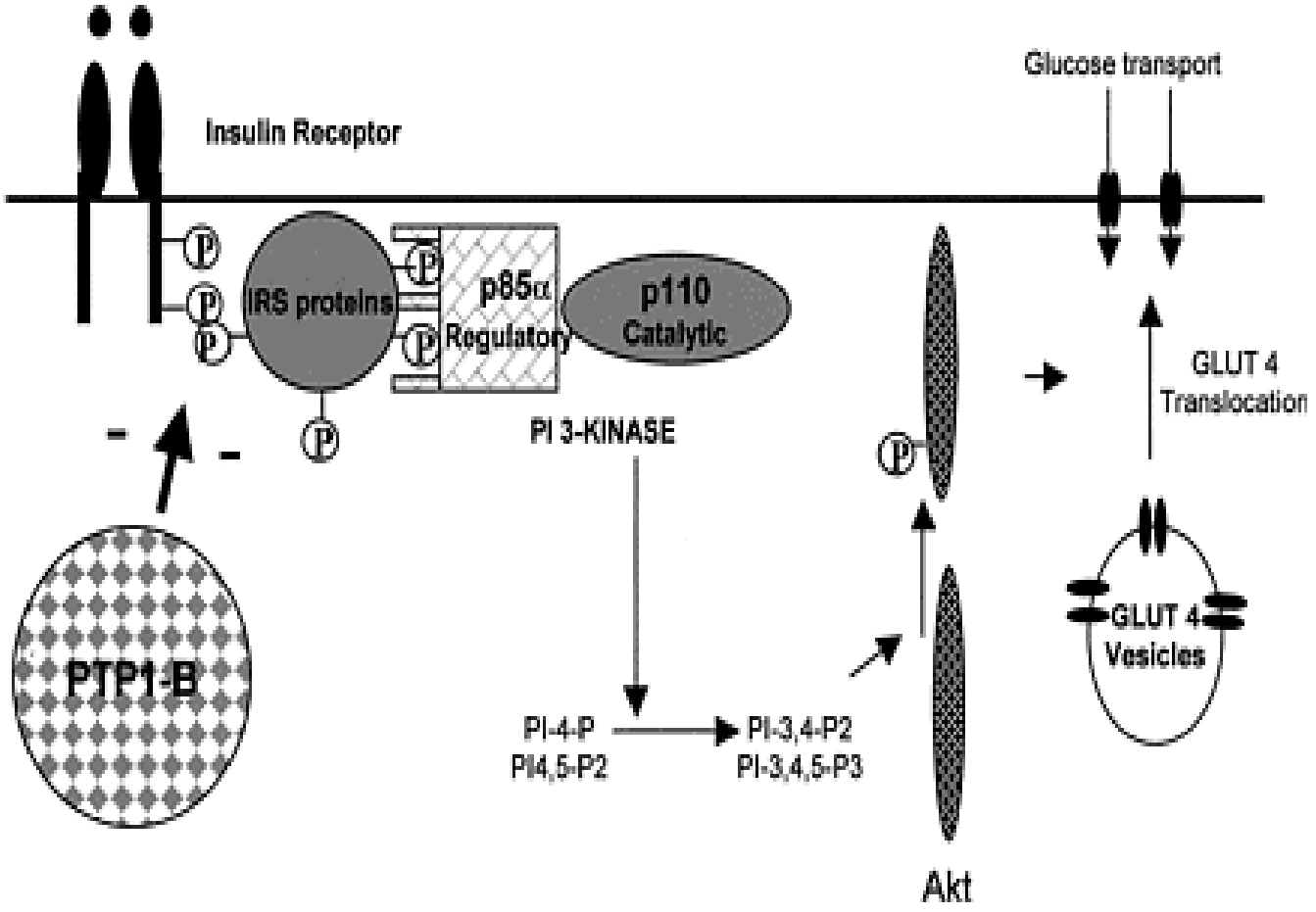
Cardiovascular Effects of Anti-Diabetic Medications in Type 2 Diabetes Mellitus

Samar Singh · Jyoti Bhat · Ping H. Wang

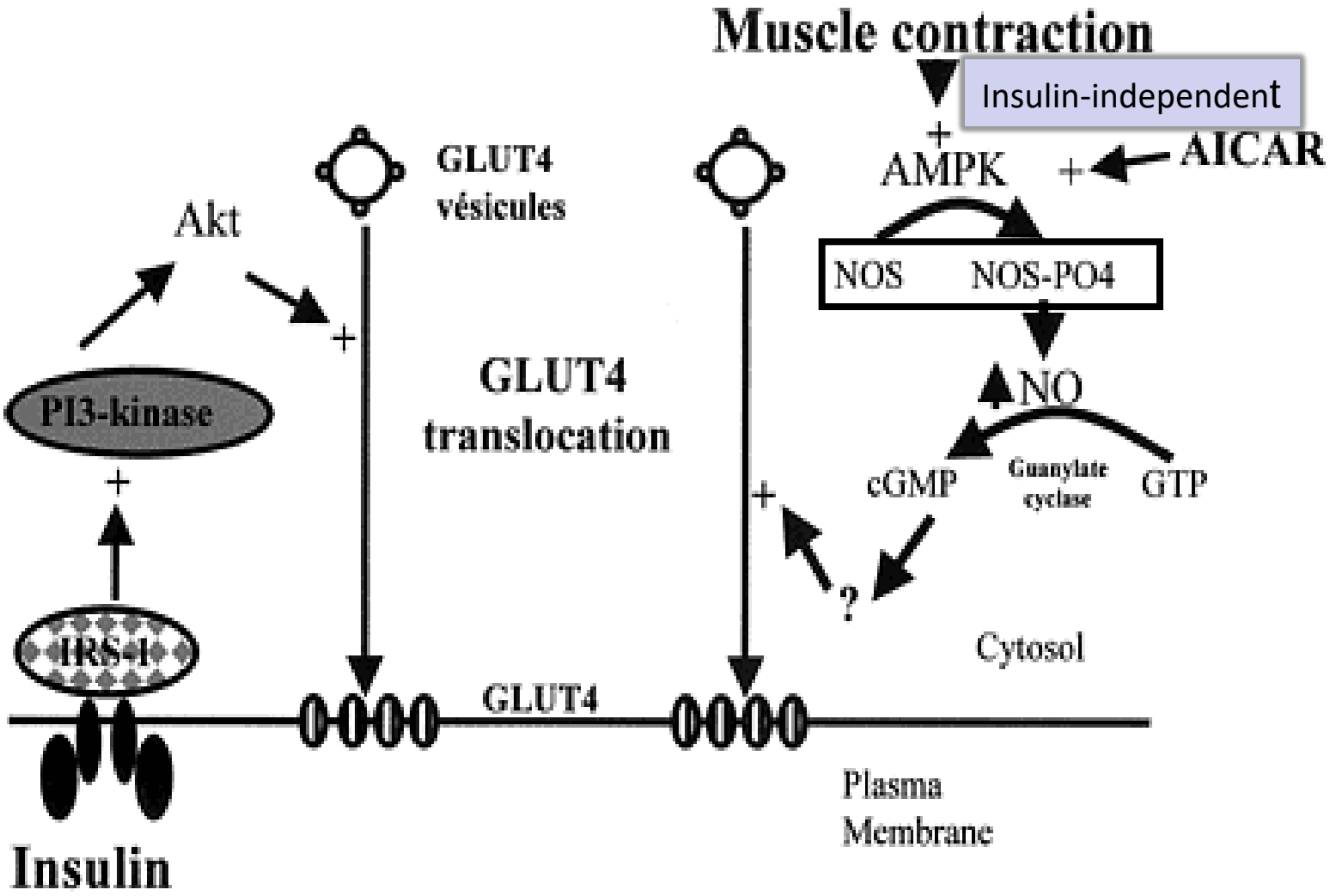
known to lower A1c by approximately 0.5-1.4 % [27]. The three drugs in this category that have been introduced in the United States are troglitazone, rosiglitazone, and pioglitazone. Of these three, troglitazone was removed from the market in 2000 due to hepatoxicity, and rosiglitazone and pioglitazone both have black box warnings due to being linked with congestive heart failure. Because of recent studies, there has been a great deal of skepticism in using TZDs mostly due to concern of congestive heart failure and increased risk of myocardial infarction with rosiglitazone and now a concern of bladder cancer with pioglitazone. Surprisingly, according to the AHA/ADA consensus

Ipoglicemizzanti

Insulin signalling and glucose uptake in muscle and adipose cells



Insulin and muscle contraction: two pathways to stimulate glucose uptake



Insuline ricombinanti

- *Insuline a breve o rapida durata d'azione*. Sono preparazioni di insulina complessata con Zn da somministrare 45-30 min prima del pasto con 5-8 h di durata d'azione.
- *Insuline ad azione intermedia*. Insulina con cinetica **di** solubilizzazione più graduale dopo iniezione. Si tratta di 2 formulazioni: Zn-insulina complessata con protamina, proteina basica, stabilizzata a pH neutro (insulina Hagedorn; NPH, isofano insulina). Durata d'azione dell'ormone fino a 24h.
- *Insulina ad azione lenta*. Si tratta di miscugli di insulina cristallina (ultra-lenta) e amorfa (semilenta) anche fino a 36 h di durata ma picchi ematici bassi che si mantengono abbastanza costanti.

Gli analoghi rapidi

- *Lyspro insulina:* insulina con modificazione della molecola di insulina introducendo sulla catena B una lisina in posizione 28 e una prolina in 29. Alla Lyspro viene poi aggiunta protamina a varie percentuali per modificare le caratteristiche farmacocinetiche

Analoghi lenti

Glargina (3 aminoacidi diversi rispetto alla insulina nativa): con queste modificazioni si ottiene un inizio di azione più lento ma effetto costante, senza picco ematico, per una durata anche fino a 24 ore. Ha efficacia ipoglicemizzante e riduzione della HbA_{1c} simile alla NPH con minore incidenza di eventi ipoglicemici notturni.

Detemir: ottenuta per rimozione della treonina nella catena β (posizione 30) e acilazione di un residuo di lisina (B29) mediante acido miristico. Questa acilazione stabilizza la associazione della molecola di insulina e permette un unico legame insulina-albumina responsabile di un lento assorbimento dai depositi sottocutanei prolungando così la durata d'azione. Insulina detemir riduce la variabilità inter-individuale nel profilo

Questa acilazione stabilizza la associazione della molecola di insulina e permette un unico legame insulina-albumina responsabile di un lento assorbimento dai depositi sottocutanei prolungando così la durata d'azione. Insulina Detemir riduce la variabilità inter-individuale nel profilo farmacocinetico e farmacodinamico della insulina.

Lyspro o Aspart vs insulina umana

I confronti tra insulina Lispro o Aspart e insulina umana regolare non hanno evidenziato differenze statisticamente significative in termini di HbA1c, ipoglicemia severa (notturna e diurna)

Detemir vs. insulina neutra

Gli studi indicano una minore incidenza di ipoglicemia notturna con insulina Detemir. Invece nei casi in cui è stato associato un ipoglicemizzante orale la differenza nell'HbA1c era a favore della associazione detmir con insulina protamina neutra di Hagedorn

Detemir vs. Glargina

non ci sono evidenza a sostegno di differenze significative in termine di efficaciae di incidenza di eventi ipoglicemici

Non sono disponibili dati sufficienti per stabilire se gli analoghi abbiano un profilo migliore rispetto alle insuline convenzionali nella riduzione delle complicanze del diabete o in termini di mortalità.

In studi di confronto tra insulina Lispro o Aspart e insulina umana regolare, condotti su donne gravide con diabete di tipo 1 o diabete gestazionale, non sono state osservate differenze statisticamente significative in termini di HbA1c, ipoglicemia severa, notturna e totale.

Apart from the well-known side effects of insulin therapy, i.e. hypoglycemia and weight gain, there have been concerns about the mitogenic potency of high levels of circulating insulin, and particularly IG. The FDA recently issued a communication to inform the public about four published observational studies, three of which suggested an increased risk of cancer associated with the use of IG [123], but due to methodological limitations, the data was considered inconclusive. Additional review of a 5-year ran-

Sulfaniluree (SU)

The sulfonylureas were introduced in the 1940s and, therefore, may be regarded as the oldest available oral antihyperglycemic drugs. Sulfonylurea stimulate insulin secretion by closing the ATP-dependent potassium (K_{ATP})-channels on the beta-cell surface [21], in a glucose-independent manner.

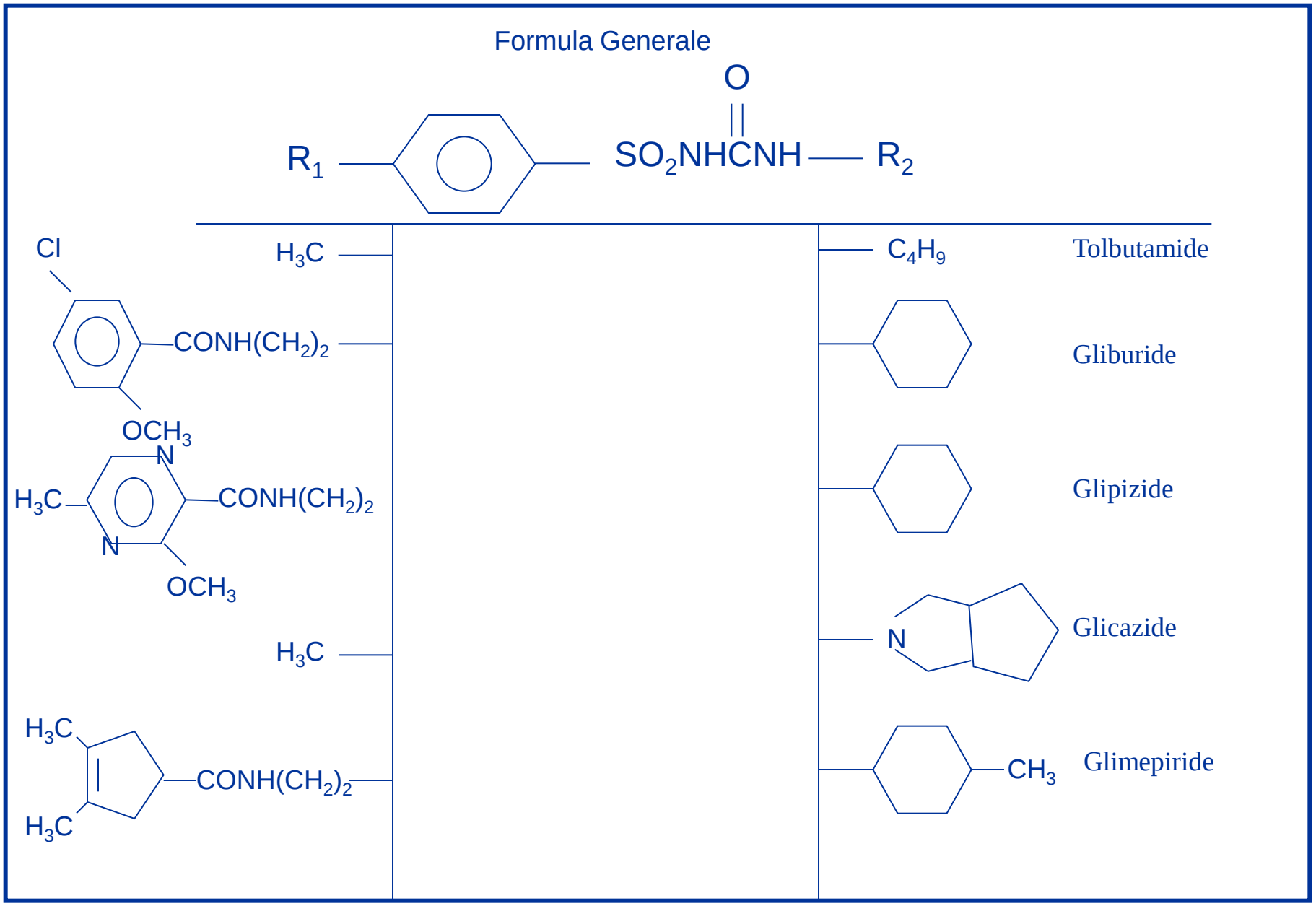
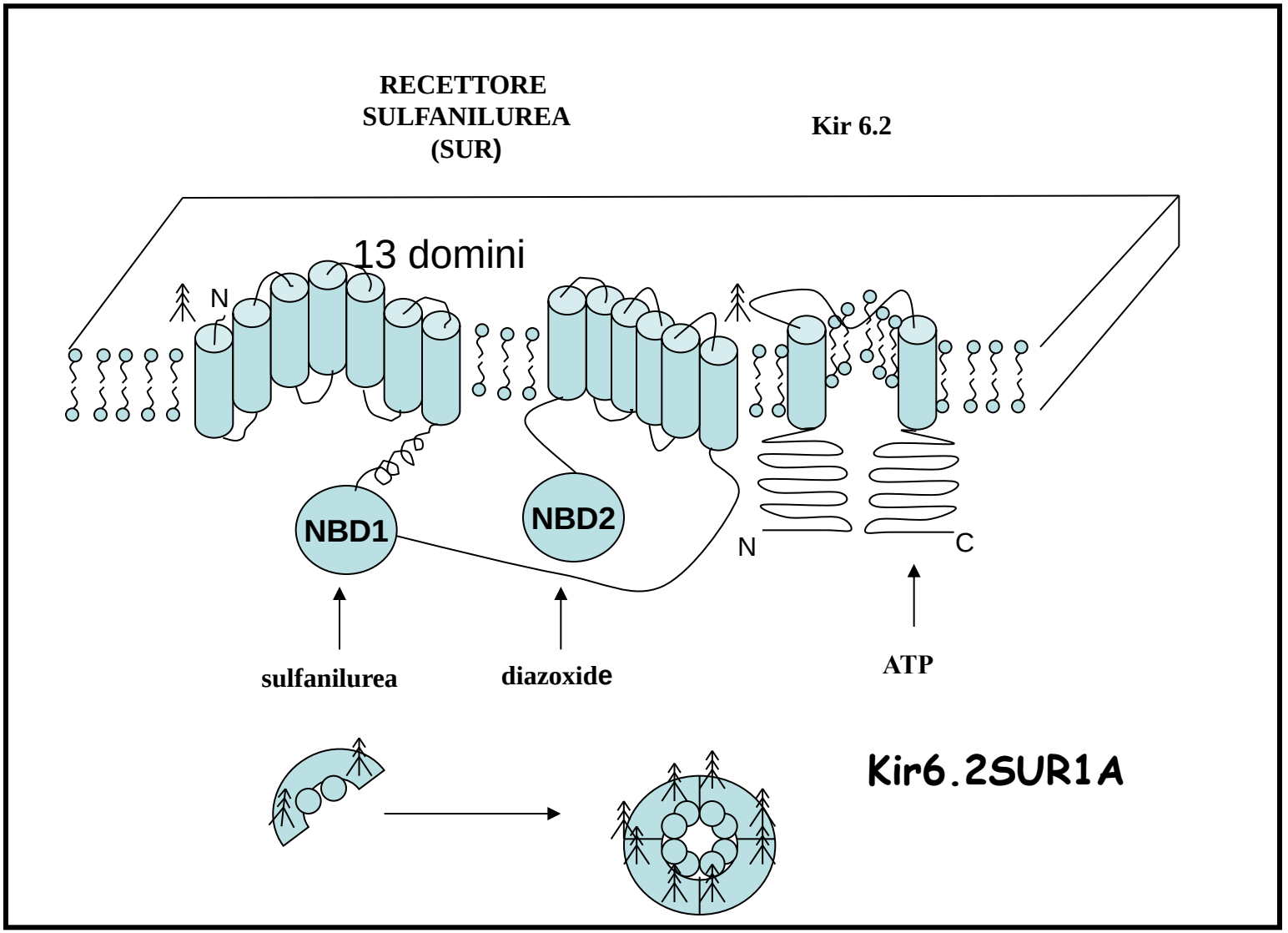


Figura 1. Struttura chimica delle varie SU.



Struttura molecolare del monomero K^+ ATP-recettore alle sulfaniluree nella cellula β pancreatica

INDICAZIONI

- SULFANILUREE

  - Generali:
    - Diabete mellito non insulino-dipendente non controllabile con la sola dietoterapia.
  - Appropriatezza di uso:
    - Episodi ipoglicemici: ridotti con glipizide (t 1/2 breve) e gliquidone (risposta insulinemica più fisiologica).
    - Potenza di effetto: glibenclamide e glipizide equipotenti con effetto superiore alle altre sulfaniluree.
    - gliclazide usata in IR di grado lieve e moderato.
    - In sostituzione a sulfaniluree di ridotta efficacia: glibenclamide.
    - Associazioni con insulina: glibenclamide, gliciclamide.
    - Compliance: clorpropamide in pz con scarsa compliance.

CONTROINDICAZIONI

- SULFANILUREE
  - Generali:
    - Diabete insulino-dipendente
    - Gravidanza
    - Allattamento
    - Insufficienza surrenale
  - Specifiche:
    - clorpropamide: grave ipotiroidismo.
    - clorpropamide, glimepiride, gliciclamide, glibenclamide in IR e insufficienza epatica.

REAZIONI AVVERSE

- SULFANILUREE
- Ipoglicemia
- Incremento ponderale
- Discrasie ematiche
- Sindrome di inappropriata secrezione di ADH (SIADH)

Increased risk of stroke in patients with chronic kidney disease after recurrent hypoglycemia. Neurology. 2014; 83:686-94.

Interazioni farmacologiche delle SU

Farmaci che spiazzano le SU dalle proteine plasmatiche

salicilati, warfarin, antiepilettici, antibiotici sulfamidici per la loro analogia strutturale con le SU.

aumento dell'effetto ipoglicemizzante.

Interazioni Farmacologiche delle SU

Farmaci che interferiscono con la frequenza di chiusura/apertura del canale al K+ della cellula b pancreatica: il diazossido e alcuni diuretici tiazidici, farmaci che aprono i canali al K+,

riducono l'effetto ipoglicemizzante delle SU.

Farmaci che interferiscono con l'assorbimento intestinale delle SU: colestiramina, antiacidi

Farmaci che potenziano l'azione delle SU agendo su recettori che controllano il rilascio di insulina:

β bloccanti, α agonisti, inibitori delle mono aminossidasi (iMAO).

Farmaci che alterano la potenza terapeutica delle SU con meccanismo non conosciuto: fluorochinoloni, enalapril, gemfibrozil, trimetoprin.

Diabetologia. 2014 Sep 10 [Epub ahead of print]

Sulfonylurea in combination with insulin is associated with increased mortality compared with a combination of insulin and metformin in a retrospective Danish nationwide study.

Benzoic Acid Derivative (Repaglinide)

Mechanism of Action. Repaglinide is a benzoic acid derivative that also stimulates insulin secretion by interacting with the ATP-sensitive K+ channels but via an apparently different receptor than the sulphonylureas. It is, therefore, regarded as a non-sulphonylurea insulin secretagogue.

From popular medicine…

Historical accounts reveal that type II diabetes existed long ago, and medicinal plants have been used for many millennia to treat this disease.

To date, the anti-diabetic activities of well over 1200 traditional plants has been reported, although scant few have been subjected to rigorous scientific evaluation for safety and efficacy in humans.

Galega officinalis

Famiglia: Leguminose

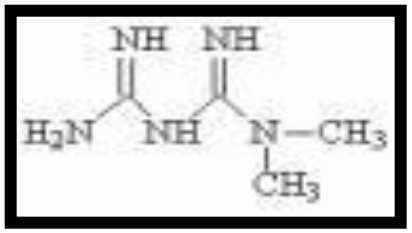
Nome volgare: Galega.capraggine

Caratteristiche: Pianta erbacea perenne **Habitat:** Luoghi umidi ed erbosi.0-1300 m. Maggio luglio

Proprietà farmaceutiche: rinfrescanti. (Droga usata: parte aerea della pianta).

Galega's juce

Ricco in derivati guanidinici tra cui

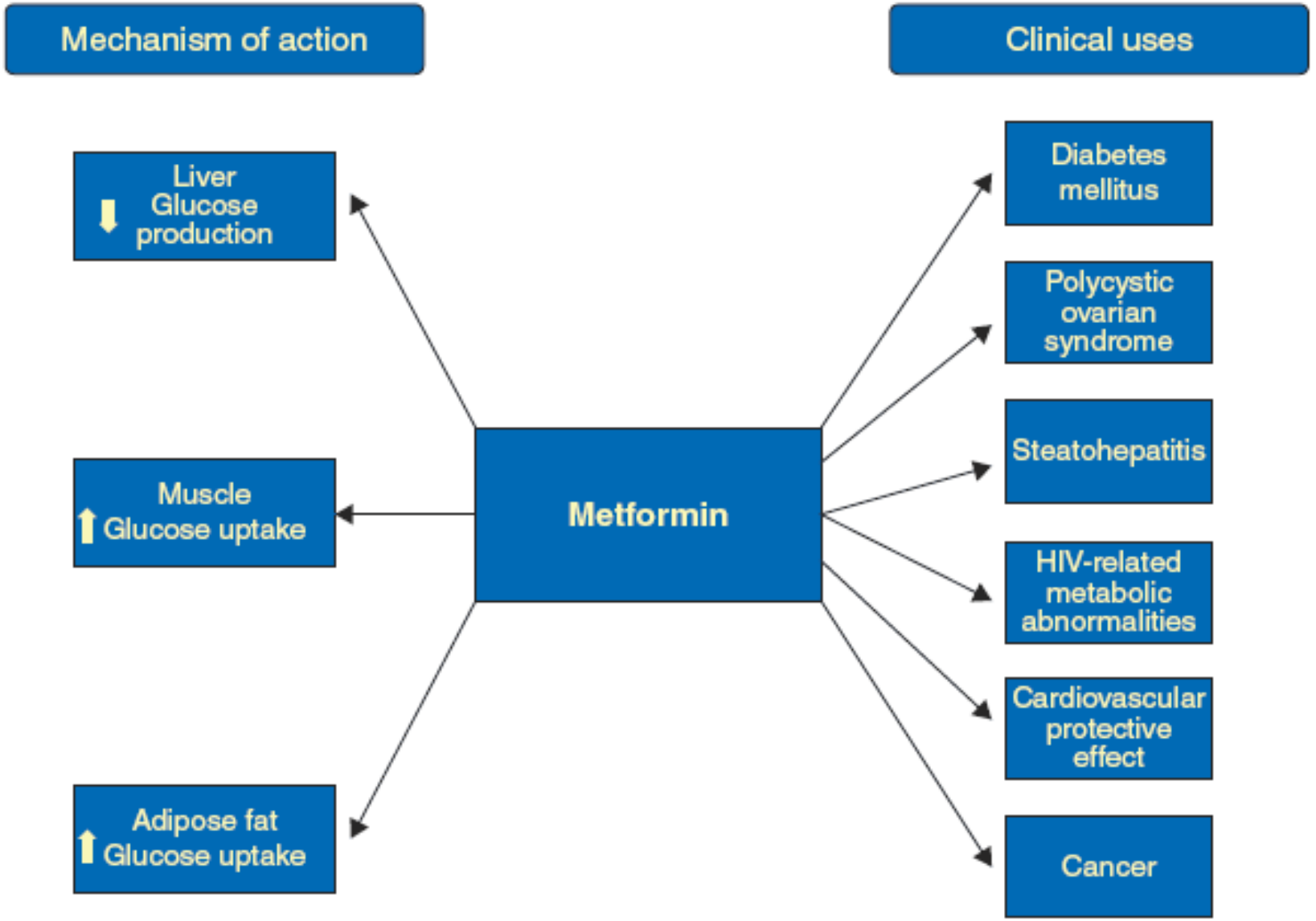


Metformin

Metformin

Approved by the FDA for use in the United States in 1995.

Its primary effect is to enhance insulin-mediated inhibition of hepatic glucose production and stimulation of glucose transport into muscle.


Mechanism of action
Clinical uses
Liver
Glucose
production
Muscle
Glucose uptake
Adipose fat
Glucose uptake
Metformin
Diabetes
mellitus
Polycystic
ovarian
syndrome
Steatohepatitis
HIV-related
metabolic
abnormalities
Cardiovascular
protective
effect
Cancer

This biguanide, which is derived from extracts of the French Lilac [12], remains the first choice agent for treatment of T2DM worldwide, because of its efficacy, low cost, weight neutrality, no increased risk of hypoglycemia, and most importantly, its proven long-term efficacy on outcome [13,

Pleyotropic effects

- **Increase of GLP-1 secretion**
- **Reduction of LDL-cholesterol**
- **Reduction of PAI-1**
- **Polyistic ovaric syndrome**
- **Reduction of insulin levels**
- **Reduction of body weight**
- **Reduction of SP**

Other effects of metformin

- Reduces lipolysis contributing to reduce free fatty acids
- Reduces uncoupling proteins activity potentially triggering metabolic acidosis

CONTROINDICAZIONI

Gravidanza

Allattamento

Insufficienza epatica

Insufficienza surrenale

Malattie cardiovascolari e respiratorie (con ipossia tissutale)

Alcolismo

Acidosi metabolica

REAZIONI AVVERSE

Disturbi gastrointestinali

Acidosi lattica (rara)

Riduzione dei livelli di vit.B_{12}

Metformin and Cancer

Metformin and Cancer Occurrence in Insulin-Treated Type 2 Diabetic Patients

Several studies have shown that metformin is associated with reduced cancer-related morbidity and mortality, due to improvement in insulin sensitivity or to the activation of AMP-activated protein kinase

Matteo Monami et al *2011Diabetes Care January vol. 34 no. 1 129-131*

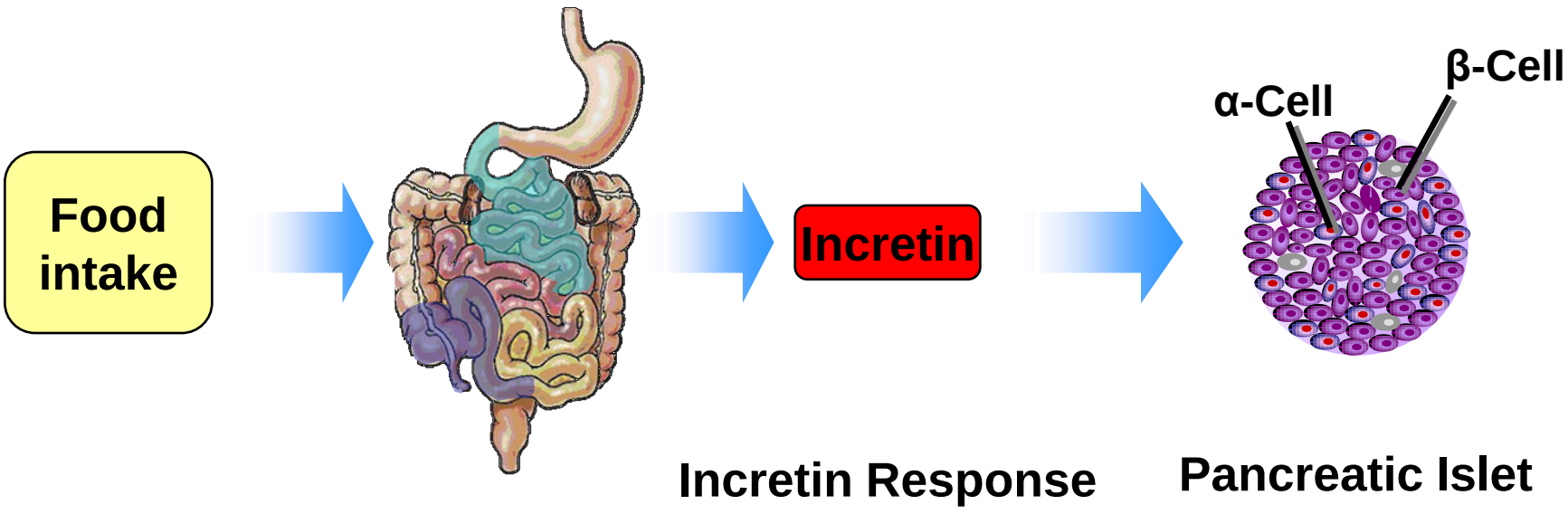
Farmaci che potenziano l'efficacia delle incretine

Incretin-based therapies

Injectable GLP-1 analogs or GLP-1 Receptor agonists

Inhibitors of DPP-IV

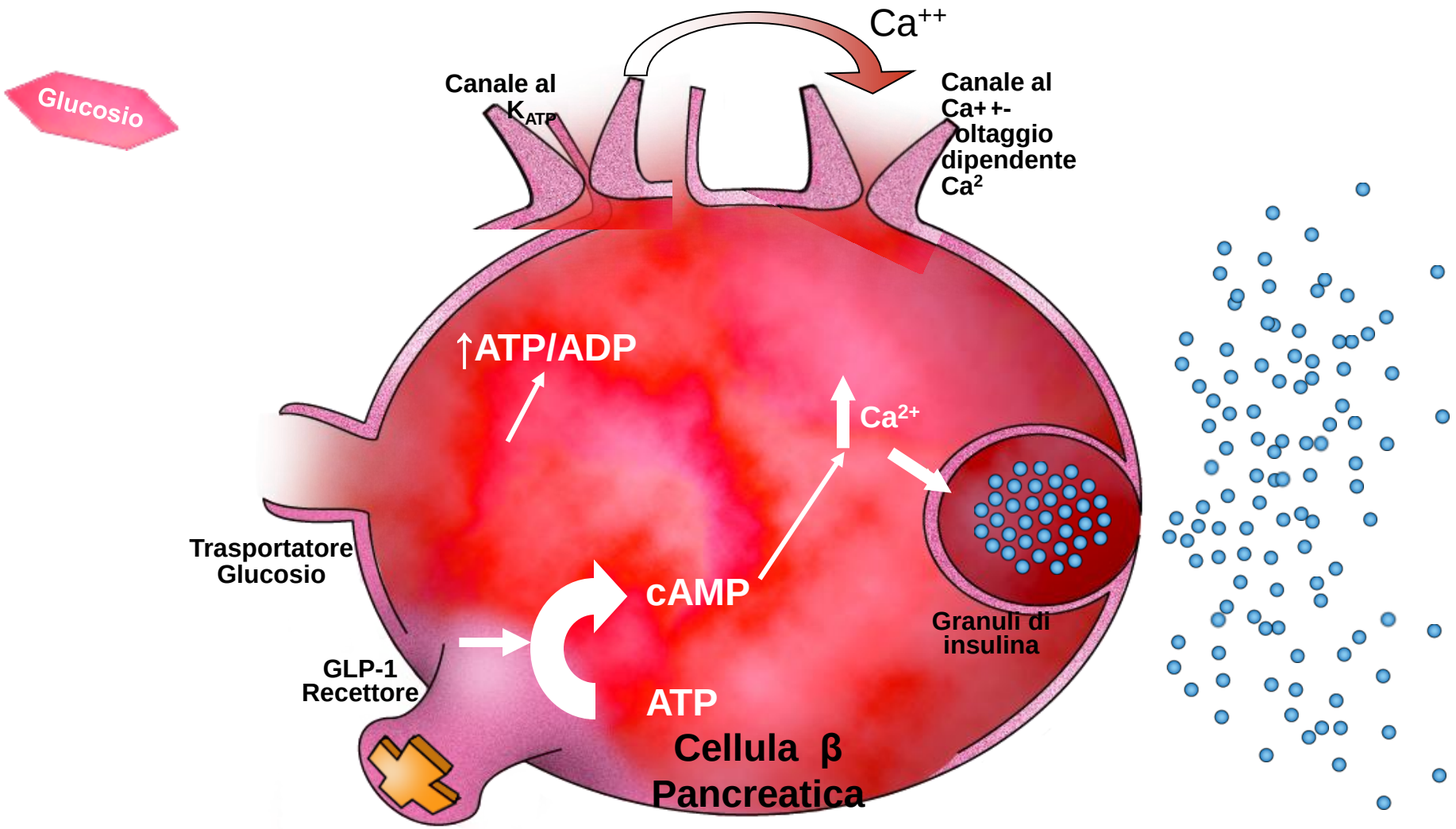
Pancreatic Islet Cells are Targets for Incretin Hormones



GLP-1=Glucagon-Like Peptide-1

Adapted from Drucker D. *Diabetes Care.* 2003;26:2929-2940. Wang Q, *et al*. *Diabetologia.* 2004;47:478-487.

L'effetto insulinotropo di GLP-1 è mediato dal glucosio



Gromada J, et al. *Pflugers Arch – Eur J Physiol.* 1998;435:583-594; MacDonald PE, et al. *Diabetes.* 2002;51:S434-S442.

Figura 2

Exenatide (Exendin-4)

- Versione sintetica del peptide trovato nelle ghiandole salivari della Gila monster
- Circa 50% identico con GLP-1umano

  Si lega a recettori per il GLP-1 sulle cellule n β cells *in vitro*

  -Resistente alla inattivazione da parte della DPP-IV

Exenatide	H **G** E G T F T S D **L** S **K Q M** E **E E** A **V R L** F I **E** W L **K N** G **G P S S G A P P P S – NH$_2$**
GLP-1 Human	H A E G T F T S D V S S Y L E G Q A A K E F I A W L V K G R – NH$_2$

Sito di inattivazione da parte della DPP-IV

Exendin-4 (Exenatide; Byetta)

Stimulates secretion of insulin in the presence of elevated blood glucose, but not during periods of hypoglycemia.

The peptide modulates gastric emptying to slow the absorption of ingestion of nutrients into the blood stream.

53% sequence identity to native GLP-1

(antibodies?)

Long-acting GLP-1 analogues

✓Liraglutide is a GLP-1 analog that shares 97% sequence identity to native GLP-1

The addition of a C16 fatty acid side chain enables once-daily dosing of liraglutide by prolonging its duration of action to over 24 h

✓ Once weekly exenatide LAR (2 mg)

Clinical use

Liraglutide 1.8 mg reduced HbA1c by 0.33% more than exenatide 10 μg twice daily. Liraglutide led to similar improvements in HbA1c compared to sulphonylureas but reduced it more than sitagliptin and rosiglitazone.

Both exenatide and liraglutide led to greater weight loss than most active comparators, including in participants not experiencing nausea.

Hypoglycaemia occurred more frequently in participants taking concomitant sulphonylurea.

Liraglutide as monotherapy in doses of 0.9 mg or above showed a significantly superior reduction in HbA1C compared to monotherapies with glimepiride or glyburide.

When liraglutide was used as add-on therapy to glimepiride in doses of 1.2 mg or above, the reduction of HbA1C was greater than that in the combination therapy of glimepiride and rosiglitazone

In clinical practice, liraglutide is a potent anti-diabetic drug whether given in combination with oral agents, insulin or following substitution of Exenatide.

It lowers weight,

HBA1c, systolic blood pressure, reactive C protein and triglyceride

Varanasi et al., Endocr Pract. 2011

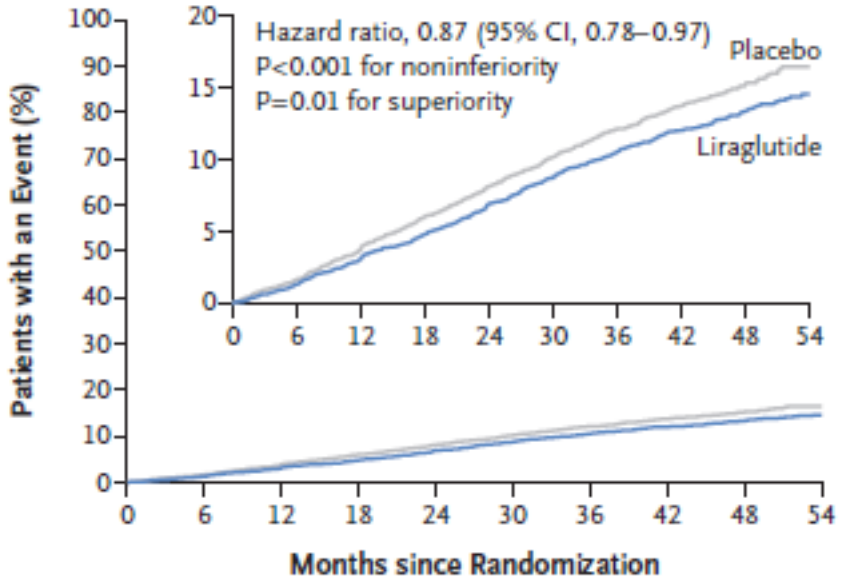
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 28, 2016 VOL. 375 NO. 4

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Steven P. Marso, M.D., Gilbert H. Daniels, M.D., Kirstine Brown-Frandsen, M.D., Peter Kristensen, M.D., E.M.B.A., Johannes F.E. Mann, M.D., Michael A. Nauck, M.D., Steven E. Nissen, M.D., Stuart Pocock, Ph.D., Neil R. Poulter, F.Med.Sci., Lasse S. Ravn, M.D., Ph.D., William M. Steinberg, M.D., Mette Stockner, M.D., Bernard Zinman, M.D., Richard M. Bergenstal, M.D., and John B. Buse, M.D., Ph.D., for the LEADER Steering Committee on behalf of the LEADER Trial Investigators*

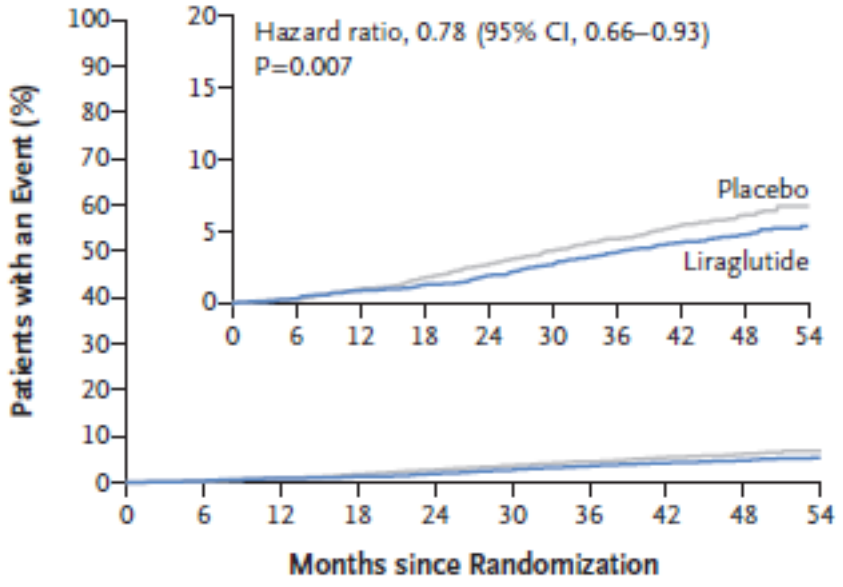
A Primary Outcome



No. at Risk

Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424
Placebo	4672	4588	4473	4352	4237	4123	4010	3914	1543	407

B Death from Cardiovascular Causes



No. at Risk

Liraglutide	4668	4641	4599	4558	4505	4445	4382	4322	1723	484
Placebo	4672	4648	4601	4546	4479	4407	4338	4267	1709	465

Liraglutide and β-cell mass

Liraglutide increased the β-cell mass by upregulating β-cell proliferation and that the proliferative action of liraglutide in β cells was mediated by activation of PI-3K/Akt, which resulted in inactivation of FoxO1 and decreased p27.

Fang et al., Mol Med Report. 2011

Liraglutide long acting (LAR) antiobesity and in the prevention of type 2 diabetes

- Liraglutide ha dimostrato di ridurre efficacemente il peso corporeo, ma anche di mantenere il calo ponderale ottenuto significativamente superiore a 3 anni rispetto al solo intervento sullo stile di vita (–6·1 [SD 7·3] vs –1·9% [6·3], p<0·0001).
- Viene anche mantenuta la perdita di peso ottenuta mediante una dieta a basso contenuto calorico (81.4 versus 48.9%; P<0.0001), con un ulteriore decremento ponderale (+6.2% [S.D. 7.3] liraglutide vs. + 0.2% [S.D. 7.0] placebo, p<0.0001) (3).
- Infine, dati recenti hanno mostrato la superiorità di Liraglutide 3 mg, associata a modificazioni dello stile di vita, rispetto alle sole modifiche dello stile di vita, nel ridurre la comparsa di diabete nei soggetti obesi (HR 0·21 (95% CI 0·13– 0·34). In tutti gli studi del programma SCALE sono emersi ulteriori benefici cardio-metabolici (riduzione della pressione arteriosa, della circonferenza vita, miglioramento del profilo lipidico).

Obesity Management Task Force of the European Association for the Study of Obesity. European Guidelines for Obesity Management in Adults, Obes Facts 2015;8:402–424

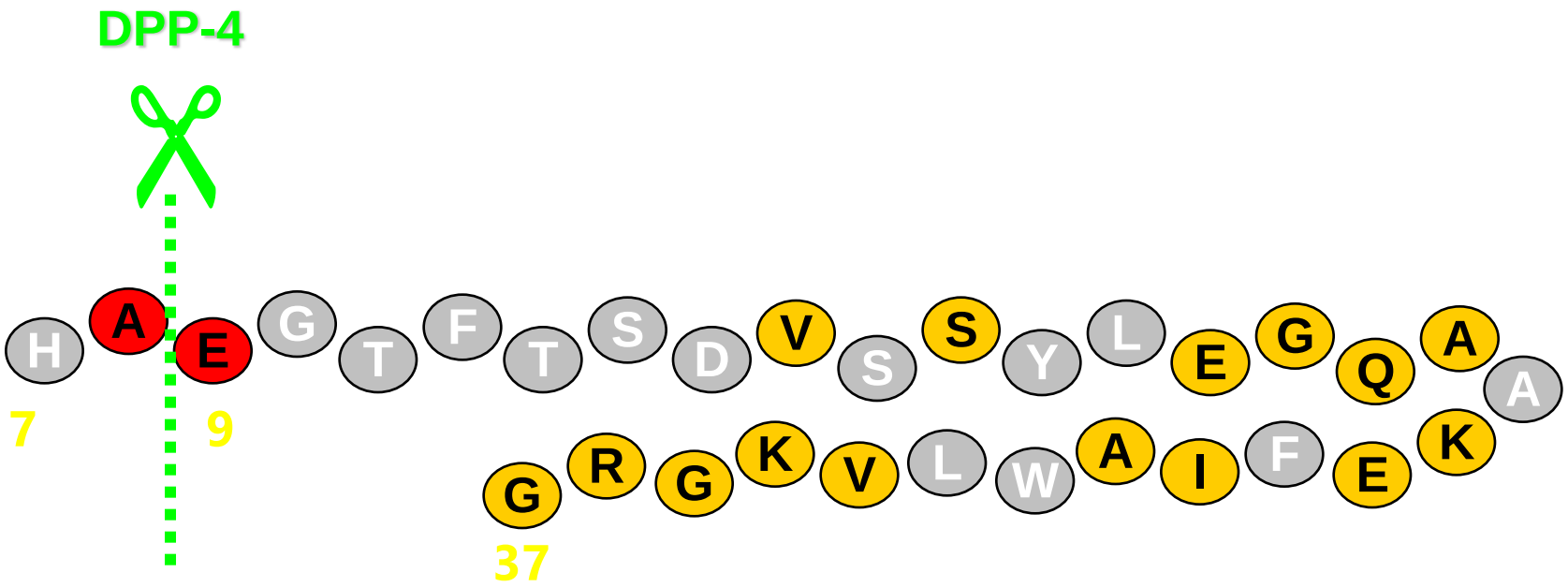
3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial, Lancet. 2017 Feb 22. pii: S01406736(17)30069-7

Liraglutide

- Like other GLP-1 analogs it delays gastric emptying, potentially affecting absorption of concomitantly administered oral drugs.

on the pharmacokinetics of the components of an oral contraceptive (ethinyl estradiol/levonorgestrel).

GLP-1 is Rapidly Degraded by the DPP-IV enzyme



$T_{½}$ = 1–2 minutes

*Amino acids shown in gold are homologous with the structure of glucagon

DPP-IV inhibitors (incretin mimetics)

These compounds may play an important role in the treatment of patients with T2DM as their potential effects go beyond glucose-lowering (weight loss, potential improvement of cardiovascular risk factors). However, to better understand their place in the management of T2DM, further experimental and clinical prospective studies are required.

Diabetes Metab. 2011; 37:477-88.

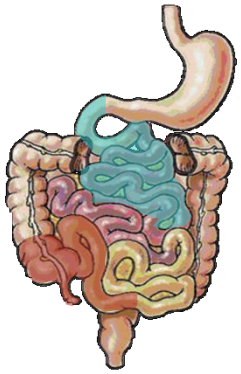
What Is DPP-IV?

- A serine protease widely distributed throughout the body WITH restricted substrate specificity: 80 AA < PEPTIDES>30 AA
- It Cleaves N-terminal amino acids of a number of biologically active peptides, including GLP-1 and GIP, substance P and NPY
- DPP-IV effects on GLP-1 and GIP proven to play a key role in incretin activity and glucose homeostasis
  - Inactivates GLP-1 >50% in ~1–2 min
  - Inactivates GIP >50% in ~7 min

DPP-4 = dipeptidyl peptidase-4; GIP = glucose-dependent insulinotropic peptide; GLP-1 = glucagon-like peptide-1; t½ = half-life

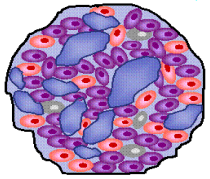
Adapted from Ahrén B. *Curr Enzyme Inhib*. 2005;1:65–73.

DPP-IV Inhibition enhances the physiological effects of incretin hormones



T2DM

Incretin Response Diminished

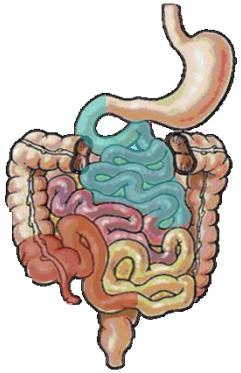


↓ Insulin

Further impaired islet function

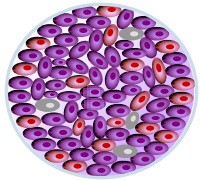
↑ Glucagon

HYPERGLYCAEMIA



DPP-4 Inhibitor

Incretin Activity Prolonged



↑ Insulin

Improved islet function

↓ Glucagon

IMPROVED GLYCAEMIC CONTROL

HGO = hepatic glucose output

Adapted from Unger RH. *Metabolism* 1974;23:581–593

Vildagliptin

è il primo inibitore della DPP-IV della serie delle gliptine approvato in Italia. Vildagliptin aumenta la semivita del GLP-1 e dell'altra incretina, il peptide insulinotropo GIP. Attraverso questa azione si ottiene il beneficio sul controllo glicemico e sulla riduzione della glicata.

Molti altri:

Sitagliptin

Saxagliptin

Linagliptin

Alogliptin

Vildagliptin

presenta un rapido assorbimento per via orale (tmax 1.5-2.0 ore) e rapidamente eliminata per via renale ($t_{1/2}$ di circa 2 ore). Per la sua breve emivita non si osservano fenomeni anche dopo somministrazione di multidose.

Vildagliptin (da 25 to 200 mg) produce una inibizione rapida e quasi totale (>95%) della DPP-IV per almeno 4 ore con associato un aumento delle concentrazioni plasmatiche di GLP-1. Vildagliptin non produce modifiche della glicemia e dell'insulina plasmatica in pazienti non diabetici.

(Light) Concerns…

- The most commonly seen adverse effect of vildagliptin in patients with type 2 diabetes is stuffy or runny nose and sore throat
- DPP-IV scavenges substance P
- DPP-4 attenuates the pro-inflammatory actions of substance P (associated with oedema and pain)
- The role of DPP-IV inhibition in patients with rheumatoid arthritis
- DPP-IV scavenges substance NPY
- pressor effects?

Indicazioni

Come per exenatide anche la somministrazione di vildagliptin si correla ad un miglioramento della funzione pancreatica e riduce la progressione della disfunzione pancreatica diabetica.

Trattamento farmacologico del diabete tipo 2 in combinazione con metformin (peraltro inibitore della DPP-IV), sulfoniluree o thiazolidinedioni in pazienti con inadeguato controllo glicemico con la sola monoterapia.

Non modifica sostanzialmente il peso corporeo .

The cardiovascular protection of gliptins, if any, is not a class effects

DPP-4 inhibition with saxagliptin did not increase or decrease the rate of ischemic events, though the rate of hospitalization for heart failure was increased.

Although saxagliptin improves glycemic control, other approaches are necessary to reduce cardiovascular risk in patients with diabetes

(N Engl J Med. 2013;369:1317-26)

Original Article

Sitagliptin on Cardiovascular Outcomes in Type 2

Jennifer B. Green, M.D., M. Angelyn Bethel, M.D., Paul W. Armstrong, M.D., John B. Buse, M.D., Ph.D., Samuel S. Engel, M.D., Jyotsna Garg, M.S., Robert Josse, M.B., B.S., Keith D. Kaufman, M.D., Joerg Koglin, M.D., Scott Korn, M.D., John M. Lachin, Sc.D., Darren K. McGuire, M.D., M.H.Sc., Michael J. Pencina, Ph.D., Eberhard Standl, M.D., Ph.D., Peter P. Stein, M.D., Shailaja Suryawanshi, Ph.D., Frans Van de Werf, M.D., Ph.D., Eric D. Peterson, M.D., M.P.H., Rury R. Holman, M.B., Ch.B., for the TECOS Study

N Engl J Med
Volume 373(3):232-242
July 16, 2015

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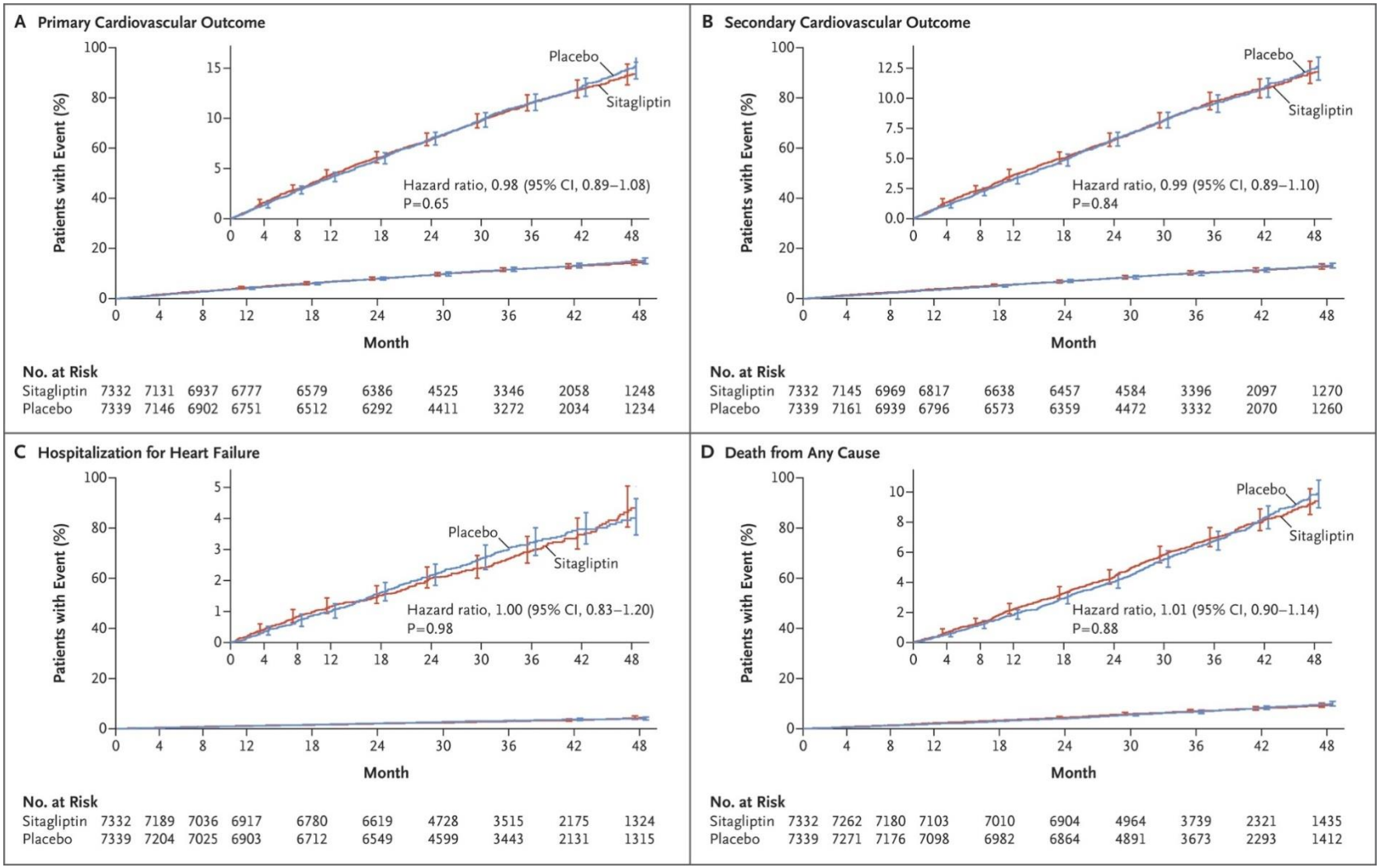

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Conclusions

Among patients with type 2 diabetes and established cardiovascular, adding sitagliptin to usual care did not appear to increase the risk of major adverse cardiovascular events, hospitalization for heart failure, or other adverse events disease, adding sitagliptin to usual care did not appear to increase the risk of major adverse cardiovascular events, hospitalization for heart failure, or other adverse events.

Adverse effects

Concern has been raised about a possible association between incretin-based therapies and adverse pancreatic effects.[15] Although acute pancreatitis was uncommon, it occurred more often in the sitagliptin group, but the difference was not significant. Pancreatic cancer was also uncommon and occurred more often in the placebo group, but again the difference was not significant.

BMJ

BMJ 2013;346:f3680 doi: 10.1136/bmj.f3680 (Published 10 June 2013)

FEATURE

DIABETES DRUGS

Has pancreatic damage from glucagon suppressing diabetes drugs been underplayed?

Incretin mimetics have been called "the darlings of diabetes treatment" and they may soon also be licensed for treating obesity. But a *BMJ* investigation has found growing safety concerns linked to the drugs' mechanism of action. **Deborah Cohen** asks why patients and doctors have not been told.

Deborah Cohen *investigations editor*

BMJ, London WC1H 9JR, UK

New Approaches to Harnessing Incretins for Improved Glucose Control

DPP-4 Inhibitors (incretin mimetics)	Incretin Analogues
• Significant HbA1c reduction	• Significant HbA1c reduction
• Weight neutral	• Weight loss (satiety)
• Oral administration	• Injection
• Almost no GI side effects	• Higher rate of GI side effects
• GLP-1 and GIP effects	• GLP-1 effects only
• Very low rate of hypoglycaemia	• Higher rate of hypoglycaemia in combination with SUs

GI = gastrointestinal

SGLT2 inhibition: a paradigm shift for a novel strategy for diabetes treatment

Bristol-Myers Squibb and AstraZeneca Collaboration

Bristol-Myers Squibb and AstraZeneca entered into a collaboration in January 2007 to enable the companies to research, develop and commercialize select investigational drugs for type 2 diabetes. The Bristol-Myers Squibb/AstraZeneca Diabetes collaboration is dedicated to global patient care, improving patient outcomes and creating a new vision for the treatment of type 2 diabetes.

The kidney has a key role in regulating glucose levels by mediating the re-absorption of glucose back into the plasma following filtration of the blood

- SGLTs activity represent a crucial evolutionary adaptation aimed to maintaining glucose homeostasis and to retaining calories;
- Diabetic patients have increased capacity for renal glucose reabsorption.

- The kidney is well engineered to perform coupled glucose and sodium reabsorption. In the S1/S2 segment of the proximal tubule, a member of the sodium glucose transporter (SGLT) family of transmembrane proteins, SGLT-2—encoded in the *SLC5* gene—is expressed at high levels and co-transports filtered glucose and sodium into the tubular cell cytoplasm.
- Downstream to the S1/S2 segment along the S3 segment of the proximal tubule, another SGLT isoform—SGLT-1, abundantly expressed in the enterocyte—also performs coupled sodium-glucose co-transport.
- At the basolateral membrane of the tubular cell, a glucose transporter of a different family, GLUT-2, affects the transfer of intracellular glucose to the interstitium by a facilitated transport process (via Na^+-K^+-ATPase).

Plasma glucose is filtered freely through the glomerular barrier

- In a 70-kg adult with a glomerular filtration rate of 120 mL · min^{-1} per 1.73 m^2 and an average, around-the-clock plasma glucose concentration of 120 mg/dL (6.7 mmol/L), ~200 g of glucose are transferred daily from the bloodstream into the preurine.
- If nothing else happened, the whole-body mass of free glucose (some 20 g in a distribution volume of 250 mL/kg) would be emptied out in less than 3 h.
- What prevents this catastrophe is, on the one hand, virtually complete glucose reabsorption at the level of the kidney and on the other hand, a precisely matched modulation of endogenous glucose release (chiefly by the liver and possibly also by the kidney itself).

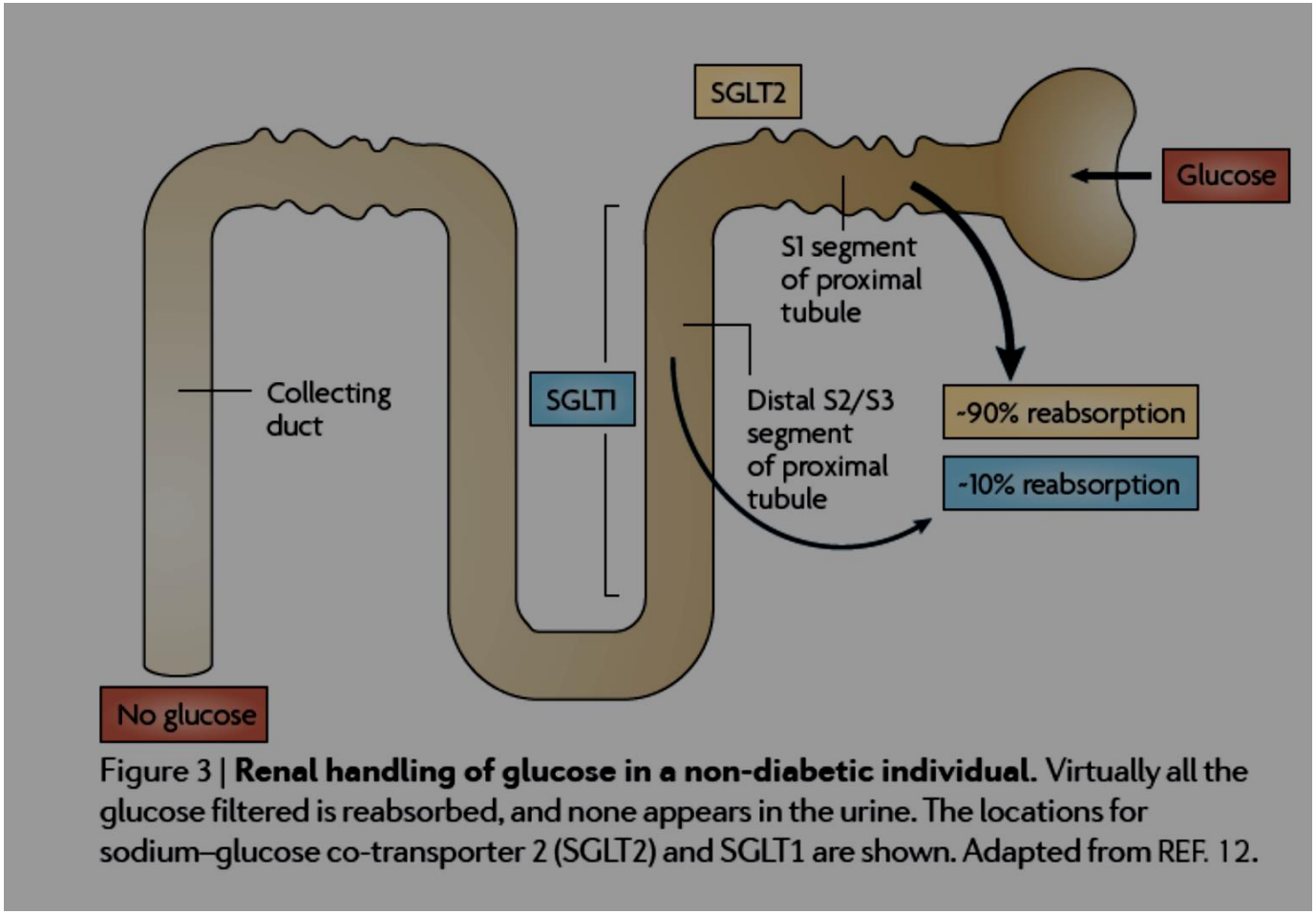


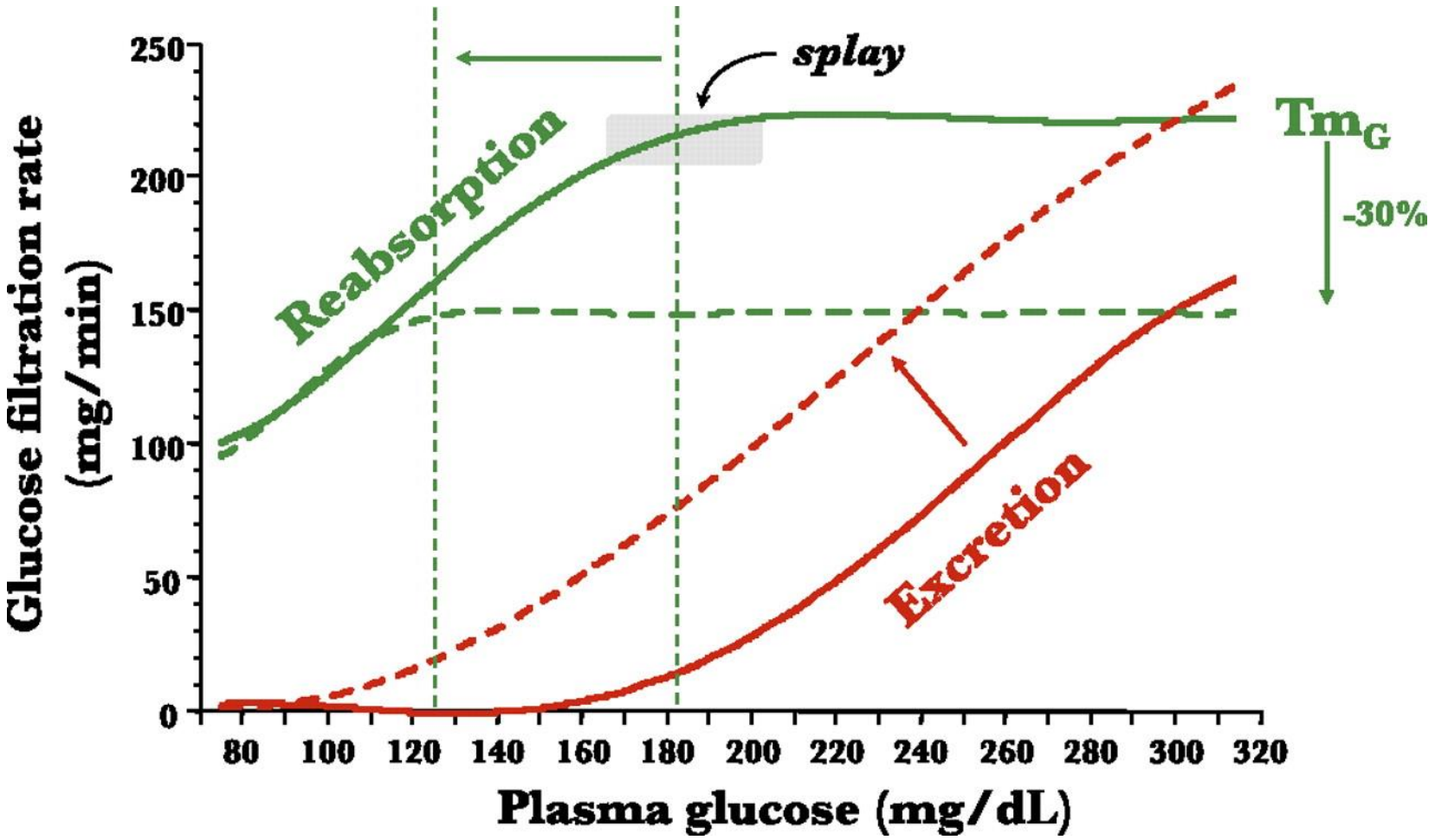
Figure 3 | **Renal handling of glucose in a non-diabetic individual.** Virtually all the glucose filtered is reabsorbed, and none appears in the urine. The locations for sodium–glucose co-transporter 2 (SGLT2) and SGLT1 are shown. Adapted from REF. 12.

Development: from Phlorizin to Dapaglifozin

- Isolated in 1835 by French chemists from the root bark of the apple tree and then characheterized as a potent inhibitors of SGLT2 and SGLT1;

- In euglycemic hyperinsulinemic clamp studies phlorizin normalised insulin sensitivity in diabetic rats, produced glycusuria, normalised fasting and post-prandial plasma glycemia and reversed insulin resistance

Renal glucose handling.



Ferrannini E Diabetes 2011;60:695-696

A paradigm shift

Glycosuria has gone a long way from a mere symptom of decompensated diabetes to a tool to learn more physiology and, in all likelihood, to help to treat glucose toxicity in man.

FORXIGA™ (dapagliflozin) approved in EU for treatment of type 2 diabetes (nov. 2012)

- FORXIGA was discovered by Bristol-Myers Squibb and is the latest product to be approved under the collaboration between Bristol-Myers Squibb and AstraZeneca, to research, develop and commercialise select investigational drugs for type 2 diabetes.
- FORXIGA tablets are approved as a once-daily oral medication in adult patients with type 2 diabetes to improve glycaemic control:
- As a monotherapy, when diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance;
- In combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.
- FORXIGA **is not indicated as a weight loss pro**duct or for the management of obesity or high blood pressure, and has only been studied for the treatment of type 2 diabetes.

- complete blockade of renal glucose reabsorption is never achieved with selective SGLT-2 inhibition. Even SGLT-2-null mice reabsorb one-third of the filtered glucose and dapaglifozin causes at most ~50% inhibition at the highest doses , whereas the nonselective inhibitor, phlorizin, completely blocks reabsorption.
- Perhaps SGLT-1 plays a greater role in the kidney than previously thought .
- Regulation of SGLT-2 expression by glycemia, binding kinetics of glucose and inhibitor concentrations in the lumen of the proximal tubule, and the impact of declining glomerular filtration are additional levels of complexity that need to be explored

FDA approves new diabetes drug, canagliflozin, despite CV concerns

March 29, 2013

Canagliflozin is the first in a new class of drug, an oral inhibitor of sodium glucose cotransporter 2 (SGLT2). Inhibition of SGLT2 reduces resorption of glucose in the kidney, resulting in increased urinary glucose excretion, with a consequent lowering of plasma glucose levels as well as weight loss.

Table 1
Pharmacokinetics of SGLT2 inhibitors in normal mice.

		C_{max} (ng/mL) (ng/g tissue)	T_{max} (h)	$t_{1/2}$ (h)	$AUC_{0-24\ h}$ (ng·h/mL) (ng·h/g tissue)	Tissue/plasma AUC ratio
Ipragliflozin	Plasma	1230	0.5	2.1	4520	1
	Kidney	18,871	0.5	4.1	126,000	28
	Liver	8074	0.5	1.2	19,300	4
	Brain	959	0.5	1.1	2090	0.5
Dapagliflozin	Plasma	1130	1	2.4	2970	1
	Kidney	5448	1	4.2	29,200	10
	Liver	4719	1	1.5	8750	3
	Brain	464	1	1.3	904	0.3
Tofogliflozin	Plasma	439	1	1.3	1010	1
	Kidney	1202	1	2.1	3170	3
	Liver	3597	1	1.5	7930	8
	Brain	157	1	1.6	315	0.3
Canagliflozin	Plasma	449	1	3.1	1620	1
	Kidney	4103	1	3.2	16,600	10
	Liver	3593	1	2.4	11,800	7
	Brain	214	1	1.9	532	0.3
Empagliflozin	Plasma	253	1	1.8	626	1
	Kidney	1570	1	2.1	4200	7
	Liver	1056	1	2.2	2930	5
	Brain	171	1	1.5	313	0.5
Luseogliflozin	Plasma	394	0.5	0.4	478	1
	Kidney	978	0.5	1.4	2690	6
	Liver	5288	0.5	0.6	7990	17
	Brain	188	0.5	0.3	157	0.3

Each mouse was treated with a single oral dose (3 mg/kg) of drug. Pharmacokinetic parameters are expressed as the mean for three animals at each time point.

Postmarketing studies required

A cardiovascular outcomes trial (CANVAS).

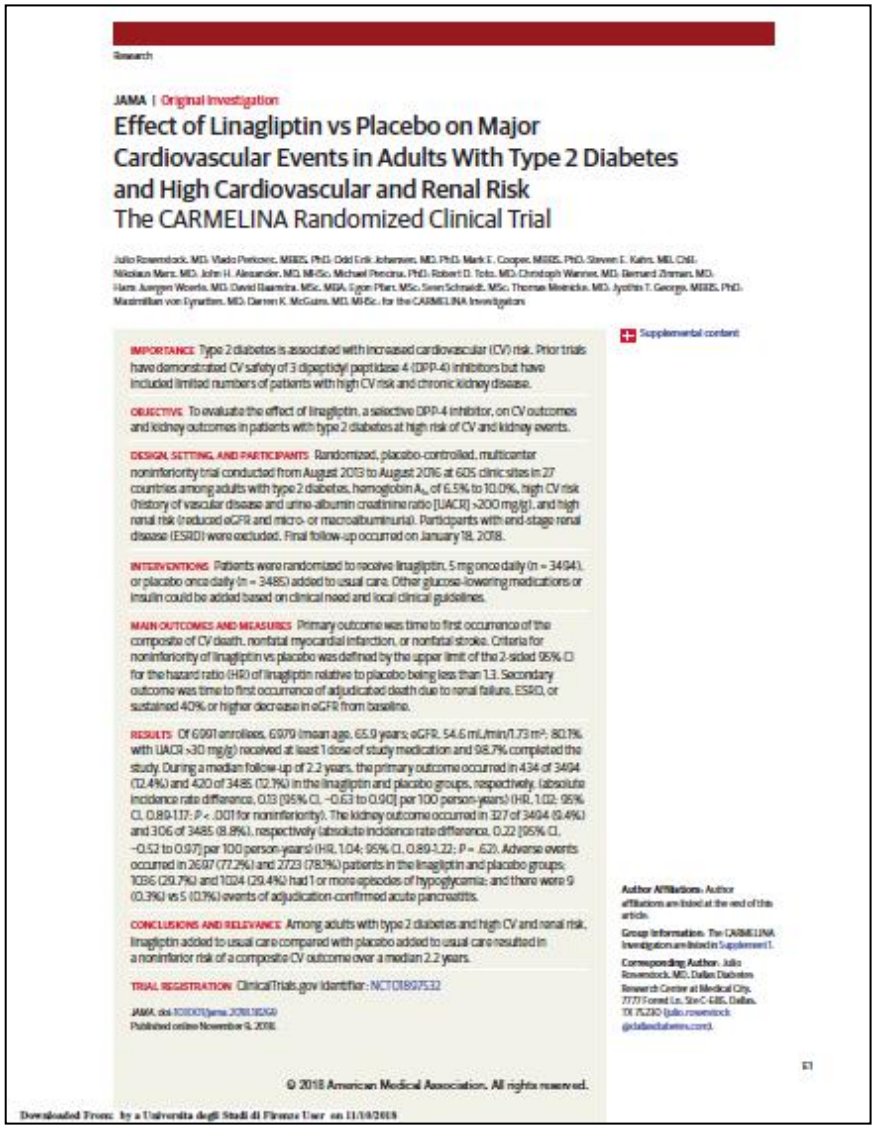
An enhanced pharmacovigilance program to monitor for malignancies, serious cases of pancreatitis, and other adverse events.

A bone-safety study.

A pediatric pharmacokinetic and pharmacodynamics study.

A pediatric safety and efficacy study.

The question of the cardiovascular safety



Research

JAMA | Original Investigation

Effect of Linagliptin vs Placebo on Major Cardiovascular Events in Adults With Type 2 Diabetes and High Cardiovascular and Renal Risk

The CARMELINA Randomized Clinical Trial

Julio Rosenstock, MD; Vlado Perkovic, MBBS, PhD; Odd Erik Johansen, MD, PhD; Mark E. Cooper, MBBS, PhD; Steven E. Kahn, MB, ChB; Nikolaus Marx, MD; John H. Alexander, MD, MHSc; Michael Pencina, PhD; Robert D. Toto, MD; Christoph Wanner, MD; Bernard Zinman, MD; Hans-Juergen Woerle, MD; David Baanstra, MSc, MBA; Egon Pfarr, MSc; Sven Schnaidt, MSc; Thomas Meinicke, MD; Jyothis T. George, MBBS, PhD; Maximilian von Eynatten, MD; Darren K. McGuire, MD, MHSc; for the CARMELINA Investigators

IMPORTANCE Type 2 diabetes is associated with increased cardiovascular (CV) risk. Prior trials have demonstrated CV safety of 3 dipeptidyl peptidase 4 (DPP-4) inhibitors but have included limited numbers of patients with high CV risk and chronic kidney disease.

OBJECTIVE To evaluate the effect of linagliptin, a selective DPP-4 inhibitor, on CV outcomes and kidney outcomes in patients with type 2 diabetes at high risk of CV and kidney events.

DESIGN, SETTING, AND PARTICIPANTS Randomized, placebo-controlled, multicenter noninferiority trial conducted from August 2013 to August 2016 at 605 clinic sites in 27 countries among adults with type 2 diabetes, hemoglobin A_{1c} of 6.5% to 10.0%, high CV risk (history of vascular disease and urine-albumin creatinine ratio [UACR] >200 mg/g), and high renal risk (reduced eGFR and micro- or macroalbuminuria). Participants with end-stage renal disease (ESRD) were excluded. Final follow-up occurred on January 18, 2018.

INTERVENTIONS Patients were randomized to receive linagliptin, 5 mg once daily (n = 3494), or placebo once daily (n = 3485) added to usual care. Other glucose-lowering medications or insulin could be added based on clinical need and local clinical guidelines.

MAIN OUTCOMES AND MEASURES Primary outcome was time to first occurrence of the composite of CV death, nonfatal myocardial infarction, or nonfatal stroke. Criteria for noninferiority of linagliptin vs placebo was defined by the upper limit of the 2-sided 95% CI for the hazard ratio (HR) of linagliptin relative to placebo being less than 1.3. Secondary outcome was time to first occurrence of adjudicated death due to renal failure, ESRD, or sustained 40% or higher decrease in eGFR from baseline.

RESULTS Of 6991 enrollees, 6979 (mean age, 65.9 years; eGFR, 54.6 mL/min/1.73 m²; 80.1% with UACR >30 mg/g) received at least 1 dose of study medication and 98.7% completed the study. During a median follow-up of 2.2 years, the primary outcome occurred in 434 of 3494 (12.4%) and 420 of 3485 (12.1%) in the linagliptin and placebo groups, respectively. (absolute incidence rate difference, 0.13 [95% CI, −0.63 to 0.90] per 100 person-years) (HR, 1.02; 95% CI, 0.89-1.17; $P < .001$ for noninferiority). The kidney outcome occurred in 327 of 3494 (9.4%) and 306 of 3485 (8.8%), respectively (absolute incidence rate difference, 0.22 [95% CI, −0.52 to 0.97] per 100 person-years) (HR, 1.04; 95% CI, 0.89-1.22; $P = .62$). Adverse events occurred in 2697 (77.2%) and 2723 (78.1%) patients in the linagliptin and placebo groups; 1036 (29.7%) and 1024 (29.4%) had 1 or more episodes of hypoglycemia; and there were 9 (0.3%) vs 5 (0.1%) events of adjudication-confirmed acute pancreatitis.

CONCLUSIONS AND RELEVANCE Among adults with type 2 diabetes and high CV and renal risk, linagliptin added to usual care compared with placebo added to usual care resulted in a noninferior risk of a composite CV outcome over a median 2.2 years.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT01897532

JAMA. doi:10.1001/jama.2018.18269
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Supplemental content

Author Affiliations. Author affiliations are listed at the end of this article.

Group Information. The CARMELINA Investigators are listed in Supplement 1.

Corresponding Author. Julio Rosenstock, MD, Dallas Diabetes Research Center at Medical City, 7777 Forest Ln, Ste C-681, Dallas, TX 75230 (julio.rosenstock@dallasdiabetes.com).

The NEW ENGLAND JOURNAL of MEDICINE

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ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

ABSTRACT

BACKGROUND

The effects of empagliflozin, an inhibitor of sodium–glucose cotransporter 2, in addition to standard care, on cardiovascular morbidity and mortality in patients with type 2 diabetes at high cardiovascular risk are not known.

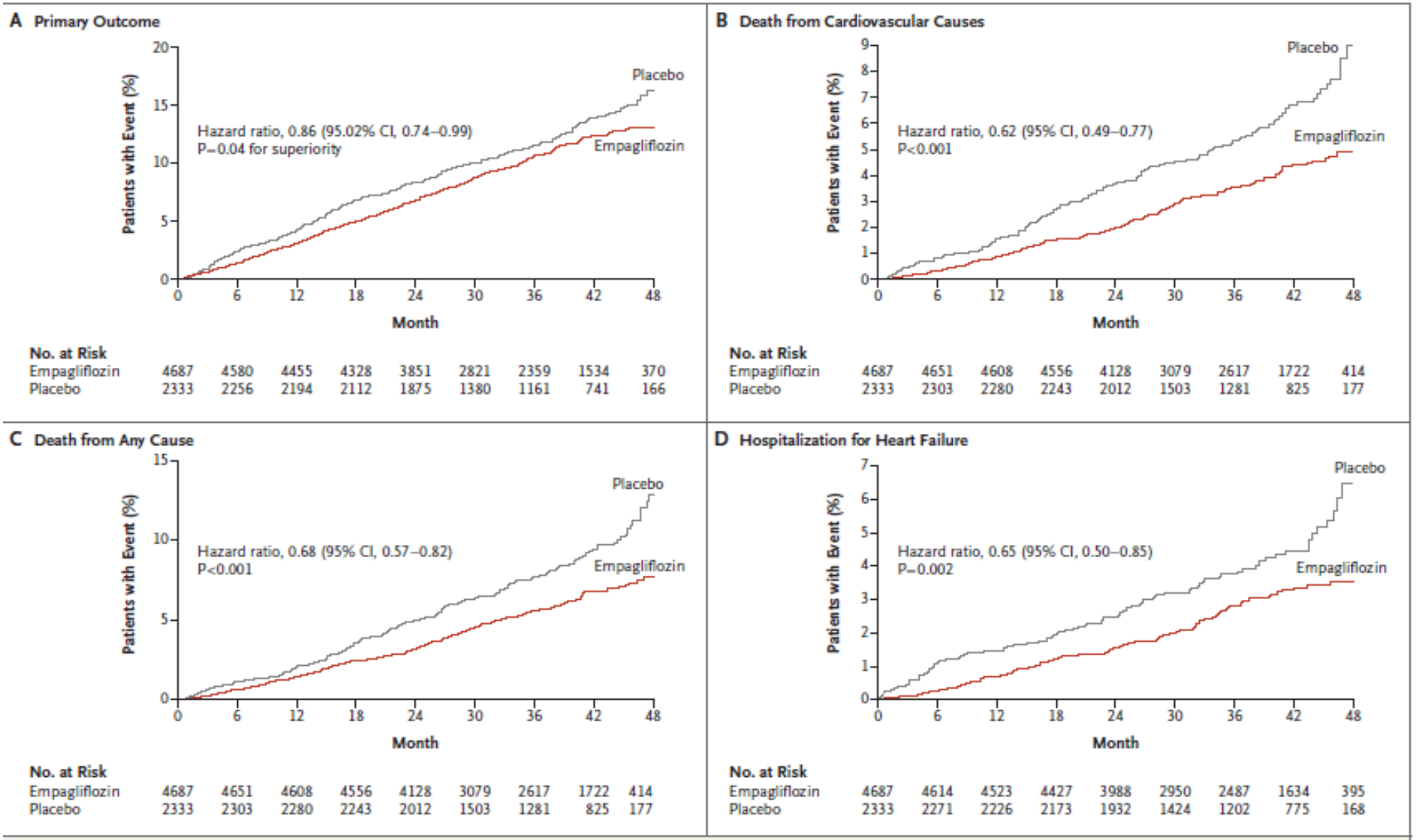

Figure 1. Cardiovascular Outcomes and Death from Any Cause.

Shown are the cumulative incidence of the primary outcome (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) (Panel A), cumulative incidence of death from cardiovascular causes (Panel B), the Kaplan–Meier estimate for death from any cause (Panel C), and the cumulative incidence of hospitalization for heart failure (Panel D) in the pooled empagliflozin group and the placebo group among patients who received at least one dose of a study drug. Hazard ratios are based on Cox regression analyses.

?

In the ischemic heart, SGLT1 and not SGLT2 is present

Glifozins have different profile of SGLT2/SGLT1 affinity

Empaglifozin and the Reduction of the cardiovascular risk: which mechanism?

Reduces triglyceride levels with a trend toward the increase of HDL

Reduces blood pressure

Reduces body weight

Reduces hospitalization for heart failure (35% relative risk reduction)

?

Cardiovascular protection is likely a class effect but . . .

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

Bruce Neal, M.B., Ch.B., Ph.D., Vlado Perkovic, M.B., B.S., Ph.D., Kenneth W. Mahaffey, M.D., Dick de Zeeuw, M.D., Ph.D., Greg Fulcher, M.D., Ngozi Erondu, M.D., Ph.D., Wayne Shaw, D.S.L., Gordon Law, Ph.D., Mehul Desai, M.D., and David R. Matthews, D.Phil., B.M., B.Ch., for the CANVAS Program Collaborative Group*

ABSTRACT

BACKGROUND

Canagliflozin is a sodium–glucose cotransporter 2 inhibitor that reduces glycemia as well as blood pressure, body weight, and albuminuria in people with diabetes. We report the effects of treatment with canagliflozin on cardiovascular, renal, and safety outcomes.

METHODS

The CANVAS Program integrated data from two trials involving a total of 10,142 participants with type 2 diabetes and high cardiovascular risk. Participants in each trial were randomly assigned to receive canagliflozin or placebo and were followed for a mean of 188.2 weeks. The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.

RESULTS

The mean age of the participants was 63.3 years, 35.8% were women, the mean duration of diabetes was 13.5 years, and 65.6% had a history of cardiovascular disease. The rate of the primary outcome was lower with canagliflozin than with placebo (occurring in 26.9 vs. 31.5 participants per 1000 patient-years; hazard ratio, 0.86; 95% confidence interval [CI], 0.75 to 0.97; P<0.001 for noninferiority; P=0.02 for superiority). Although on the basis of the prespecified hypothesis testing sequence the renal outcomes are not viewed as statistically significant, the results showed a possible benefit of canagliflozin with respect to the progression of albuminuria (hazard ratio, 0.73; 95% CI, 0.67 to 0.79) and the composite outcome of a sustained 40% reduction in the estimated glomerular filtration rate, the need for renal-replacement therapy, or death from renal causes (hazard ratio, 0.60; 95% CI, 0.47 to 0.77). 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.

CONCLUSIONS

In two trials involving patients with type 2 diabetes and an elevated risk of cardiovascular disease, patients treated with canagliflozin had a lower risk of cardiovascular events than those who received placebo but a greater risk of amputation, primarily at the level of the toe or metatarsal. (Funded by Janssen Research and Development; CANVAS and CANVAS-R ClinicalTrials.gov numbers, NCT01032629 and NCT01989754, respectively.)

From the George Institute for Global Health, Faculty of Medicine, UNSW Sydney (B.N., V.P.), the Charles Perkins Centre (B.N.), and the Royal North Shore Hospital (V.P., G.F.), University of Sydney, and the Faculty of Medicine, University of New South Wales (B.N.) — all in Sydney; Imperial College London, London (B.N.), and the Oxford Centre for Diabetes, Endocrinology, and Metabolism and Harris Manchester College, University of Oxford, Oxford (D.R.M.) — both in the United Kingdom; the Stanford Center for Clinical Research, Department of Medicine, Stanford University School of Medicine, Stanford, CA (K.W.M.); the University Medical Center Groningen, University of Groningen, Groningen, the Netherlands (D.Z.); and Janssen Research and Development, Raritan, NJ (N.E., W.S., G.L., M.D.). Address reprint requests to Dr. Neal at the George Institute for Global Health, UNSW Sydney, Level 5, 1 King St., Newtown, NSW 2042, Australia, or at bneal@georgeinstitute.org.au.

*A complete list of investigators in the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program is provided in the Supplementary Appendix, available at NEJM.org.

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Ottobre 2018

FDA approves Canaglifozin (INVOKANA) for the reduction of cardiovascular risk in diabetic patients with high cardiovascular risk

INVOKANA is now the only antidiabetic tretament approved to reduce the cardiovascular risk of the diabetic patient

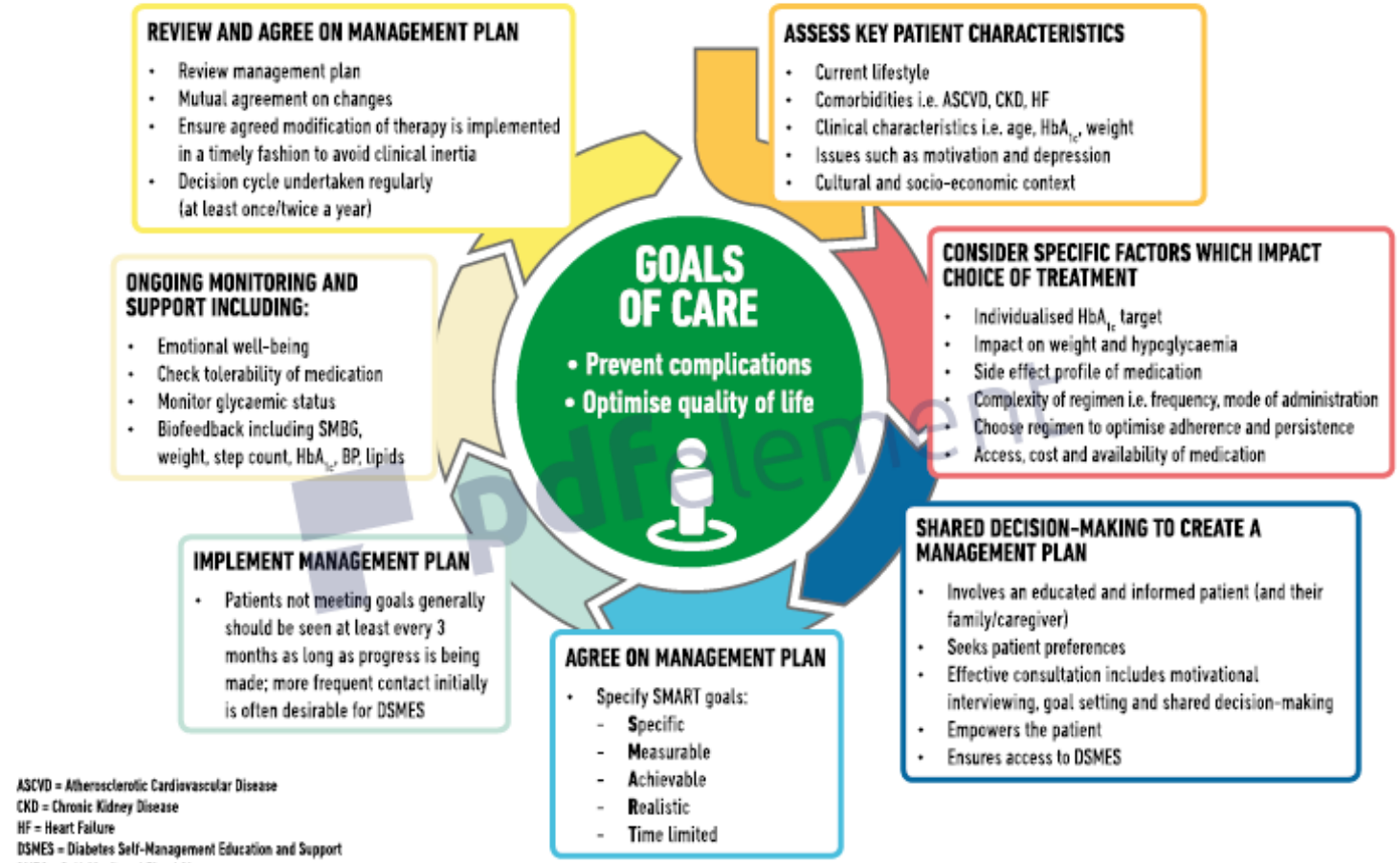
Diabetologia
https://doi.org/10.1007/s00125-018-4729-5

CONSENSUS REPORT

Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

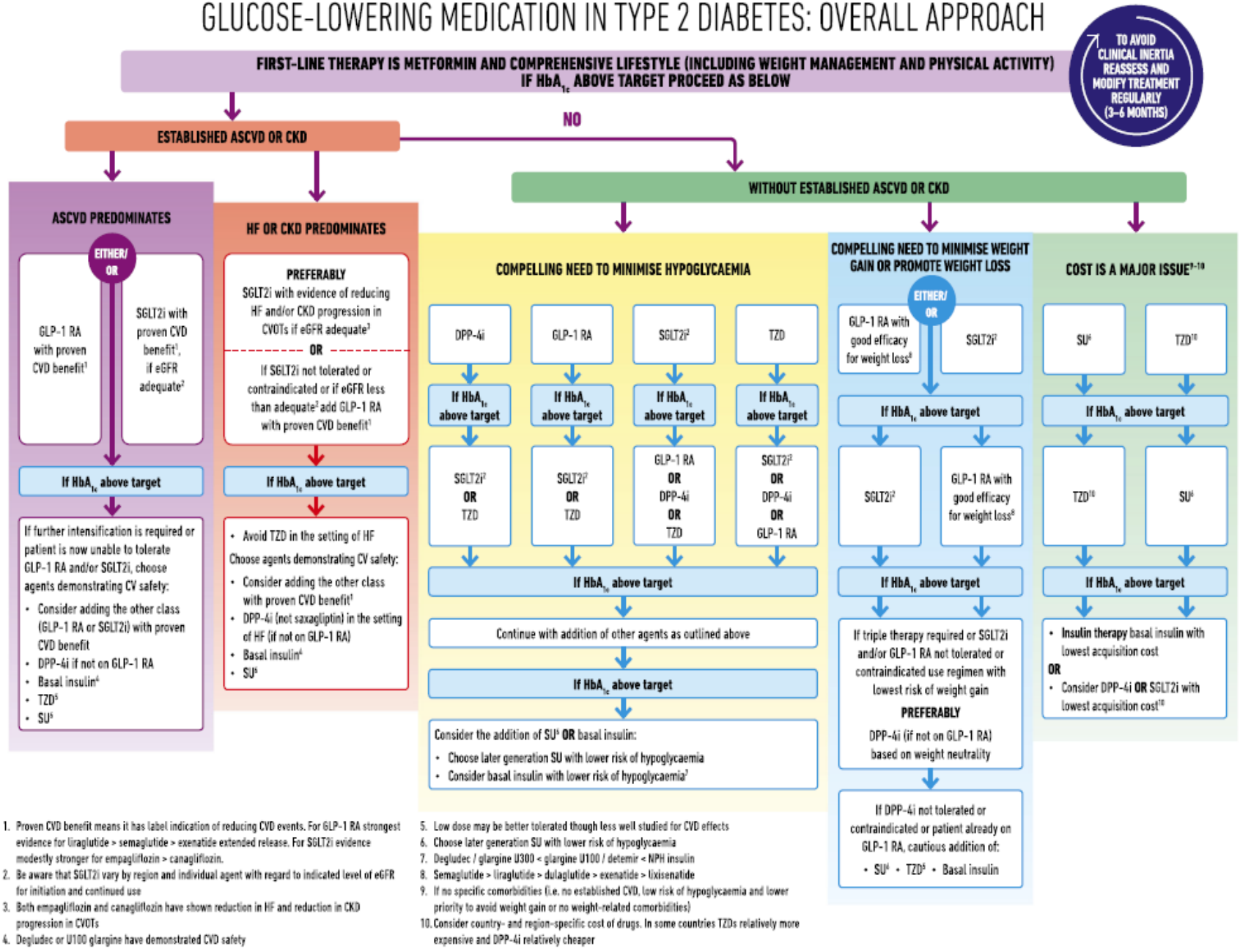
Melanie J. Davies[1,2] · David A. D'Alessio[3] · Judith Fradkin[4] · Walter N. Kernan[5] · Chantal Mathieu[6] · Geltrude Mingrone[7,8] · Peter Rossing[9,10] · Apostolos Tsapas[11] · Deborah J. Wexler[12,13] · John B. Buse[14]

DECISION CYCLE FOR PATIENT-CENTRED GLYCAEMIC MANAGEMENT IN TYPE 2 DIABETES



ASCVD = Atherosclerotic Cardiovascular Disease
CKD = Chronic Kidney Disease
HF = Heart Failure
DSMES = Diabetes Self-Management Education and Support
SMBG = Self-Monitored Blood Glucose

Fig. 1 Decision cycle for patient-centred glycaemic management in type 2 diabetes



1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU with lower risk of hypoglycaemia
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e. no established CVD, low risk of hypoglycaemia and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

Fig. 2 Glucose-lowering medication in type 2 diabetes: overall approach