IL PAZIENTE

DIABETICO / IPERGLICEMICO IN OSPEDALE

Partiamo da lontano……

National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2·7 million participants

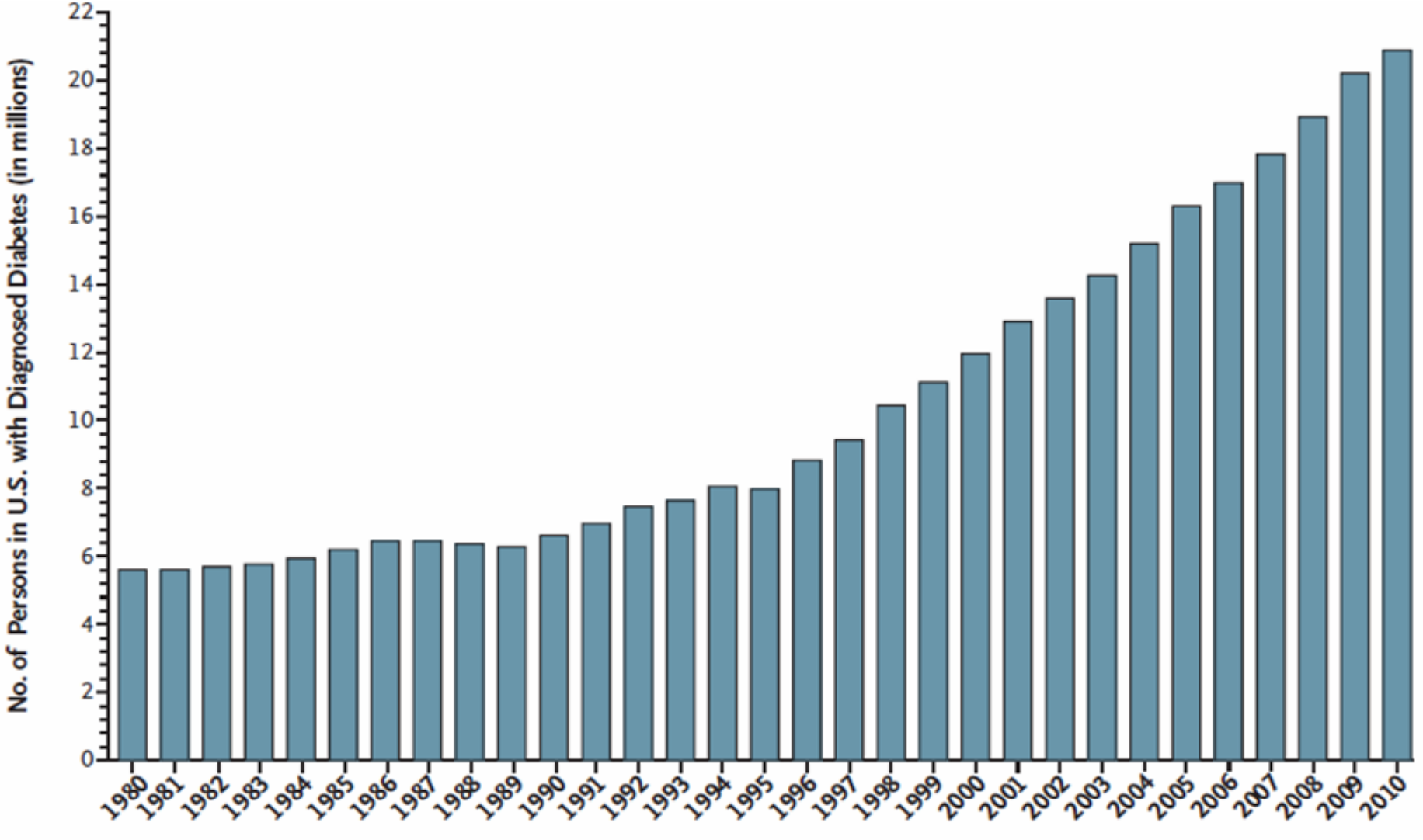
Goodarz Danaei, Mariel M Finucane*, Yuan Lu, Gitanjali M Singh, Melanie J Cowan, Christopher J Paciorek, John K Lin, Farshad Farzadfar, Young-Ho Khang, Gretchen A Stevens, Mayuree Rao, Mohammed K Ali, Leanne M Riley, Carolyn A Robinson, Majid Ezzati, on behalf of the Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group (Blood Glucose)†*

"Glycaemia and diabetes are rising globally, driven both by population growth and ageing and by increasing age-specific prevalences.

Effective preventive interventions are needed, and health systems should prepare to detect and manage diabetes and its sequelae."

Danaei G. Lancet 2011, published online June 25

Number of Persons of the Population with Diagnosed Diabetes in the United States, 1980–2010.



Polonsky KS: NEJM 2012;367:1332.

Diabetes in the Population

Prevalence of diabetes (in patients aged 20-79 years) in 2011 and estimated in 2030:

- **Global estimated number in 2011: 366 million (prevalence: 8.3%)**
- **Global estimated number in 2030: 552 million (prevalence: 10%)**
- **51% increase in the number of diabetic patients in the world**

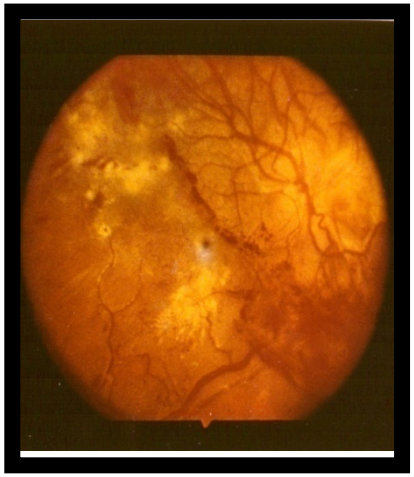
IDF Diabetes Atlas 5th edition; Nov 2011. www.idf.org

Diabete e pre-diabete in Liguria sono molto comuni

In ogni famiglia della Liguria c'è o ci sarà nei prossimi anni una persona con il diabete o un soggetto pre-diabetico

Diabete noto in Liguria: 85000

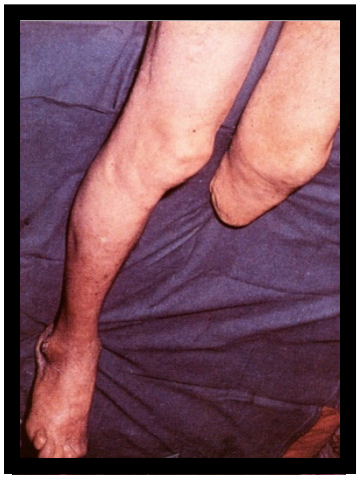
Diabete: complicanze gravissime e disabilitanti



Prima causa
di cecità

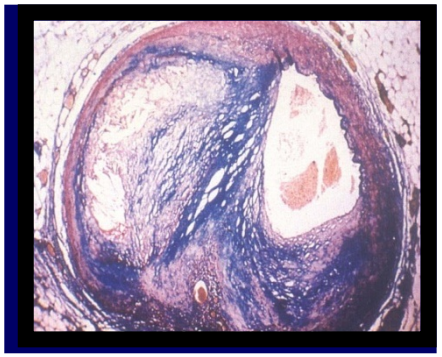
Causa maggiore
di insufficienza
renale & dialisi

Diabete



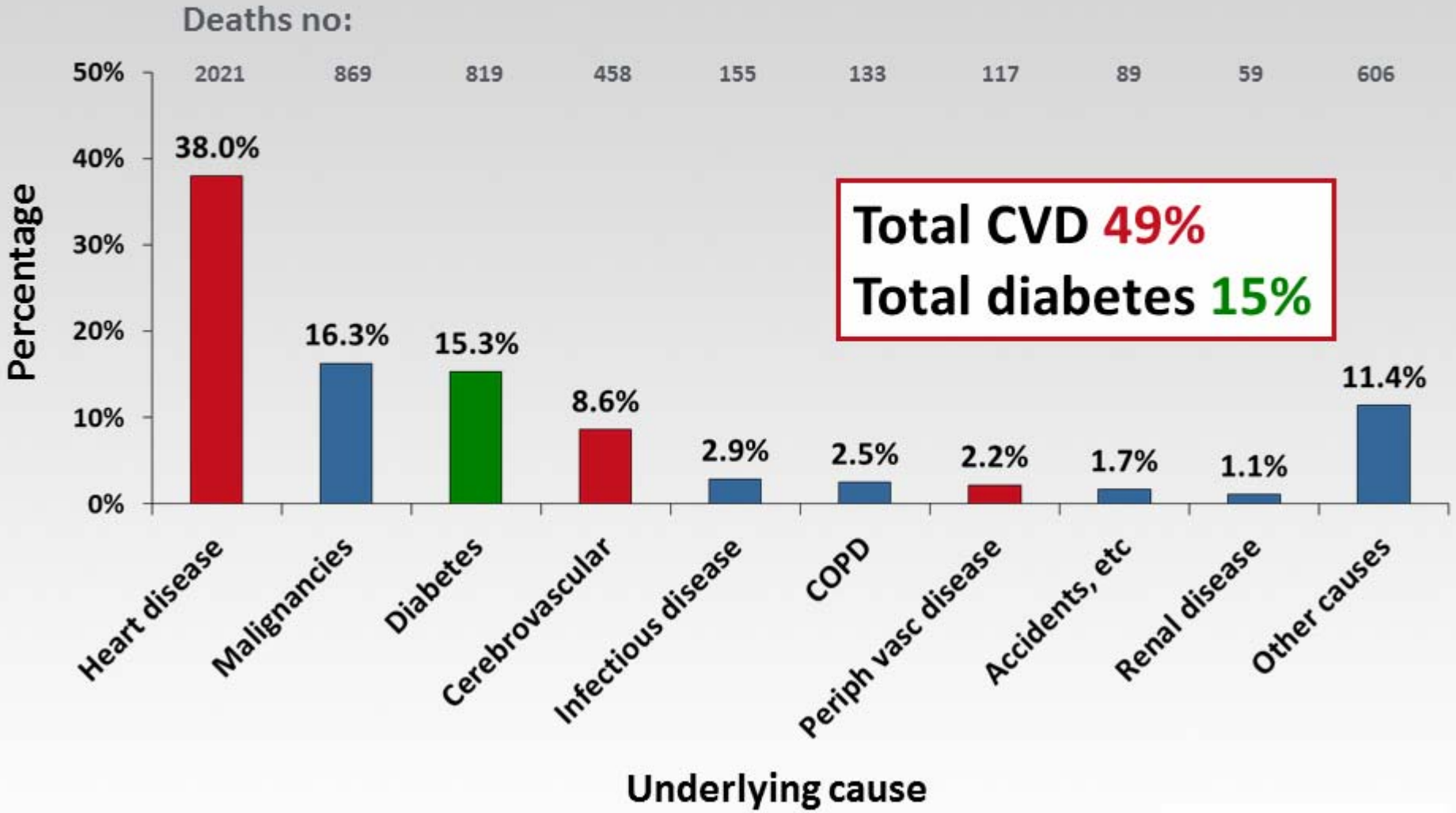
Prima causa
di amputazione
non traumatica

Concausa
nel 40-50% di
infarti e ictus



Mortality Reasons in Diabetes

Population-Based Data from North Dakota



Tierney EF, et al. *Am J Public Health.* 2001;91(1):84-92.

Diagnostic Criteria

	Fasting Glucose mg/dL	2-h OGTT mg/dL	Random Glucose mg/dL	A1c
Normal	<100	<140	<200	<5.7%
Prediabetes	100-125 (IFG)	140-199 (IGT)		5.7-6.4%
Diabetes	≥ 126	≥ 200	≥ 200	≥ 6.5%

Note: In the absence of unequivocal hyperglycemia, result(s) should be confirmed by repeat testing.

ADA. I. Classification and Diagnosis. *Diabetes Care* 2012;35(suppl 1):S12.

Prevention, Prevention, Prevention!

- Refer patients with IGT, IFG, or A1C 5.7–6.4% to ongoing ***support program***
  - Target weight loss = 7% of total body weight
  - Minimum of 150 min/week of moderate physical activity
- Medications shown to ***delay progression*** of IGT/IFG to T2DM
  - Metformin (US DPP, NEJM 2002)
  - Acarbose (STOP-NIDDM, Lancet 2002)
  - Pioglitazone (ACT NOW, presentation 2008)
- Consider metformin for prevention of type 2 diabetes if IGT, IFG, or A1C 5.7–6.4%
  - Especially for those with BMI >35 kg/m^2, age <60 years, and women with prior GDM

ADA. IV. Prevention/Delay of Type 2 Diabetes. *Diabetes Care* 2012;35(suppl 1):S16

Vari tipi di diabete

DM tipo 2

- Alta prevaleza (90%)
- Insulino resistenza + insulino carenza
- Genetica
- Esordio graduale
- Di solito in età più tardiva
- Associato a obesità / sindrome metabolica
- Preceduto talvolta da IFG
- Non soggetto a chetosi
- Da non trattare necessariamente con insulina
- Complicanze micro e macro vascolari

DM tipo1

- Bassa prevalenza (5-10%)
- Insulino carenza assoluta (insulite distruttiva)
- Genetica meno rilevante
- Esordio spesso acuto
- A qualunque età ma di solito nel giovane
- Spesso associato a dimagramento
- Soggetto a chetosi
- Da trattare necessariamente con insulina ab initio
- Complicanze micro e macro vascolari

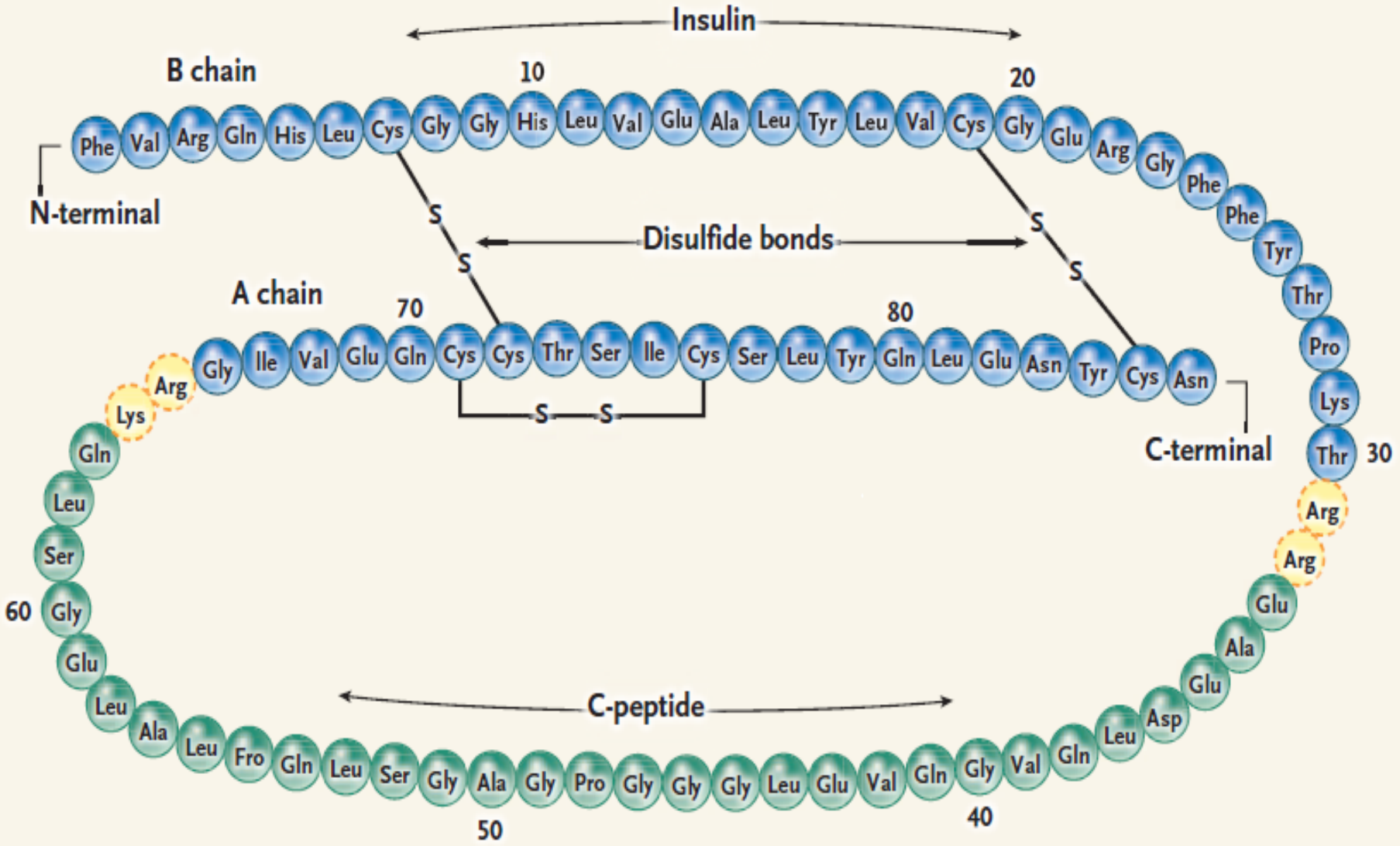
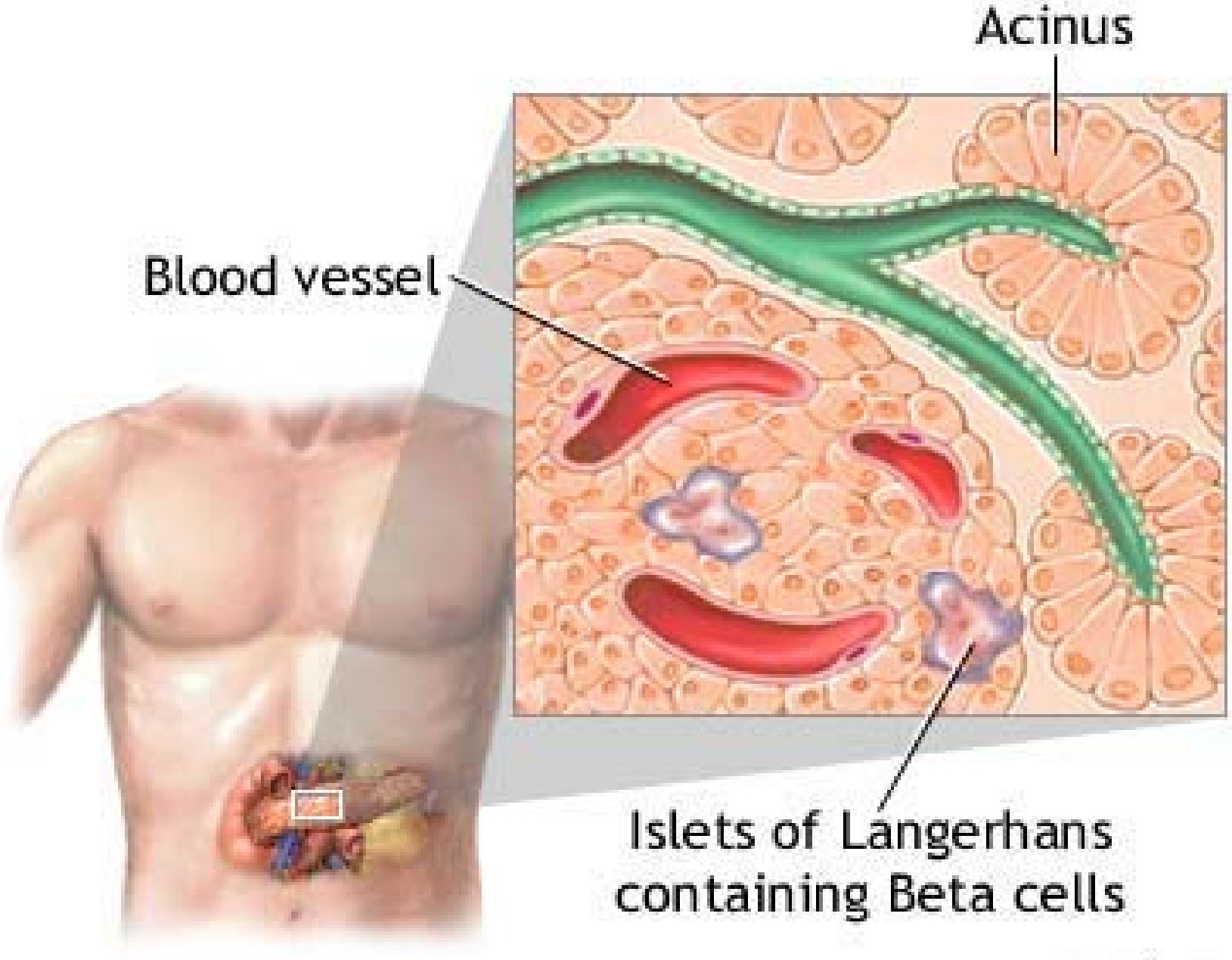
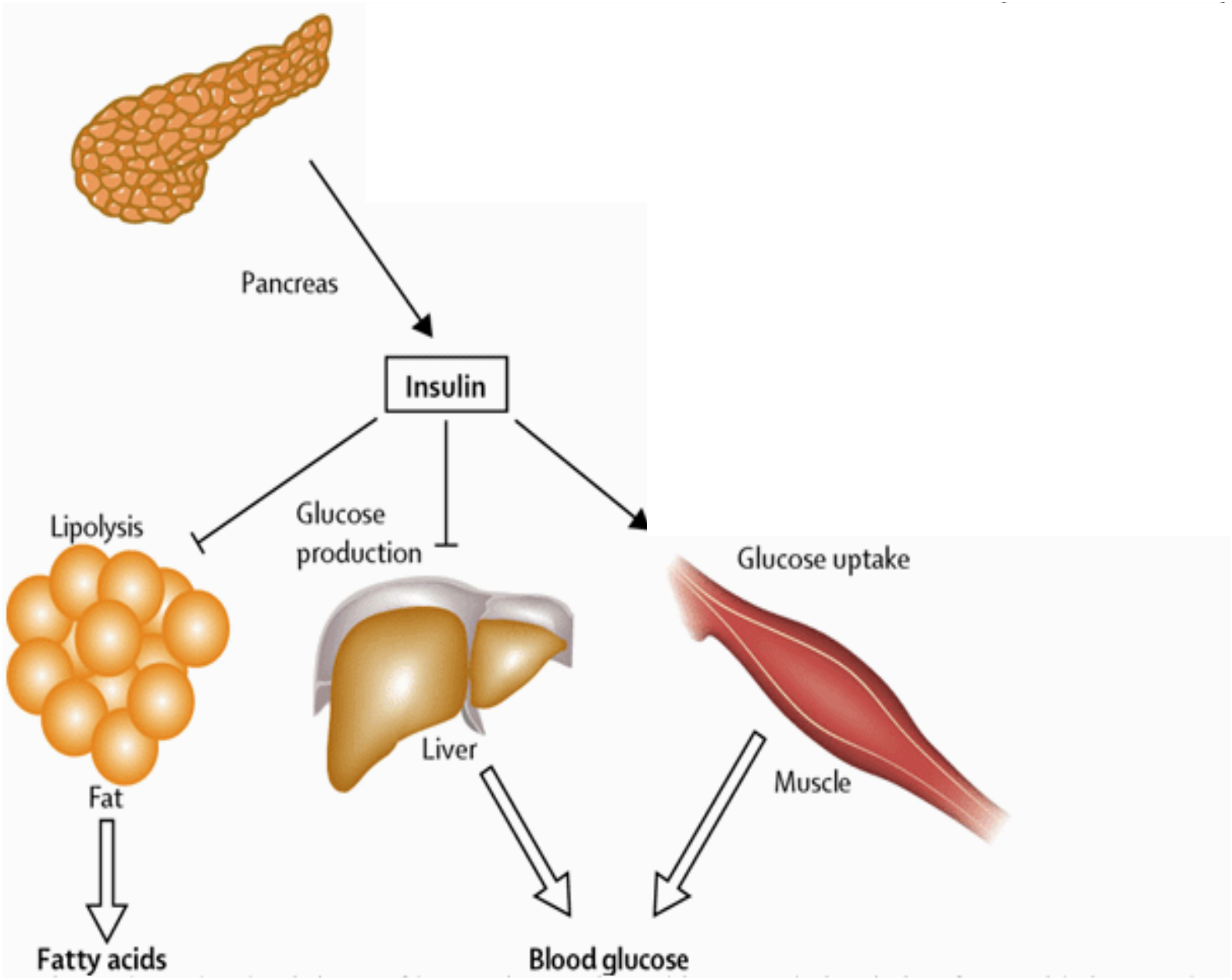


Figure 2. The Structure of Human Proinsulin.

Proinsulin is converted to insulin by proteolytic converting enzymes that remove the connecting peptide (C-peptide) and the lysine-arginine (Lys-Arg) and arginine-arginine (Arg-Arg) sequences of dibasic amino acids, leaving the mature insulin molecule, which consists of A and B chains connected by disulfide bonds.


Acinus
Blood vessel
Islets of Langerhans
containing Beta cells

A cosa serve l'insulina



Effetti dell'Insulina:

	Stimola	Inibisce
◆ *Fegato*		
	sintesi del glicogeno	glicogenolisi
	sintesi dei trigliceridi	chetogenesi
		gluconeogenesi
◆ *Muscolo Scheletrico*		
	captazione del glucosio	
	sintesi proteica	catabolismo proteico
	glicogeno sintesi	glicogenolisi
◆ *Tessuto Adiposo*		
	captazione del glucosio	
	deposito di trigliceridi	lipolisi

Promuove i processi anabolici

Inibisce i processi catabolici.

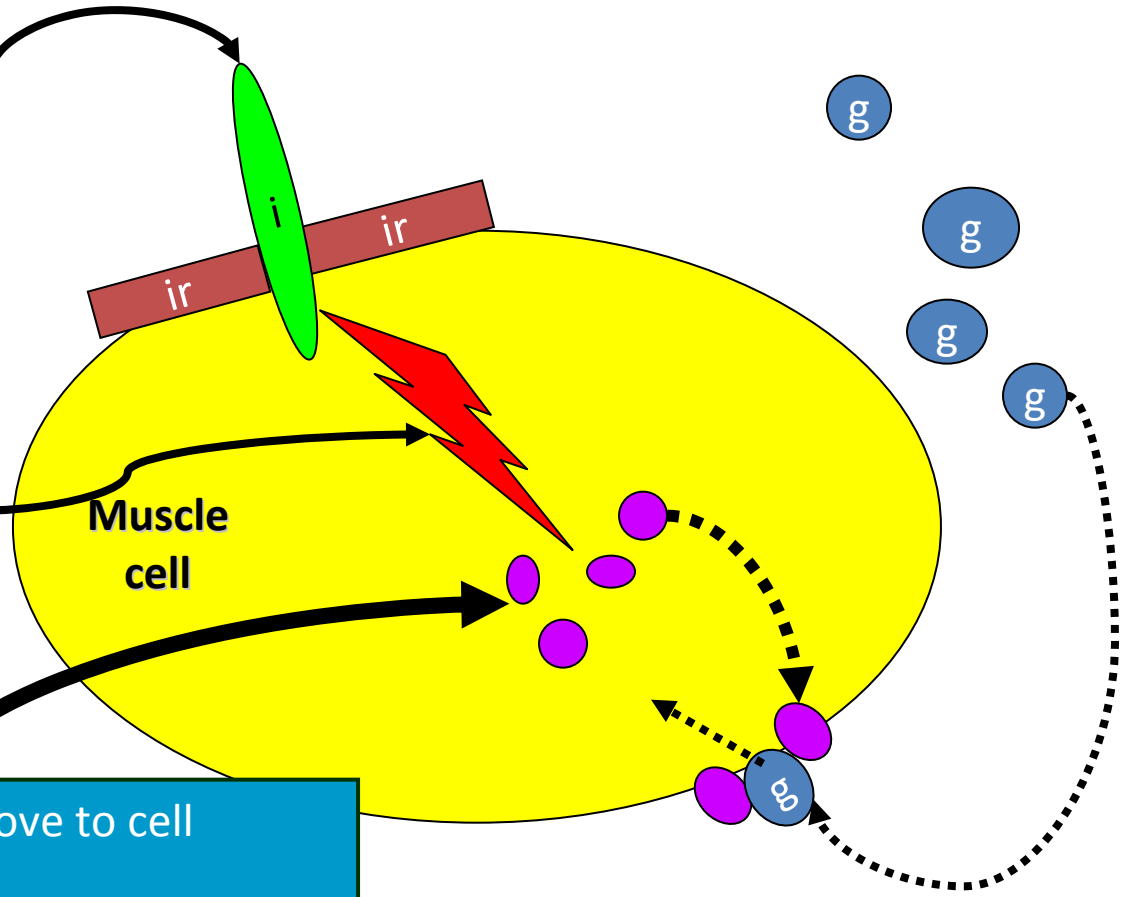
Insulin Action: muscle

1. Insulin Binds to insulin receptor

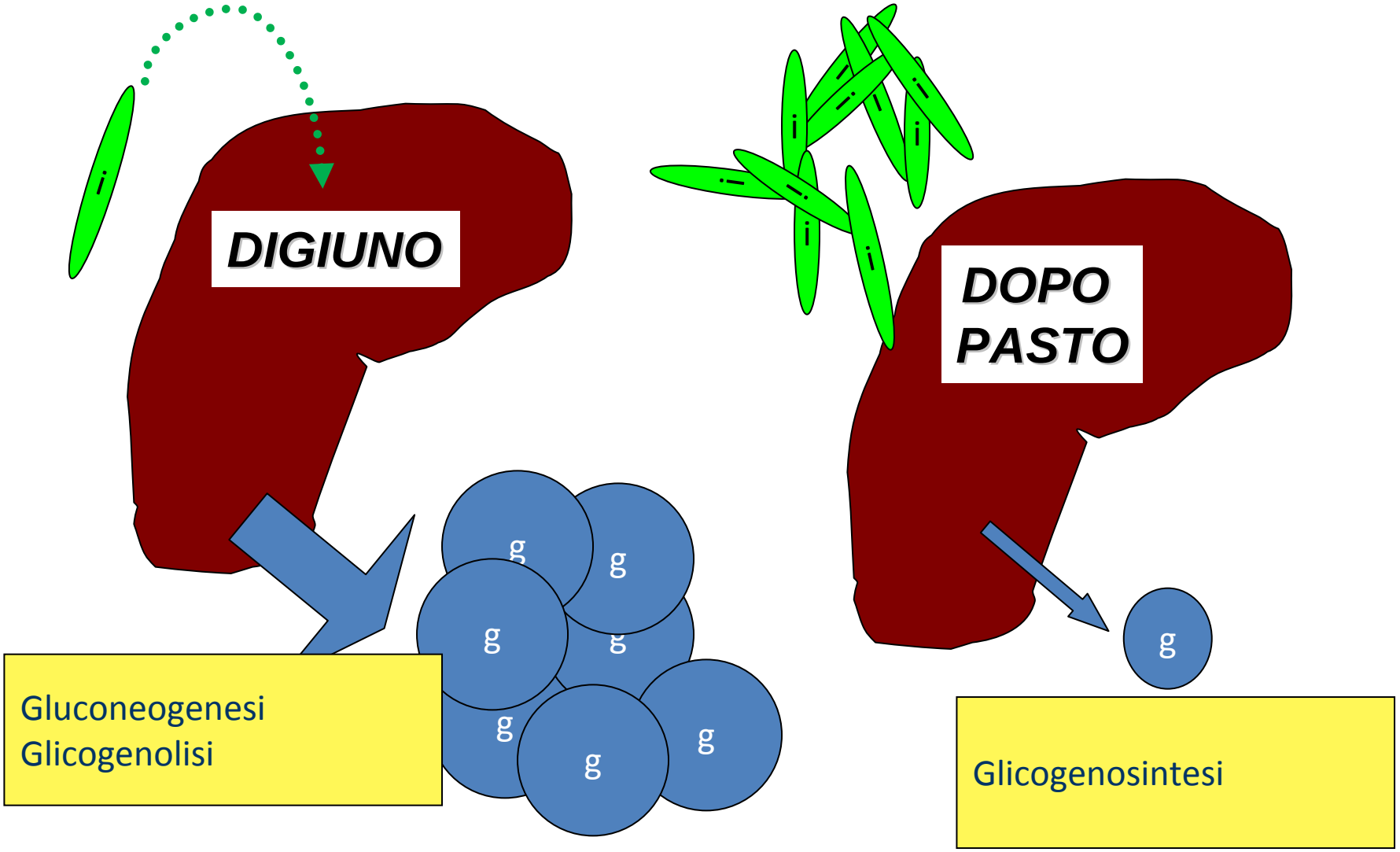
2. Binding signals glucose transporters to move to cell surface

3. Glucose transporters move to cell surface (e.g. GLUT4)

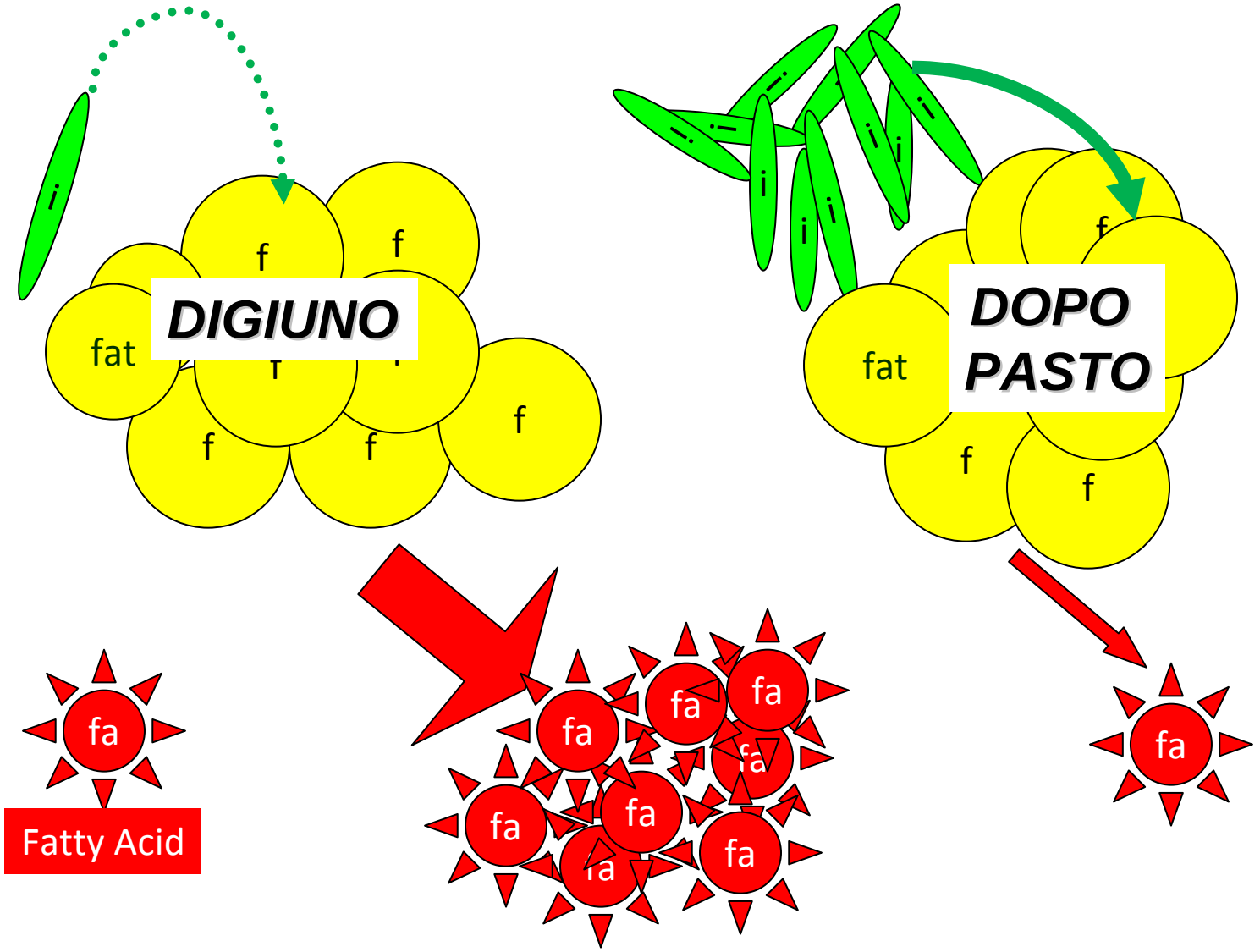
4. Glucose enters cell



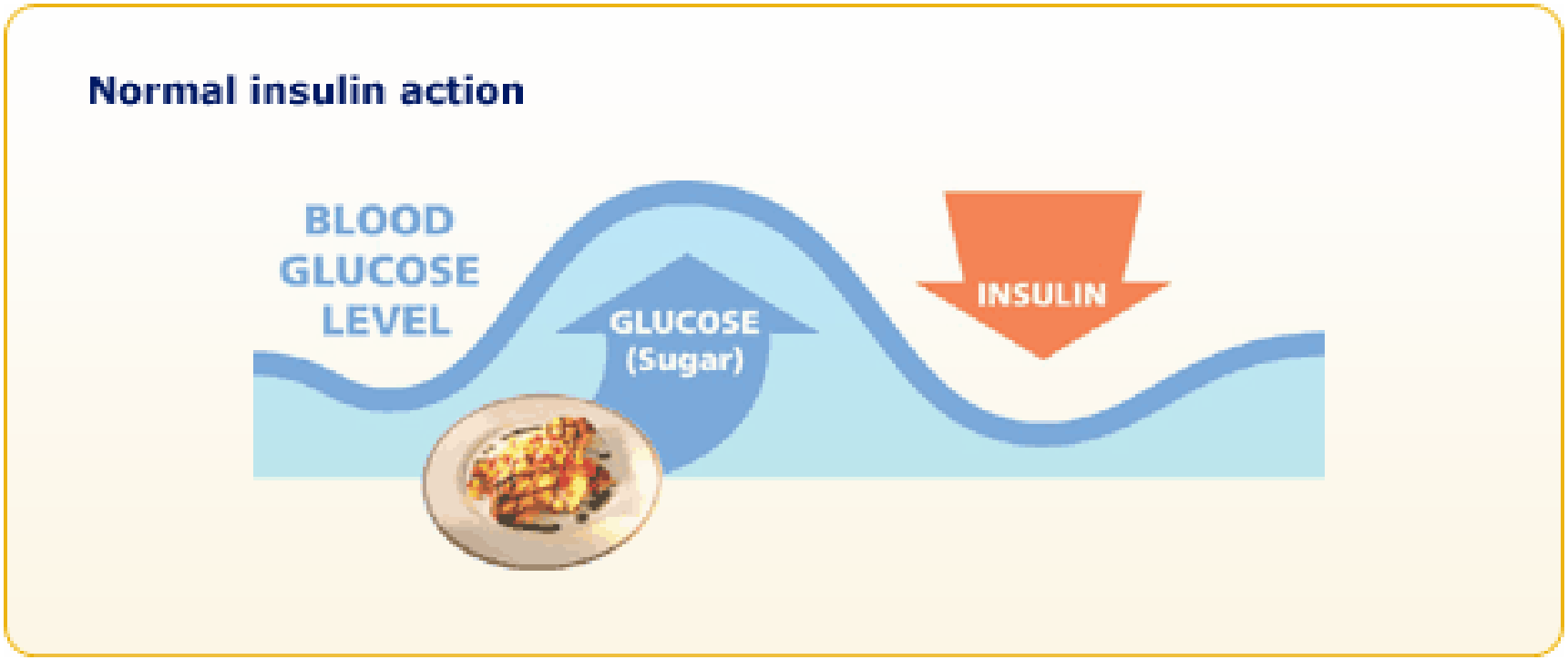
Insulin Action: Liver



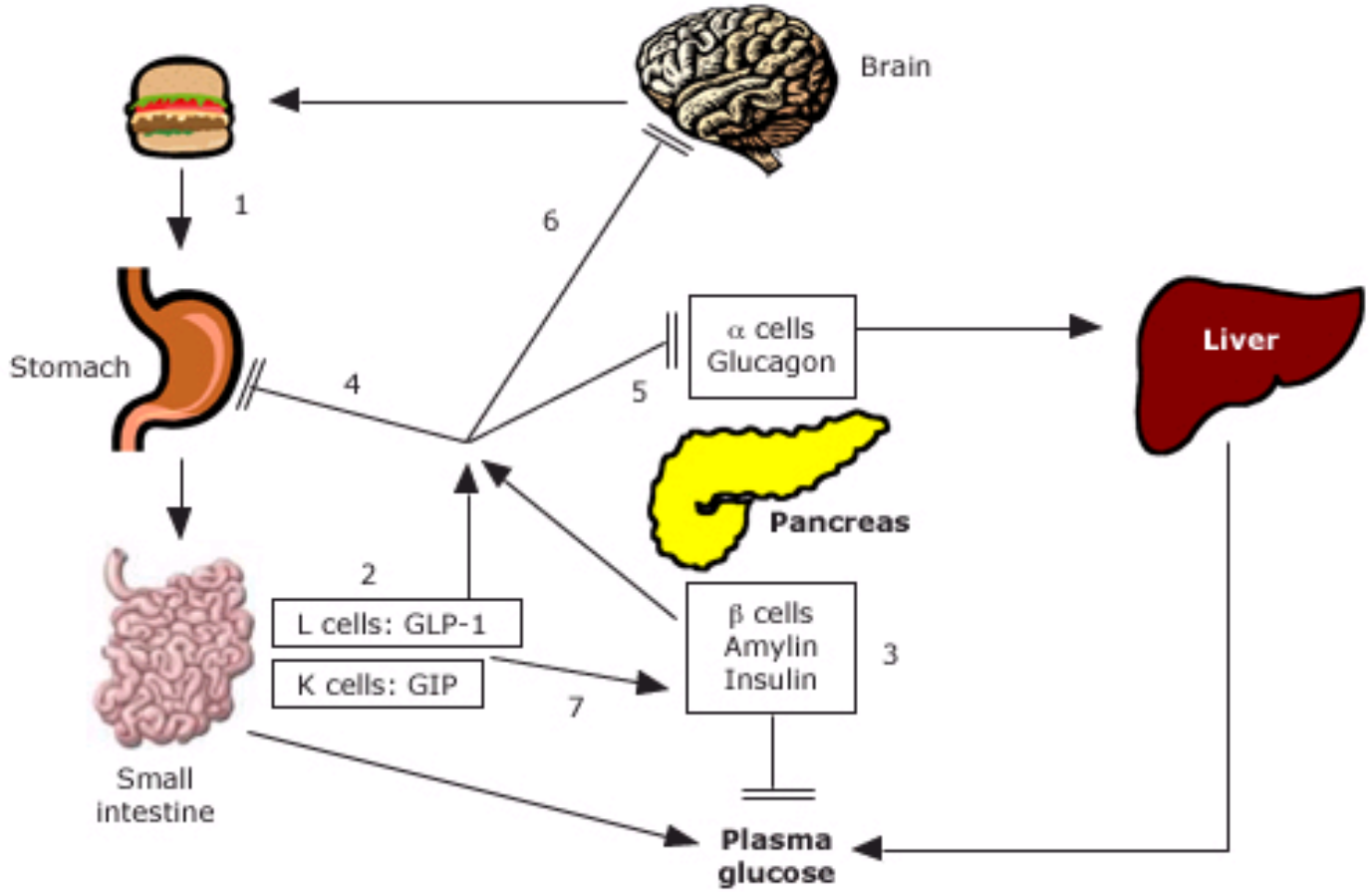
Insulin Action: Fat



A cosa serve l'insulina



Multihormonal regulation of glucose



In healthy individuals, (1) ingestion of food results in (2) release of gastrointestinal peptides (GLP-1 and GIP) as well as (3) pancreatic beta cell hormones (insulin and amylin). GLP-1 and amylin, in particular, have inhibitory effects on (4) gastric emptying, (5) glucagon release, and (6) appetite. (7) Following the absorption of food, GLP-1 and GIP promote insulin secretion, otherwise known as the incretin effect. In diabetes, these steps are disrupted.

Qualcosa può andare storto…..

Vari tipi di diabete

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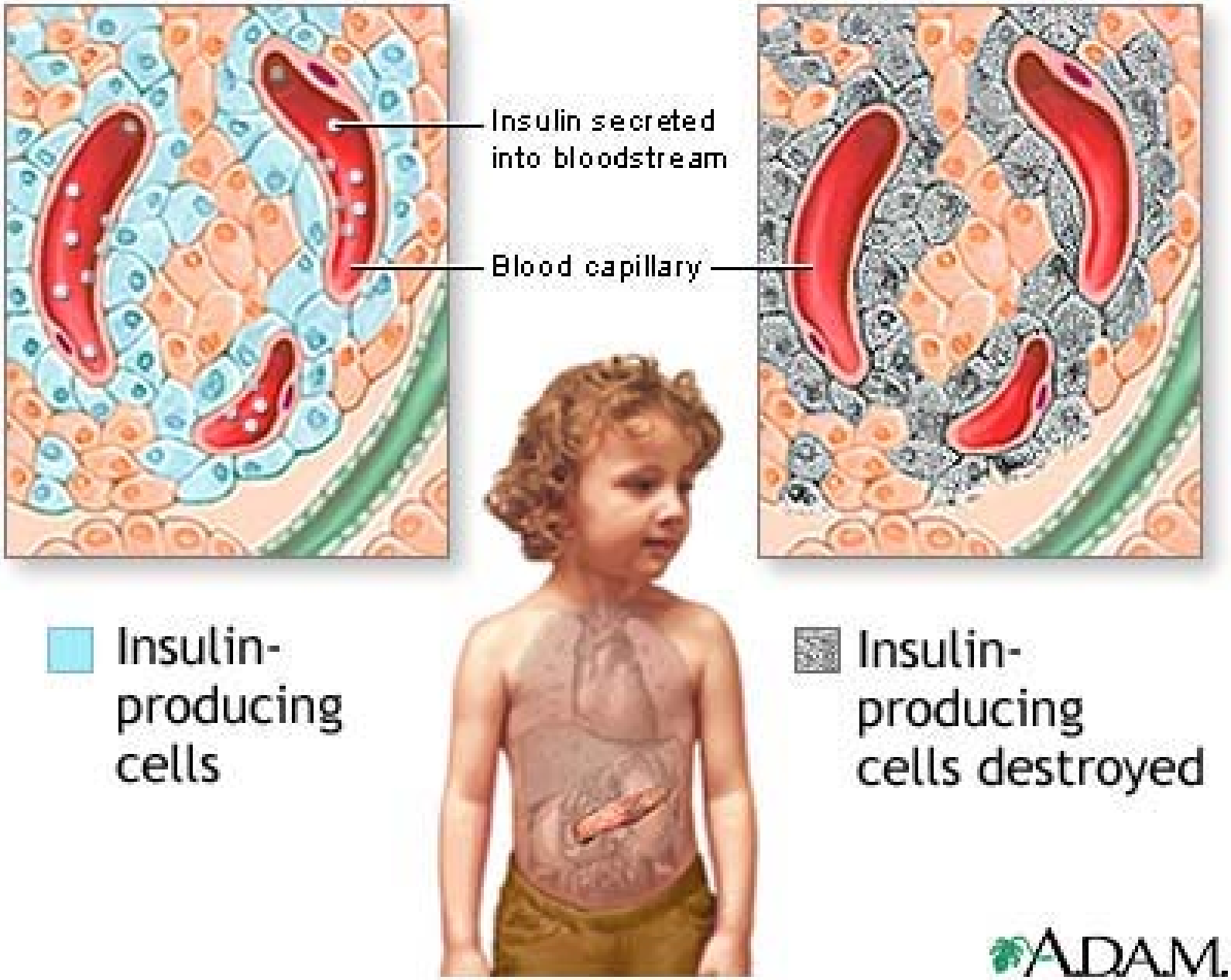
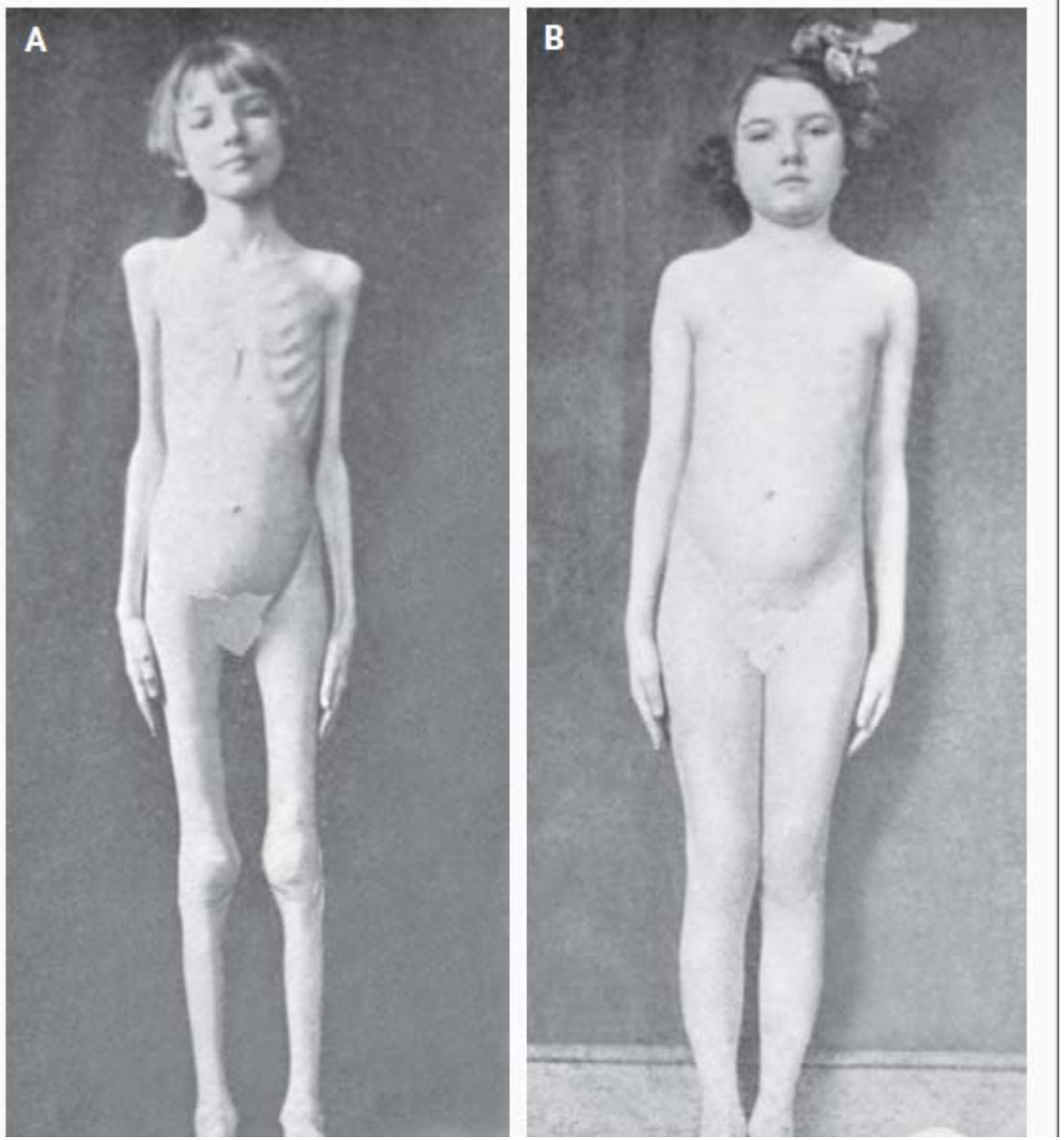
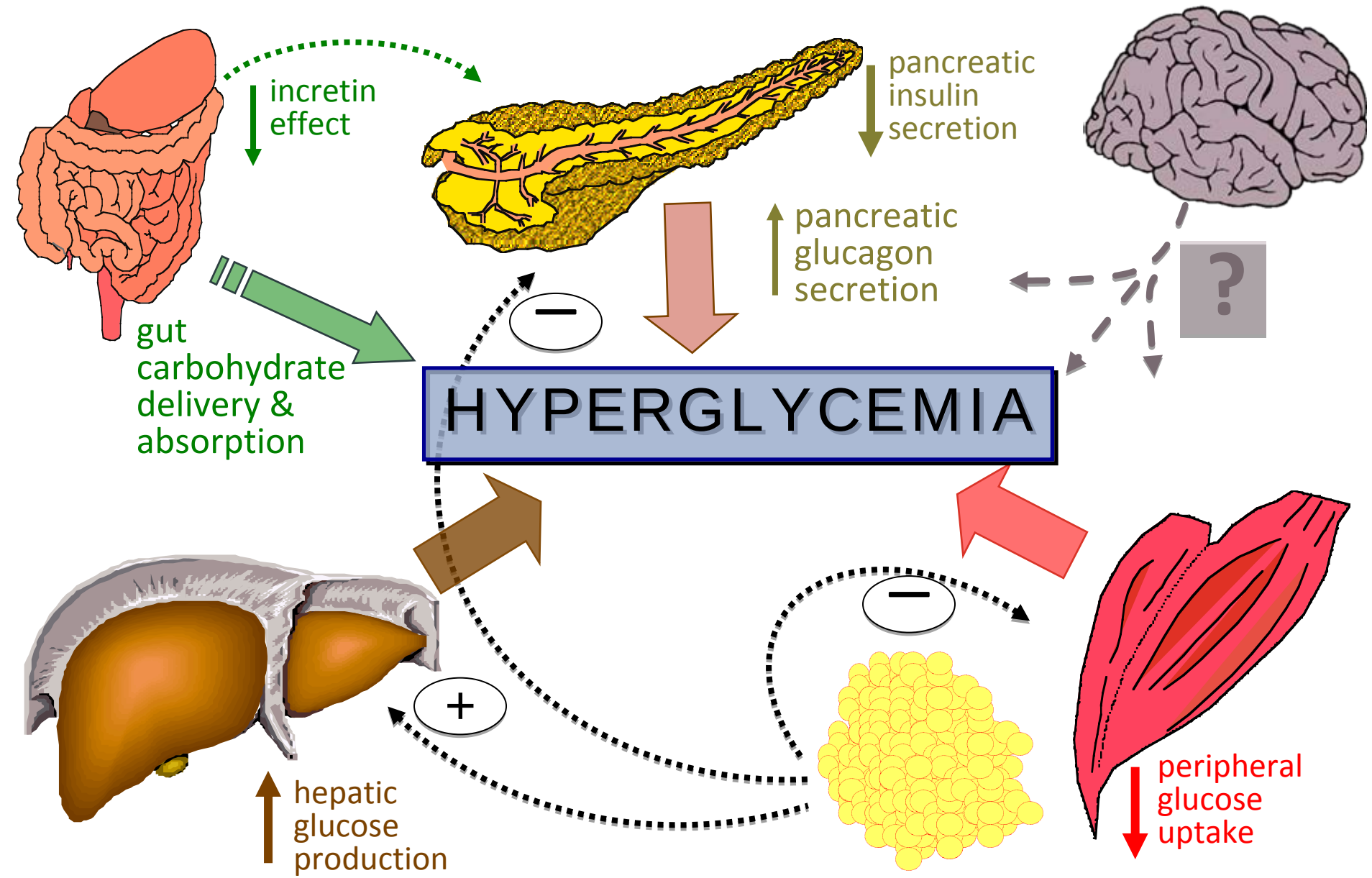
- Soggetto a chetosi
- Da trattare necessariamente con insulina ab initio
- Complicanze micro e macro vascolari


Insulin secreted into bloodstream
Blood capillary
Insulin-producing cells
Insulin-producing cells destroyed
A.D.A.M.



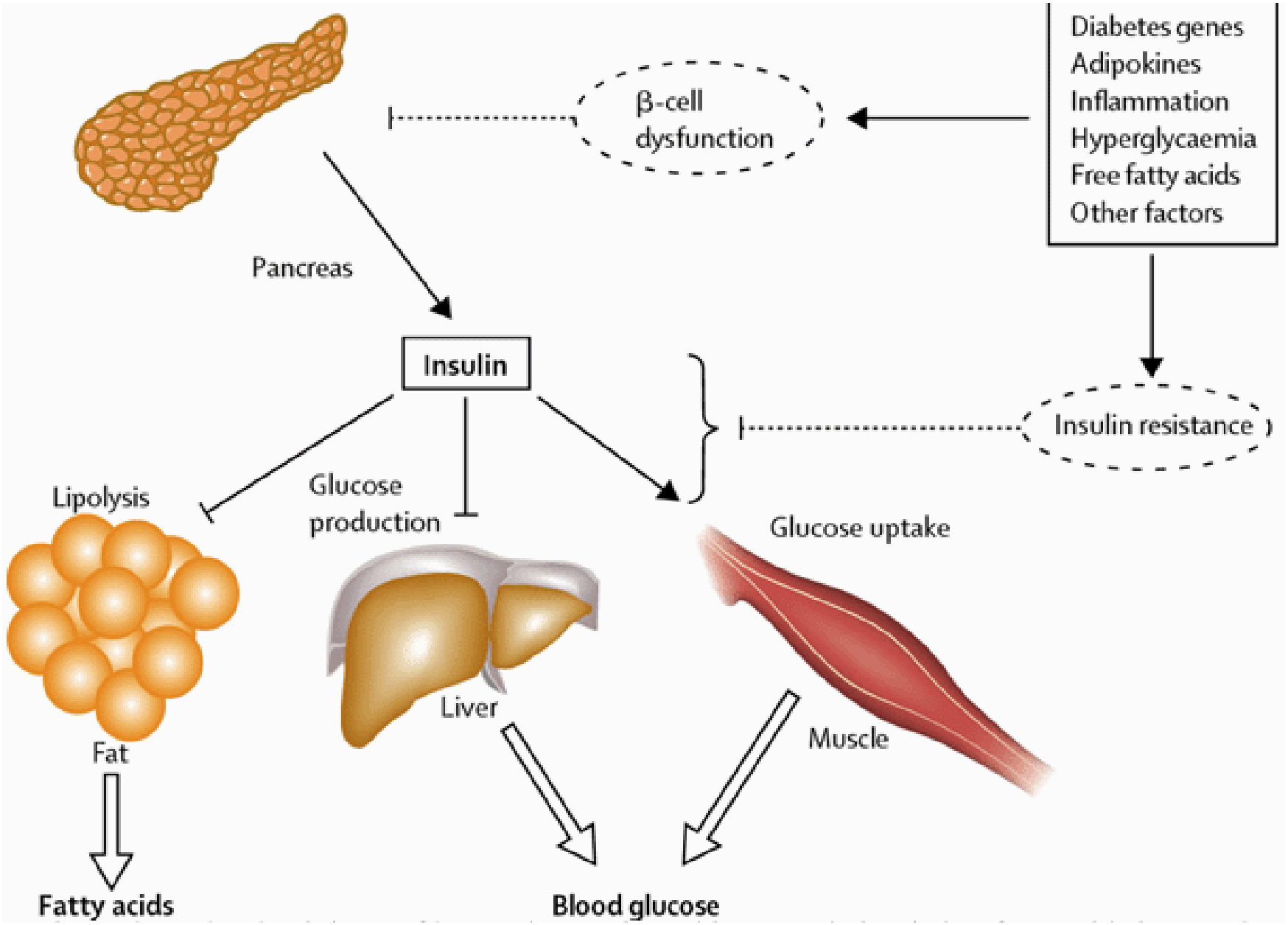
Effects of Insulin Therapy.
These photographs from 1922, in a case described by Geyelin, show a young girl with insulin-deficient diabetes before treatment with insulin (Panel A) and after treatment (Panel B).

Main Pathophysiological Defects in T2DM

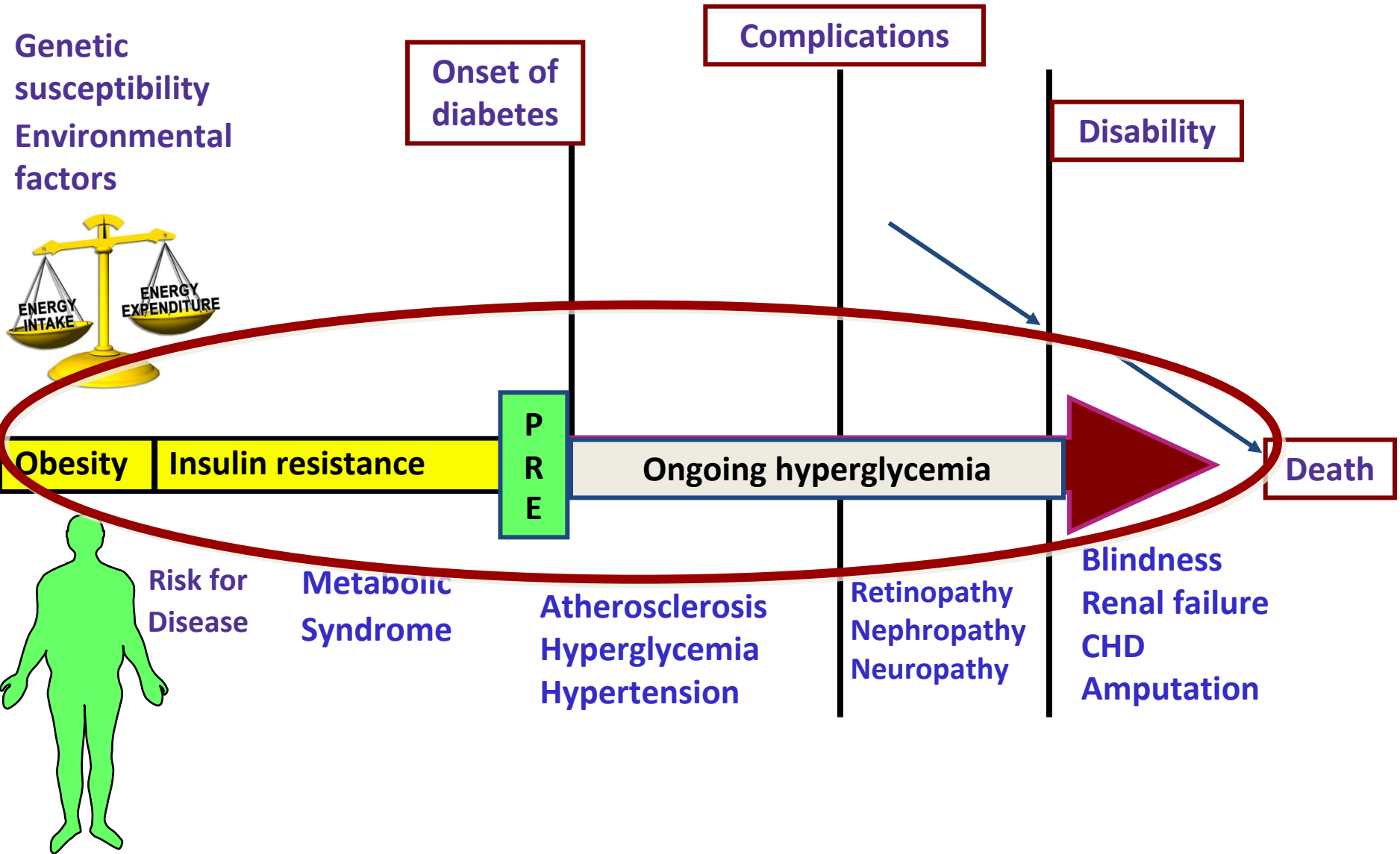


Adapted from: Inzucchi SE, Sherwin RS in: *Cecil Medicine* 2011

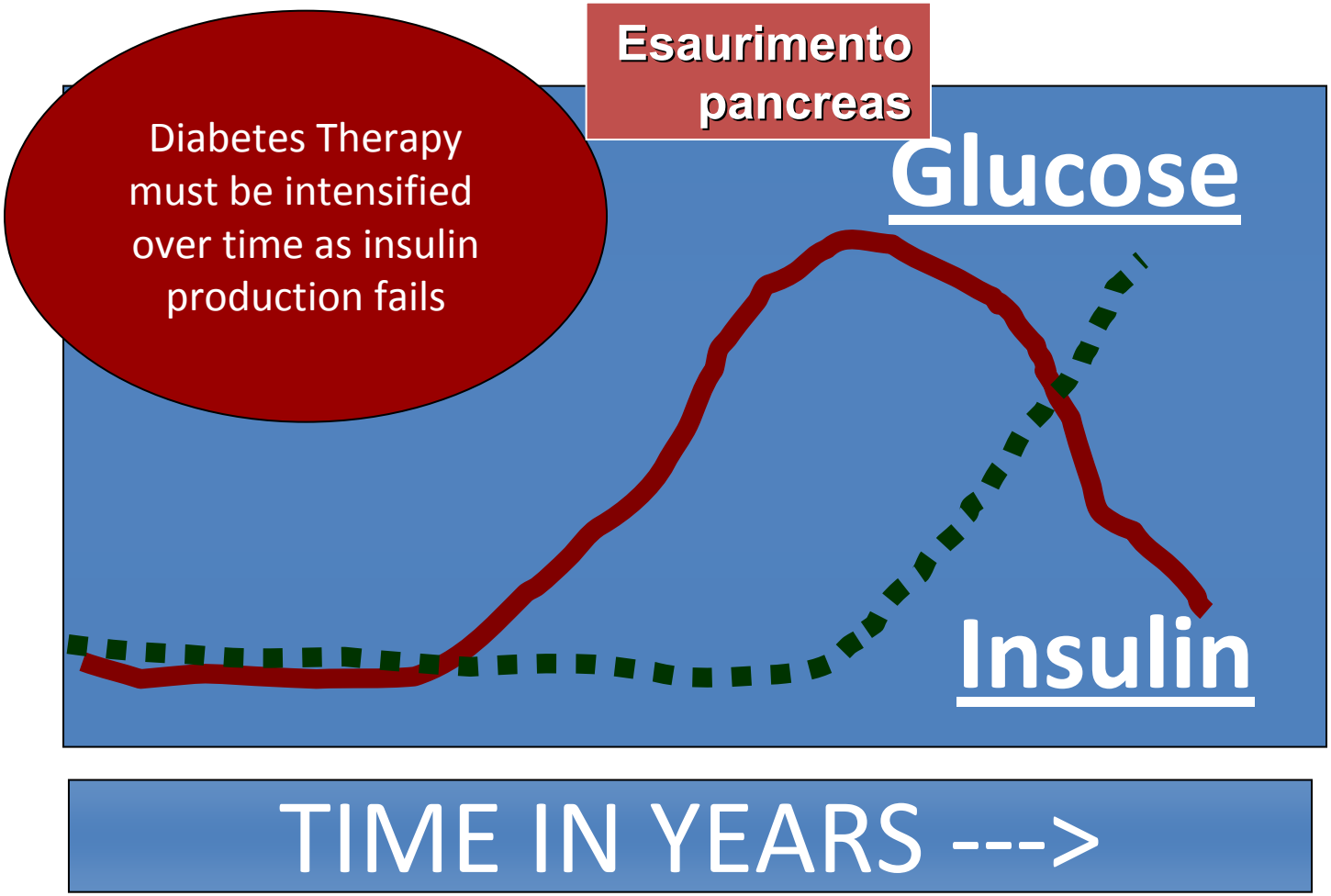
Diabete tipo 2



Natural History of Type 2 Diabetes

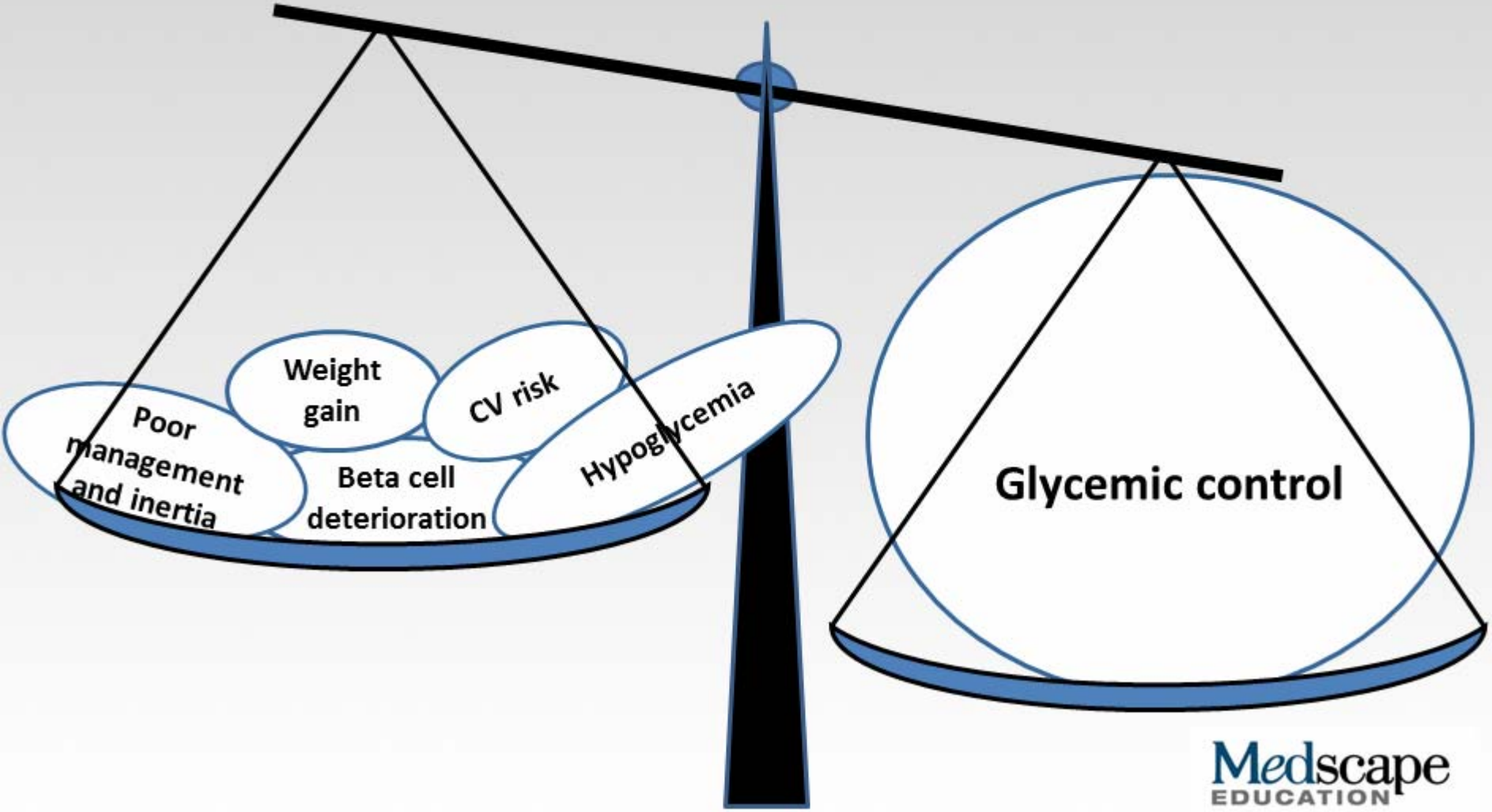


Beta cell exhaustion



Need for Personalized Care

The Benefits and Risks of Diabetes Therapy Must Be Assessed for Each Patient



Medscape EDUCATION

Detection devices

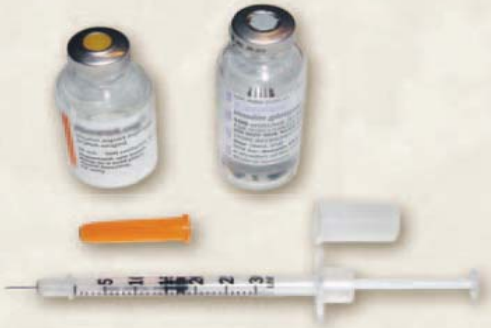
Detection of diabetes has progressed from use of the saccharometer in the 1800s to measure urine density (a proxy for urinary glucose content) to instruments that monitor blood glucose levels at home.

Insulin syringes

Insulin syringes were initially glass and were used on multiple occasions, with needles that were also reused. Insulin pens, which became available in the 1990s, allow patients to vary the injected dose and to administer insulin discreetly.

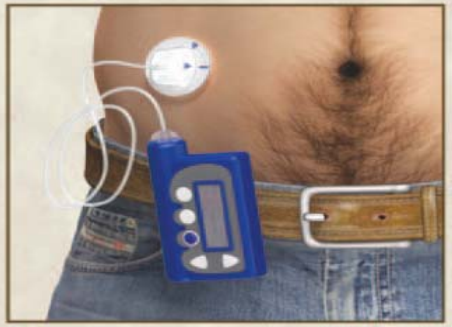
Insulin preparations

The first highly refined form of insulin was extracted from porcine or bovine pancreas. Recombinant human insulin is now readily available.



Insulin pumps

The first insulin pumps, such as the Mill Hill infuser (near right), were invented in 1976 and weighed more than 0.5 kg. Current pumps are much smaller and more portable. Pumps that simultaneously infuse insulin and monitor glucose, allowing instantaneous feedback, are currently under investigation.



3. ANTI-HYPERGLYCEMIC THERAPY

- Therapeutic options: Lifestyle

- Weight optimization

- Healthy diet

- Increased activity level

Diabetes Care, Diabetologia. 19 April 2012 [Epub ahead

3. ANTI-HYPERGLYCEMIC THERAPY

- Therapeutic options:

Oral agents & non-insulin injectables

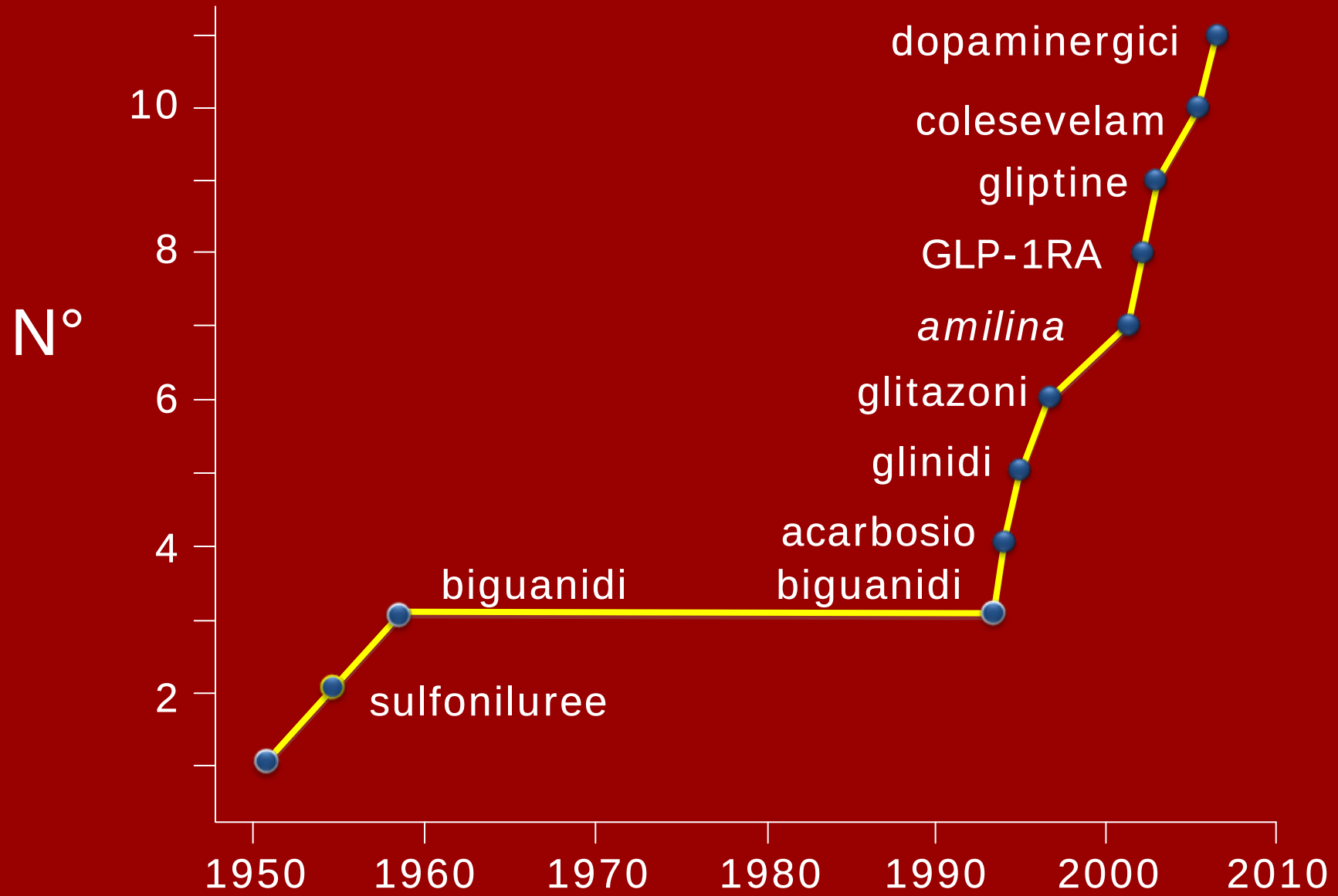
Oral

- *Biguanides*
- *Sulfonylureas*
- *Meglitinides*
- *Thiazolidinediones*
- *Alpha Glucosidase inhibitors*
- *Incretin Enhancers (DPP-IV inhibitors)*
- *Resin binder*
- *SLGT2 Inhibitors*

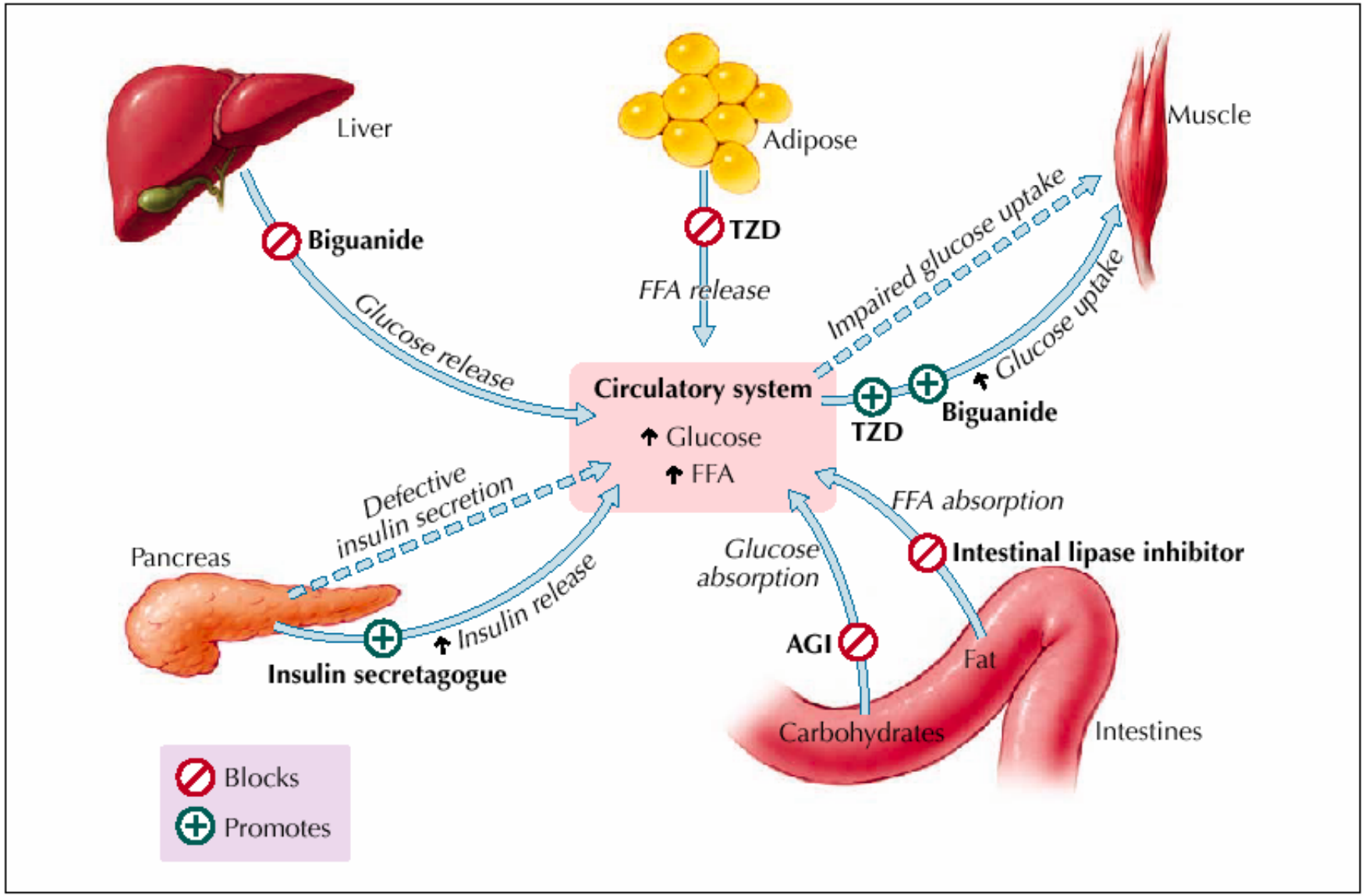
Parenteral

- *Amylin analogs*
- *Incretin mimetics*

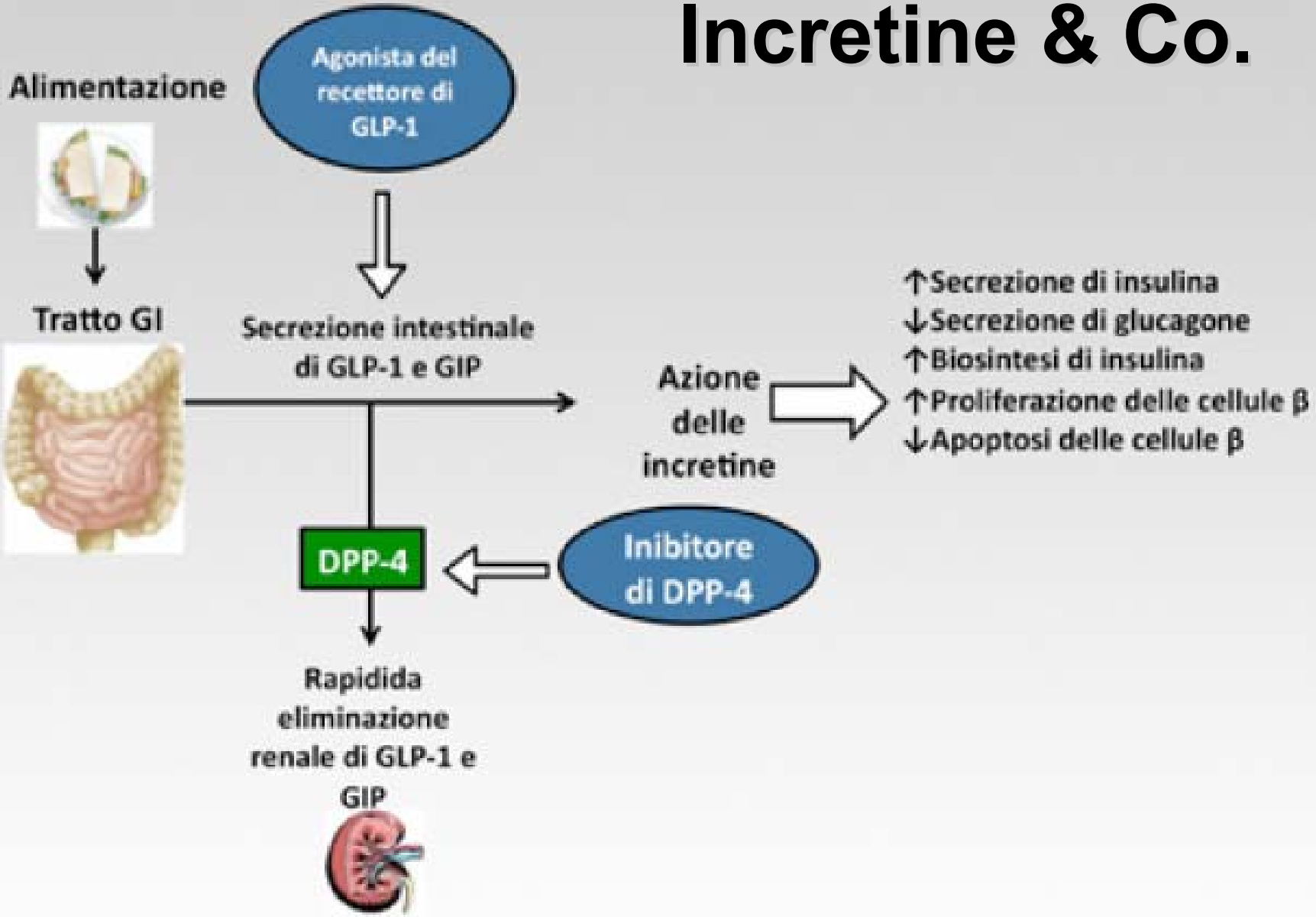
Classi di farmaci disponibili (USA)



Dove agiscono?



Incretine & Co.



Davidson JA. *Mayo Clin Proc. 2010; 85:S27*

Actions of Incretin-Based Therapies for Type 2 Diabetes: GLP-1 Receptor Agonists and DPP-4 Inhibitors

	Action	GLP-1 Receptor Agonists[1,2]	DPP-4 Inhibitors[1,2]
	↑ Insulin production	+++	++
	↑ First-phase insulin response	+++	++
	↓ Glucagon; glucose output	+++	+
	↓ Gastric emptying	Delayed	No effect
	↓ Food intake	Decreased	No effect

1. DeFronzo RA, et al. *Curr Med Res Opin.* 2008;24(10)2943-2952.
2. Drucker DJ, Nauck MA. *Lancet.* 2006;368:1696-1705.

Pharmacology – Incretin Enhancers

Class	**DPP-4 inhibitors (incretin enhancers)**
Compound	• **Sitagliptin (Januvia 100 mg) (Janumet 50/1000, 50/850)** • **Vildagliptin (Galvus 50 mg) (Eucreas 50/1000,50/850)** • **Saxagliptin (Ongliza 5 mg)** • **Linagliptin (Tradjenta®)**
Mechanism	Inhibits DPP-4 activity, prolongs survival of endogenously released incretin hormones
Action(s)	• Active GLP-1 concentration ↑ • Insulin secretion ↑ • Glucagon secretion ↓
Advantages	• No hypoglycemia • Weight "neutrality"
Disadvantages	• Occasional reports of urticaria/angioedema • Cases of pancreatitis observed • Long-term safety unknown (cancer ?)
Cost	High

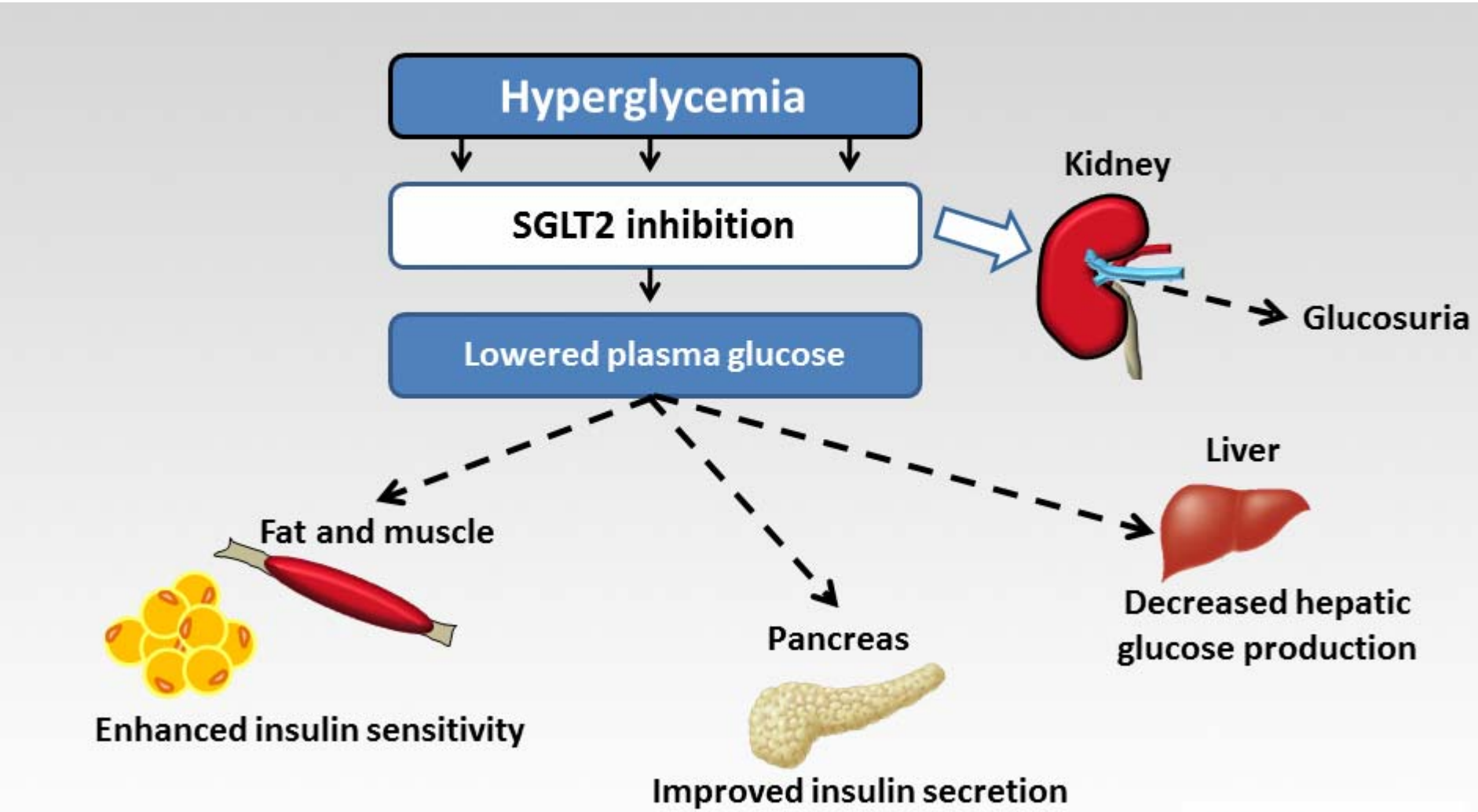
ADA. V. Diabetes Care. *Diabetes Care* 2012;35(suppl 1):S22.
Adapted with permission from Silvio Inzucchi, Yale University.

Pharmacology – Incretin Mimetics

Class	**GLP-1 receptor agonists (incretin mimetics)**
Compound	• **Exenatide (Byetta®)** • **Liraglutide (Victoza®)**
Mechanism	Activates GLP-1 receptors (β-cells/endocrine pancreas; brain/autonomous nervous system
Action(s)	• Insulin secretion ↑ (glucose-dependent) • Glucagon secretion ↓ (glucose-dependent) • Slows gastric emptying • Satiety ↑
Advantages	• Weight reduction • Potential for improved β-cell mass/function
Disadvantages	• Gastrointestinal side effects (nausea, vomiting, diarrhea) • Cases of acute pancreatitis observed • C-cell hyperplasia/medullary thyroid tumors in animals (liraglutide) • Injectable • Long-term safety unknown
Cost	High

ADA. V. Diabetes Care. *Diabetes Care* 2012;35(suppl 1):S22.
Adapted with permission from Silvio Inzucchi, Yale University.

Reversal of hyperglycemia → Reversal of "glucotoxicity"



Medscape EDUCATION

Del Prato, S. *Diabetic Medicine*. 2009;26:1185-1192.

SGLT2 Inhibitors in Phase 3 Development

- Empagliflozin
- ***Canagliflozin***
- ***Dapagliflozin***
- Ipragliflozin

Summary of Key Benefits and Risks of Medications

	Metformin	DPP-4 Inhibitor	GLP-1 Agonist	Sulfonylurea	Glinide	TZD	Colesevelam	AGI	Insulin	Pramlintide
Benefits										
PPG - lowering	Mild	Moderate	Moderate to Marked	Moderate	Moderate	Mild	Mild	Moderate	Moderate to Marked	Moderate to Marked
FPG - lowering	Moderate	Mild	Mild	Moderate	Mild	Moderate	Mild	Neutral	Moderate to Marked	Mild
Nonalcoholic fatty liver disease (NAFLD)	Mild	Neutral	Mild	Neutral	Neutral	Moderate	Neutral	Neutral	Neutral	Neutral
Risks										
Hypoglycemia	Neutral	Neutral	Neutral	Moderate	Mild	Neutral	Neutral	Neutral	Moderate to Severe	Neutral
GI Symptoms	Moderate	Neutral	Moderate	Neutral	Neutral	Neutral	Moderate	Moderate	Neutral	Moderate
Risk of use with renal insufficiency	Severe	Reduce Dosage	Moderate	Moderate	Neutral	Mild	Neutral	Neutral	Moderate	Neutral
Contraindicated if liver failure or predisposition to lactic acidosis	Severe	Neutral	Neutral	Moderate	Moderate	Moderate	Neutral	Neutral	Neutral	Neutral
Heart failure/Edema	Contra-indicted in CHF	Neutral	Neutral	Neutral	Neutral	Mild/ Moderate Contra-indicted in class 1, 4 CHF	Neutral	Neutral	Neutral Unless with TZD	Neutral
Weight Gain	Benefit	Neutral	Benefit	Mild	Mild	Moderate	Neutral	Neutral	Mild to Moderate	Benefit
Fractures	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate	Neutral	Neutral	Neutral	Neutral
Drug-Drug Interactions	Neutral	Neutral	Neutral	Moderate	Moderate	Neutral	Neutral	Neutral	Neutral	Neutral

Drug Pearls

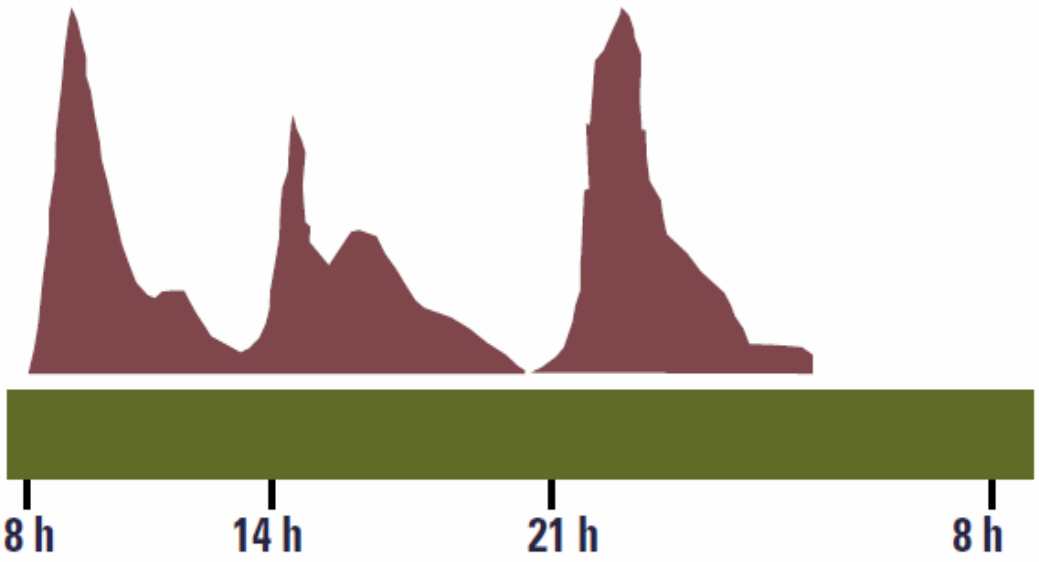
Medication	PRO	CON
Metformin	Low cost, A1c lowering, + CV effects, weight loss, PCOS	Renal or hepatic impairment
Sulfonylurea	Low cost, A1c lowering	Hypoglycemia, treatment failure
Meglitinides	Erratic meals, renal insufficiency	Hypoglycemia, treatment failure
Pioglitazone	Insulin resistance, decrease in adipose tissue, TG reduction	Edema, wt gain, CI with HF class III and IV
α-glucosidase inhibitors	Patients with constipation	Long duration of T2DM, patients with GI problems
DPP-4	Well tolerated	? long term safety
GLP-1 agonists	Obese patients	GI side effects
Amylin analogs	Poor PPG control despite insulin therapy	GI side effects
Insulin	Flexible treatment (basal, basal bolus, etc)	Hypoglycemia, weight gain

Typical A1c Reductions

Monotherapy	Route of Administration	A1c (%) Reduction
Sulfonylurea	PO	1.5-2.0
Metformin	PO	1.5
Glitazones	PO	1.0-1.5
Meglitinides	PO	0.5-2.0
α-glucosidase inhibitors	PO	0.5-1.0
DPP-4	PO	0.5-0.7
GLP-1 agonists	Injectable	0.8-1.5
Amylin analogs	Injectable	0.6
Insulin	Injectable	Open to target

Unger J et al. Postgrad Med 2010; 122: 145-57

Secrezione fisiologica dell'insulina

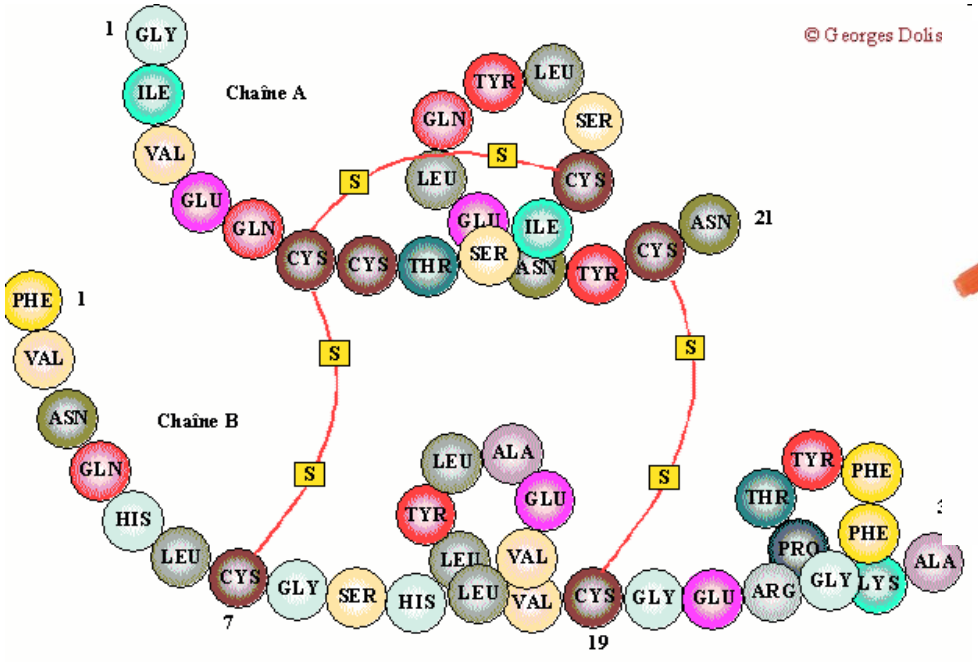


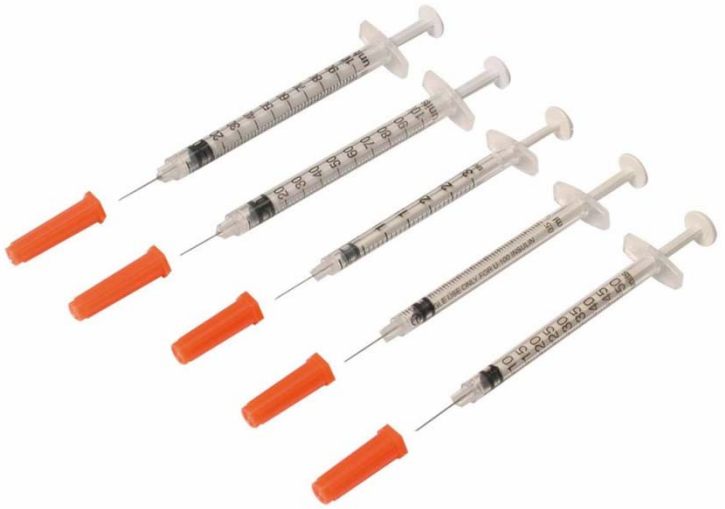
PHG = produzione epatica di glucosio

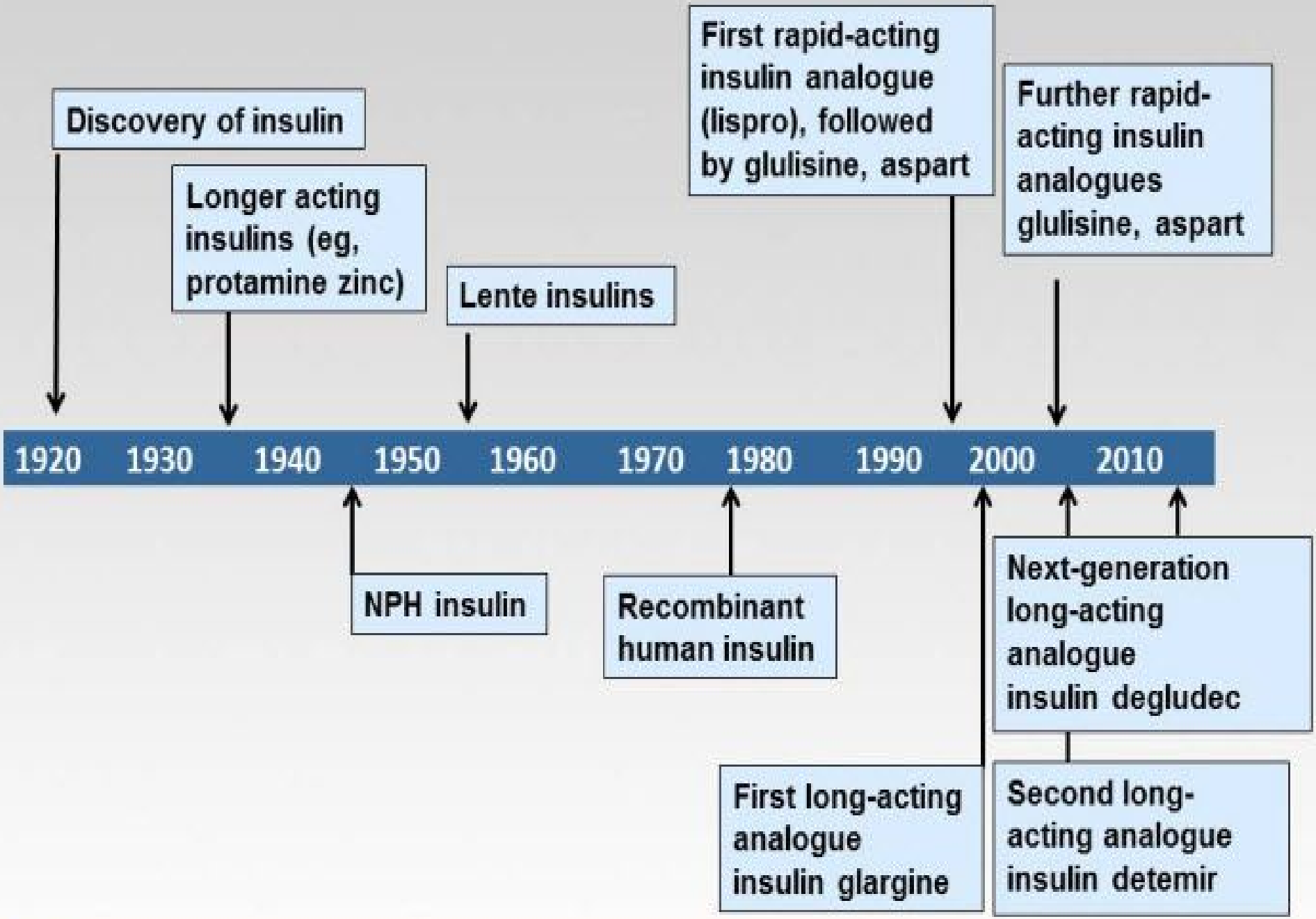
- **Secrezione insulinica prandiale**
  - Limita l'iperglicemia successiva al pasto
  - Effetto immediato con picco in un'ora circa
  - 50% delle richieste giornaliere totali 10-20% per ciascun pasto (1 U/8-10 g di zuccheri)
- **Secrezione insulinica basale**
  - Sopprime la produzione di glucosio tra i pasti e durante la notte (PHG = 5-10 g glucosio/ora)
  - Livelli pressochè costanti
  - 50% delle richieste giornaliere (0,5-1 U/ora)

INSULINA :

QUALE , COME E PERCHE’






Discovery of insulin
Longer acting insulins (eg, protamine zinc)
Lente insulins
First rapid-acting insulin analogue (lispro), followed by glulisine, aspart
Further rapid-acting insulin analogues glulisine, aspart
1920
1930
1940
1950
1960
1970
1980
1990
2000
2010
NPH insulin
Recombinant human insulin
Next-generation long-acting analogue insulin degludec
First long-acting analogue insulin glargine
Second long-acting analogue insulin detemir

Caratteristiche delle principali insuline presenti in commercio

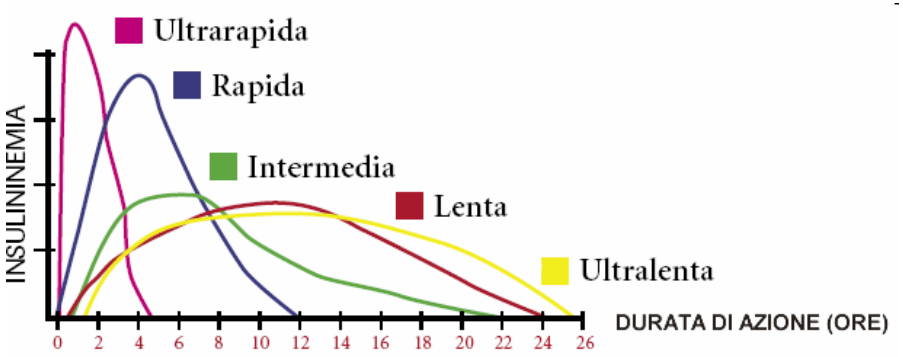
Tipi di insulina	Inizio dell'azione	Picco (ore)	Durata dell'azione (ore)
Insuline umane			
Regolare (Actrapid®)	0,5-1 ora	2-4	10-20
NPH Humulin NPH®)	1-3 ore	4-12	10-20
Analoghi			
Glulisina (Apidra®)	10-15 min	1	4-5
Lispro (Humalog pen®)	10-15 min	1	4-5
Aspart (Novorapid®)	10-15 min	1	4-5
NPL (Humalog NPL®)	1-3 ore	4-12	10-20
Glargine (Lantus®)	1-2 ore	Nessuno	≤24
Detemir (Levemir®)	1-2 ore	Nessuno	12-18
Premiscelate			
75% NPL/ 25% Lispro (Humalog Mix25®)	5-15	Duplice	10-16
70% NPH/ 30% Aspart (Novomix30®)	5-15	Duplice	10-16

I tempi d'azione di ciascuna insulina possono variare nei diversi individui e, nella stessa persona, in funzione del momento della somministrazione e della dose somministrata. Pertanto, le indicazioni riportate in questa tabella vanno considerate solo come racomandazioni di carattere generale.

Antonio Pérez Pérez et al. Tratamiento de la hiperglucemia en el hospital - Hospital management of hyperglycemia. Conferencia de Consenso. Med Clin (Barc). 132:465–475; 2009

PROBLEMI CON LE INSULINE UMANE

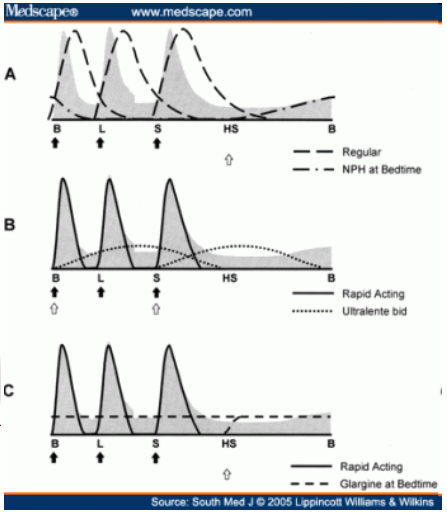
- **Problemi con le insuline umane rapide**
  - Da somministrarsi 30-45 min prima del pasto
  - Assorbimento variabile da diverse sedi di iniezione
  - Rischio di ipoglicemie tra i pasti
  - Aumento di peso corporeo



- **Problemi con le insuline umane intermedie / lente / ultralente**
  - Assorbimento erratico
  - Insufficiente insulinizzazione “basale” (soprattutto all’alba)
  - Rischio di ipoglicemie notturne
  - Aumento di peso corporeo

CARATTERISTICHE DEGLI ANALOGHI

- **Analoghi rapidi (lispro, aspart, glulisina)**
  - Somministrabili prima, durante, dopo i pasti (flessibilità)
  - Picco d'azione fisiologico, dose e sede indipendente (migliore glicemia dopo pasto)
  - Durata d'azione relativa al pasto (minor rischio di ipoglicemie tra i pasti)



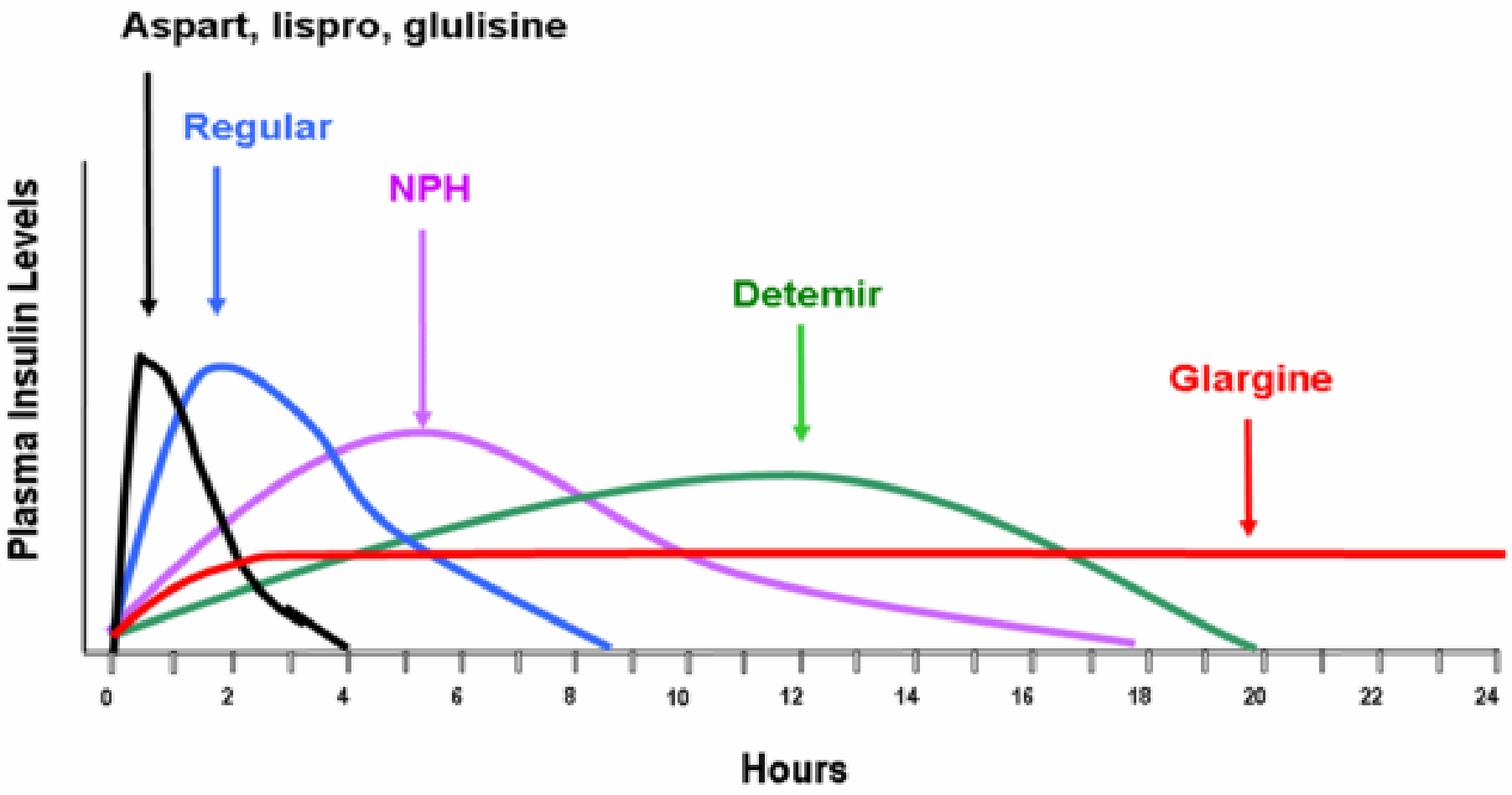
- **Analoghi basali (glargine, detemir, degludec)**
  - Assorbimento più riproducibile (minore variabilità glicemica, minor rischio di ipoglicemia)
  - Sufficiente durata d'azione (minore ricorso a più somministrazioni giornaliere)
  - Assenza di picco d'azione (minor rischio di ipoglicemia)

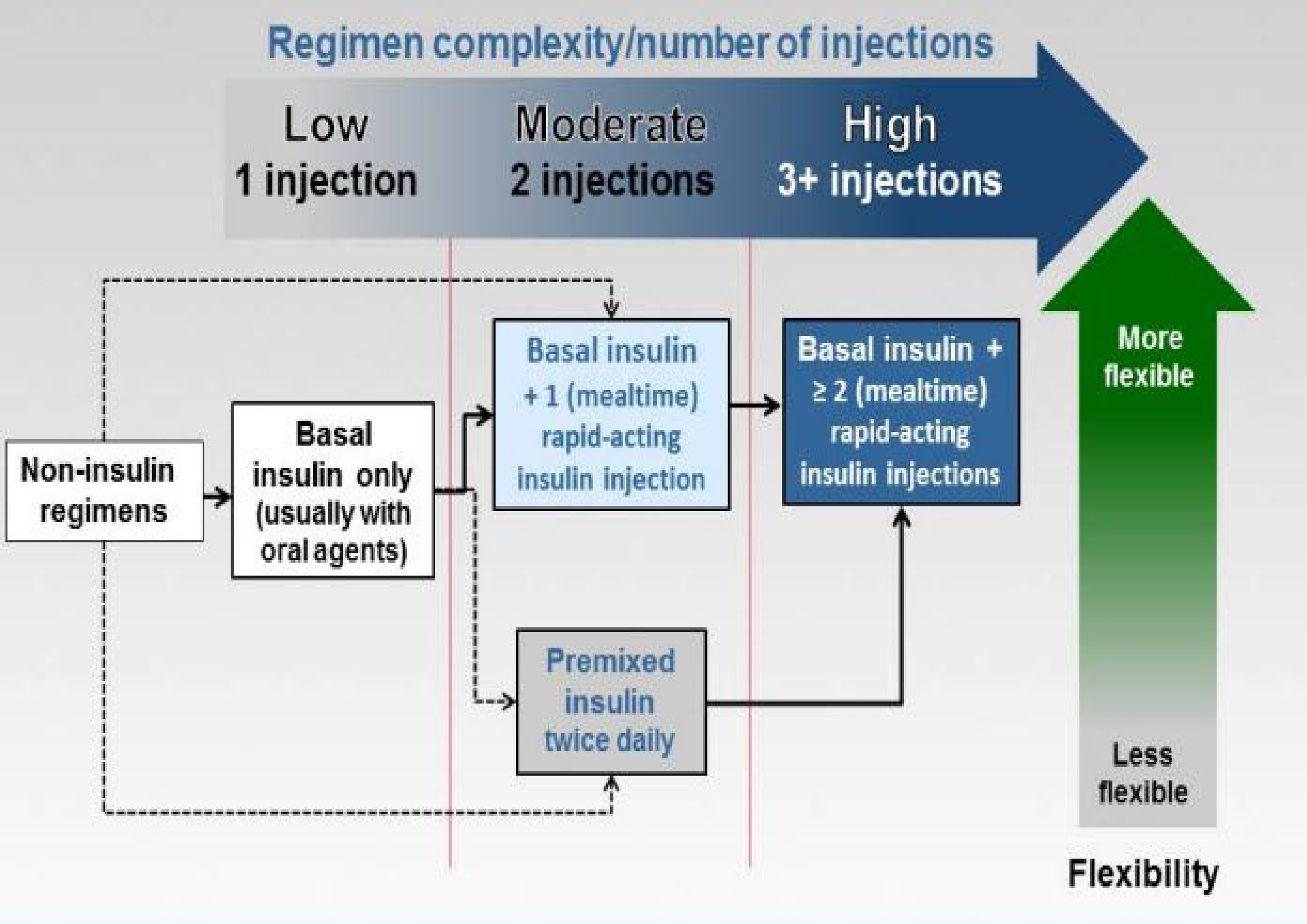
ANALOGHI RAPIDI

- Insulina Lyspro
- Insulina Aspart
- Insulina Glulisina

ANALOGHI AD AZIONE RITARDATA

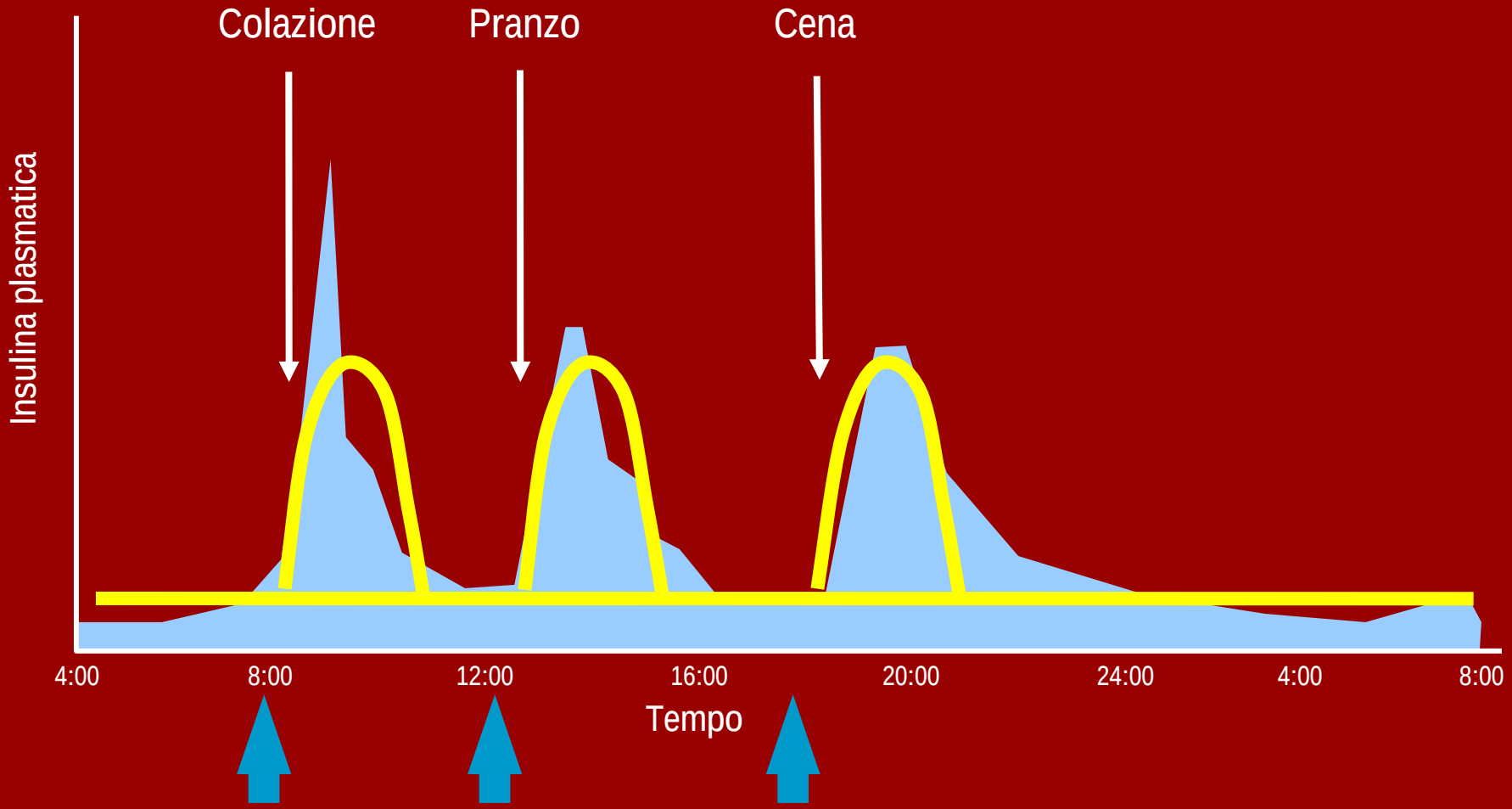
- Insulina Glargine
- Insulina Detemir
- Insulina Degludec


Aspart, lispro, glulisine
Regular
NPH
Detemir
Glargine
Plasma Insulin Levels
0
2
4
6
8
10
12
14
16
18
20
22
24
Hours



Diabetes Care. 2012;35(6):1364-1379

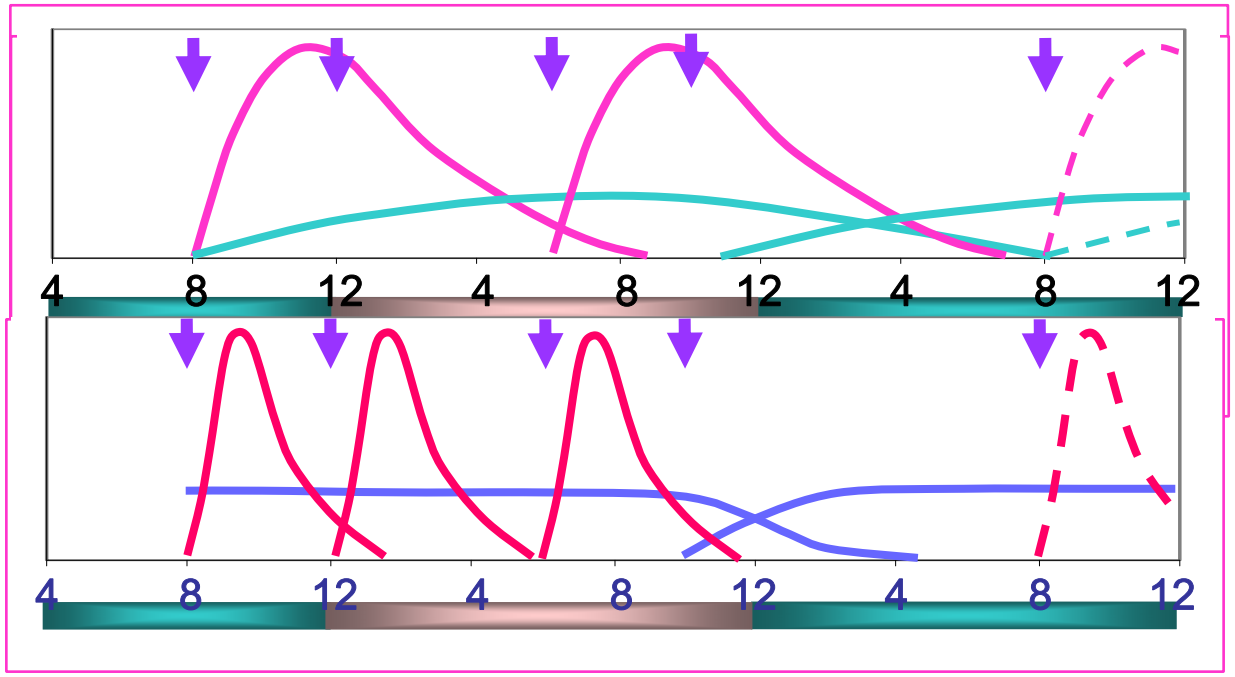
Mimare la risposta fisiologica: insulina basale e prandiale



Adapted from White JR Jr, et al. *Postgrad Med.* 2003;113:30-36

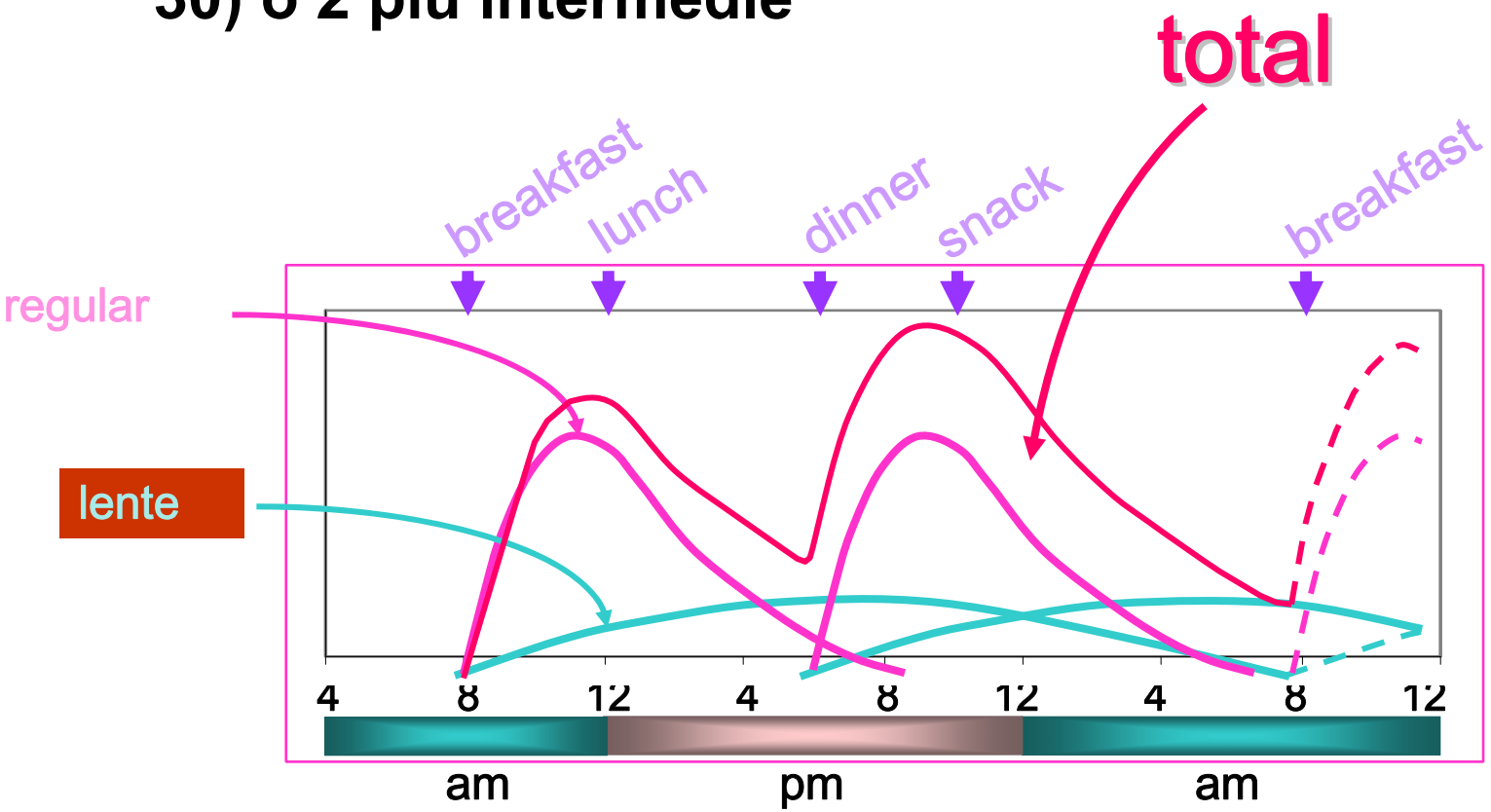
Regimi di trattamento insulinico

- **Terapia Insulinica Intensiva**
  - **Frequenti controlli glicemici**
  - **3 o più iniezioni al giorno**
  - **Individualizzata**

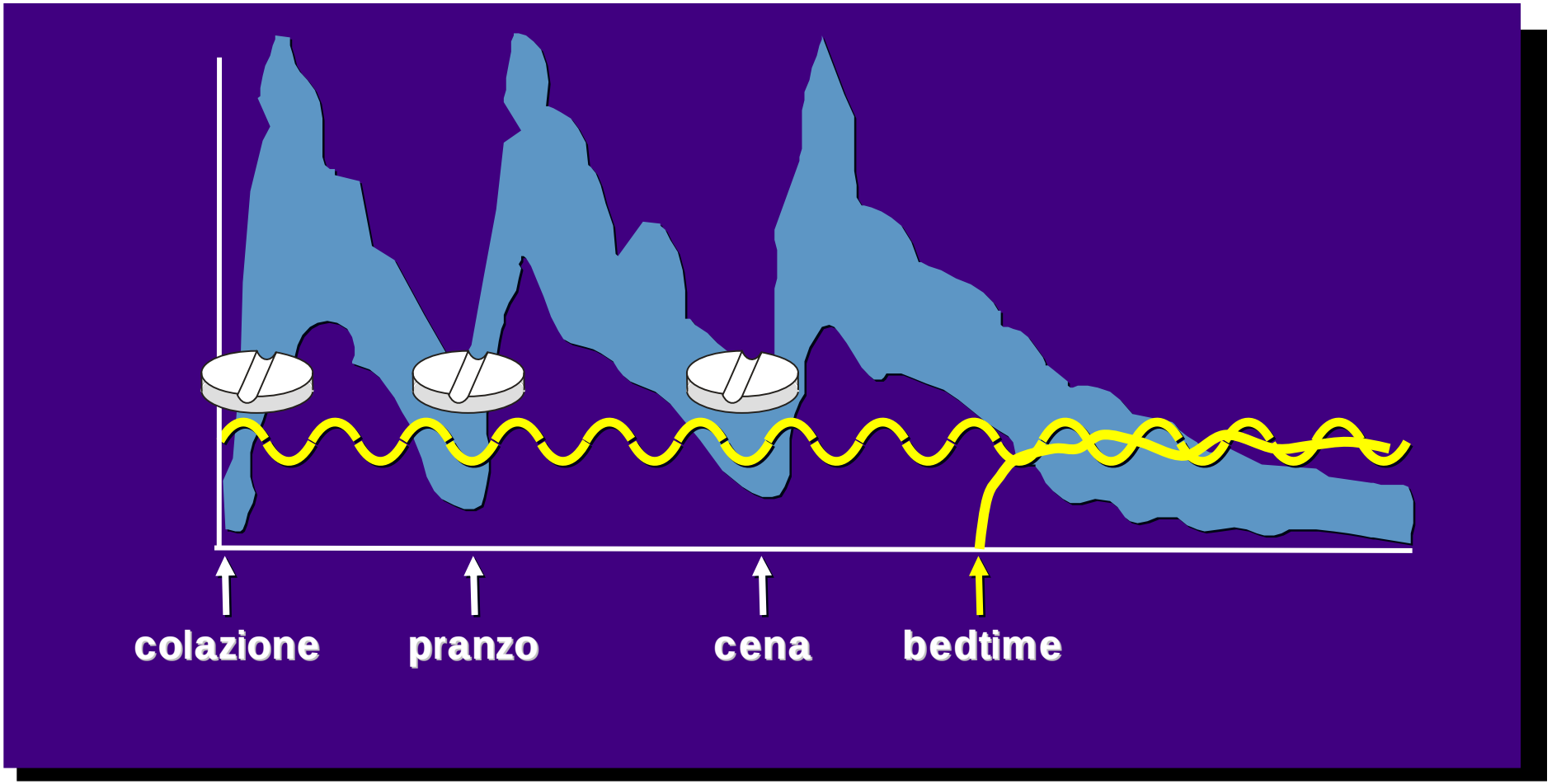


Regimi di trattamento insulinico

- **Terapia Insulinica Convenzionale**
  - **1 o 2 iniezioni sottocutanee al giorno**
  - **Miscela di rapida o ultrarapida e intermedia (es. 30) o 2 più intermedie**



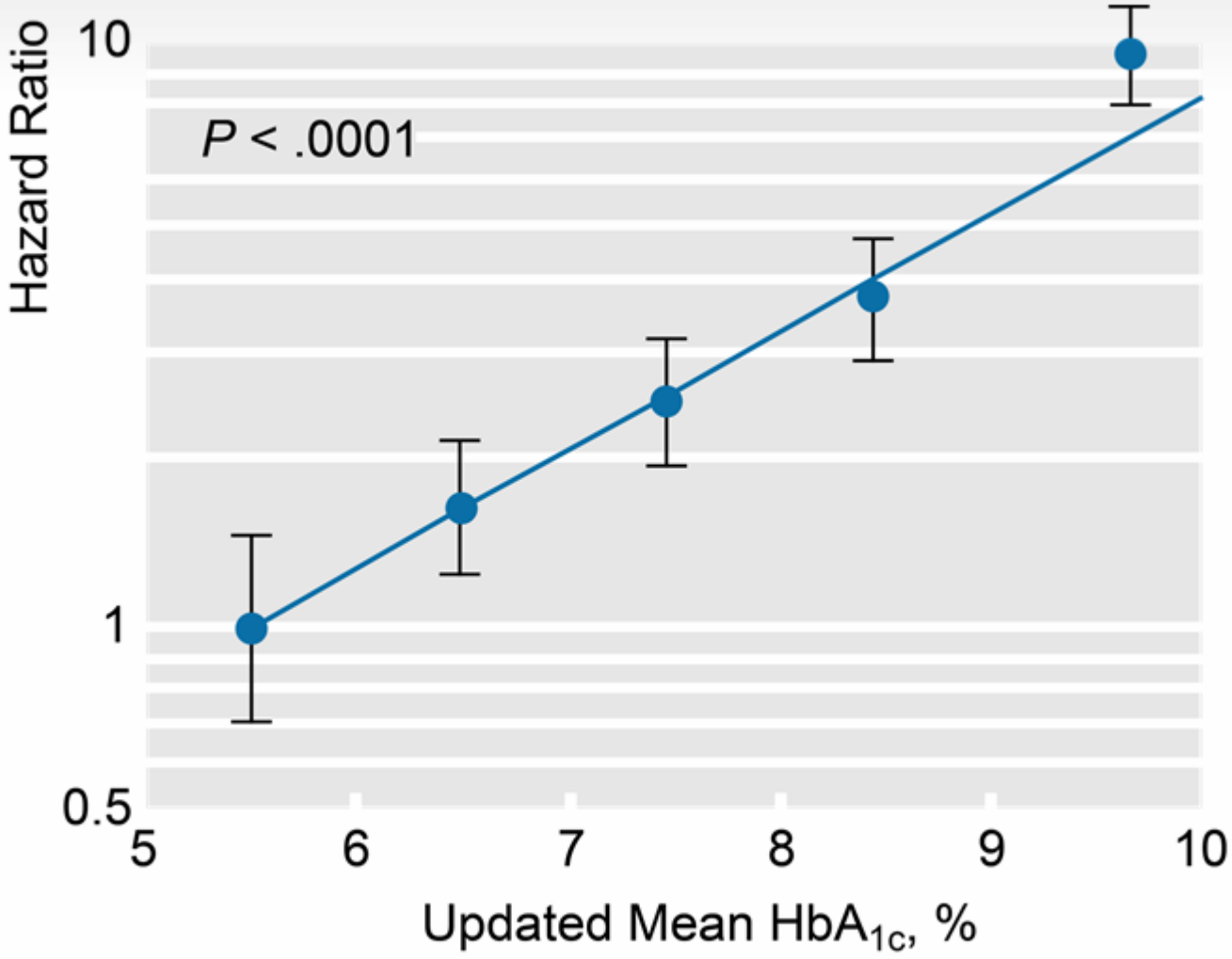
Terapia Combinata



La terapia mista rispetto alla sola terapia insulinica determina la riduzione di circa il 25 – 30% del fabbisogno insulinico

Perché?

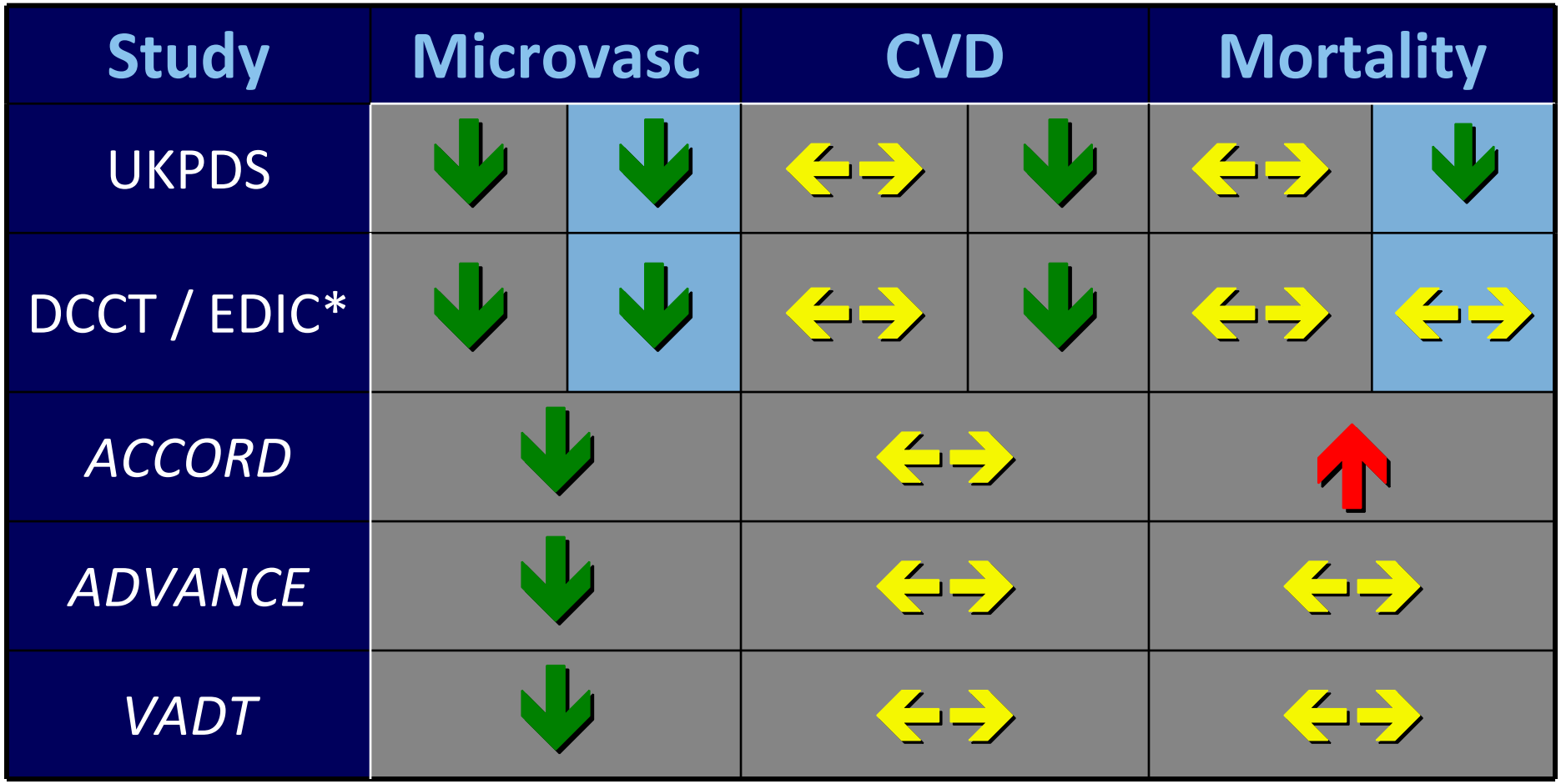
Microvascular Endpoints



37% decrease per 1% reduction in HbA_{1c}

From Stratton IM, et al. *BMJ*. 2000;321:405-412. Republished with permission.

Impact of Intensive Therapy for Diabetes: Summary of Major Clinical Trials



Kendall DM, Bergenstal RM. © International Diabetes Center 2009

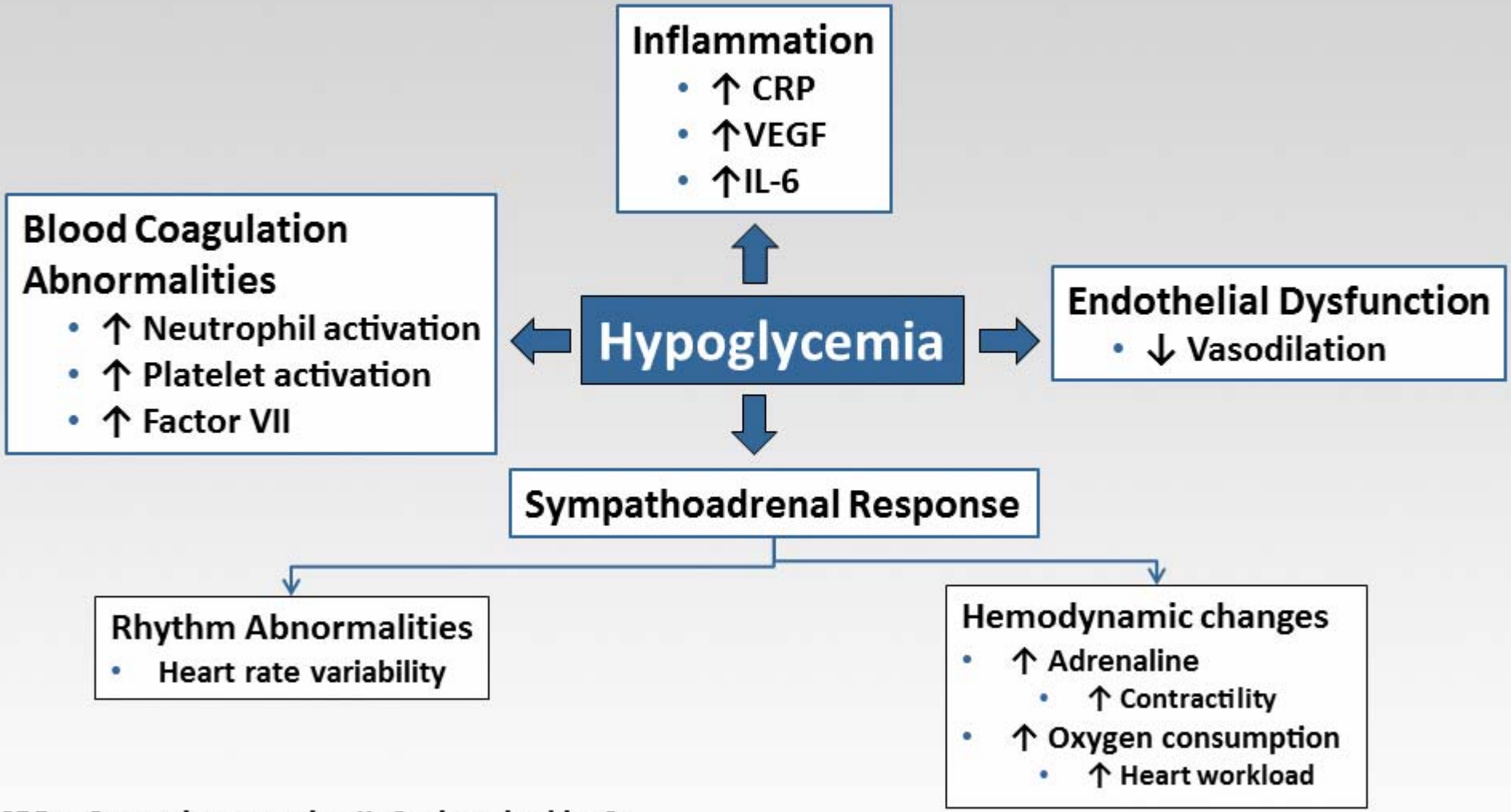
UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352:854.
Holman RR et al. *N Engl J Med*. 2008;359:1577. DCCT Research Group. N Engl J Med 1993;329;977.
Nathan DM et al. *N Engl J Med*. 2005;353:2643. Gerstein HC et al. *N Engl J Med.* 2008;358:2545.
Patel A et al. N Engl J Med 2008;358:2560. Duckworth W et al. N Engl J Med 2009;360:129. (erratum:
Moritz T. *N Engl J Med* 2009;361:1024)

Initial Trial

Long Term Follow-up

* in T1DM

Cardiovascular Consequences of Hypoglycemia

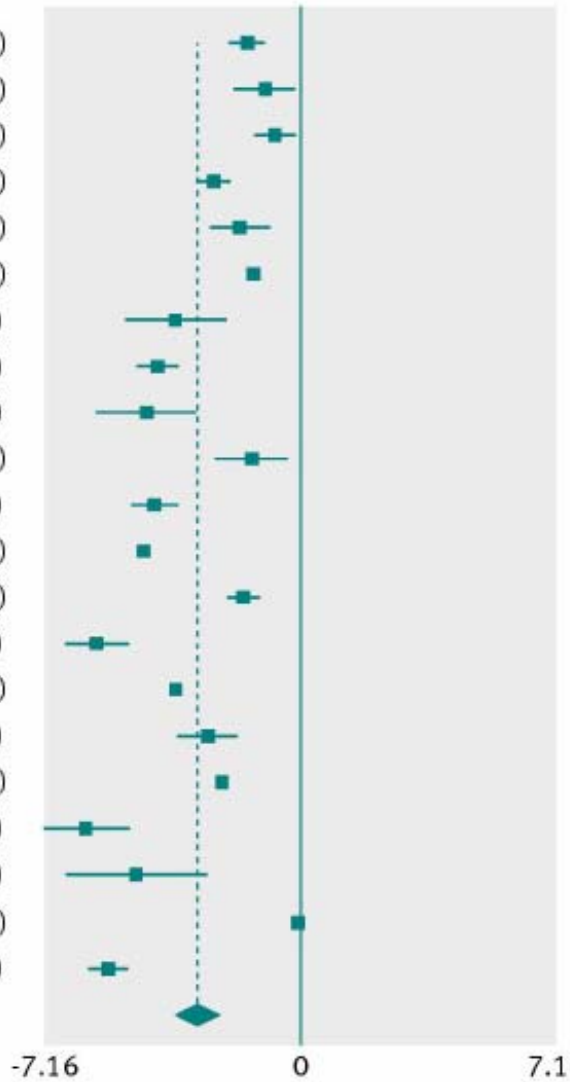


CRP = C-reactive protein; IL-6 = interleukin 6;
VEGF = vascular endothelial growth factor

Desouza CV, et al. *Diabetes Care.* 2010;33(6):1389-1394.

Meta-analysis of change in body weight (kg) in included trials after at least 20 weeks of treatment, using random effects model

Trial	No of patients: GLP-1R agonist group	No of patients: Control group	Mean change (standard deviation): GLP-1R agonist group	Mean change (standard deviation): Control group	Weight (%)	Weighted mean difference (95% CI)
Bergenstal 2010	160	166	-2.3 (3.0)	-0.8 (0.3)	4.98	-1.50 (-1.97 to -1.03)
Buse 2004	129	123	-1.6 (3.4)	-0.6 (3.3)	4.74	-1.00 (-1.83 to -0.17)
Kendall 2005	241	247	-1.6 (3.1)	-0.9 (3.1)	4.93	-0.70 (-1.26 to -0.14)
Pratley 2010	221	219	-3.4 (3.0)	-1.0 (1.8)	4.98	-2.42 (-2.88 to -1.96)
Moretto 2008	78	78	-3.1 (2.7)	-1.4 (2.7)	4.74	-1.70 (-2.53 to -0.87)
Nauck 2009	242	122	-2.8 (0.2)	-1.5 (0.3)	5.09	-1.30 (-1.36 to -1.24)
Garber 2009	246	248	-2.5 (7.8)	1.0 (7.9)	4.21	-3.50 (-4.89 to -2.11)
Diamant 2010	233	223	-2.6 (3.1)	1.4 (3.0)	4.93	-4.00 (-4.55 to -3.45)
DeFronzo 2010	45	45	-2.8 (3.4)	1.5 (3.4)	4.21	-4.30 (-5.69 to -2.91)
Russell-Jones 2009	230	114	-1.8 (5.0)	-0.4 (4.1)	4.59	-1.38 (-2.38 to -0.38)
Heine 2005	282	267	-2.3 (3.9)	1.8 (4.0)	4.86	-4.10 (-4.76 to -3.44)
Astrup 2009	93	98	-7.2 (0.5)	-2.8 (0.5)	5.08	-4.40 (-4.54 to -4.26)
Elkin 2010	20	20	-3.2 (0.5)	-1.6 (0.9)	4.99	-1.60 (-2.04 to -1.16)
Davies 2009	118	117	-2.7 (3.4)	3.0 (3.4)	4.72	-5.71 (-6.57 to -4.85)
Rosenstock 2010	73	70	-5.1 (0.5)	-1.6 (0.5)	5.08	-3.50 (-3.66 to -3.34)
Zinman 2009	178	177	-2.0 (4.0)	0.6 (4.0)	4.74	-2.60 (-3.43 to -1.77)
Apovian 2010	96	98	-6.2 (0.5)	-4.0 (0.5)	5.08	-2.19 (-2.34 to -2.04)
Bergenstal 2009	124	124	-1.9 (3.8)	4.1 (5.4)	4.44	-6.00 (-7.16 to -4.84)
Bunck 2009	36	33	-3.6 (3.6)	1.0 (4.6)	3.59	-4.60 (-6.56 to -2.64)
Marre 2009	234	114	-0.2 (0.0)	-0.1 (0.6)	5.08	-0.10 (-0.22 to 0.02)
Nauck 2007	253	248	-2.5 (3.2)	2.9 (3.0)	4.94	-5.40 (-5.94 to -4.86)
Overall; P=0.00					100.00	-2.90 (-3.59 to -2.22)



Vilsboll T : *BMJ 2012;344:d7771*

Come?

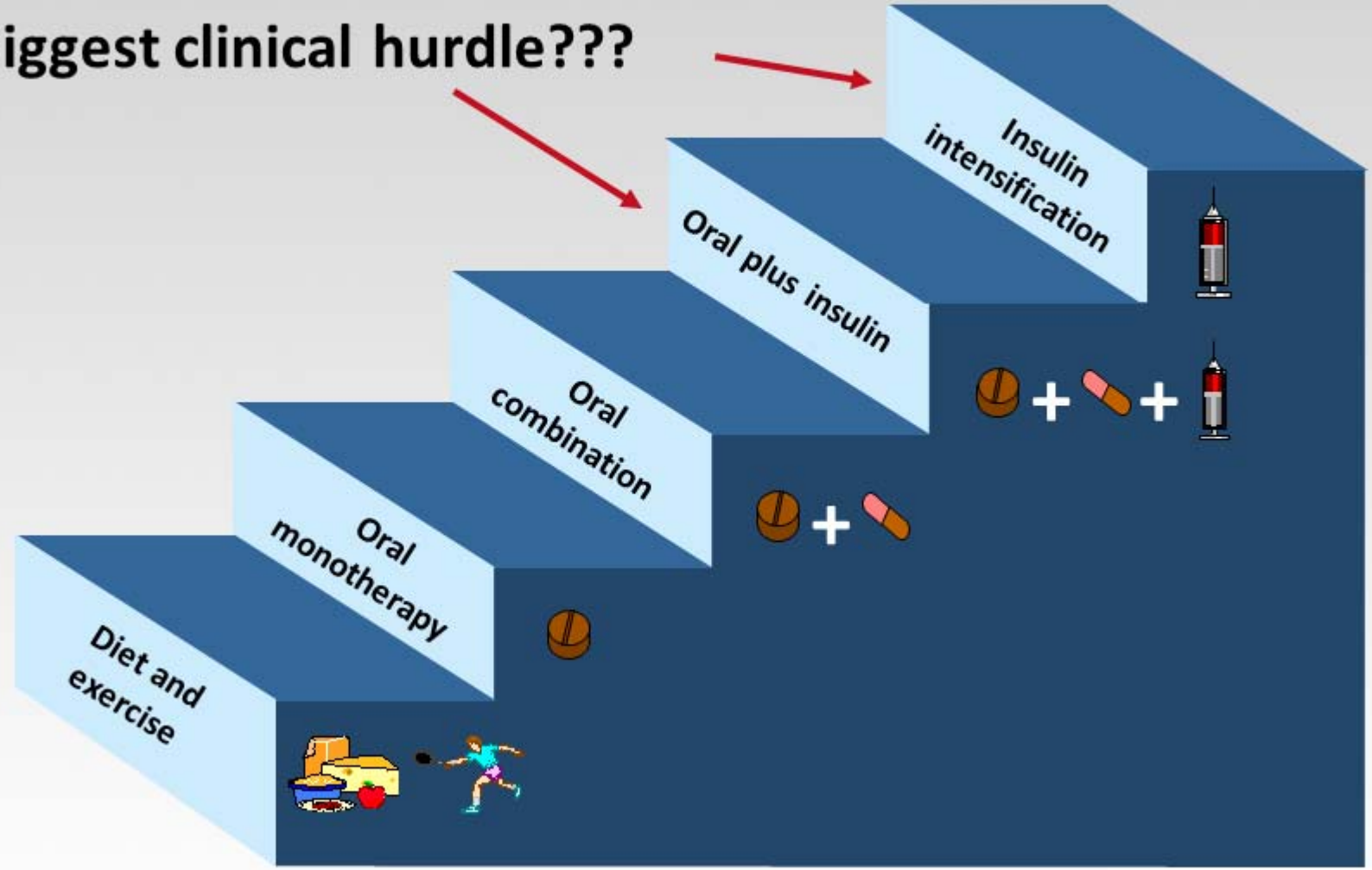
Nonadherence:
A Problem of Epidemic Proportions

- **Nonadherence in chronic diseases: 50% by 1 year[a]**
- **In Europe, nonadherence costs 125 billion Euros and contributes to 200,000 deaths per annum[b]**
- **3 in 10 stop their medicines before first supply runs out[c]**
- **25% take less than recommended dose[c]**
- **33% do not fill the prescriptions they are given[c]**

a. World Health Organization. http://apps.who.int/medicinedocs/en/d/Js4883e/
b. Friends of Europe. http://www.friendsofeurope.org/Contentnavigation/Events/Eventsoverview/tabid/1187/EventType/EventView/EventId/841/EventDateID/845/PageID/5043/JustwhatthedoctororderedAnEUresponsetomedicationnonadherence.aspx
c. National Council on Patient Information and Education. http://www.talkaboutrx.org/documents/enhancing_prescription_medicine_adherence.pdf

Medscape EDUCATION

Stepwise Management of T2D:
Insulin Initiation and Intensification

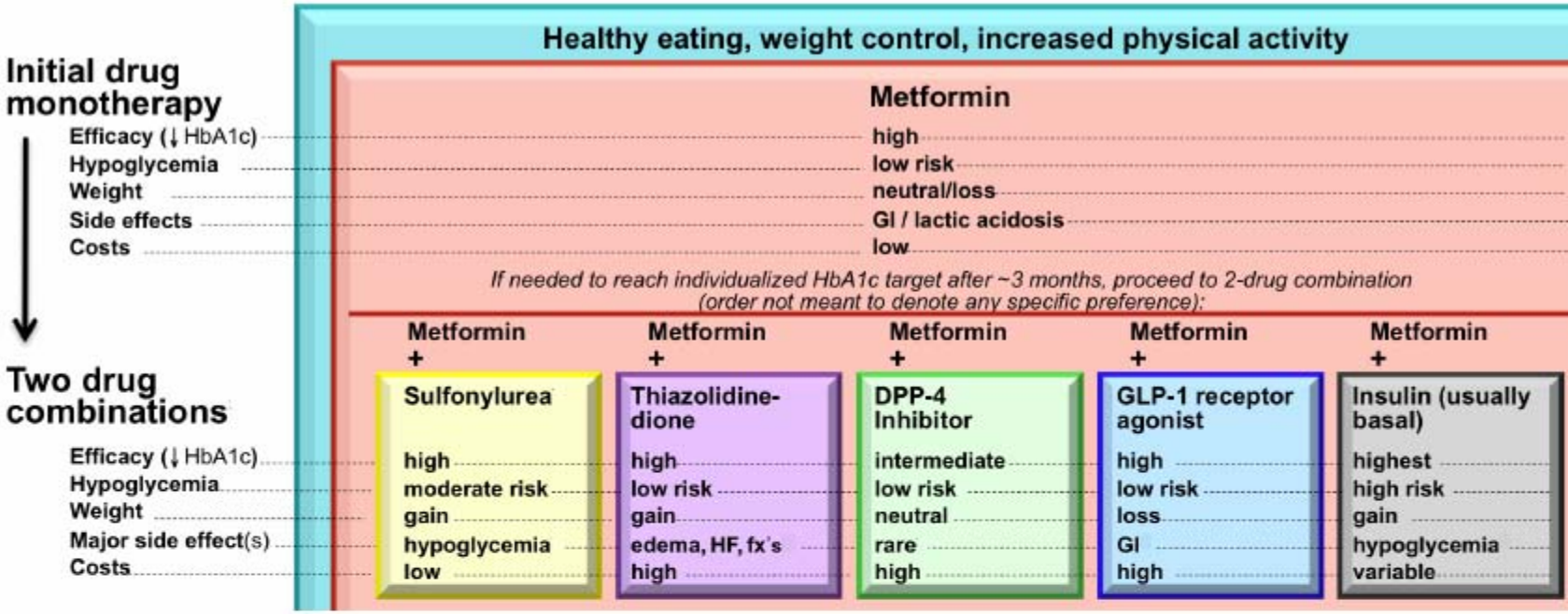


Slide courtesy of Kamlesh Khunti, MD, PhD, MBChB.

Medscape EDUCATION

T2DM Antihyperglycemic Therapy: General Recommendations

Diabetes Care, Diabetologia. 19
[Epub ahead of print]



T2DM Antihyperglycemic Therapy: General Recommendations

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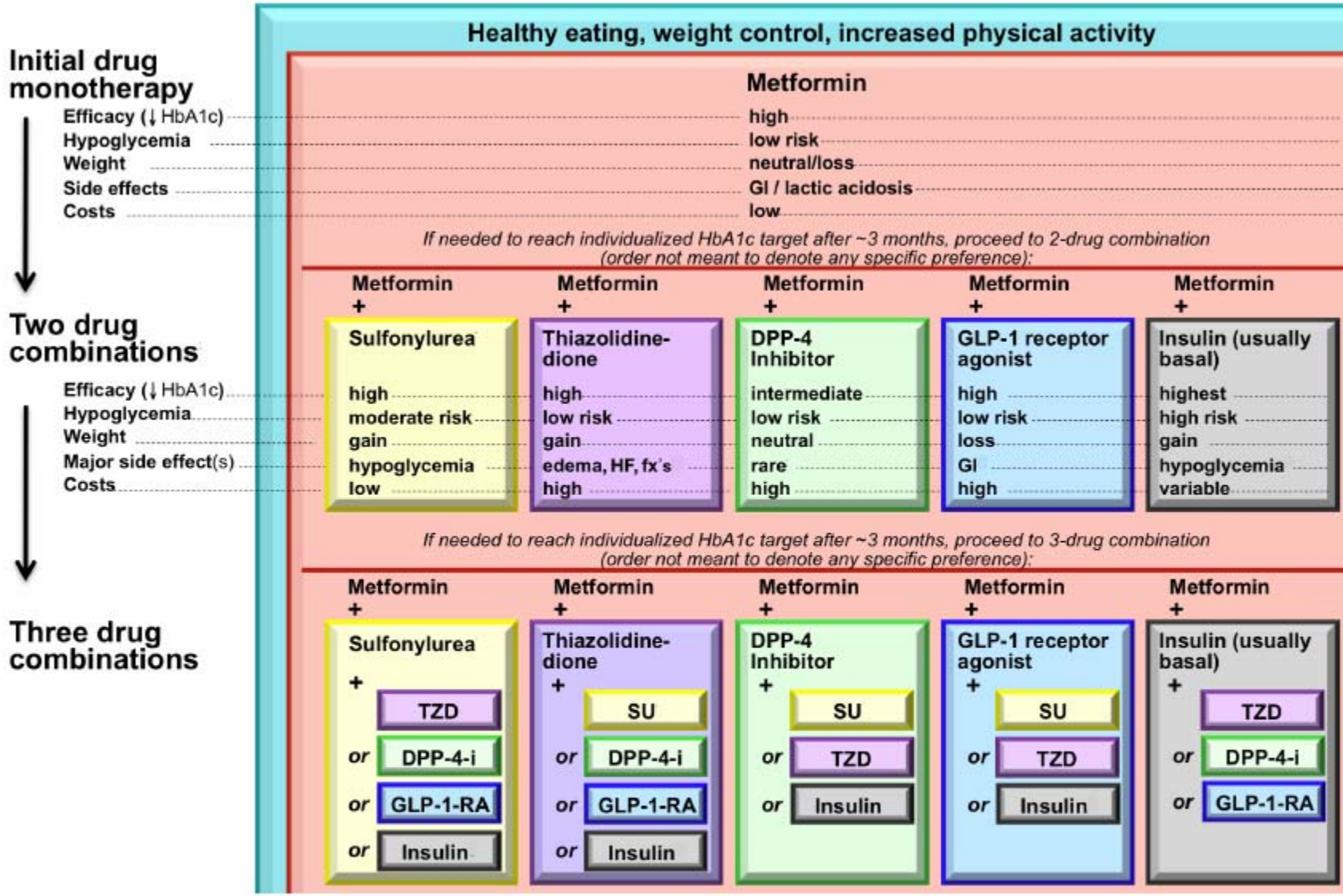

T2DM Antihyperglycemic Therapy: General Recommendations

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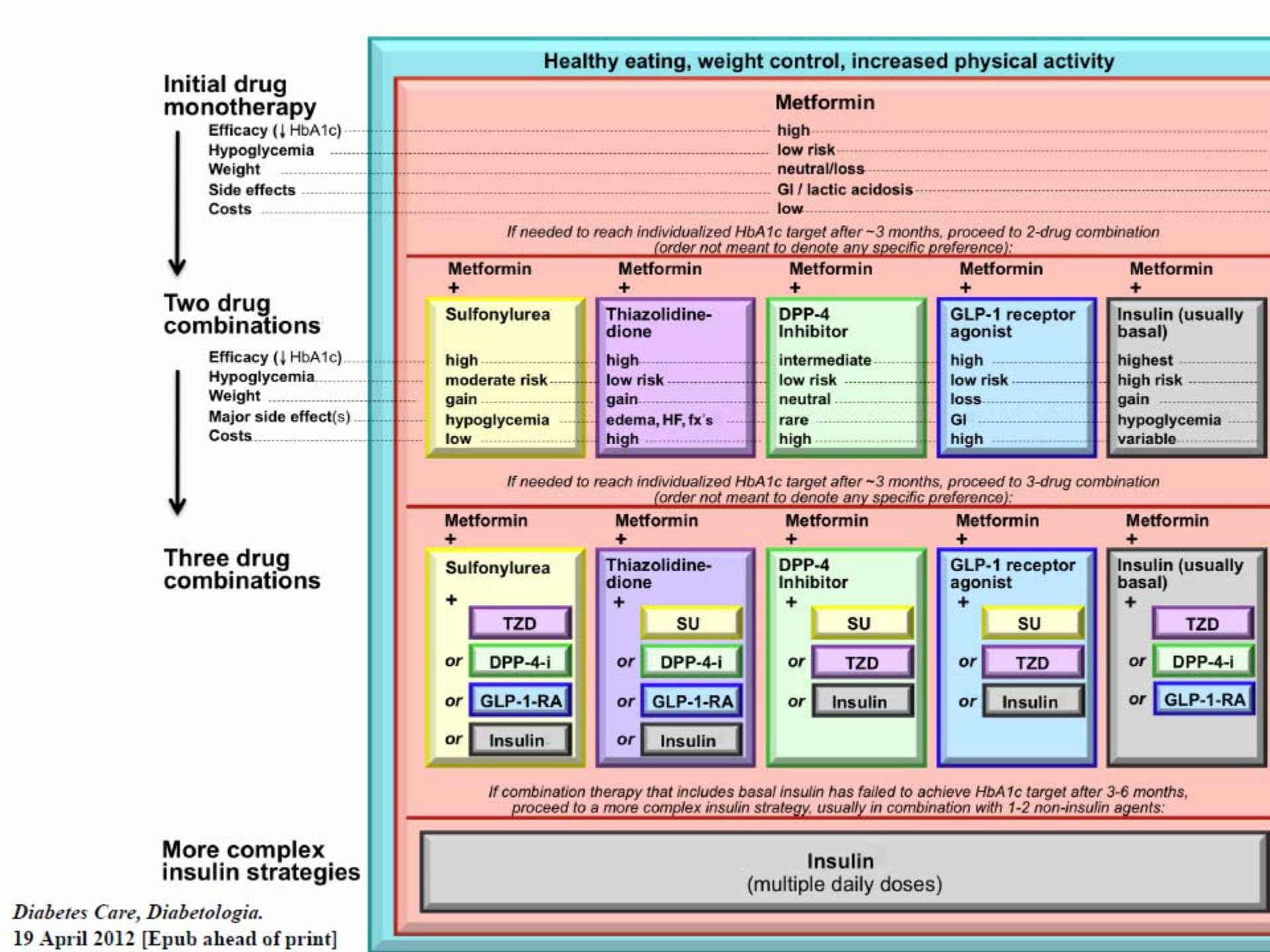


Diabetes Care, Diabetologia.
19 April 2012 [Epub ahead of print]

If HbA1c target not reached after 3 months with metformin, add a second drug treatment

Two-drug combinations	Metformin + Sulfonylurea	Metformin + Thiazolidinedione	Metformin + DPP-4 inhibitor	Metformin + GLP-1 receptor agonist	Metformin + Insulin (usually basal)
Efficacy	High	High	Intermediate	High	Highest
Hypoglycemia	Moderate risk	Low risk	Low risk	Low risk	High risk
Weight	Gain	Gain	Neutral	Loss	Gain
Major side effect	Hypoglycemia	Edema, HF, Fxs	Rare	GI	Hypoglycemia
Costs	Low	High	High	High	Variable

If HbA1c target not reached after 3 months with metformin and second drug, add a third drug treatment

Three-drug combinations	Metformin +									
	Sulfonylurea		Thiazolidinedione		DPP-4 inhibitor		GLP-1 receptor agonist		Insulin (usually basal)	
	+	TZD	+	SU	+	SU	+	SU	+	TZD
	or	DPP-4-i	or	DPP-4-i	or	TZD	or	TZD	or	DPP-4-i
	or	GLP-1-RA	or	GLP-1-RA	or	Insulin	or	Insulin	or	GLP-1-RA
	or	Insulin	or	Insulin						

Treatment should be individualized by considering the characteristics of each drug treatment

POSITION STATEMENT

Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach

Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

Silvio E. Inzucchi, MD[1]
Richard M. Bergenstal, MD[2]
John B. Buse, MD, PHD[3]
Michaela Diamant, MD, PHD[4]
Ele Ferrannini, MD[5]
Michael Nauck, MD[6]
Anne L. Peters, MD[7]
Apostolos Tsapas, MD, PHD[8]
Richard Wender, MD[9]
David R. Matthews, MD, DPHIL[10,11,12]

DIABETES CARE : 2012;35:1364

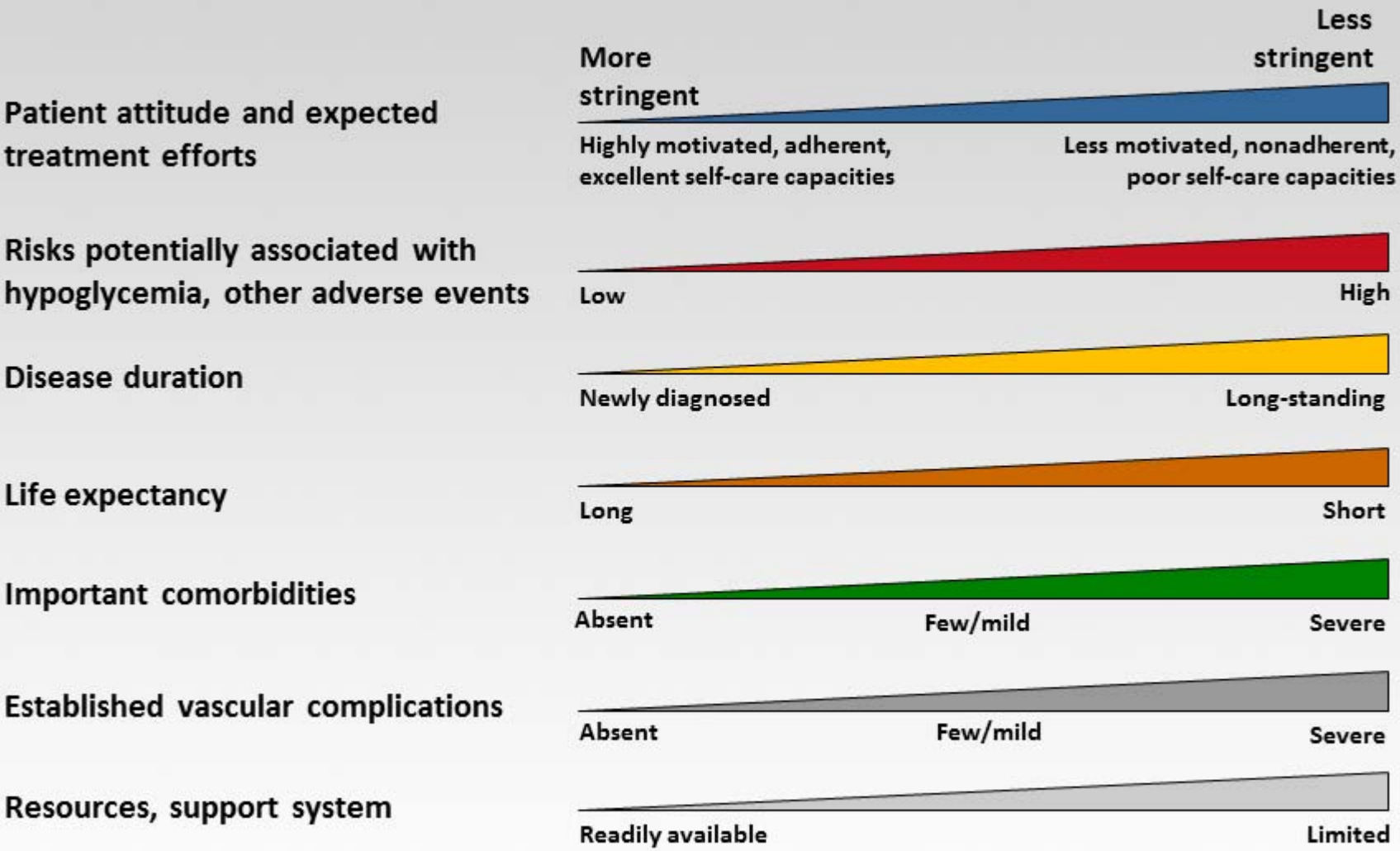
1. Patient-Centered Approach

"…providing care that is respectful of and responsive to individual patient preferences, needs, and values - ensuring that patient values guide all clinical decisions."

- **Gauge patient's preferred level of involvement.**
- **Explore, where possible, therapeutic choices.**
- **Utilize decision aids.**
- **<u>Shared</u> decision making – final decisions re: lifestyle choices ultimately lies with the patient.**

Diabetes Care, Diabetologia. 19 April 2012 [Epub ahead of print]

ADA/EASD Position Statement on T2D: Individualized Management of Hyperglycemia



Adapted from Inzucchi SE, et al. *Diabetologia*. 2012;55(6):1577-1596.

4. OTHER CONSIDERATIONS

- **Comorbidities**
  - **Coronary Disease** ----->
  - Heart Failure
  - Renal disease
  - Liver dysfunction
  - Hypoglycemia

- Metformin: CVD benefit (UKPDS)
- Avoid hypoglycemia
- ? SUs & ischemic preconditioning
- ? Pioglitazone & ↓ CVD events
- ? Effects of incretin-based therapies

Diabetes Care 2012;35:1364–1379
Diabetologia 2012;55:1577–1596

4. OTHER CONSIDERATIONS

- **Comorbidities**
  - Coronary Disease
  - **Heart Failure** ---------->
  - Renal disease
  - Liver dysfunction
  - Hypoglycemia

- Metformin: May use unless condition is unstable or severe
- Avoid TZDs
- ? Effects of incretin-based therapies

Diabetes Care 2012;35:1364–1379
Diabetologia 2012;55:1577–1596

4. OTHER CONSIDERATIONS

- **Comorbidities**
  - Coronary Disease
  - Heart Failure
  - **Renal disease** ------>
  - Liver dysfunction
  - Hypoglycemia

- Increased risk of hypoglycemia
- Metformin & lactic acidosis
  - US: stop @SCr ≥ 1.5 (1.4 women)
  - UK: half-dose @GFR < 45 &
    stop @GFR < 30
- Caution with SUs (esp. glyburide)
- DPP-4-i's – dose adjust for most
- Avoid exenatide if GFR < 30

Diabetes Care 2012;35:1364–1379
Diabetologia 2012;55:1577–1596

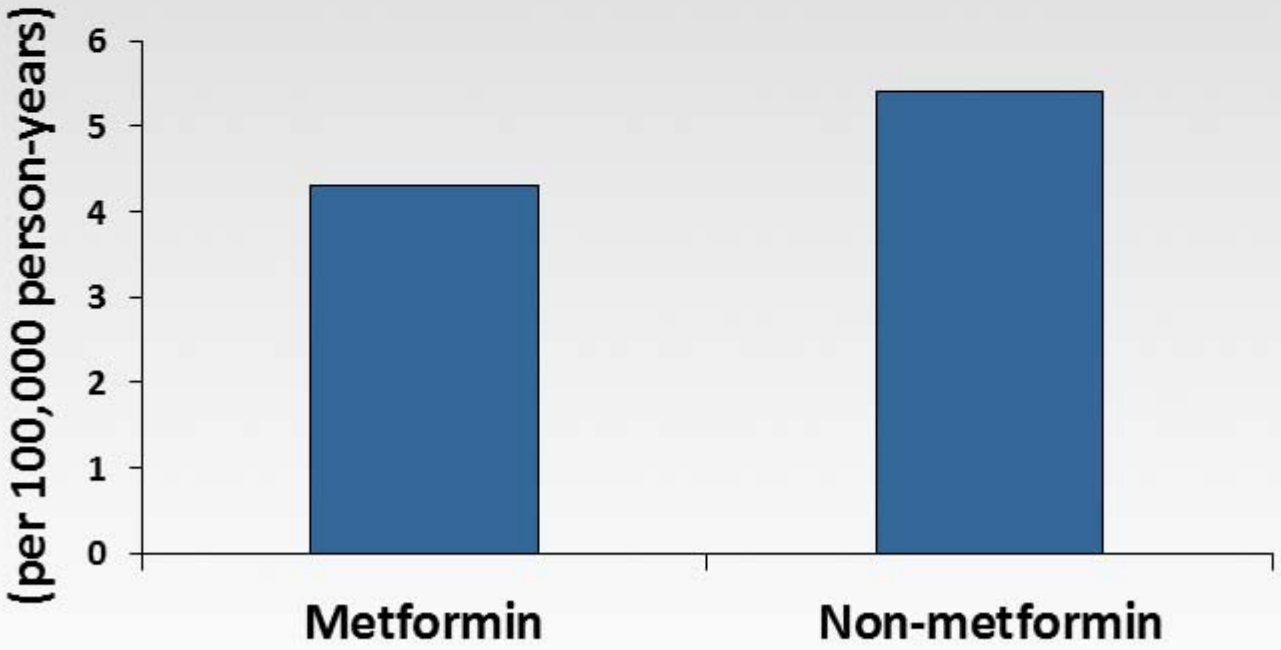
Dosing of Antihyperglycemic Thearpy in Renal Impairment

	Creatinine Clearance (mL/min)		
	30–49	15–29	<15 (dialysis)
Metformin	–	–	–
Sulfonylureas	Consider dose reduction	–	–
Repaglinide	Use with caution		
Nateglinide	Consider dose reduction		
Acarbose/Miglitol	Up to 25 mL/min	–	–
Pioglitazone	Not to be used in dialysis patients		
Sitagliptin	1 x 50 mg/day	1 x 25 mg/day	1 x 25 mg/day
Vildagliptin	Not recommended		
Saxagliptin	1 x 2.5 mg/day	1 x 2.5 mg/day with caution	1 x 2.5 mg/day with caution
Linagliptin	1 x 5 mg/day (no dose adjustment required)		

– Contraindications Acceptable

Incidence of Lactic Acidosis Not Different in Metformin-Treated Patients

Pooled data from 347 comparative trials and cohort studies revealed no cases of fatal or nonfatal lactic acidosis in 70,490 patient-years of metformin use or in 55,451 patient-years in the non-metformin group.



Medscape EDUCATION

Salpeter SR, et al. *Cochrane Database Syst Rev*. 2010;(4):CD002967.

4. OTHER CONSIDERATIONS

- **Comorbidities**
  - Coronary Disease
  - Heart Failure
  - Renal disease
  - **Liver dysfunction** --->
  - Hypoglycemia

- Most drugs not tested in advanced liver disease
- Pioglitazone may help steatosis
- Insulin best option if disease severe

Diabetes Care 2012;35:1364–1379
Diabetologia 2012;55:1577–1596

4. OTHER CONSIDERATIONS

- **Comorbidities**
  - Coronary Disease
  - Heart Failure
  - Renal disease
  - Liver dysfunction
  - **Hypoglycemia** ⟶

- Emerging concerns regarding association with increased morbidity / mortality
- Proper drug selection is key in the hypoglycemia prone

Diabetes Care 2012;35:1364–1379
Diabetologia 2012;55:1577–1596

What Is Hypoglycemia?

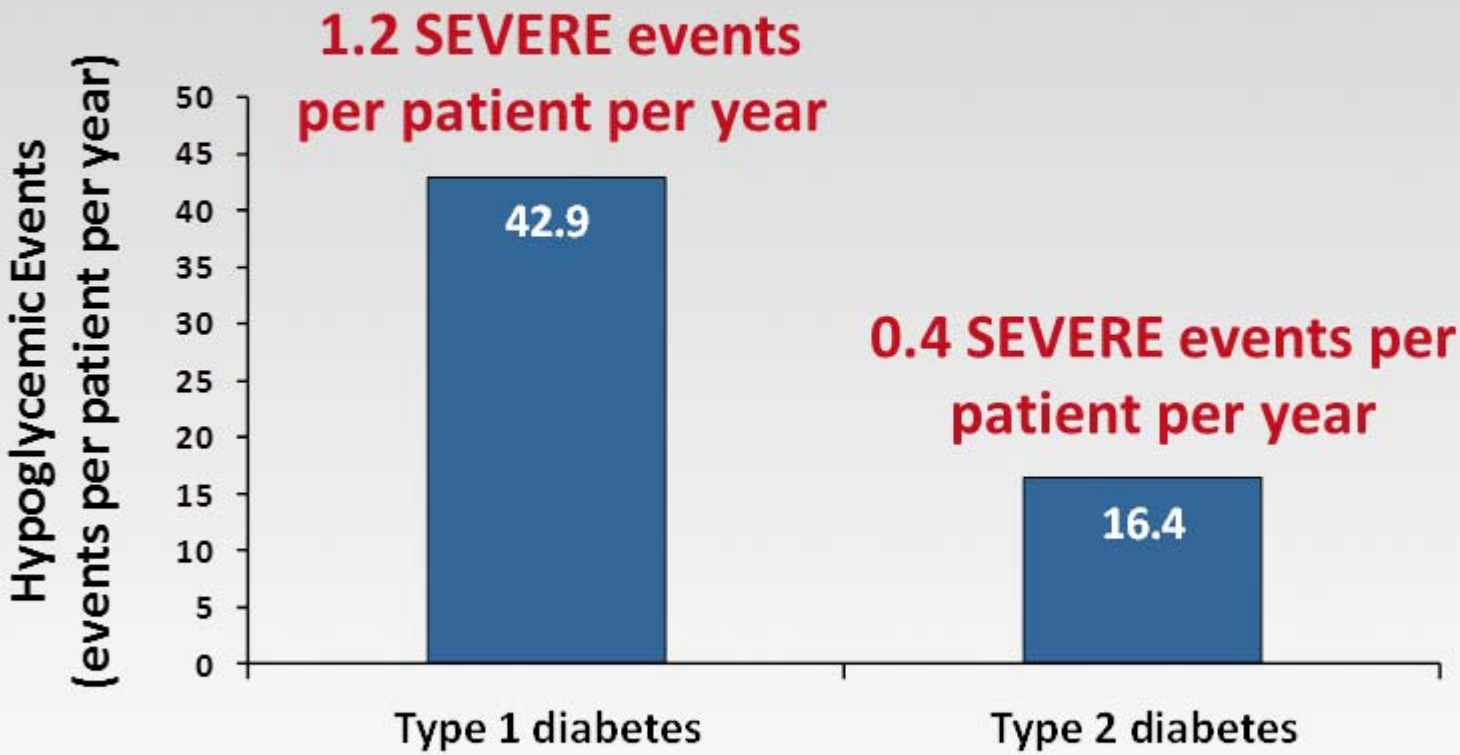
< 55 mg/dl

- Low plasma glucose causing neuroglycopenia
- Clinical definition of hypoglycemia:
  - Mild: self-treated
  - Severe: requiring help for recovery
- Biochemical definition of low plasma glucose:
  - 3.0 mmol/L (< 54.1 mg/dL) (EMA 2006)[a]
  - 3.9 mmol/L (≤ 70 mg/dL) (ADA 2005, EMA 2012)[b]
  - 4.0 mmol/L (< 72 mg/dL) for clinical use in patients treated with insulin or an insulin secretagogue (CDA 2002)[c]

ADA = American Diabetes Association; CDA = Canadian Diabetes Association; EMA = European Medicines Agency

a. EMA. CPMP/EWP/1080/00. 2006;
b. ADA. *Diabetes Care.* 2005;28(5):1245-1249; EMA. CPMP/EWP/1080/00. Rev .1 2012
c. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee *Can J Diabetes.* 2008;32(Suppl 1):S1-S201.

Patients With Type 1 and 2 Diabetes Experience Frequent Hypoglycemic Events



Medscape EDUCATION

Donnelly LA, et al. *Diabetic Med*. 2005;22(6):749-755.

Ma non dimentichiamo una visione “internistica” del problema

La “recluta”

HbA1C : 6.5

Il “veterano”

HbA1C : 7-7.5

Il “reduce ferito “

HbA1C : 8

ADA. V. Diabetes Care. *Diabetes Care* 2012;35(suppl 1):S18-19.