V Corso Aggiornamento Ame
in Endocrinologia Clinica

AGRIGENTO
Museo Archeologico

20/22 MARZO
2014

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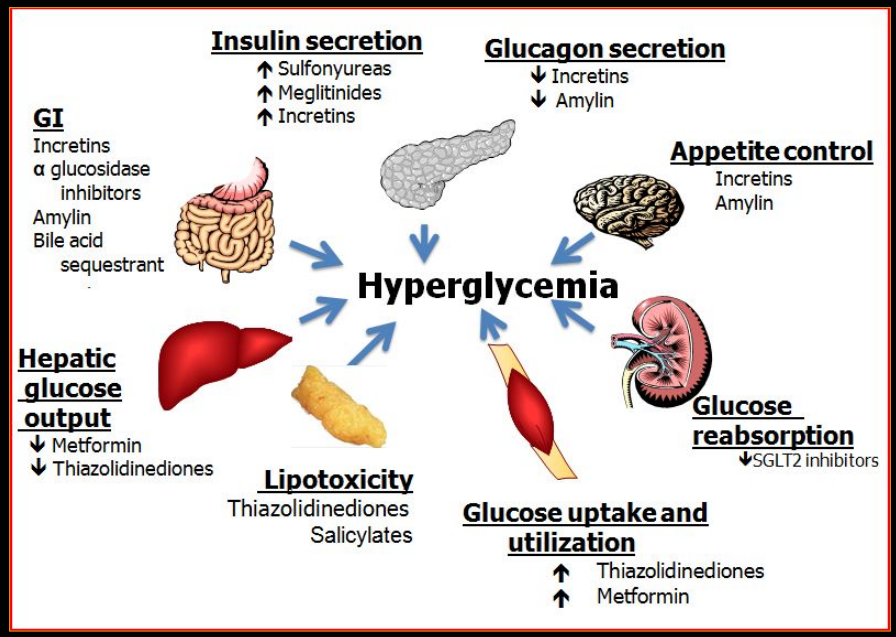
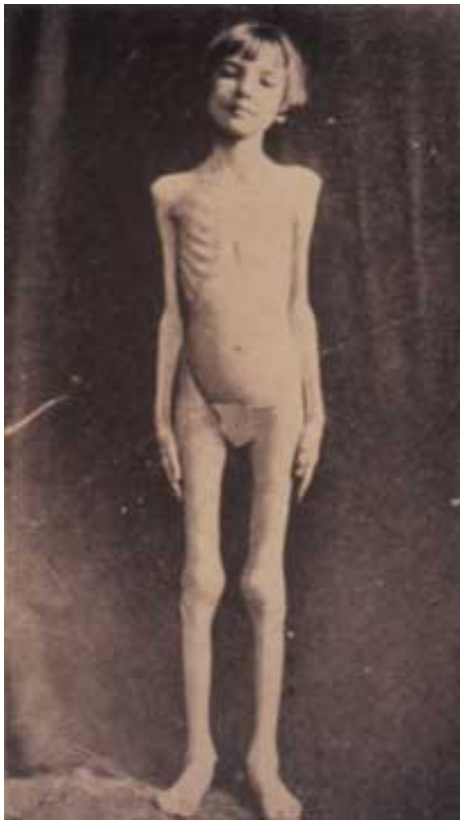
U.O.C. di Endocrinologia
Ospedale Garibaldi-Nesima
Catania

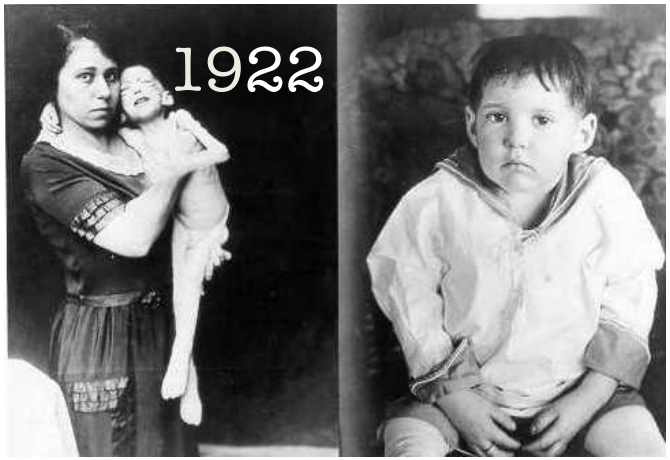
Aggiornamenti sul Trattamento del Diabete Mellito

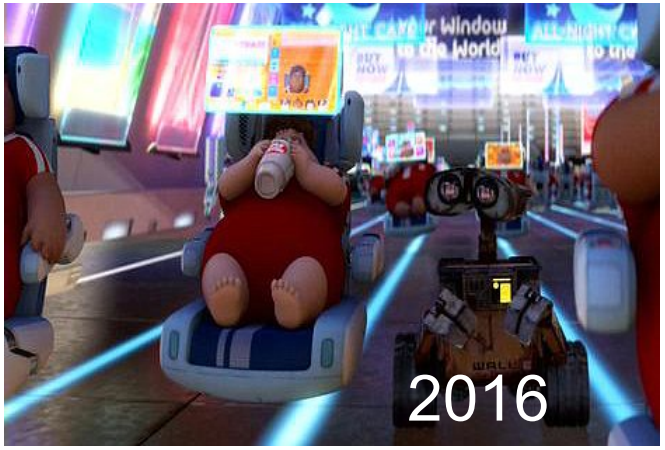


La malattia diabetica nel passato



La malattia diabetica tra passato e futuro





92 anni fa

...e fra 92 anni?

1797

John Rollo

The English military doctor John Rollo (1749-1809) was able to demonstrate the presence of sugar in the blood indirectly. He devised a low carbohydrate diet, which he tested successfully on an overweight subject, Captain Meredith. The diet consisted of milk and limewater for breakfast and supper; plain

Read More »

Late 1850s

Priorry

French physician, Priorry, advises diabetes patients to eat extra large quantities of sugar as a treatment for diabetes. Later, Ernst

"This won't be the last time that strange and unhelpful treatments for diabetes will be tried"

1870s

Apollinaire Bouchardat

French physician Apollinaire Bouchardat notices the disappearance of glycosuria (the presence of glucose in the urine) in some of his diabetes patients during the rationing of food in Paris while under seige by Germany during the Franco-Prussian War. He formulates the idea of individualized diets for

Read More »

Late 1800s

Locked Up

Italian diabetes specialist Catoni isolates his patients under lock and key in order to get them to follow their diets.

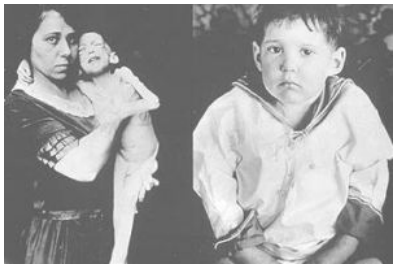
1900-1915 – fra le varie terapia del diabete:

- ***la "cura dell'avena" (otto once di farina d'avena mescolati con otto once di burro, da assumere ogni due ore)***
- ***la dieta del latte,***
- ***la cura del riso o delle patate***
- ***oppio***
- ***sovralimentazione per compensare la perdita di liquidi e di peso.***

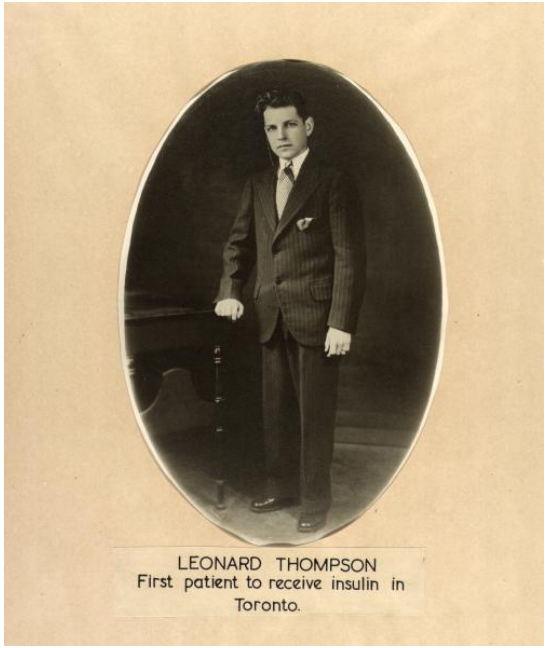
Chetoacidosi Diabetica

Mortalità dall'epoca della prima descrizione

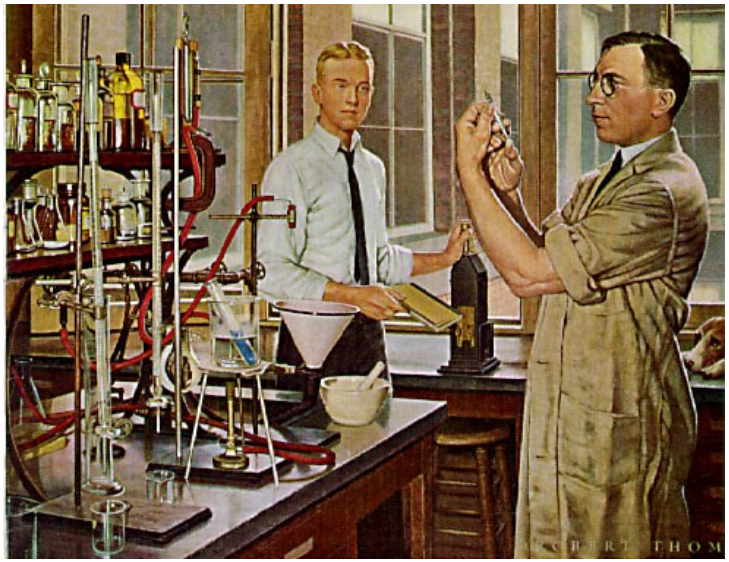
1921

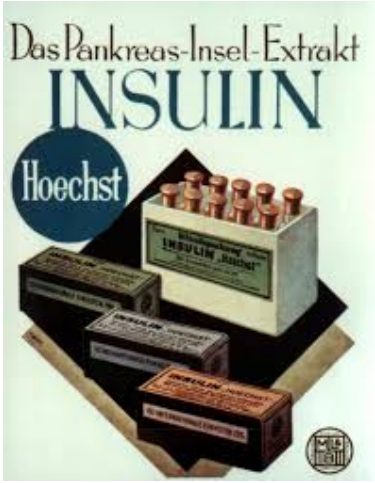


1922

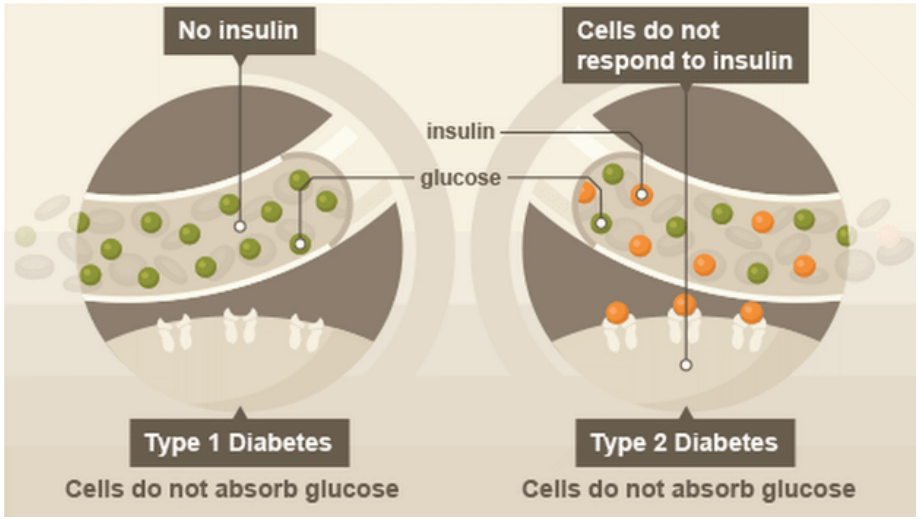


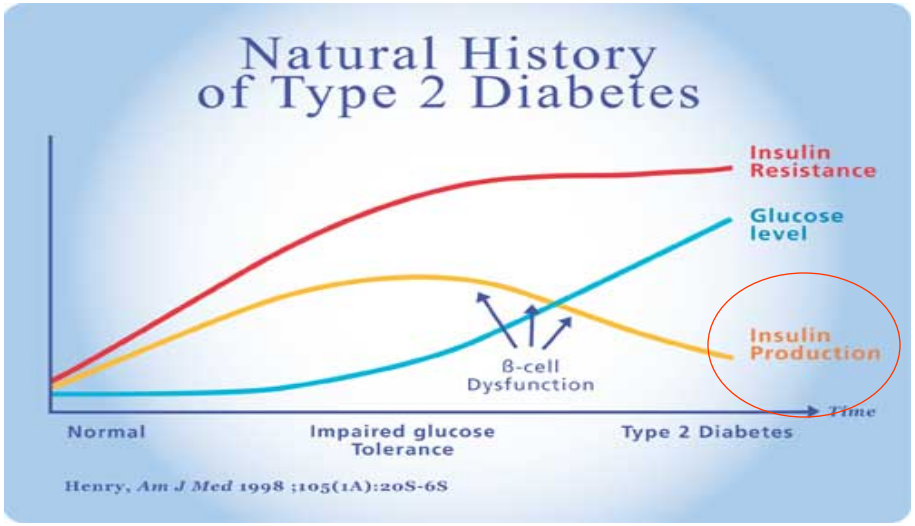
Le prime insuline



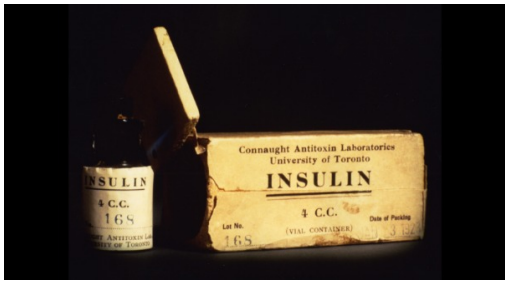


Types of diabetes





1920 | 1930 | 1940 | 1950 | 1960 | 1970 | 1980 | 1990 | 2000 | 2010



Brief history of insulin therapy

1922	First clinical use of insulin
1920s	Short-acting bovine and porcine pancreas extracts
1930s	Improved purification
	Protamine-insulin complexes reported
1940s	NPH (neutral protamine Hagedorn) introduced
1950s	Lente and ultralente insulins
1970s	Highly purified (monocomponent) insulins
1980s	Premixed biphasic insulins
	Insulin pumps for CSII (continuous subcutaneous insulin infusion)
	Biosynthetic human insulin
	Pen injection devices
1990s	Rapid-acting insulin analogues
2000s	Long-acting insulin analogues

1922- Pancreas extracts
1978 - Genetech, recombinant insulin

1936 - Protamin zinc insulin
1946- Neutral Protamin Hagedorn NPH Novo
1953 - Lente, ultralente, semilente

Modified insulin
1995 - Lispro insulin (onset 10-15 min; peak 30-60 min; duration 3-5 hrs)
2001- Insulin glargine (activity after 4+5 hrs; sustained to 24 hrs; no peak)

Principali farmaci ipoglicemizzanti diversi da insulina

Tolbutamide1956

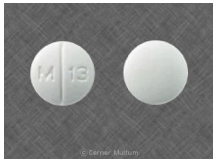
Glibenclamide 1969

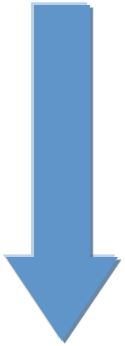
Metformina 1957 (USA 1995)

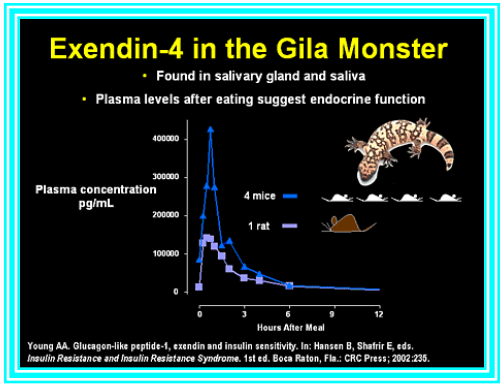
Acarbosio 1995

Glitazonici 1999

Exenatide 2005







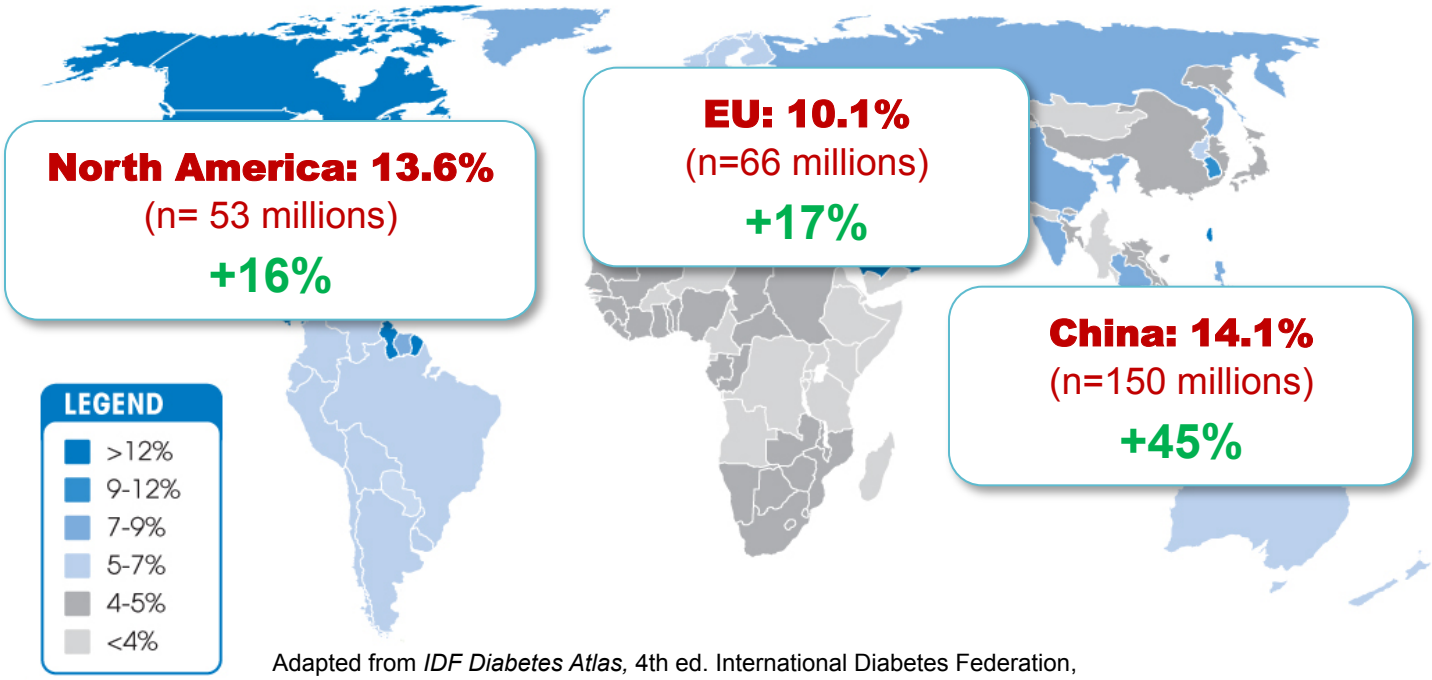

diabetes
glucose
risk
blood
insulin
cells
type
diagnosed
causes
pancreas
body
factors
prevention
people
system
immune
disease
produces
Gestational
Symptoms
history
age
produced
family
percent
person
autoimmune
million
beta
main
food
growth
Preventing
Find
help
diabetic
source
sugar
body's
form
Get
energy
eat
large
older
passes
little
types
information
know
known
present
must


THIS IS HOW
TSUNAMI IS
MADE!!


dreamstime.com

Diabetes, a growing global epidemic likely to affect ~500 million people by 2030

Prevalence (%) estimates of diabetes* (age 20-79 years, 2030)[1a]

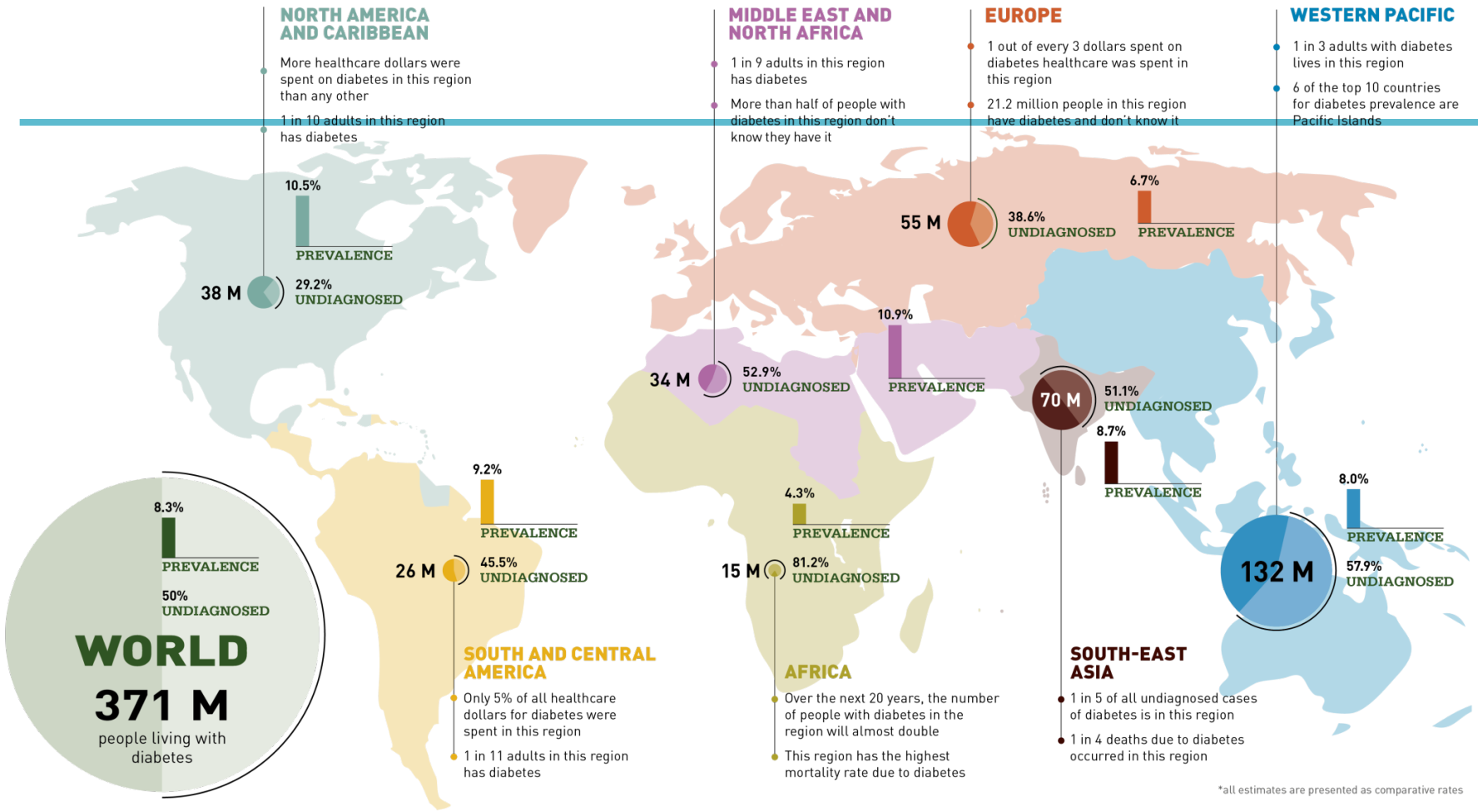


Adapted from *IDF Diabetes Atlas,* 4th ed. International Diabetes Federation, 2009.

>90% of diabetic patients have type 2 diabetes[1]

*All cases of diabetes, including type 1 and type 2 diabetes, and impaired glucose tolerance (IGT), in patients aged 20-79 years.
[a]Absolute number of cases and national prevalence

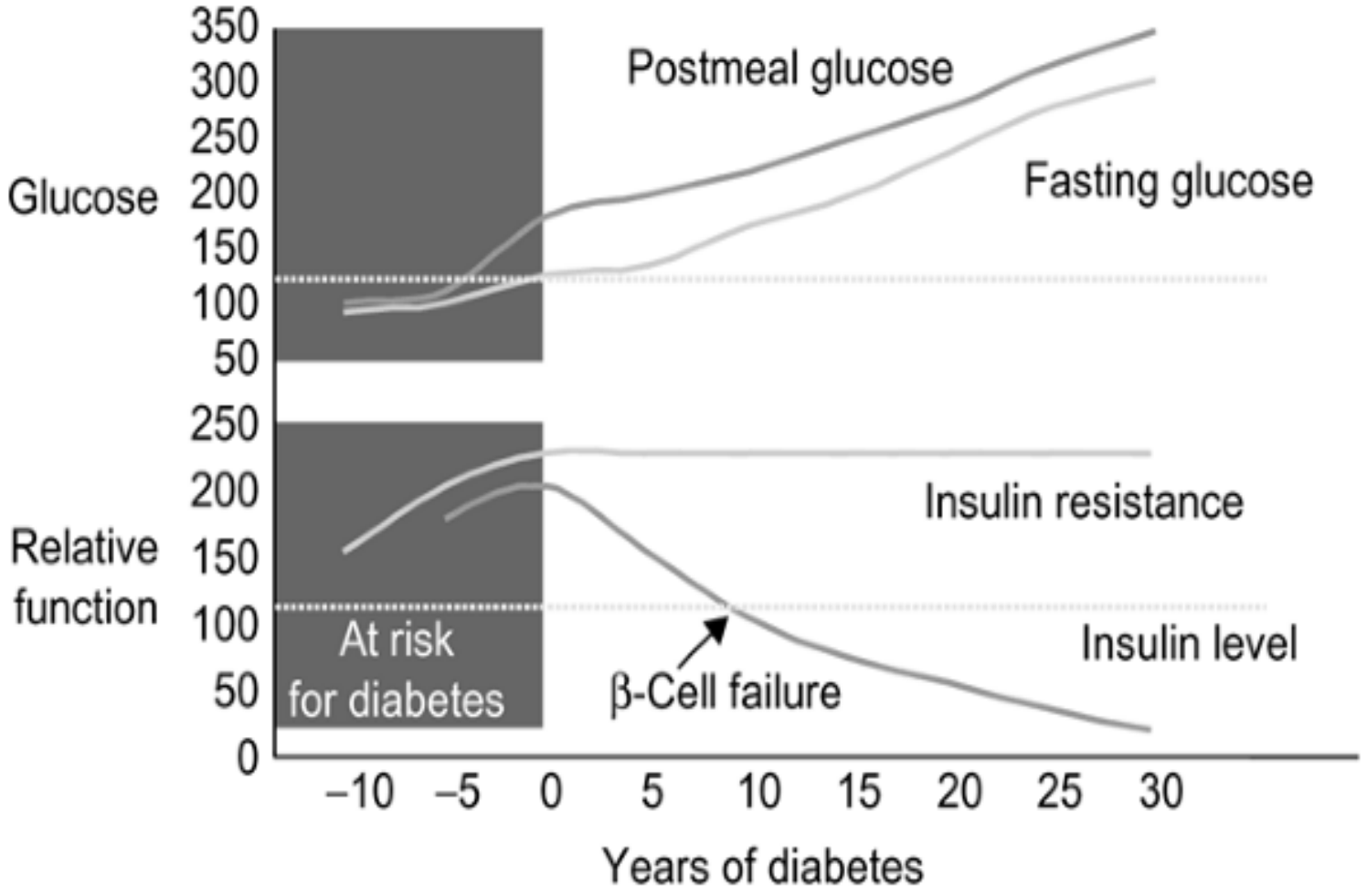
[1]International Diabetes Federation. IDF Diabetes Atlas, 4th ed. Brussels, Belgium: International Diabetes Federation, 2009. http://www.idf.org/diabetesatlas, accessed July 6th 2011.



+30% rispetto al 2010

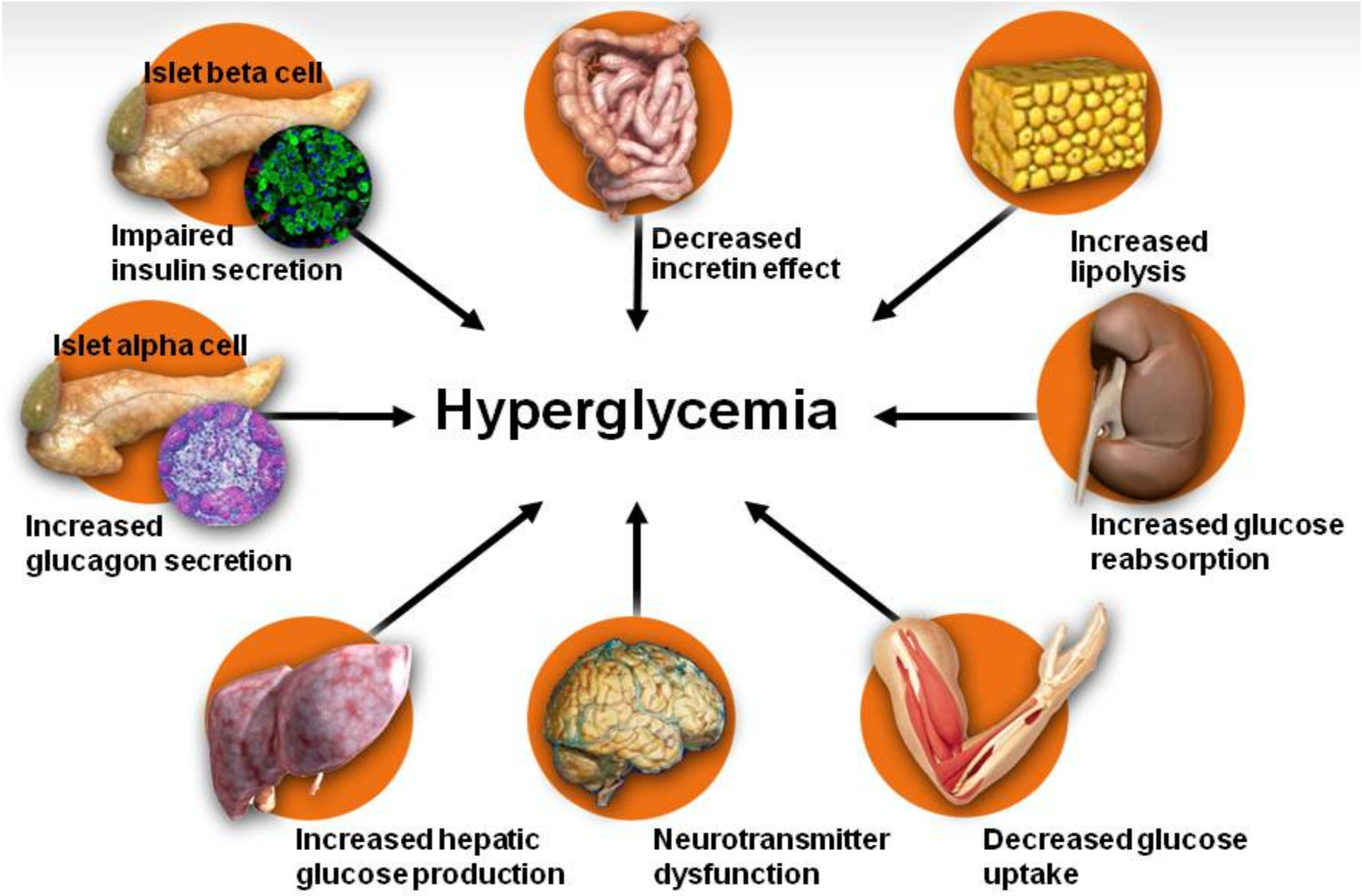
IDF Diabetes Atlas 5th Edition 2012 Update

Natural History of T2D and β-cell Function



Bergenstal R, et al. *Endocrinology.* Philadelphia, PA: WB Saunders Co;2001:821-835.

Ominous Octet



DeFronzo RA. *Diabetes.* 2009;58:773-795.

Pathophysiologic approach to therapy in T2DM

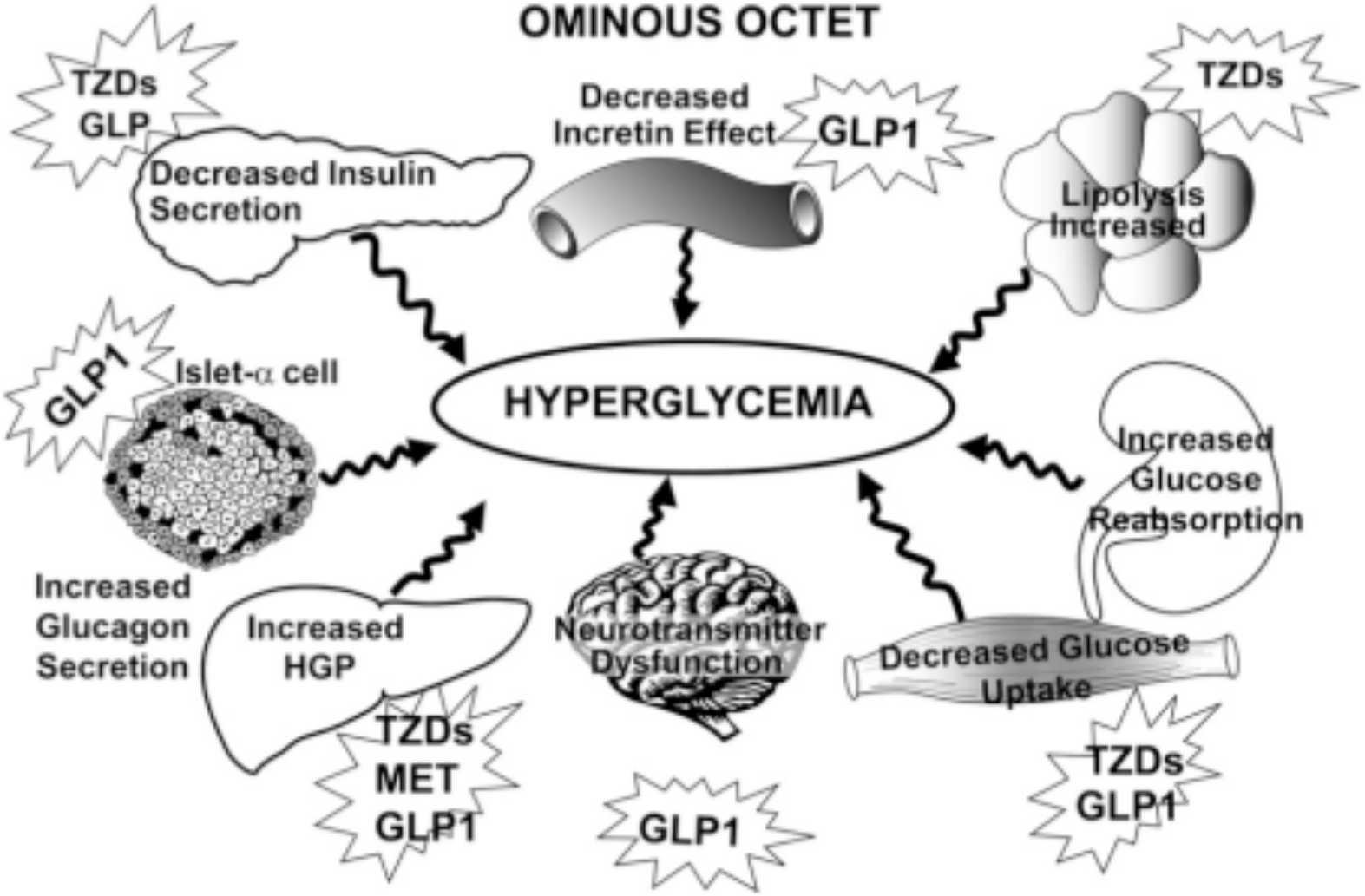


Figure 1—*The ominous octet (3) depicting the mechanism and site of action of antidiabetes medications based upon the pathophysiologic disturbances present in T2DM.*

Diabetes Care, 36: Suppl 2, Aug 2013

Farmaci di prossima introduzione

- Incretine
  - Exenatide LAR (once weekly, Astra Zeneca)
    - Consists of microspheres composed of a biodegradable poly(lactide- co-glycolide) polymeric matrix that contain the peptide exenatide.
  - Lixisenatide (once daily, Sanofi)
    - The peptide differs from exendin-4 in that two amino acids at the C-terminal end have been exchanged for seven different amino acids)
  - Dulaglutide (once weekly, Lilly)
    - GLP-1 peptide fused to IgG that exhibits extended biological activity due to its increased half-life (~90 h) compared with native GLP-1
  - Albiglutide (once weekly, SKF)
    - Fusion peptide consisting of two molecules of a GLP-1 analogue covalently bound to human serum albumin
- Gliptine (Inibitori DDP-4)
  - Linagliptin (Boheringer)
  - Alogliptin (Takeda)
- Insuline
  - Deglutec (basal insulin, NovoNordisk)
- **Inibitori Na-glucose cotrasporter**

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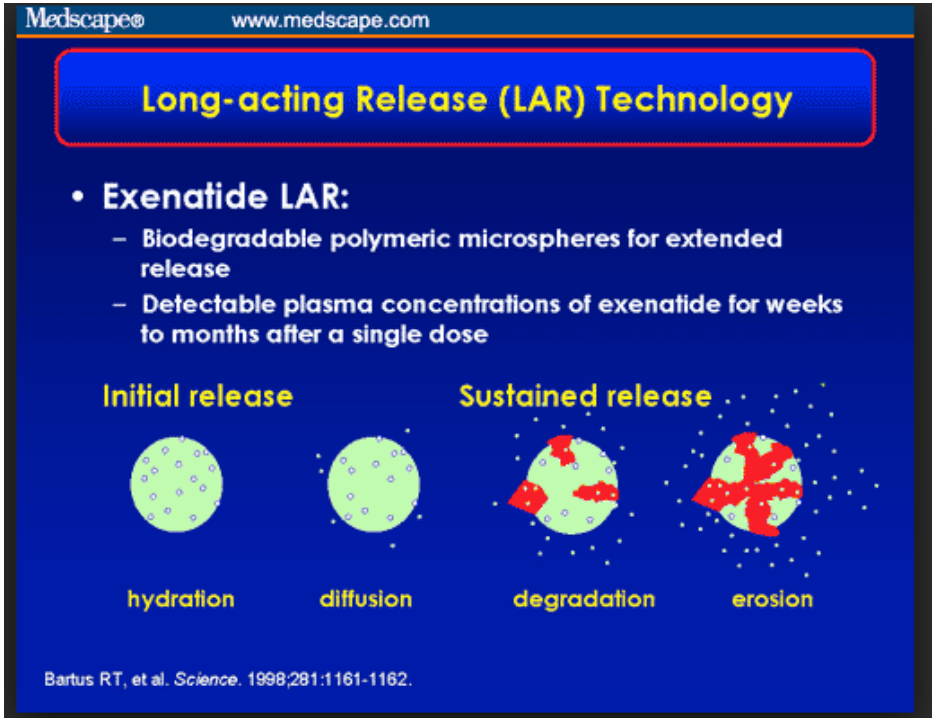
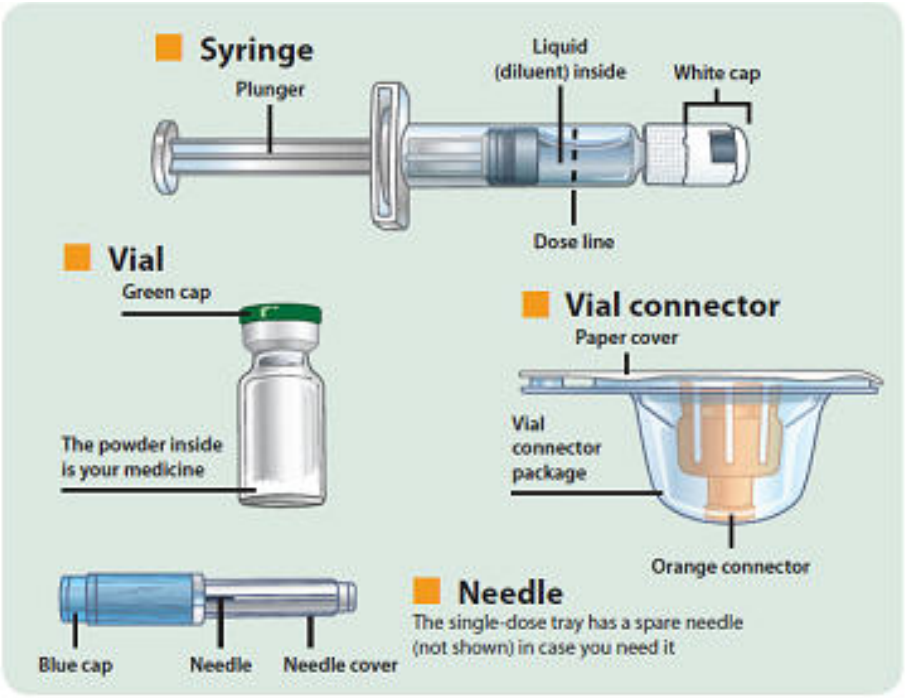
Exenatide LAR (Bydureon, Astra Zeneca)





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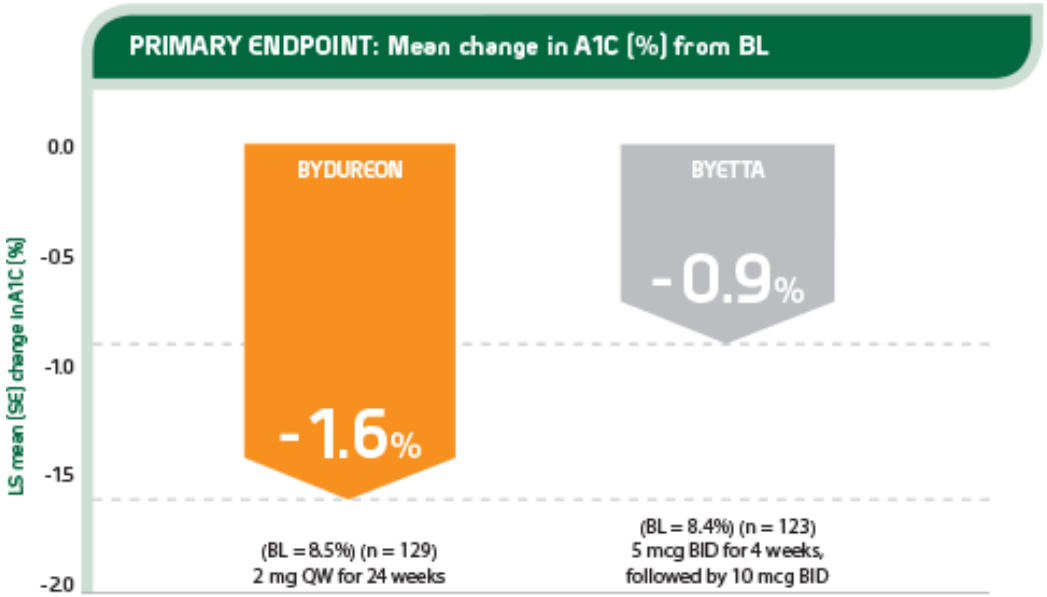

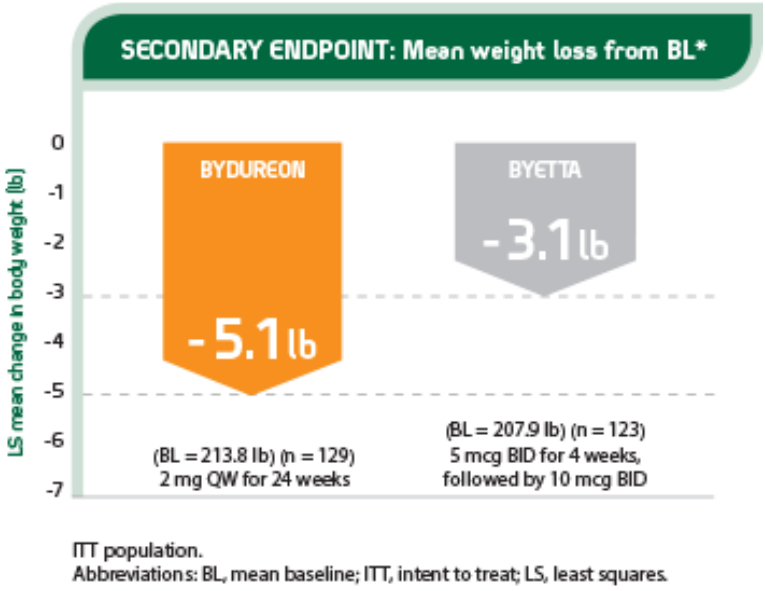

ITT population.
Abbreviations: BL, mean baseline; ITT, intent to treat; LS, least squares.
P < .001 vs comparator.

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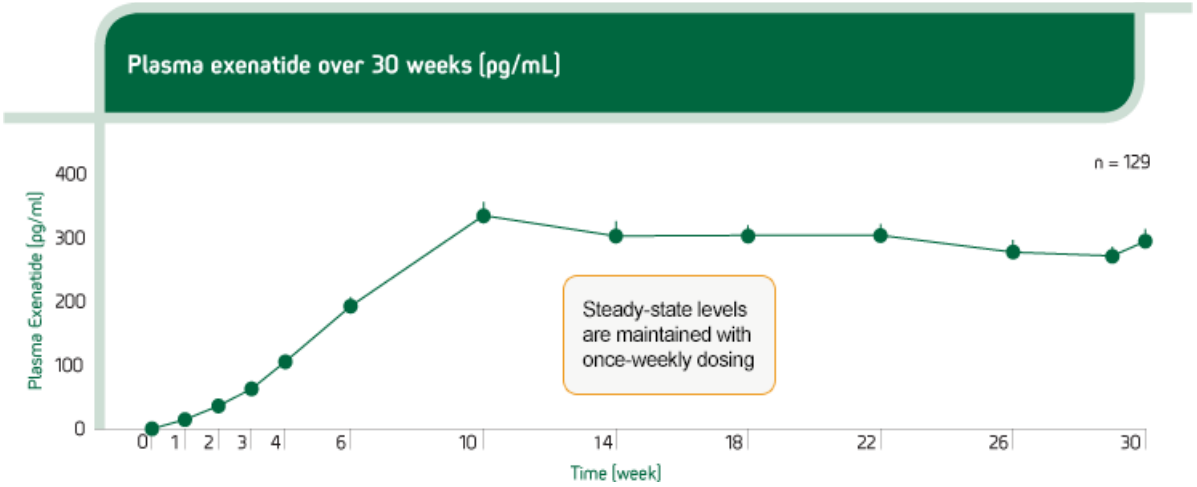

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Table 1 | Comparison of short-acting versus long-acting GLP-1 receptor agonists

Parameters	Short-acting GLP-1 receptor agonists	Long-acting GLP-1 receptor agonists
Compounds	Exenatide Lixisenatide	Albiglutide Dulaglutide Exenatide-LAR Liraglutide
Half-life	2–5 h	12 h–several days
Effects		
Fasting blood glucose levels	Modest reduction	Strong reduction
Postprandial hyperglycaemia	Strong reduction	Modest reduction
Fasting insulin secretion	Modest stimulation	Strong stimulation
Postprandial insulin secretion	Reduction	Modest stimulation
Glucagon secretion	Reduction	Reduction
Gastric emptying rate	Deceleration	No effect
Blood pressure	Reduction	Reduction
Heart rate	No effect or small increase (0–2 bpm)	Moderate increase (2–5 bpm)
Body weight reduction	1–5 kg	2–5 kg
Induction of nausea	20–50%, attenuates slowly (weeks to many months)	20–40%, attenuates quickly (~4–8 weeks)

Abbreviations: GLP-1, glucagon-like peptide 1; LAR, long-acting release.

Meier JJ. GLP-1 receptor agonists for individualized treatment of type 2diabetes mellitus. Nat Rev Endocrinol. 2012 Dec; 8(12):728-42. doi:10.1038/nrendo.2012.140. Epub 2012 Sep 4. Review. PubMed PMID: 22945360.

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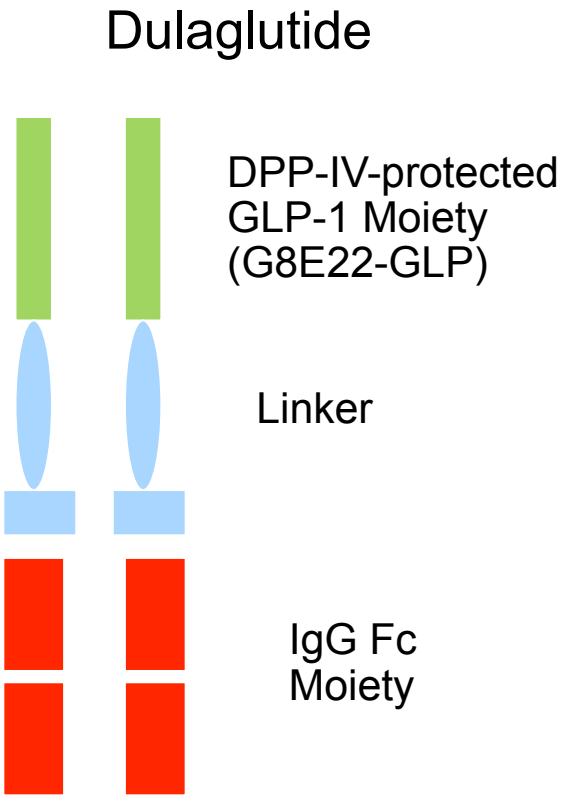
Dulaglutide

- Dulaglutide-- a novel, long-acting glucagon-like peptide 1 (GLP-1) analog[1]
  - Fused to immunoglobulin G (IgG4) Fc modified for reduced immunoreactivity
  - Amino acid substitutions in GLP-1 moiety protect from inactivation by DPP-IV
  - Large size (~60K daltons) reduces renal clearance



In the AWARD-6 study, once-weekly dulaglutide 1.5 mg achieved the primary endpoint of **non-inferiority to once-daily liraglutide 1.8 mg**, as measured by the reduction of hemoglobin A1c (HbA1c) from baseline at 26 weeks. The drug is currently under review at both the FDA and EMA

1. Glaesner, et al. *Diabetes Metab Res Rev* 2010;26:287-96.
2. Investigator's Brochure, LY2189265, Eli Lilly and Company, 3-Nov-2010.

Farmaci di prossima introduzione

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Albiglutide

The Lancet Diabetes & Endocrinology, Early Online Publication, 6 February 2014
doi:10.1016/S2213-8587(13)70214-6Cite or Link Using DOI

Once-weekly albiglutide versus once-daily liraglutide in patients with type 2 diabetes inadequately controlled on oral drugs (HARMONY 7): a randomised, open-label, multicentre, non-inferiority phase 3 study

Dr Richard E Pratley MD [a] , Prof Michael A Nauck MD [b], Prof Anthony H Barnett MD [c], Mark N Feinglos MD [d], Fernando Ovalle MD [e], Illana Harman-Boehm MD [f], June Ye PhD [g], Rhona Scott BSc[Hons] [h], Susan Johnson MD [g], Murray Stewart DM [i], Julio Rosenstock MD [j], for the HARMONY 7 study group

Interpretation

Patients who received once-daily liraglutide had greater reductions in HbA_{1c} than did those who received once-weekly albiglutide. Participants in the albiglutide group had more injection-site reactions and fewer gastrointestinal events than did those in the liraglutide group.

Funding GlaxoSmithKline.

Farmaci di prossima introduzione

- Gliptine (Inibitori DDP-4)

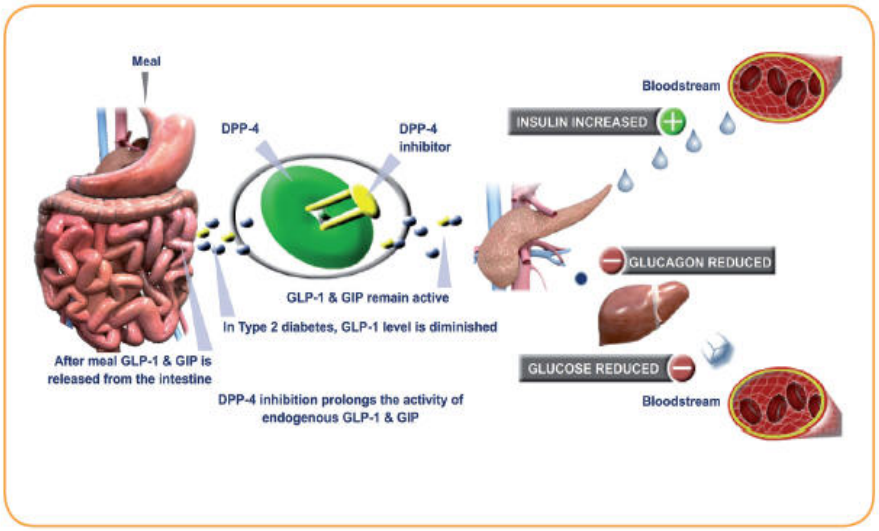


Figure 4. The mode of action of a DPP-4 inhibitor.

Sitagliptin (MSD)

Vildagliptin (Novartis)

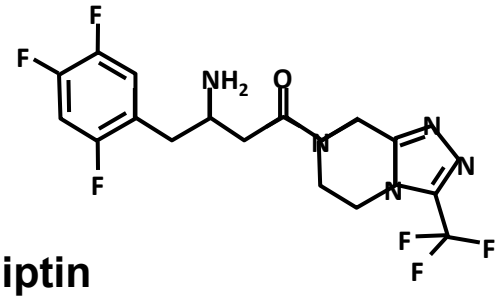
Saxagliptin (AstraZeneca)

Linagliptin (Boheringer)

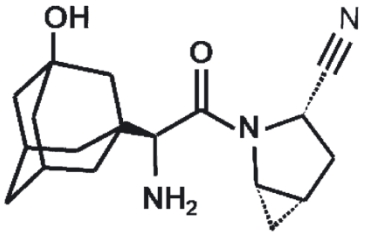
Alogliptin (Takeda)

Linagliptin – un inibitore del DPP-4 con una speciale struttura chimica a base xantinica

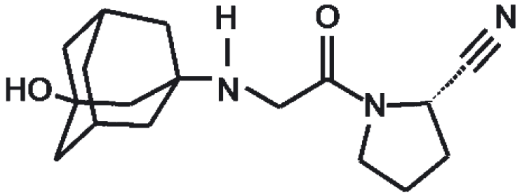
Inibitori del DPP-4 dipeptidomimetici



Sitagliptin



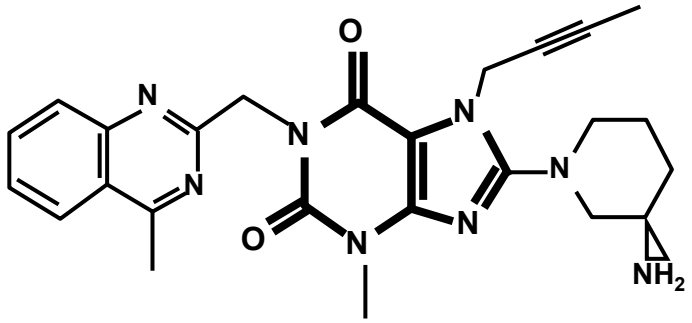
Saxagliptin



Vildagliptin

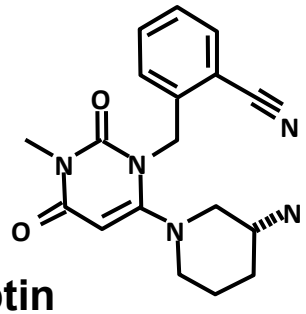
Inibitori del DPP-4 peptidomimetici

Inibitori del DPP-4 che si legano direttamente al sito attivo dell'enzima



Linagliptin

Struttura a base xantinica



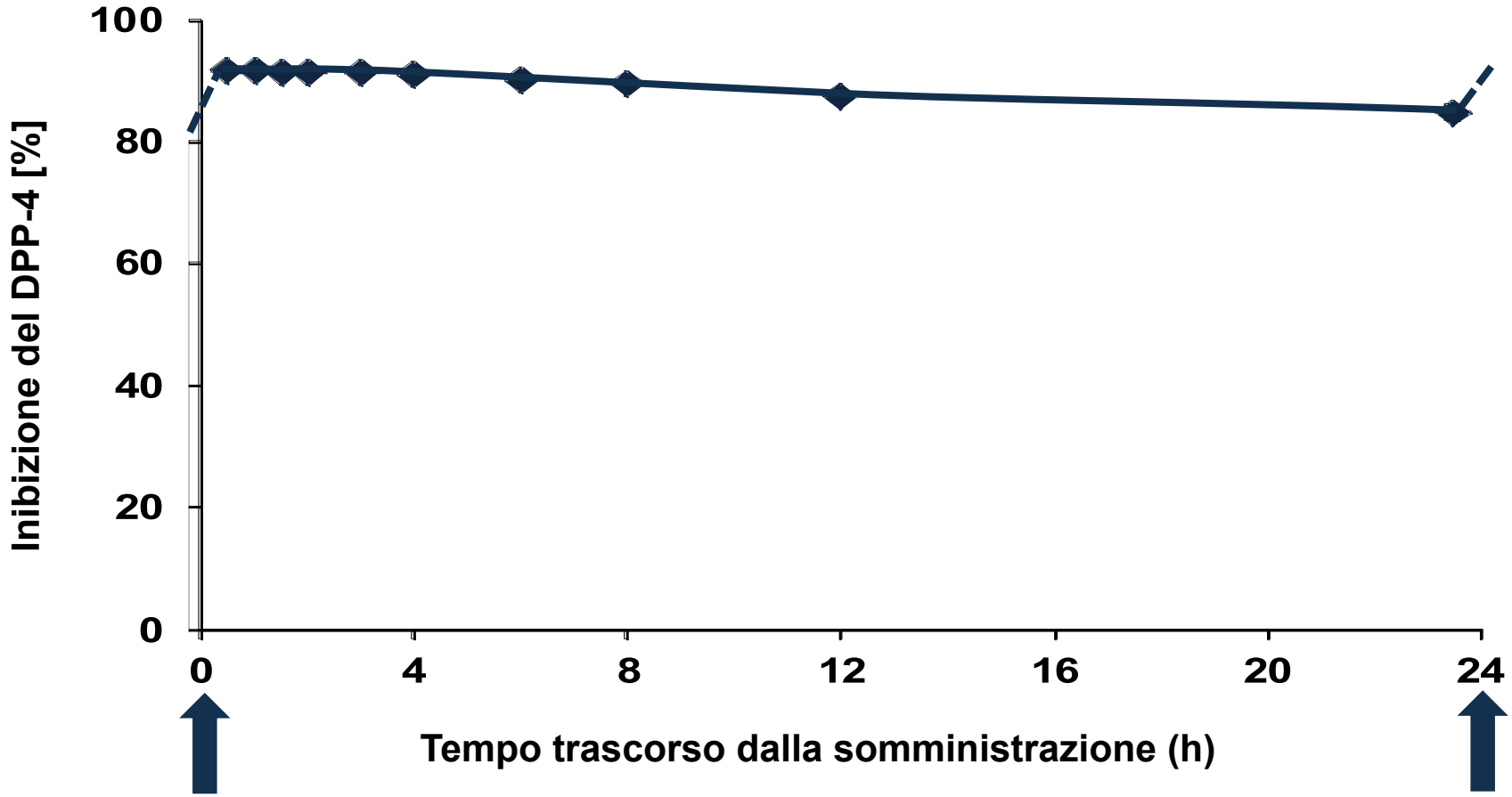
Alogliptin

Inibitori del DPP-4 non peptidomimetici

Adattato da Deacon CF. *Diabetes Obes Metab*. 2011; 13: 7–18.

Linagliptin determina un'inibizione del DPP-4 di lunga durata nei pazienti affetti da diabete mellito di tipo 2

I livelli plasmatici allo steady state vengono raggiunti già dopo la terza somministrazione, con un' inibizione del DPP-4 >91% ai livelli massimi

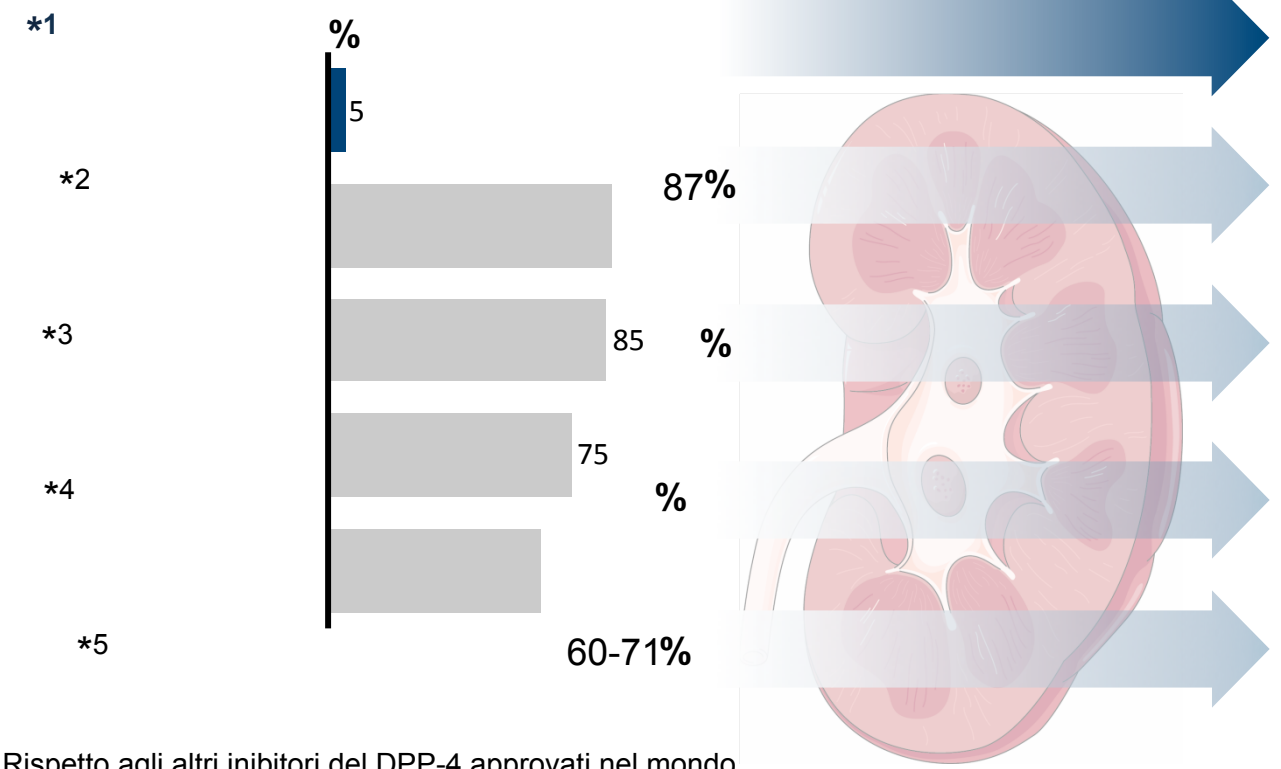


Adattato da Heise T et al. *Diabetes Obes Metab*. 2009;11(8):786–94

Linagliptin SmP

Linagliptin è l'unico inibitore del DPP-4 escreto principalmente per via biliare e intestinale*

Percentuale di escrezione renale



Nessuna necessità di aggiustamento della dose e/o ulteriore monitoraggio farmacologico[1]

Tutti gli altri inibitori del DPP-4 sono escreti principalmente per via renale

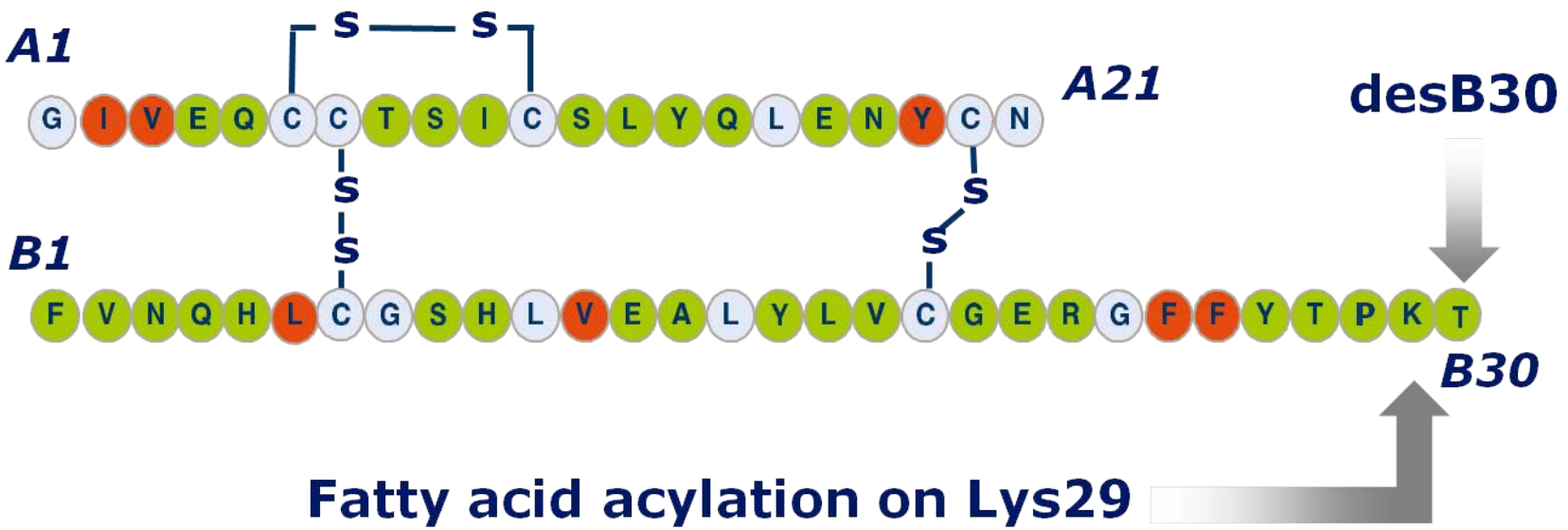
Tutti richiedono un aggiustamento della dose o non sono consigliabili in pazienti con compromissione renale.
Può essere inoltre necessario un monitoraggio farmacologico dei reni

- Rispetto agli altri inibitori del DPP-4 approvati nel mondo

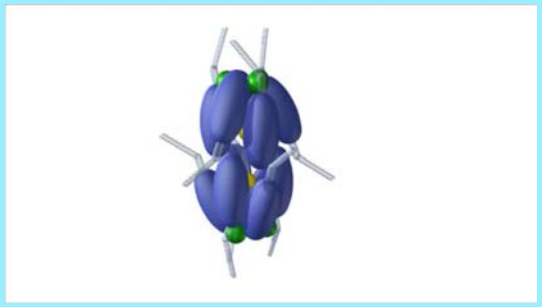
Dati raccolti da più studi, comprendenti i metaboliti e il farmaco non modificato; escrezione dopo somministrazione di dose singola di farmaco marcato [14C]

1. Foglio illustrativo USA di linagliptin
2. Vincent SH et al. *Drug Metab Dispos.* 2007;35(4): 533–538
3. He H, et al. *Drug Metab. Dispos.*2009 37(3):545–554
4. Foglio illustrativo USA di saxagliptin
5. Christopher R et al. *Clin Ther.* 2008;30(3):513–527.

Insulin degludec: design

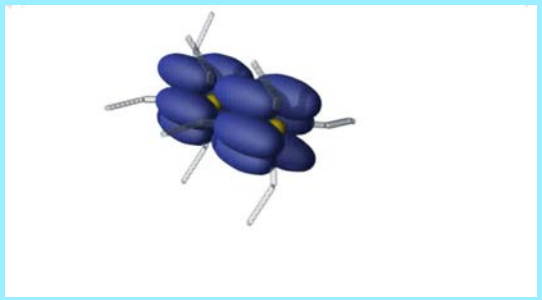


Novo Nordisk publication in preparation

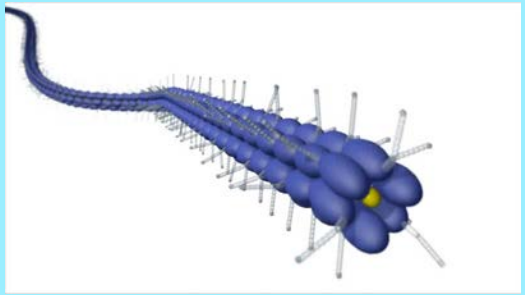


Phenol Zn^{2+}

After injection, phenol is lost and the dihexamer poles open at both ends

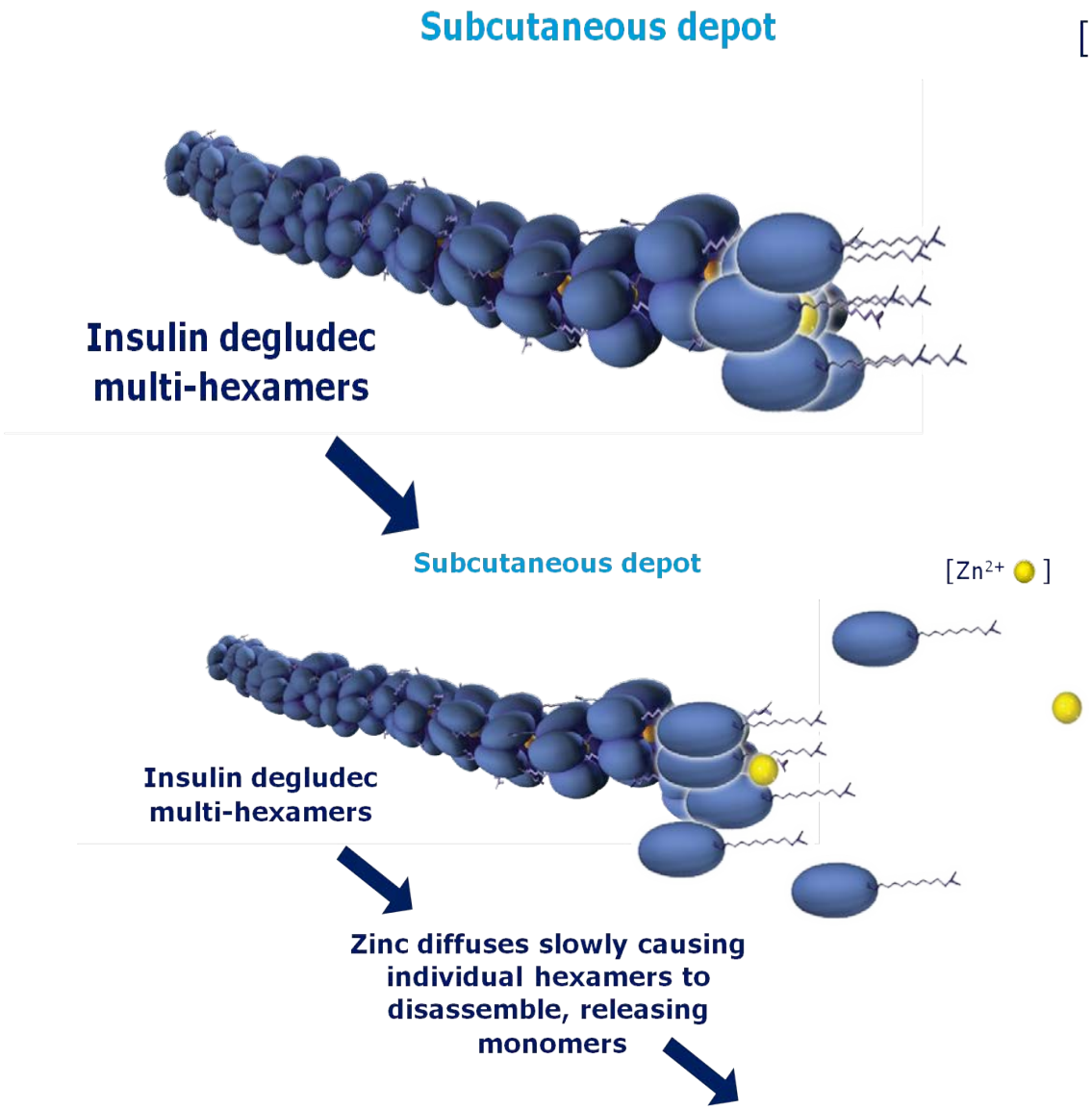


Dihexamers link up to form long soluble multihexamer chains



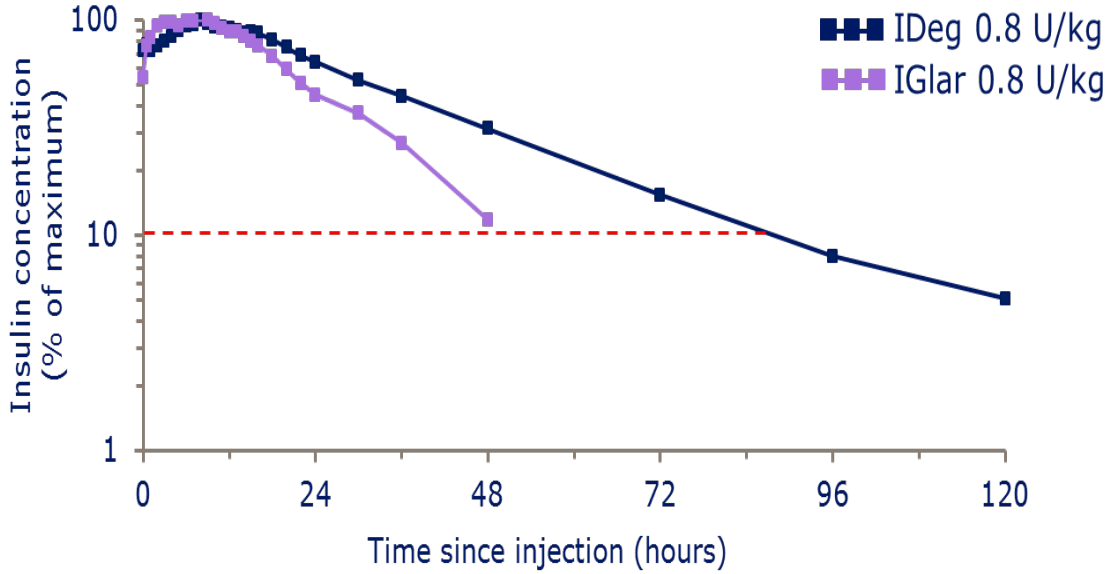
With the gradual loss of Zn^{2+}, the multihexamers release insulin degludec monomers

Insulin degludec: slow release following injection



Novo Nordisk publication in preparation

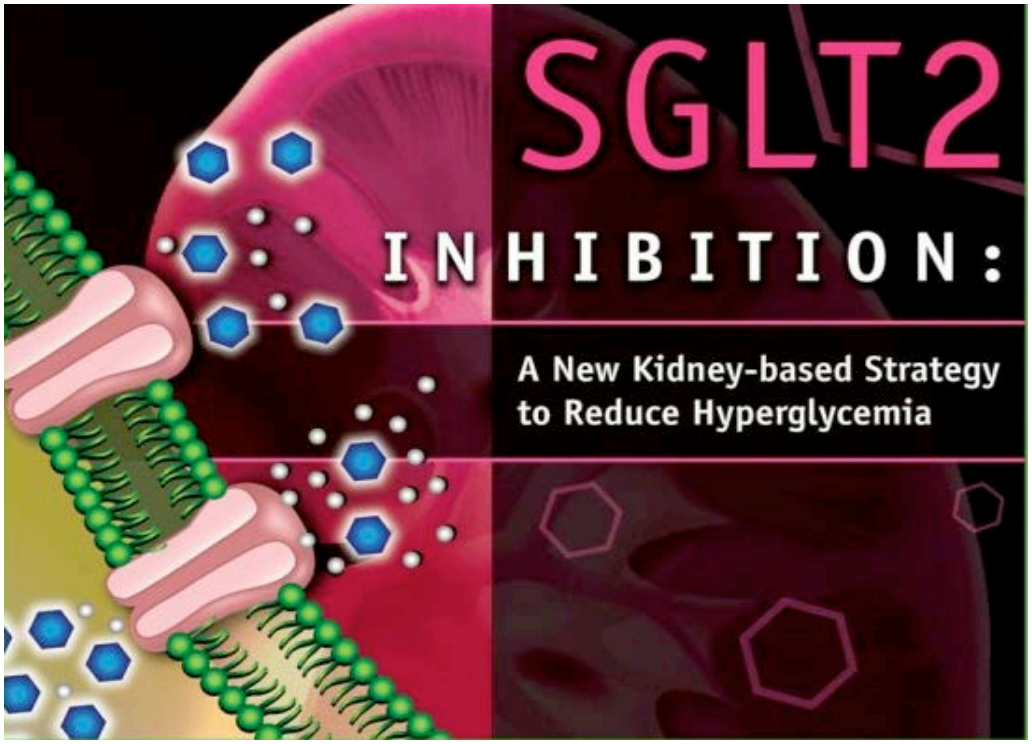
Superior PK&PD (pharmacokinetic and pharmacodynamic profile *vs* Iglar)

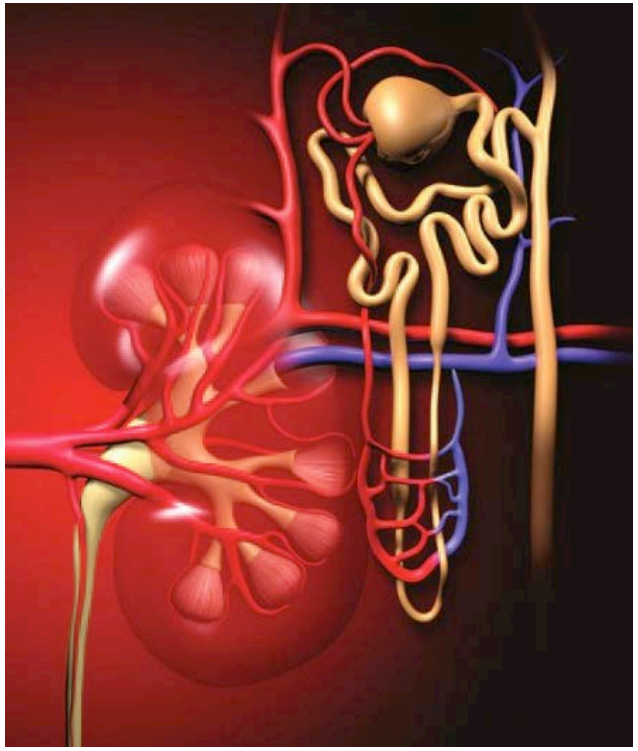


	IDeg			IGlar		
	0.4 U/kg	0.6 U/kg	0.8 U/kg	0.4 U/kg	0.6 U/kg	0.8 U/kg
Half-life (hours)	25.9	27.0	23.9	11.8	14.0	11.9
Mean half-life	**25.4**			**12.5**		

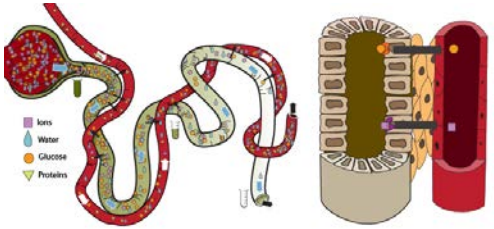
IDeg, insulin degludec; IGlar, insulin glargine

Heise *et al. Diabetes* 2011;60(Suppl. 1):LB11; Heise *et al. Diabetologia* 2011;54(Suppl. 1):S425


SGLT2
INHIBITION:
A New Kidney-based Strategy
to Reduce Hyperglycemia



The Kidneys Play an Important Role in Glucose Control

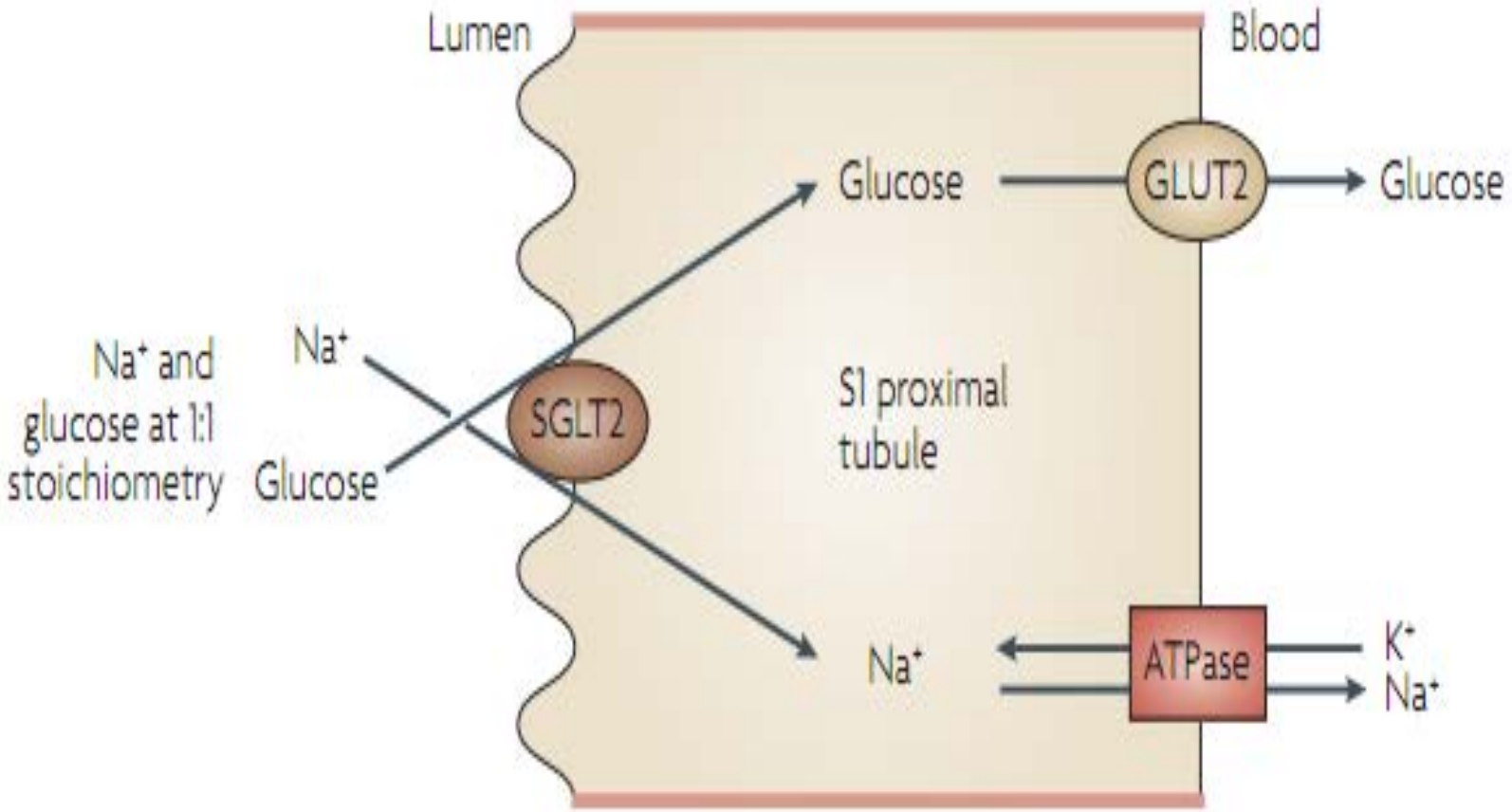


Normal Renal Glucose Physiology

- 180 g of glucose is filtered each day
- Virtually all glucose reabsorbed in the proximal tubules & reenters the circulation
- SGLT2 reabsorbs about 90% of the glucose
- SGLT1 reabsorbs about 10% of the glucose
- Virtually no glucose excreted in urine

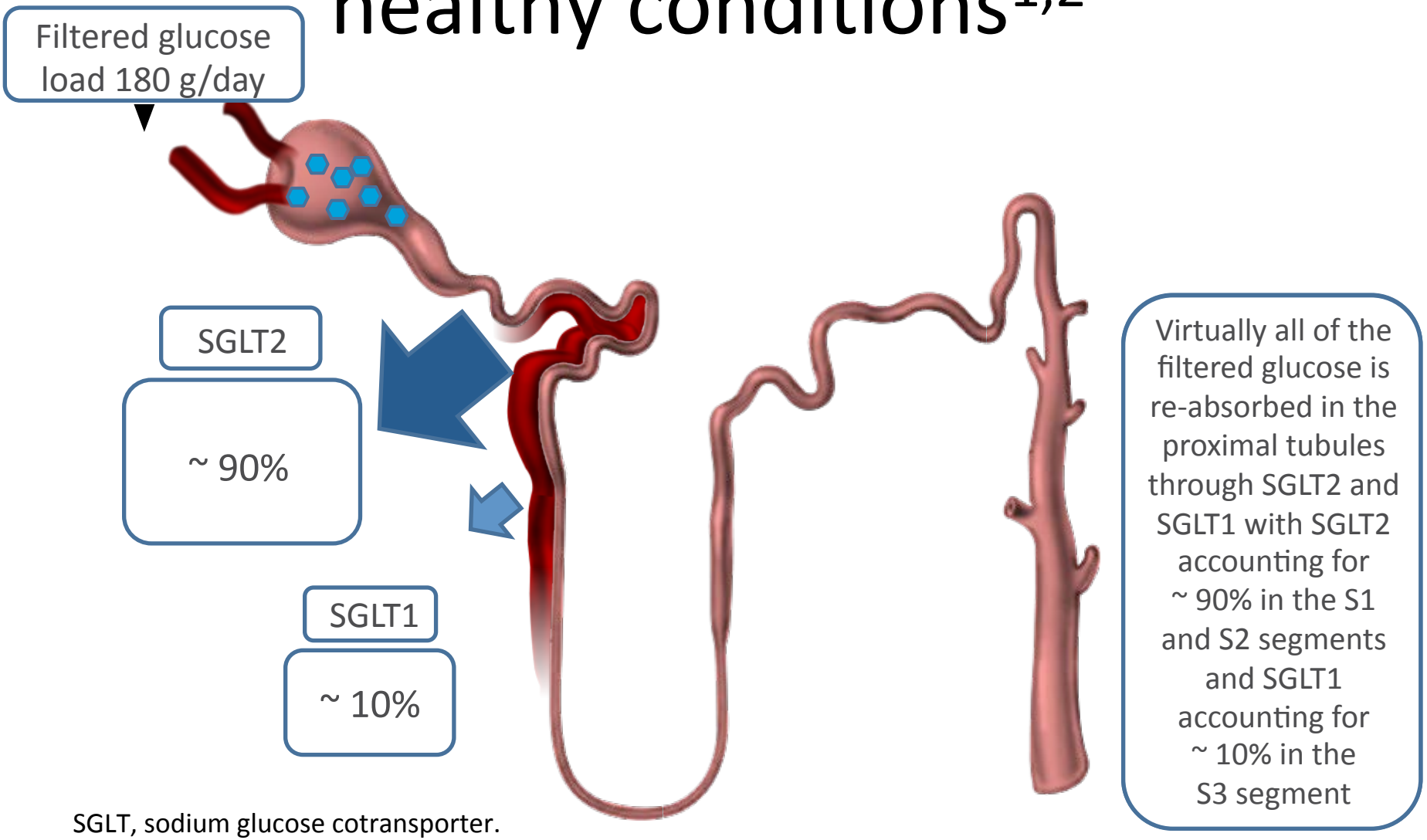
Mather, A & Pollock, C. *Kidney International*. 2011;79:S1-S6.

Renal Glucose Transport



Chao, EC & Henry RR. *Nature Reviews Drug Discovery*. 2010;9:551-559.

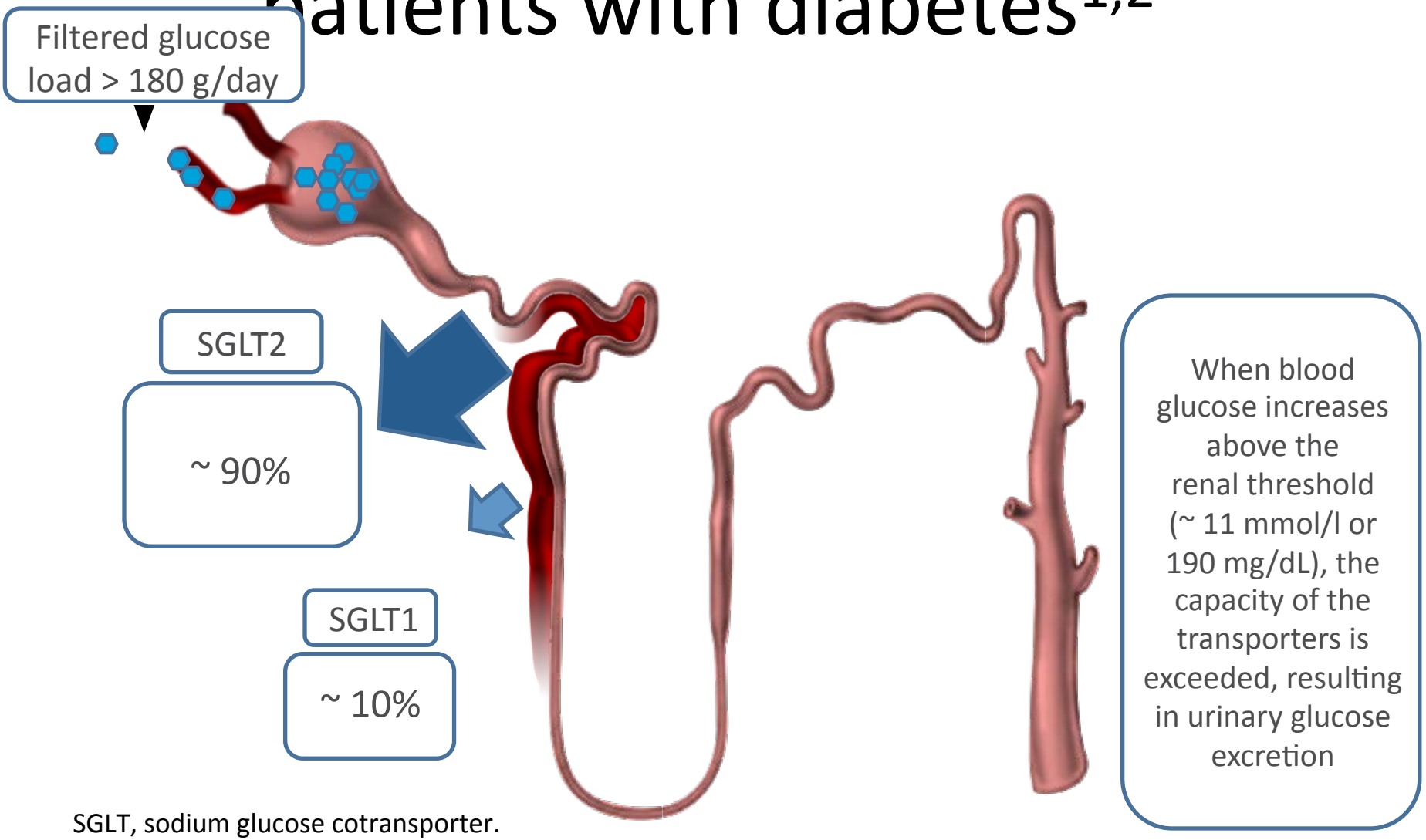
Renal glucose re-absorption under healthy conditions[1,2]



SGLT, sodium glucose cotransporter.

1. Adapted from: Gerich JE. *Diabet Med*. 2010;27:136–142; 2. Bakris GL, et al. *Kidney Int*. 2009;75;1272–1277.

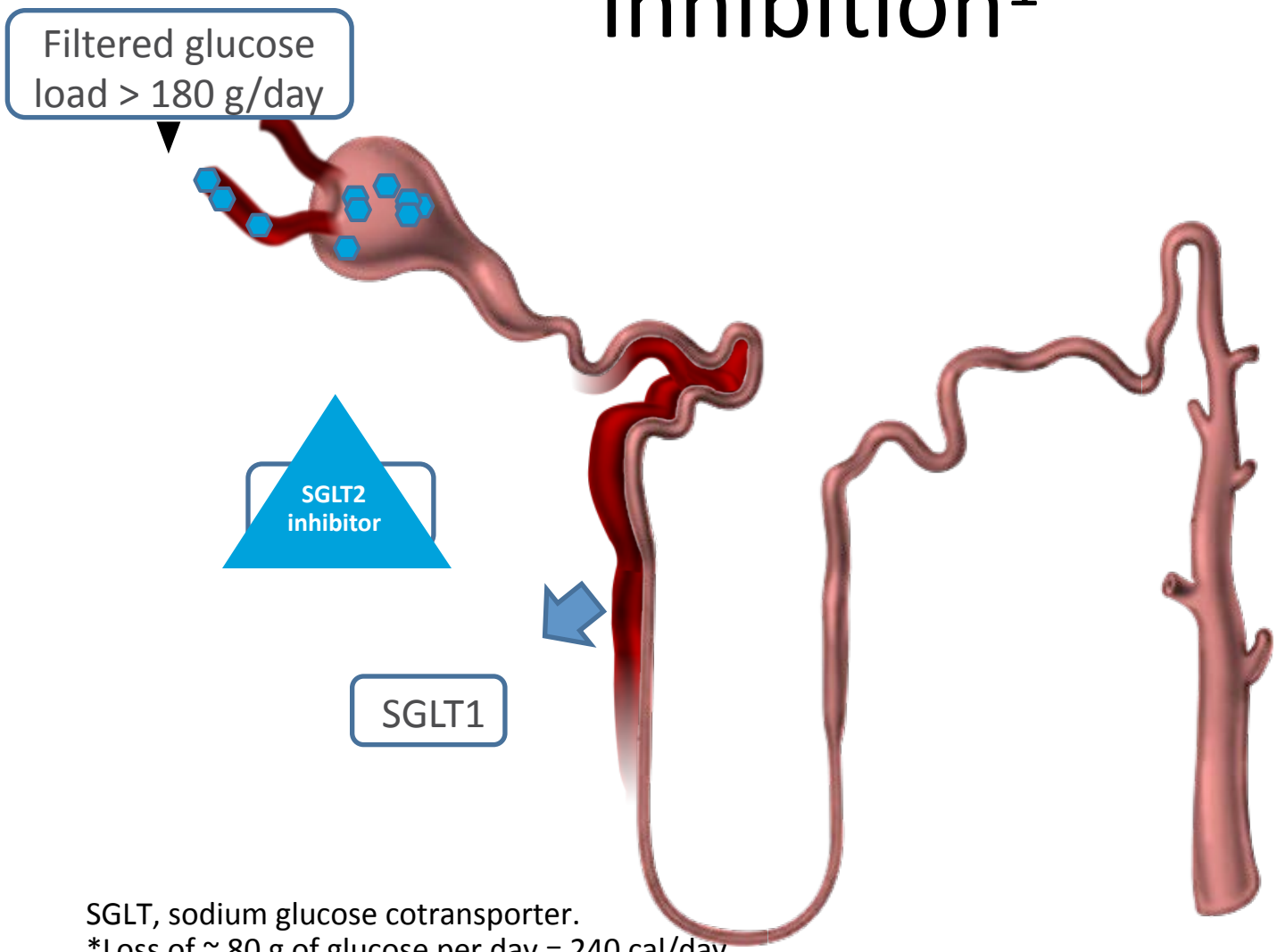
Renal glucose re-absorption in patients with diabetes[1,2]



SGLT, sodium glucose cotransporter.

1. Adapted from: Gerich JE. *Diabet Med*. 2010;27:136–142; 2. Bakris GL, et al. *Kidney Int*. 2009;75;1272–1277.

Urinary glucose excretion via SGLT2 inhibition[1]

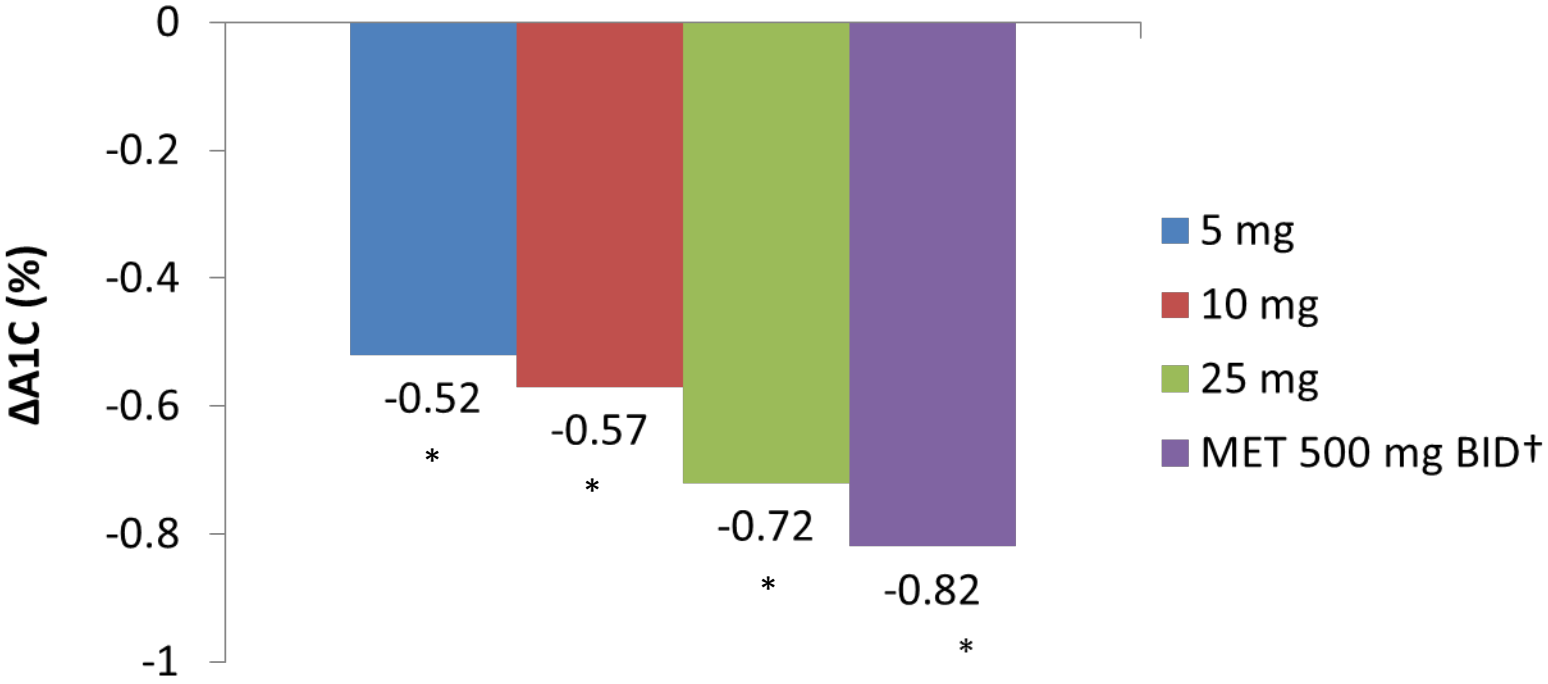


SGLT2 inhibitors reduce glucose re-absorption in the proximal tubule, leading to urinary glucose excretion* and osmotic diuresis

SGLT, sodium glucose cotransporter.
*Loss of ~ 80 g of glucose per day = 240 cal/day.
1. Bakris GL, et al. *Kidney Int*. 2009;75;1272–1277.

Empagliflozin: Change in A1C

Randomized, double-blind, 12 week trial comparing empagliflozin and open-label metformin



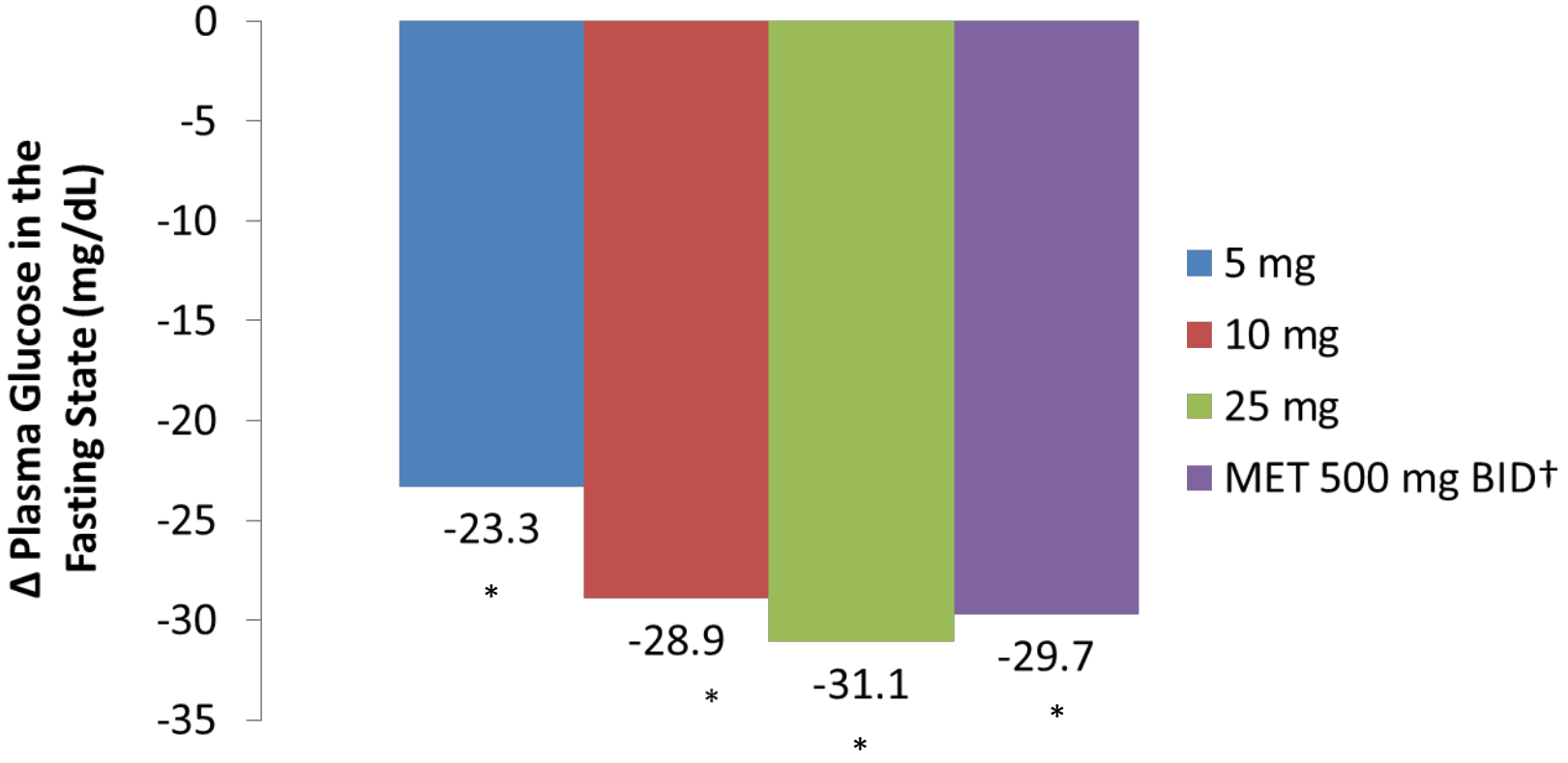
*P<.001 vs. placebo

†500 mg BID for four weeks, then 1000 mg BID or the maximum tolerate dose

Ferrannini E, et al. Abstract 877. EASD 2010.

Empagliflozin: Change in Plasma Glucose in the Fasting State

Randomized, double-blind, 12 week trial comparing empagliflozin and open-label metformin



*P<.001 vs. placebo

†500 mg BID for four weeks, then 1000 mg BID or the maximum tolerate dose

Ferrannini E, et al. Abstract 877. EASD 2010.

Monotherapy Study: Summary and Conclusion

- Increased incidence of urinary tract and genital infections with dapagliflozin treatment:
  - Events suggestive of urinary tract infection were 4%, 4.6%, 12.5%, and 5.7% for placebo, DAPA 2.5mg, 5mg, and 10mg groups, respectively
  - Events suggestive of genital infections were 1.3%, 7.7%, 7.8%, and 12.9% for placebo, DAPA 2.5mg, 5mg, and 10mg groups, respectively

- Hypoglycemic events occurred in 2.7%, 1.5%, 0%, and 2.9% in patients in placebo, DAPA 2.5mg, 5mg, and 10mg groups, respectively

Ferrannini E, et al. *Diabetes Care.* 2010;33(10):2217-2224.

Perspectives on SGLT2 Inhibition

- Potential advantages
  - Insulin Independence
  - Weight loss (75g urine glucose = 300kcal/day)
  - Low risk of hypoglycemia
  - Blood pressure lowering?
- Concerns
  - Polyuria
  - Electrolyte disturbances
  - Bacterial urinary tract infections
  - Fungal genital infections
  - Malignancies

New Classes Presently in Development

- Long-acting GLP-1 receptor agonists
- Ranolazine
- **Dual & Pan PPAR agonists**
- **11 Hydroxysteroid Dehydrogenase (HSD)- 1 inhibitors**
- Fructose 1,6-bisphosphatase inhibitors
- Glucokinase activators
- **G protein-coupled Receptor (GPR)- 40 & -119 agonists**
- Protein Tyrosine Phosphatase (PTB)- 1b inhibitors
- Camitine- Palmitoyltransferase (CPT)- 1 inhibitors
- Acetyl COA Carboxylase (ACC)- 1 & -2 inhibitors
- Glucagon receptor antagonists
- Salicylate derivatives
- Immunomodulatory drugs
- **Sodium- Glucose Cotransporter (SGLT) {-1} & -2 inhibitors**

Chinese Herbal Medicine Tianqi Reduces Progression From Impaired Glucose Tolerance to Diabetes: A Double-Blind, Randomized, Placebo-Controlled, Multicenter Trial

JCEM THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

Lian et al , China

Published Online: January 16, 2014

A combination of 10 Chinese medicinal herbs in a capsule, known as **Tianqi,** reduced progression to type 2 diabetes in people with impaired glucose tolerance (IGT) in a randomized controlled trial in China.

This is the first study to show that a Chinese herbal medicine can "reduce the progression of prediabetes to diabetes," says study author Chun-Su Yuan, MD, PhD, from the Tang Center for Herbal Medicine Research at the University of Chicago, Illinois. Tianqi "could provide a new option for diabetes management, using herbal medicine alone or as an adjuvant to currently used therapies," he noted.

"Although no direct comparison has been made between Tianqi and antidiabetic prescription drugs, our data indicate that this Chinese herbal medicine had similar effects to metformin," reported Dr. Yuan.

Dr. Yuan said the key herb in the combination was Huanglian (Coptidis Rhizoma). "The critical component of this herb is berberine, which has been reported to have good antidiabetic effects," he told *Medscape Medical News* in an interview. "Huanglian has been used traditionally in Chinese medicine in treating diabetic symptoms."

Promise and Risks of Natural Products for Hyperglycemia

Gregory A. Nichols, PhDDisclosures

March 12, 2014

Il diabete non si cura solo con i farmaci

THE UNMET NEEDS: TREATMENT

- Better education
- Effective behavioural therapy
- Preservation of B-cell function
- Specific prevention of complications
- Better monitoring of control
- Prevention of cardiovascular disease
- Societal interventions
- INDIVIDUALISED THERAPY

PRIORITIES FOR THE MANAGEMENT OF TYPE 2 DM

Key Challenges

- Prevention
- Behavioural change
- Cellular and molecular mechanisms
- Genetic basis??
- Stem cell therapy
- B-cell replacement/regeneration
- Safe, effective insulin sensitisers
- Anti-obesity agents
- CVD prevention

Diabetes: a big business

Is There Investment Upside In The Future Of Treating Diabetes?

Feb. 10, 2014 8:01 AM ET

Brian Nichols, NicholsToday (348 clicks)
Value, research analyst, biotech, author
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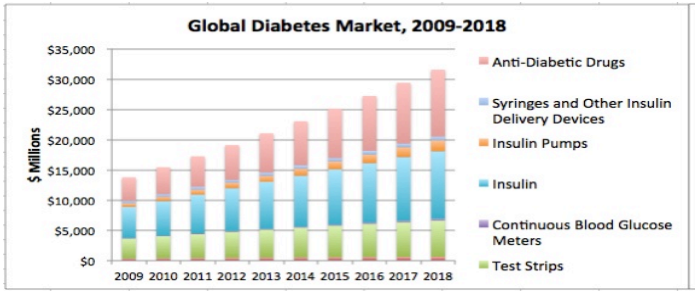
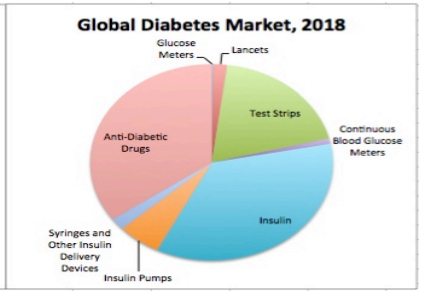
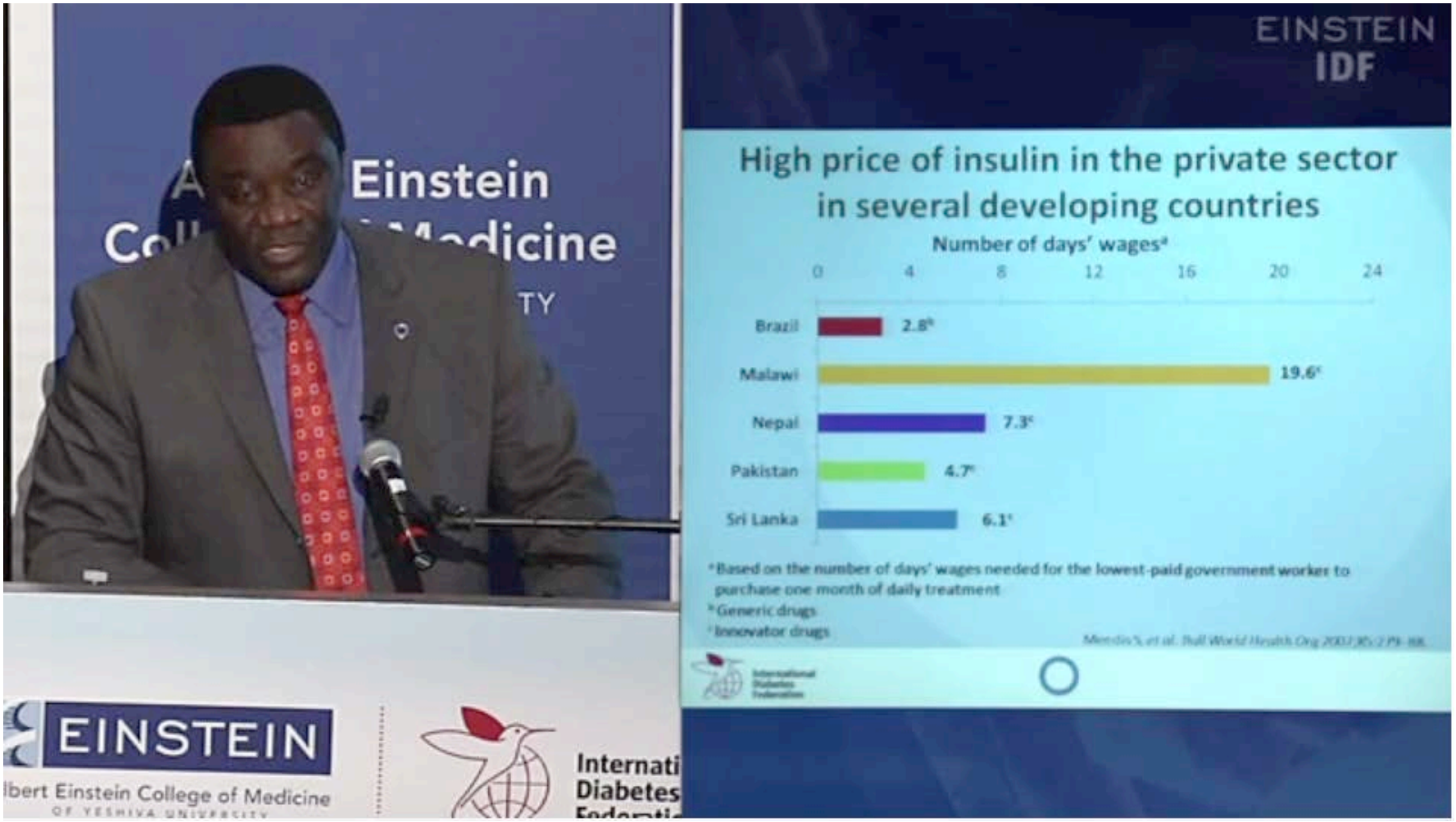
According to recent data, the type 2 diabetes market will grow to $50 billion by 2021. This, of course, does not take into account type 1 diabetes, which also is a large industry. Therefore, with this market being so large, there are clearly great gains to be created, with new leaders and drugs that will emerge to reap the benefits.

The problem is that this market is well saturated with numerous products, as it has produced some of the biggest blockbusters, but also quite a few duds that were unable to compete with the long-line of current diabetes drugs.

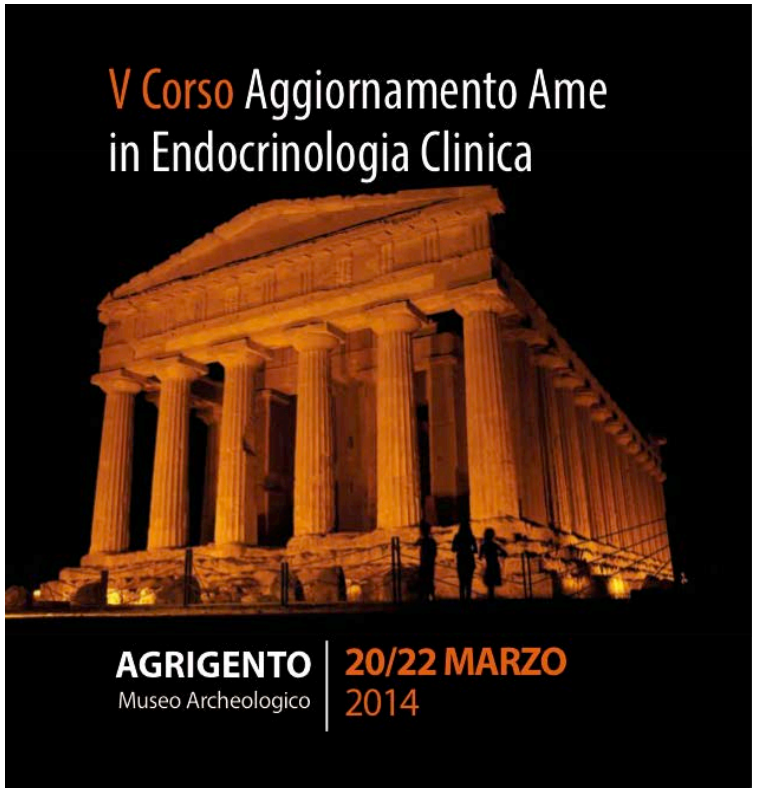




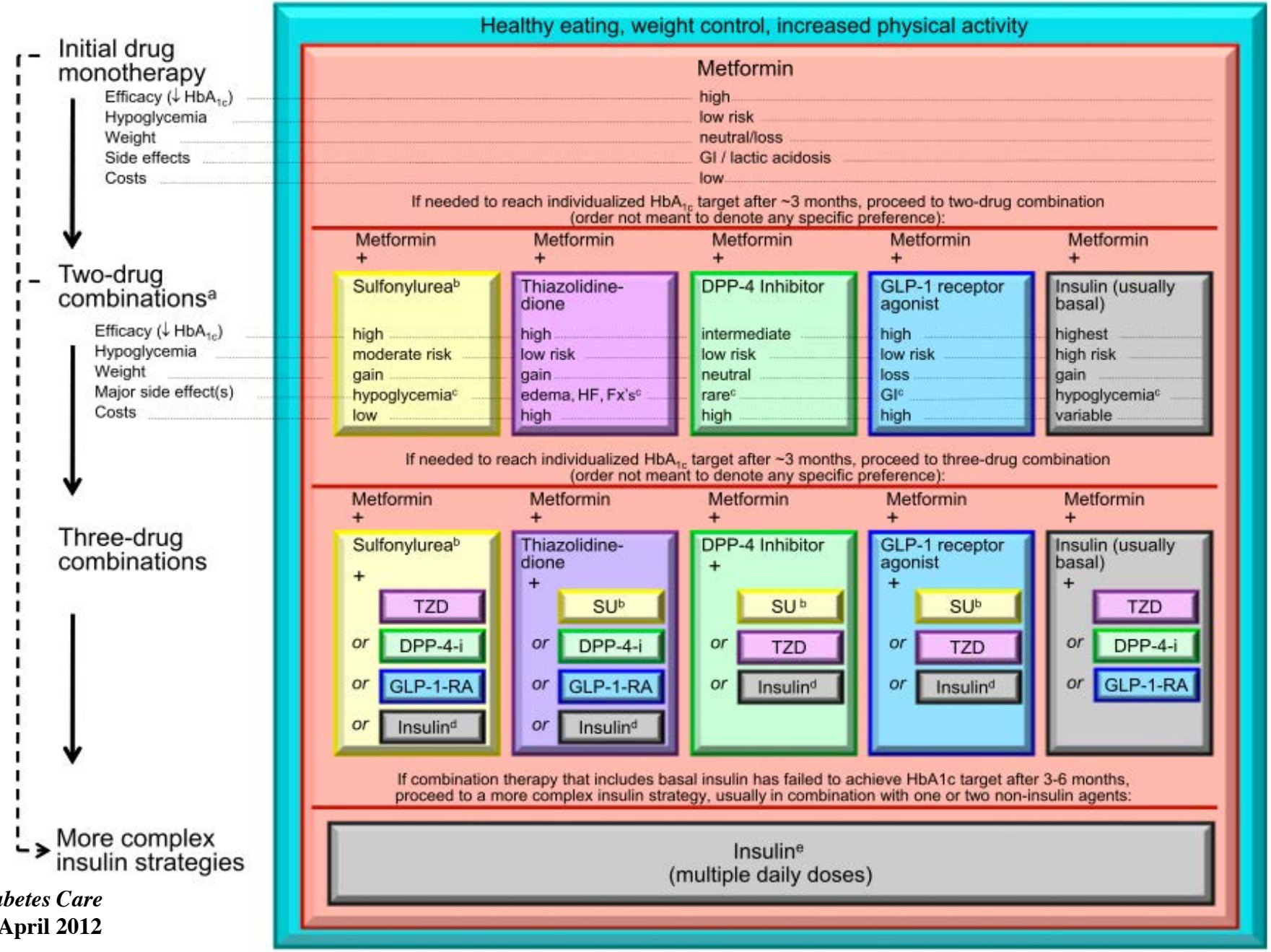
Il diabete nei paesi poveri



Global Diabetes Symposium,: IDF Vision for the Future of Global Diabetes
Professor Jean Claude Mbanya, president of the International Diabetes Federation (IDF), presents at the Global Diabetes Symposium: Finding the Way to Global Action. September 18, 2011.


V Corso Aggiornamento Ame
in Endocrinologia Clinica
AGRIGENTO
Museo Archeologico
20/22 MARZO
2014

Fine



Diabetes Care
19 April 2012