University of Rome "Tor Vergata"

Physical Activity & Health Promotion

2020/2021

Endocrinology

&

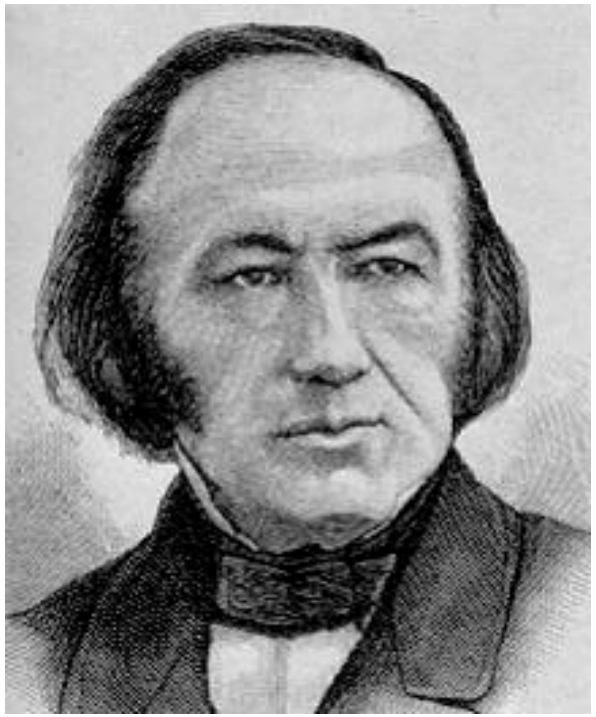
Physical activity

www.endocrinologiamoretti.it

Università di Roma Tor Vergata

Dr.ssa Katia Andreadi

Claude Bernard: the father of endocrinology



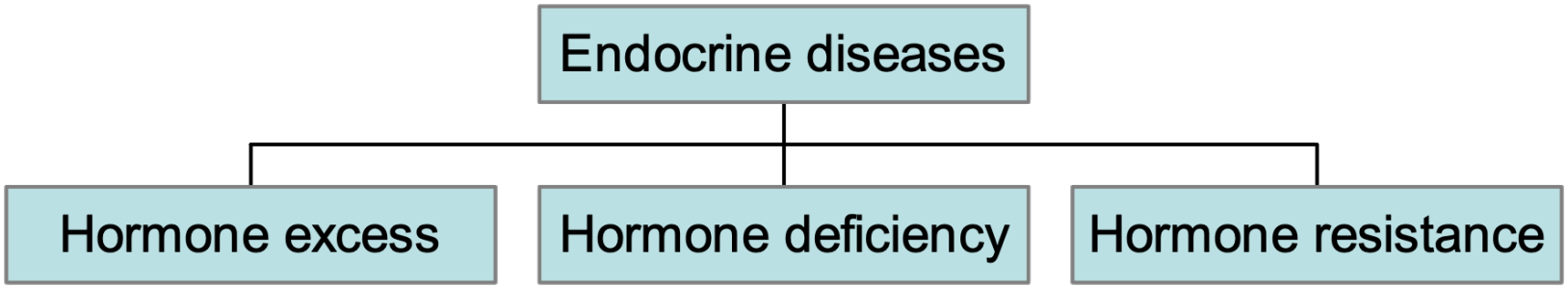
More than 100 years ago Claude Bernard stated that the endocrine system regulates the internal milieu of an animal. The "internal secretions" or hormones were liberated by one part of the body, traveled via the bloodstream to distant targets cells.

Principal functions of the endocrine system

- Maintenance of the internal environment in the body (maintaining the optimum biochemical environment).
- Integration and regulation of growth and development.
- Control, maintenance and instigation of sexual reproduction, including gametogenesis, coitus, fertilization, fetal growth and development and nourishment of the newborn.

Endocrinology Disorders

- Pituitary Disorders
- Thyroid Disorders
- Adrenal Disorders
- Gonadal Disorders
- Calcium Disorders
- Lipid Disorders


Endocrine diseases
Hormone excess
Hormone deficiency
Hormone resistance

Classes of hormones

- The hormones fall into two general classes based on their solubility in water.
  - The water soluble hormones are the catecholamines (epinephrine and norepinephrine) and peptide/protein hormones.
  - The lipid soluble hormones include thyroid hormone, steroid hormones and Vitamin D3

Regulation of hormone secretion

- Sensing and signaling: a biological need is sensed, the endocrine system sends out a signal to a target cell whose action addresses the biological need. Key features of this stimulus response system are:
  - receipt of stimulus
  - synthesis and secretion of hormone
  - delivery of hormone to target cell
  - evoking target cell response
  - degradation of hormone

Feedback control

- Negative feedback is most common: for example, LH from pituitary stimulates the testis to produce testosterone which in turn feeds back and inhibits LH secretion
- Positive feedback is less common: examples include LH stimulation of estrogen which stimulates LH surge at ovulation

Control of hormonal secretion

- **Humoral**
- **Neural**
- **Hormonal**

Substrate-hormone control

- **glucose and insulin: as glucose increases it stimulates the pancreas to secrete insulin**

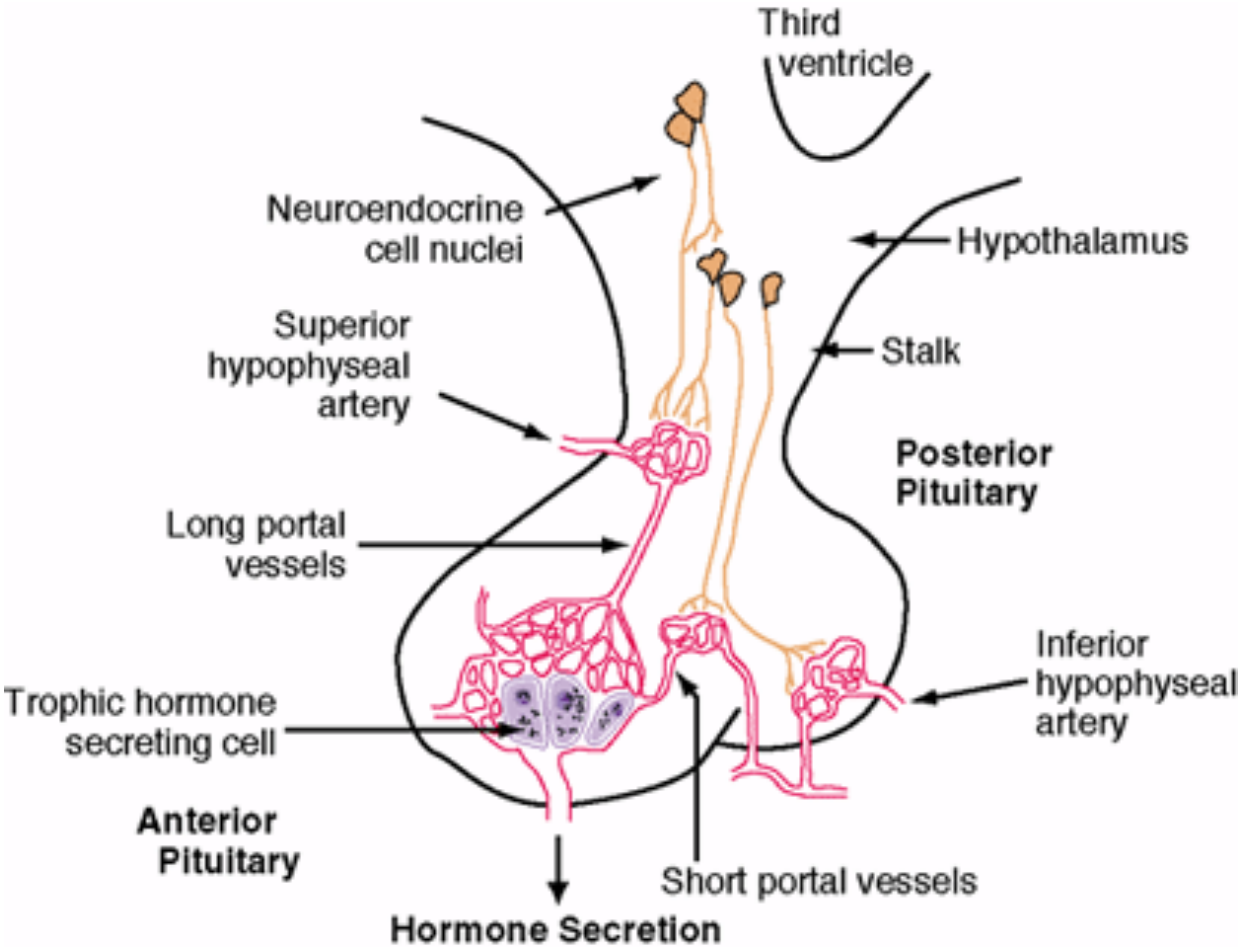
Chronotropic control

- Endogenous neuronal rhythmicity
- Diurnal rhythms, circadian rhythms (growth hormone and cortisol), Sleep-wake cycle; seasonal rhythm

Neural control

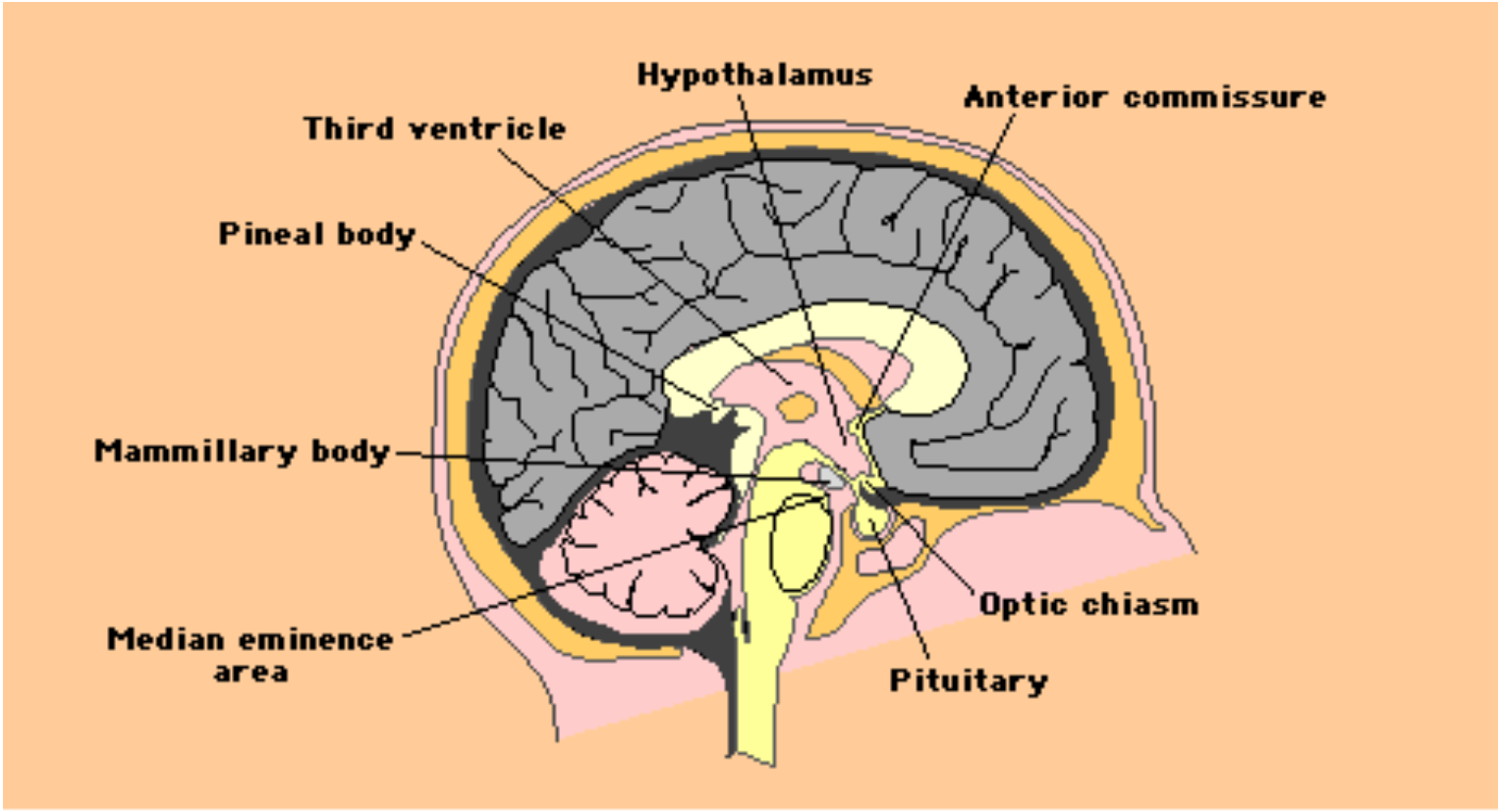
- Neural input to hypothalamus stimulates synthesis and secretion of releasing factors which stimulate pituitary hormone production and release

Hypothalamic–Pituitary Axis



Pituitary Gland

- Located within the sella tursica
- Contiguous to vascular and neurologic structures
  - Cavernous sinuses
  - Cranial nerves
  - Optic chiasm
- Hypothalamic neural cells synthesize specific releasing and inhibiting hormones
  - Secreted directly into the portal vessels of the pituitary stalk
- Blood supply derived from the superior and inferior hypophyseal arteries



Anatomy of the hypothalamic-pituitary axis Lateral view of the brain showing the relationship of the hypothalamus to the median eminence and the pituitary gland. (Adapted from Krieger, DT, in: Neuroendocrinology, Krieger, DT, Hughes, JC (Eds), Sinauer Associates, Sunderland, MA, 1980, p. 4.)

Pituitary Gland

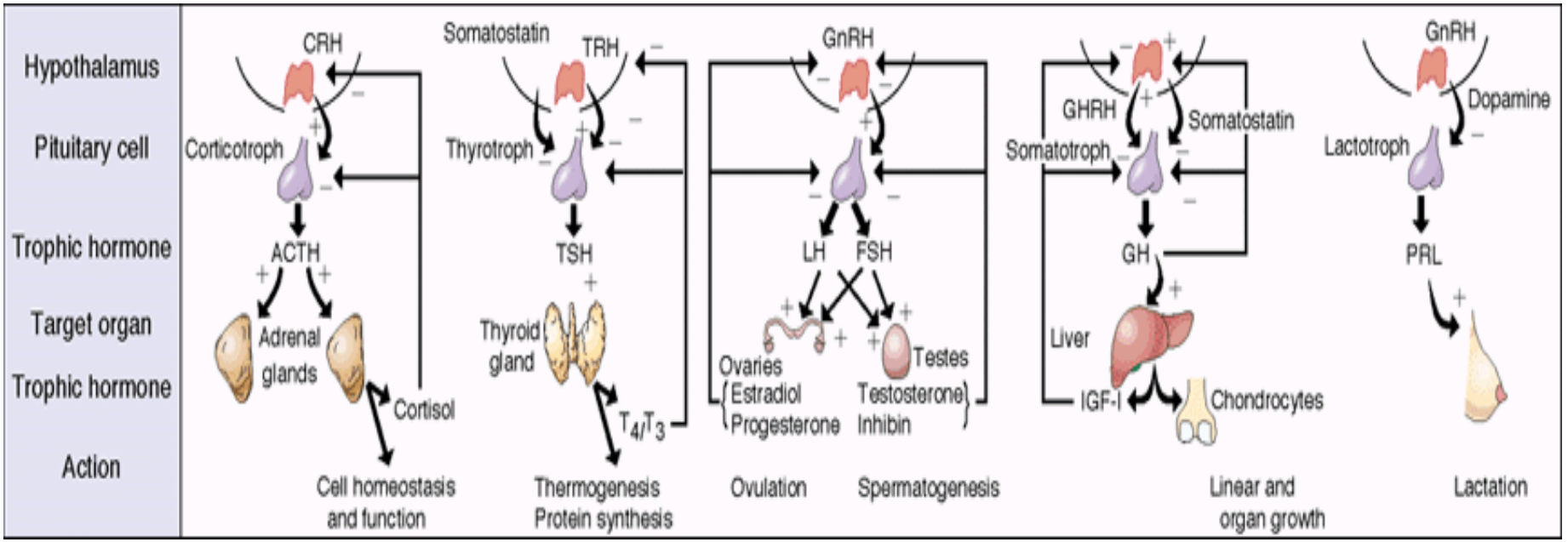
- Anterior pituitary gland
  - Secrete various trophic hormones
  - Disease in this region may result in ***syndromes of hormone excess or deficiency***

- Posterior pituitary gland
  - More of a terminus of axons of neurons in the supraoptic and paraventricular nuclei of the hypothalamus
  - Storehouse for the hormones
  - The main consequence of disease in this area is ***disordered water homeostasis***

Anterior Pituitary Gland

- Anterior Pituitary "Master gland"
  - Major blood source: hypothalamic-pituitary portal plexus
    - Allows transmission of hypothalamic peptide pulses without significant systemic dilution
    - Consequently, pituitary cells are exposed to sharp spikes of releasing factors and in turn release their hormones as discrete pulses
  - Production of six major hormones:
    - Prolactin (PRL)
    - Growth hormone (GH)
    - Adrenocorticotropin hormone (ACTH)
    - Luteinizing hormone (LH)
    - Follicle-stimulating hormone (FSH)
    - Thyroid-stimulating hormone (TSH)

Anterior Pituitary Gland

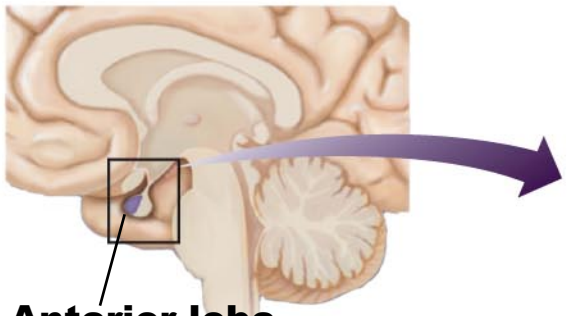


Anterior Pituitary Gland

- Anterior Pituitary "Master gland"
  - Secreted in a **pulsatile** manner
  - Elicits specific responses in peripheral target tissues
  - **Feedback control** at the level of the hypothalamus and pituitary to modulate pituitary function exerted by the hormonal products of the peripheral target glands
  - Tumors cause characteristic **hormone excess** syndromes
  - Hormone deficiency
    - may be inherited or acquired

Pituitary-Hypothalamic Relationships

- Anterior Lobe (adenohypophysis):
  - Originates as an out-pocketing of the oral mucosa
  - Hypophyseal portal system
    - Primary capillary plexus
    - Hypophyseal portal veins
    - Secondary capillary plexus
- Carries releasing and inhibiting hormones to the anterior pituitary to regulate hormone secretion



Anterior lobe of pituitary

Hypothalamus

Hypothalamic neurons synthesize GHRH, GHIH, TRH, CRH, GnRH, PIH.

Superior hypophyseal artery

① When appropriately stimulated, hypothalamic neurons secrete releasing or inhibiting hormones into the primary capillary plexus.

② Hypothalamic hormones travel through portal veins to the anterior pituitary where they stimulate or inhibit release of hormones made in the anterior pituitary.

Hypophyseal portal system

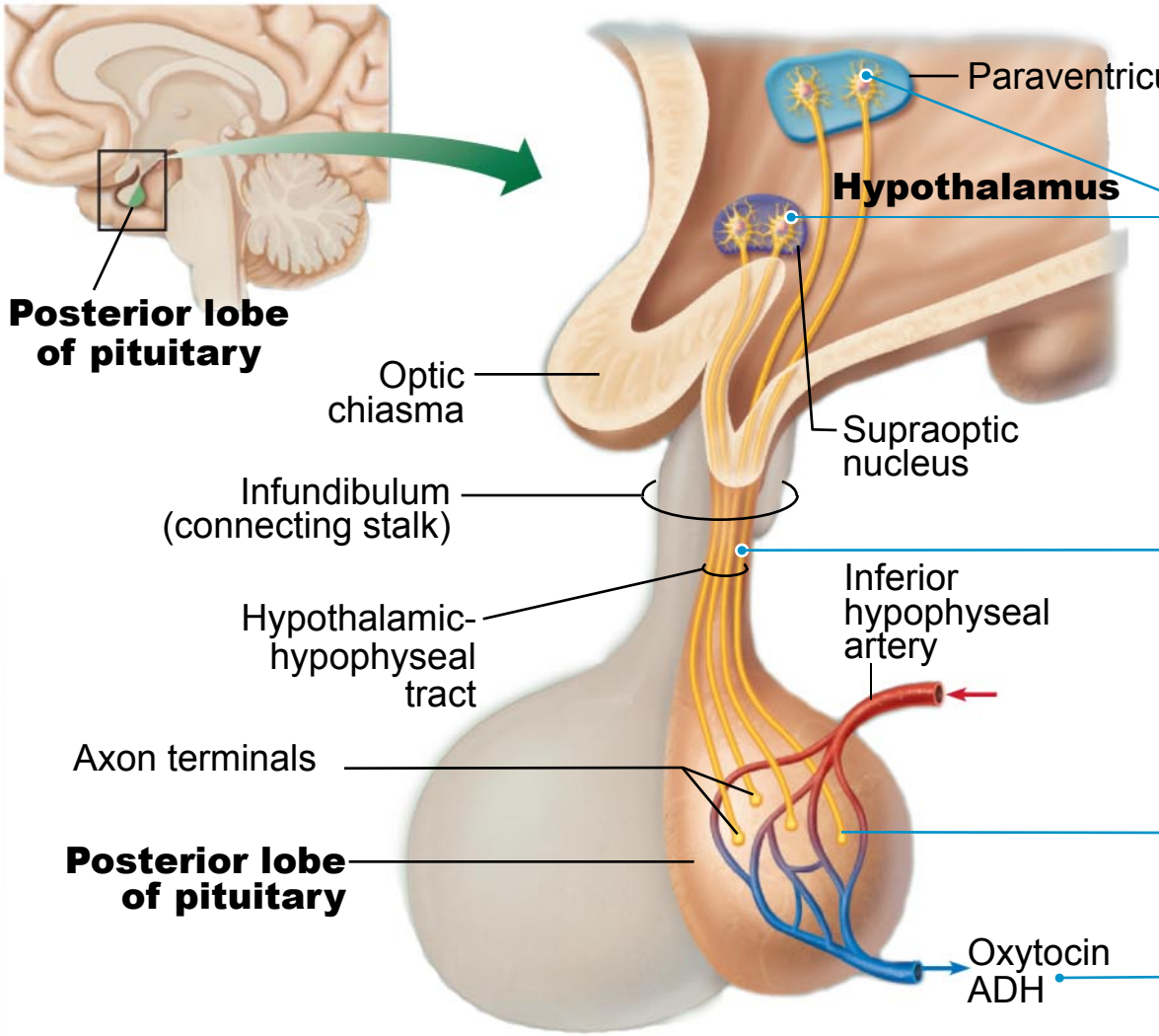
- Primary capillary plexus
- Hypophyseal portal veins
- Secondary capillary plexus

A portal system is two capillary plexuses (beds) connected by veins.

③ In response to releasing hormones, the anterior pituitary secretes hormones into the secondary capillary plexus. This in turn empties into the general circulation.

GH, TSH, ACTH, FSH, LH, PRL

Anterior lobe of pituitary

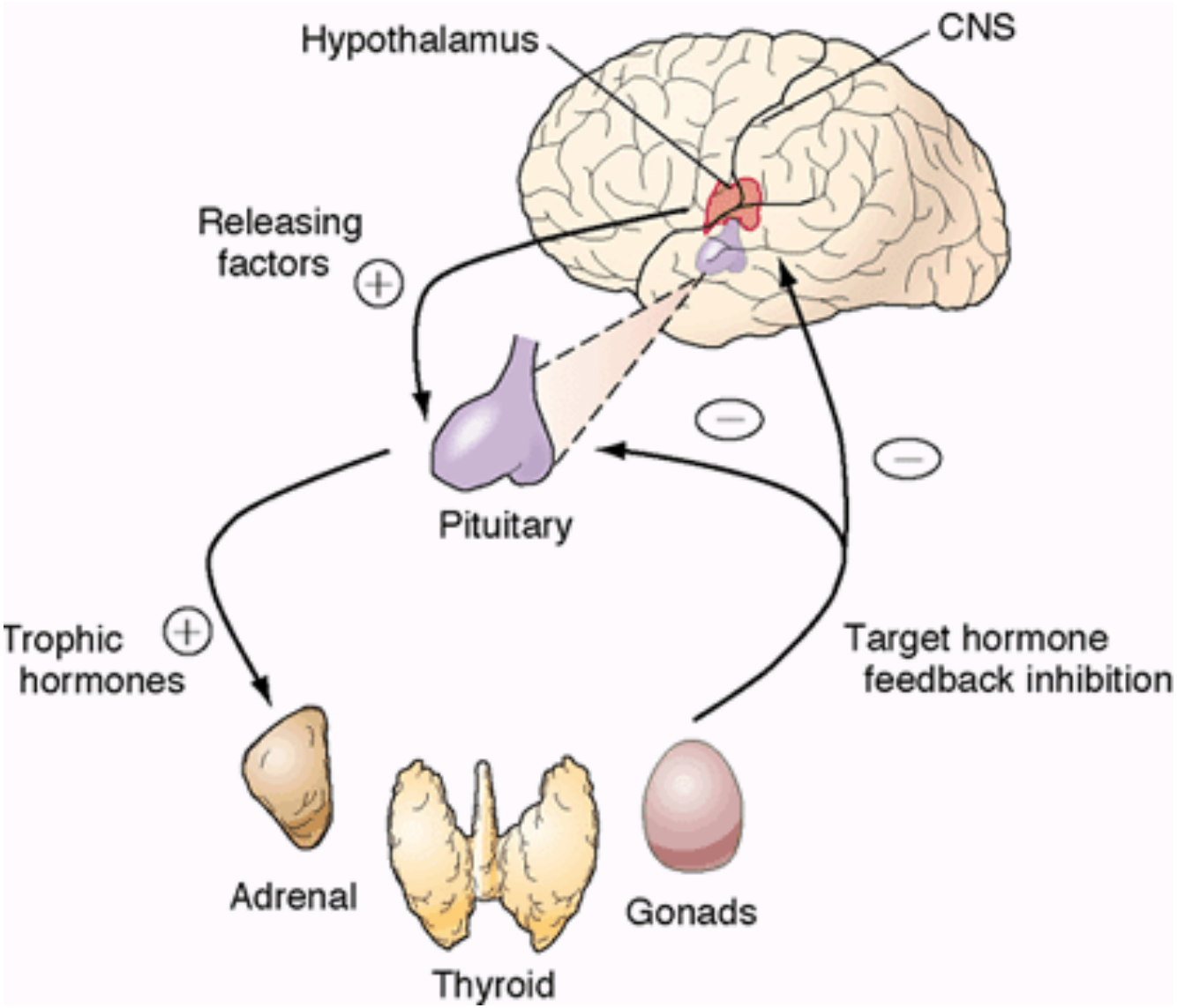


① Hypothalamic neurons synthesize oxytocin or antidiuretic hormone (ADH).

② Oxytocin and ADH are transported down the axons of the hypothalamic- hypophyseal tract to the posterior pituitary.

③ Oxytocin and ADH are stored in axon terminals in the posterior pituitary.

④ When hypothalamic neurons fire, action potentials arriving at the axon terminals cause oxytocin or ADH to be released into the blood.


Hypothalamus
CNS
Releasing factors
+
−
−
Pituitary
Trophic hormones
+
Target hormone feedback inhibition
Adrenal
Gonads
Thyroid

Gonadotropin Deficiency

Women

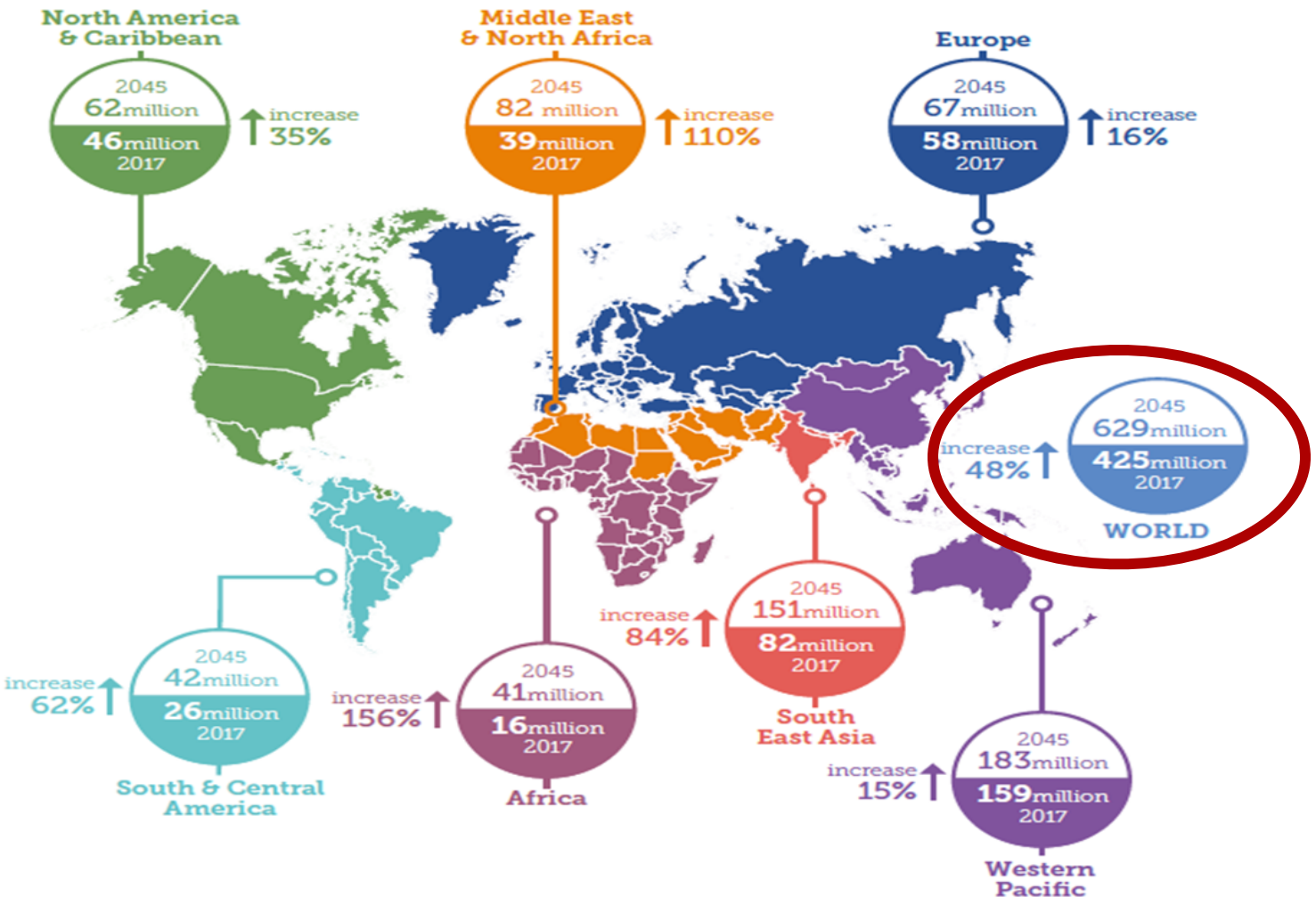
- Oligomenorrhea or amenorrhea
- Loss of libido
- Vaginal dryness or dyspareunia
- Loss of secondary sex characteristics (estrogen deficiency)

Men

- Loss of libido
- Erectile dysfunction
- Infertility
- Loss of secondary sex characteristics (testosterone deficiency)
- Atrophy of the testes
- Gynecomastia (testosterone deficiency)

Type 2 Diabetes

Diabetes mellitus numbers according IDF



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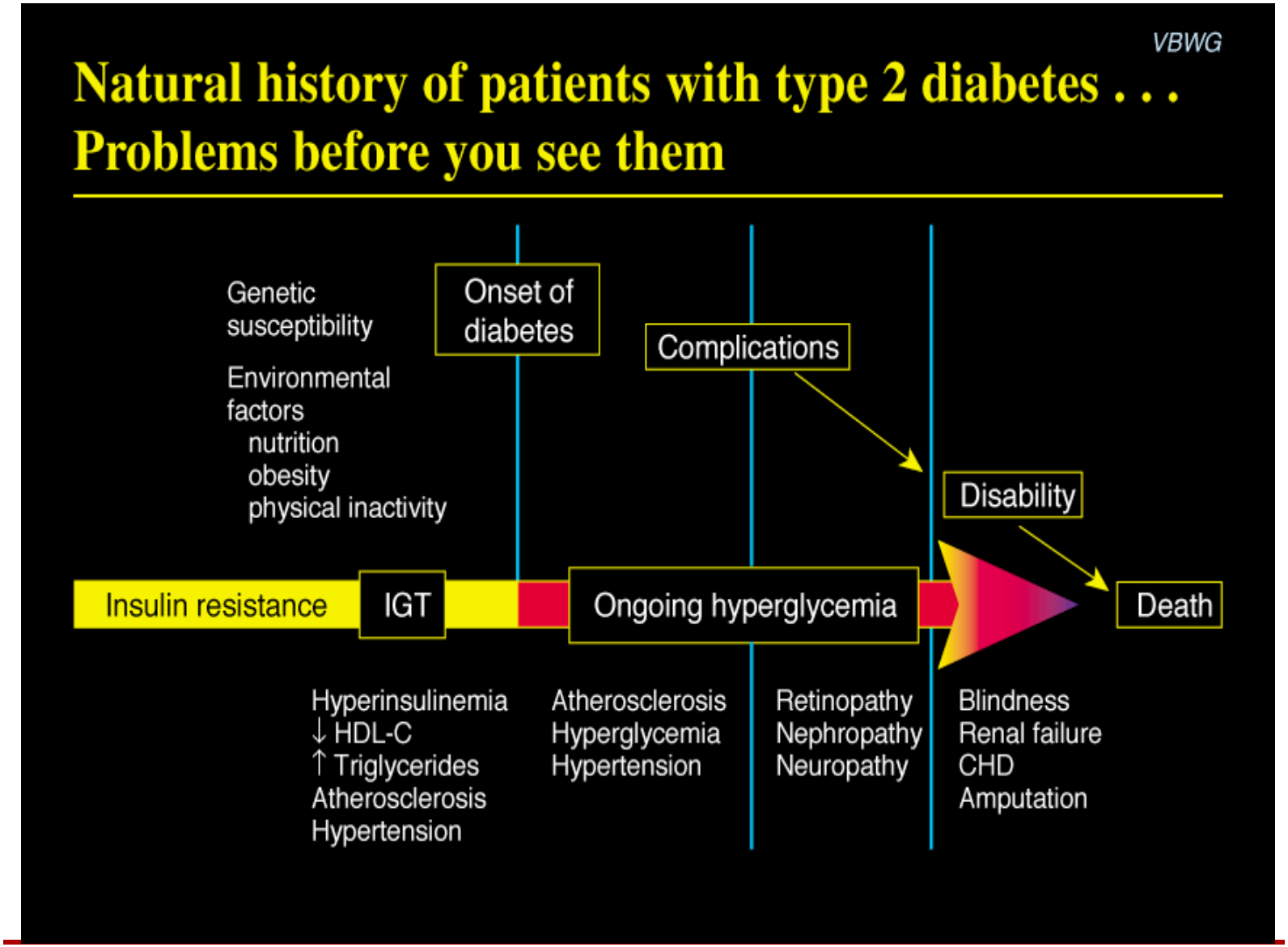
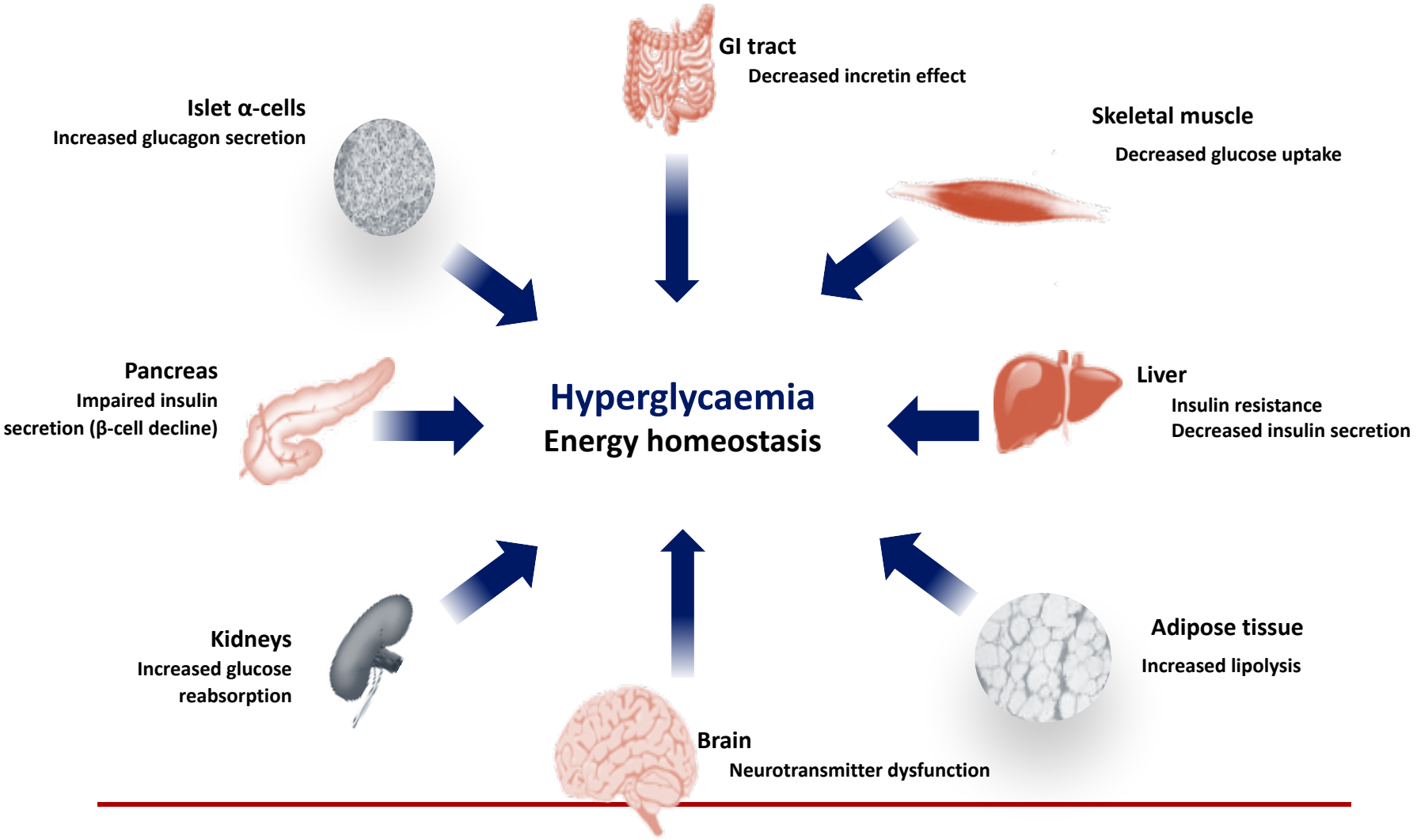
International Diabetes Federation



Pathogenesis of type 2 diabetes

The ominous octet



GI, gastrointestinal 1. DeFronzo. *Diabetes* 2009;58:773–95

Type 2 diabetes

- ✓ Patients frequently undiagnosed for many years.
- ✓ May present with hyperglycaemia symptoms.
- ✓ Coma is rare in type 2 diabetes.
- ✓ May progress to an absolute state of insulin deficiency.

Pathogenesis of Type 2 diabetes

- **Cause:** a combination of impaired insulin secretion and insensitivity of target tissues to insulin.
- Impaired insulin secretion due to beta cell malfunction can be associated with:

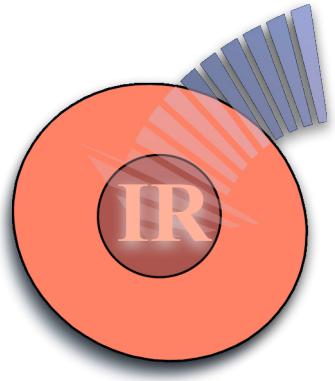
1. Incorrect secretion pattern.
2. Ratio of proinsulin to insulin.
3. Amyloid deposits.
4. Slow destruction of beta cells

Mechanisms for insulin resistance

1. Receptor numbers are decreased. (Often seen in obese and aged patients.)
2. Receptor structure is abnormal.
3. Insulin resistance at post receptor events.

What is insulin resistance?

- Major defect in individuals with type 2 diabetes[1]
- Reduced biological response to insulin[1–3]
- Strong predictor of type 2 diabetes[4]
- Closely associated with obesity[5]



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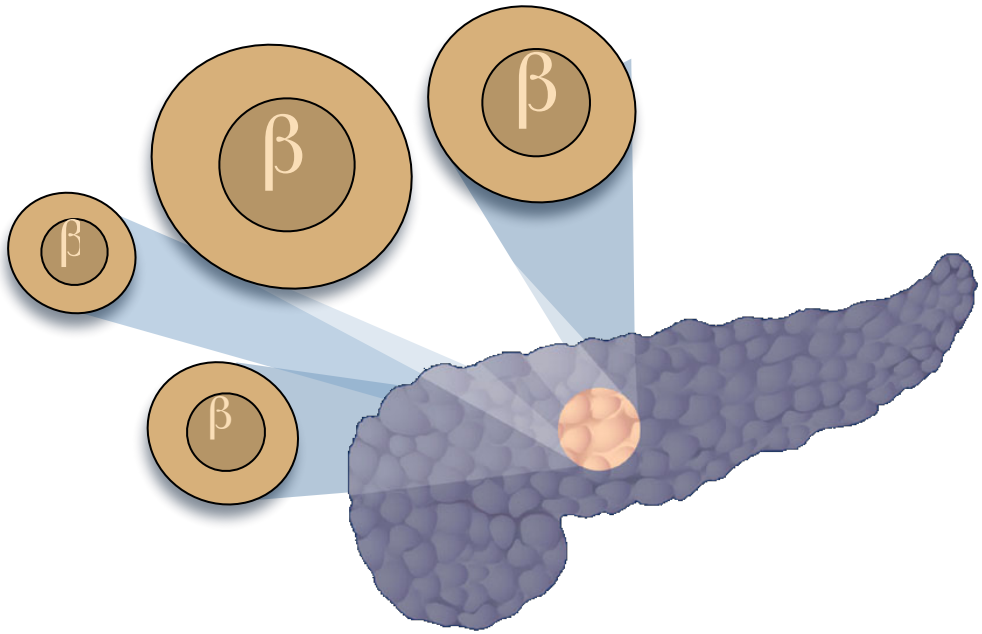
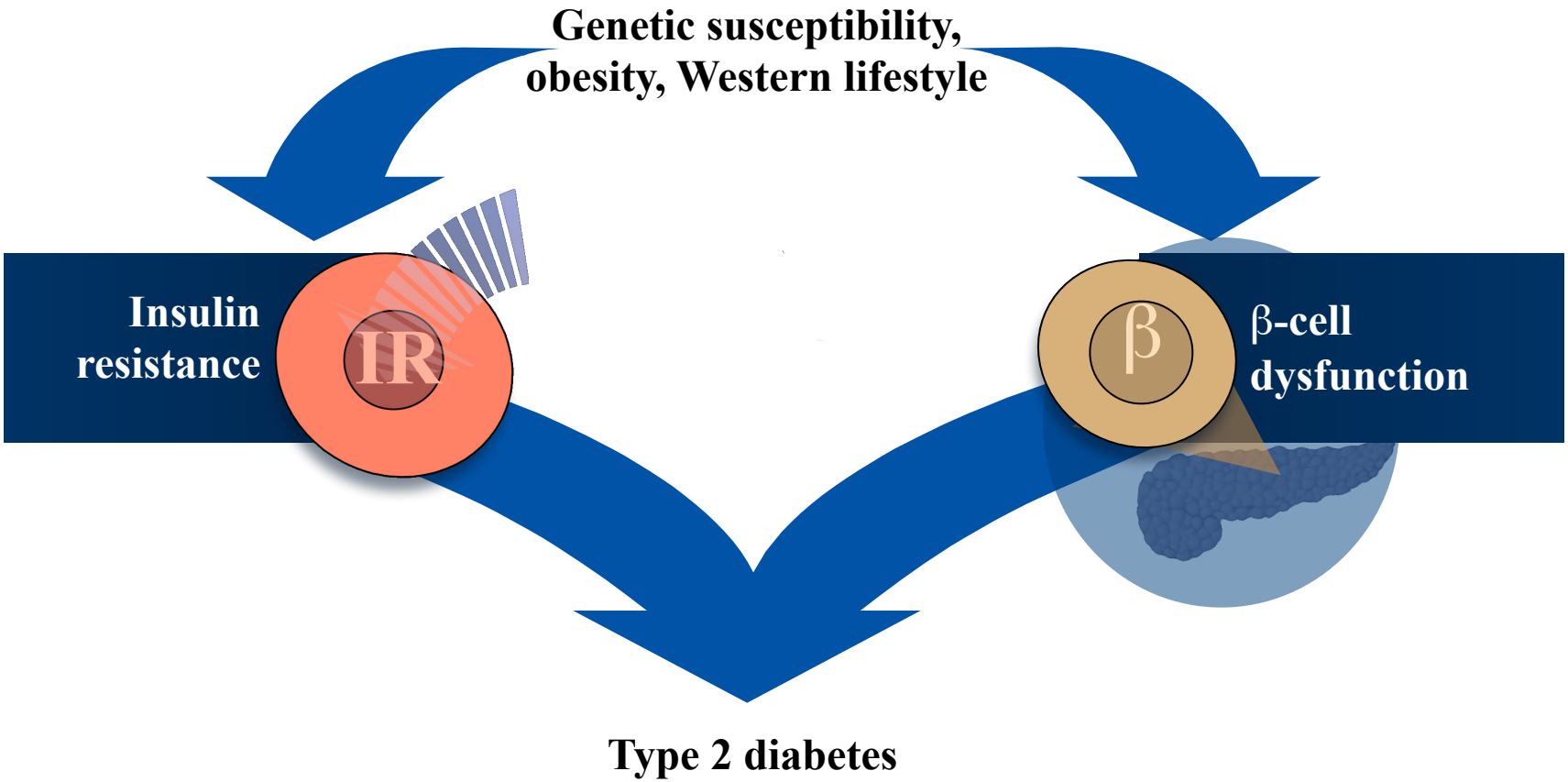
American Diabetes Association. *Diabetes Care* 1998; 21:310–314.
Beck-Nielsen H & Groop LC. *J Clin Invest* 1994; 94:1714–1721. [3]Bloomgarden ZT. *Clin Ther* 1998; 20:216–231.
Haffner SM, *et al. Circulation* 2000; 101:975–980. [5]Boden G. *Diabetes* 1997; 46:3–10.

What is β-cell dysfunction?

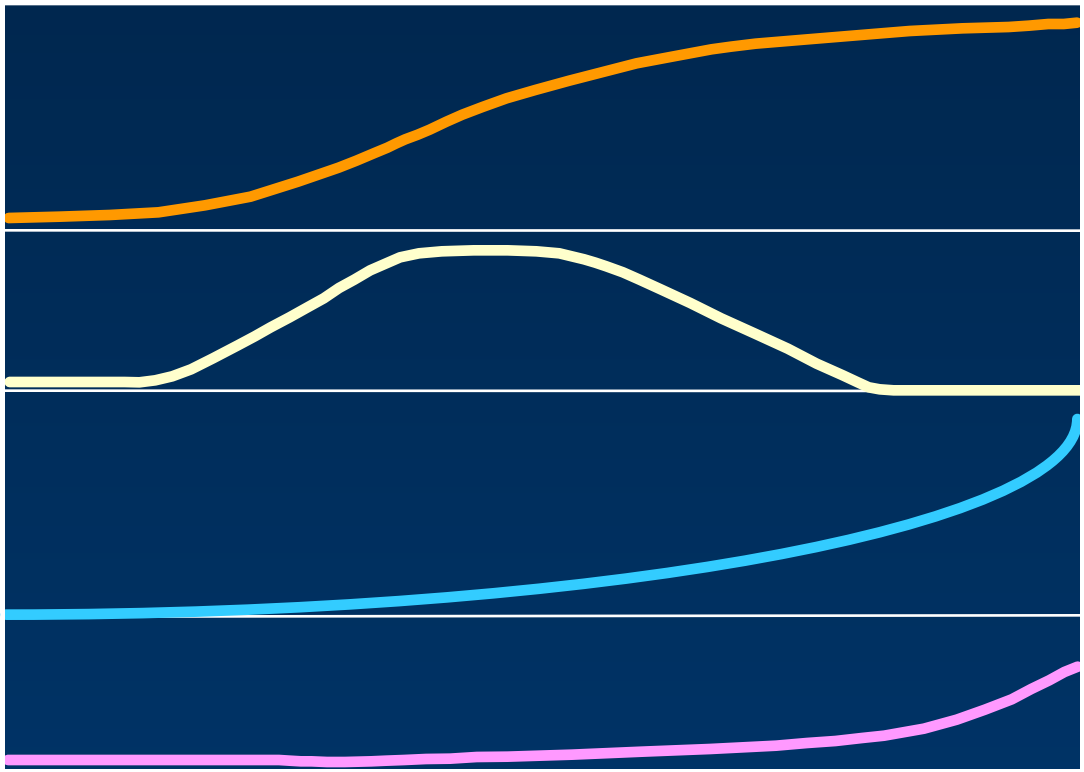
- Major defect in individuals with type 2 diabetes
- Reduced ability of β-cells to secrete insulin in response to hyperglycemia



Insulin resistance and β-cell dysfunction are core defects of type 2 diabetes



How do insulin resistance and β-cell dysfunction combine to cause type 2 diabetes?



*IGT = impaired glucose tolerance

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Adapted from *Type 2 Diabetes BASICS*. International Diabetes Center (IDC), Minneapolis, 2000.

Clinical features of Type 2 diabetes

- Diagnosis due to presence of complications.(At least 30% patients have complications at diagnosis).
- Symptoms are mild, gradual onset. Classic diabetic symptoms may be present.
- Type 2 diabetics are usually:

  over 40 years, fat (“apple obesity”) and no ketones are present.

Those at Risk of developing Type 2 Diabetes

- Gestational Diabetes
- Family History
- Ethnicity
- Obesity
- Physical Inactivity
- Age
- IGT/IFG
- Polycystic Ovary Syndrome

Risk factors for type 2 diabetes

- Hypertension
- Dyslipidaemia
- Abdominal obesity
- Overweight
- Insulin Resistance

Metabolic Syndrome/ Syndrome X

Prevention of type 2 diabetes

Lifestyle modification

- Diabetes Prevention Program
- Finnish Diabetes Prevention Study

Comparisons of Type 2 Diabetes

Type 2 (90-95%)

Gradual onset

May be Asymptomatic

Often no weight loss

Usually obese

Not ketotic

C-peptide detectable

No markers of autoimmunity present

Family history

Onset usually >40 years old

Diagnosis of Diabetes

Diagnosis cannot be made from:

- Blood glucose strips read visually or by a

- Urine testing

- Glycosalated Haemoglobin - HbA1c

Glucose Tolerance Test

- 3 days of unrestricted diet and exercise
- Evening meal as normal the night before
- Overnight fast of 8-14 hours

TEST

- Fasting blood on the morning
- Drink 75g of anhydrous glucose in 250-300ml water over 5 mins
- Blood sample 2 hours later
- No smoking during the test

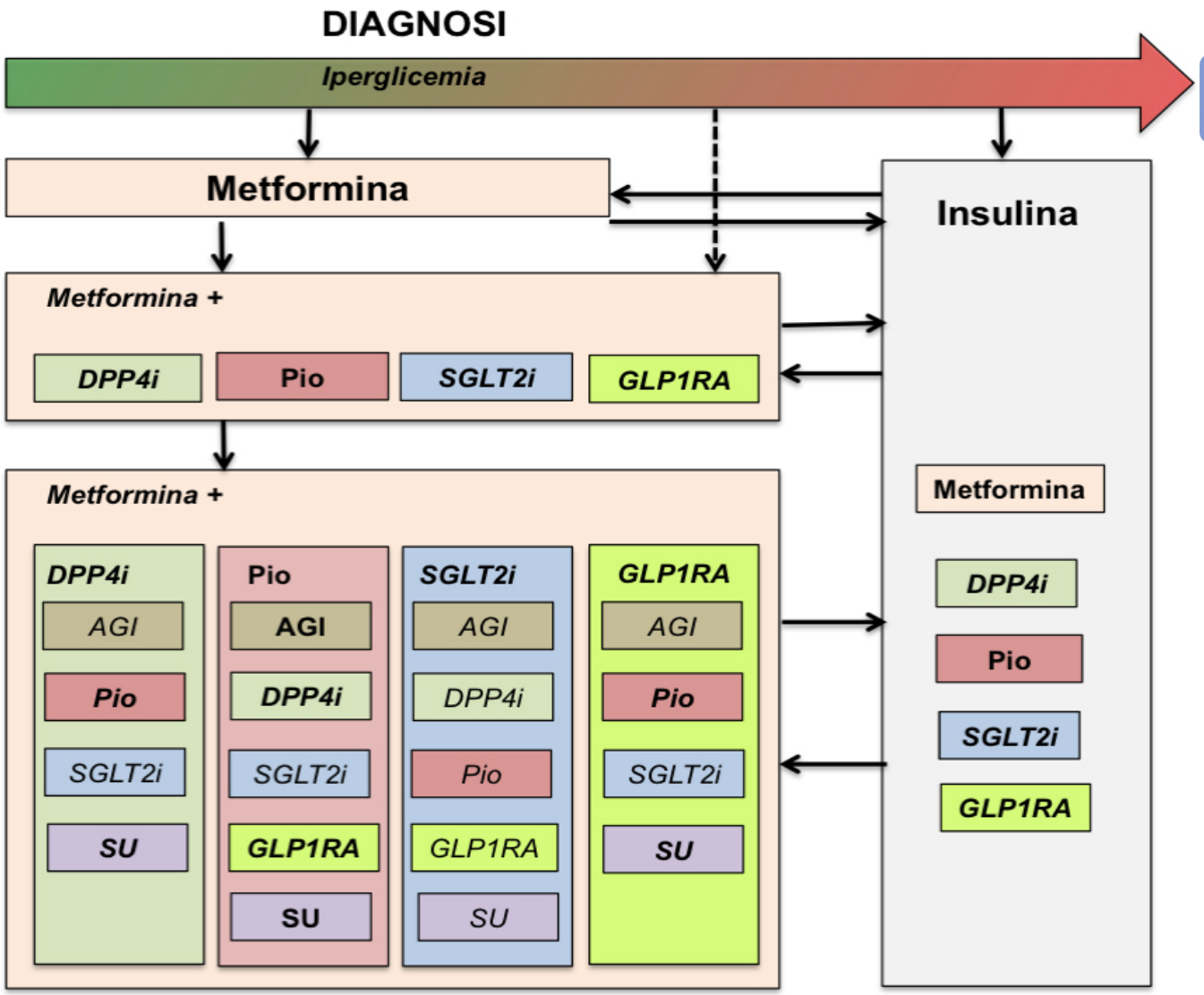
DIAGNOSIS AFTER AN OGTT

	Impaired Fasting Glucose (IFG)	Impaired Glucose Tolerance (IGT)	Diabetes
Fasting Venous Plasma Glucose	6.1 mmol/l to 6.9 mmol/l	<7.0 mmol/l	≥ 7.0 mmol/l
2 hr post	< 7.8 mmo/l	≥7.8 mmol/l up to 11.1 mmol/l	≥11.1 mmol/l (WHO,2006)

Impaired Glucose Regulation

- Impaired Glucose Tolerance (IGT)
  - Abnormalities in glucose regulation in the post-prandial state.
  - More common in women

- Impaired Fasting Glucose (IFG)
  - Elevated fasting glucose concentrations, but lower than those required to diagnose diabetes
  - More common in men


DIAGNOSI
Iperglicemia
Metformina
Insulina
Metformina +
DPP4i
Pio
SGLT2i
GLP1RA
Metformina +
DPP4i
AGI
Pio
SGLT2i
SU
Pio
AGI
DPP4i
SGLT2i
GLP1RA
SU
SGLT2i
AGI
DPP4i
Pio
GLP1RA
SU
GLP1RA
AGI
Pio
SGLT2i
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Metformina
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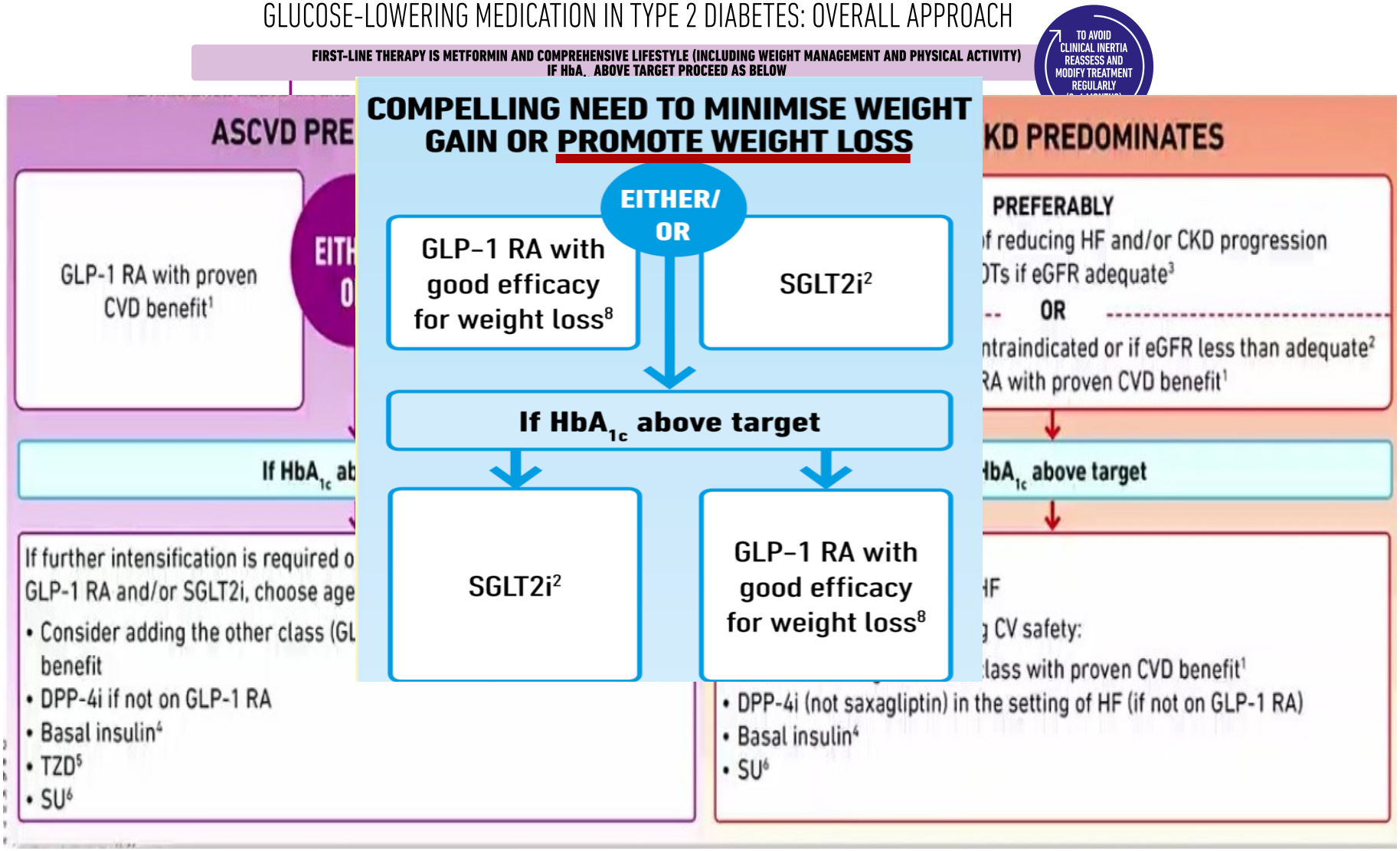
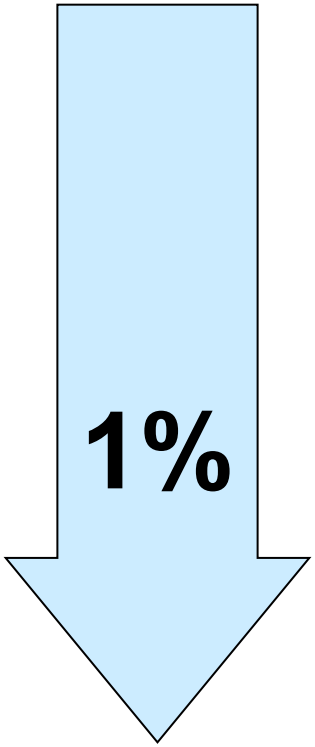
GLP1RA

GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH

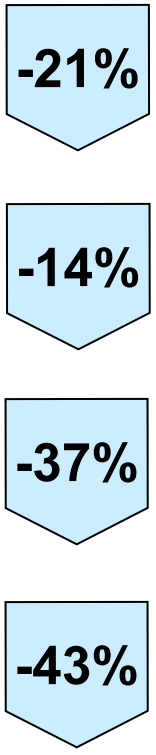


Lessons from UKPDS:
Better control means fewer complications

EVERY 1%
reduction in HBA_{1C}



REDUCED RISK*



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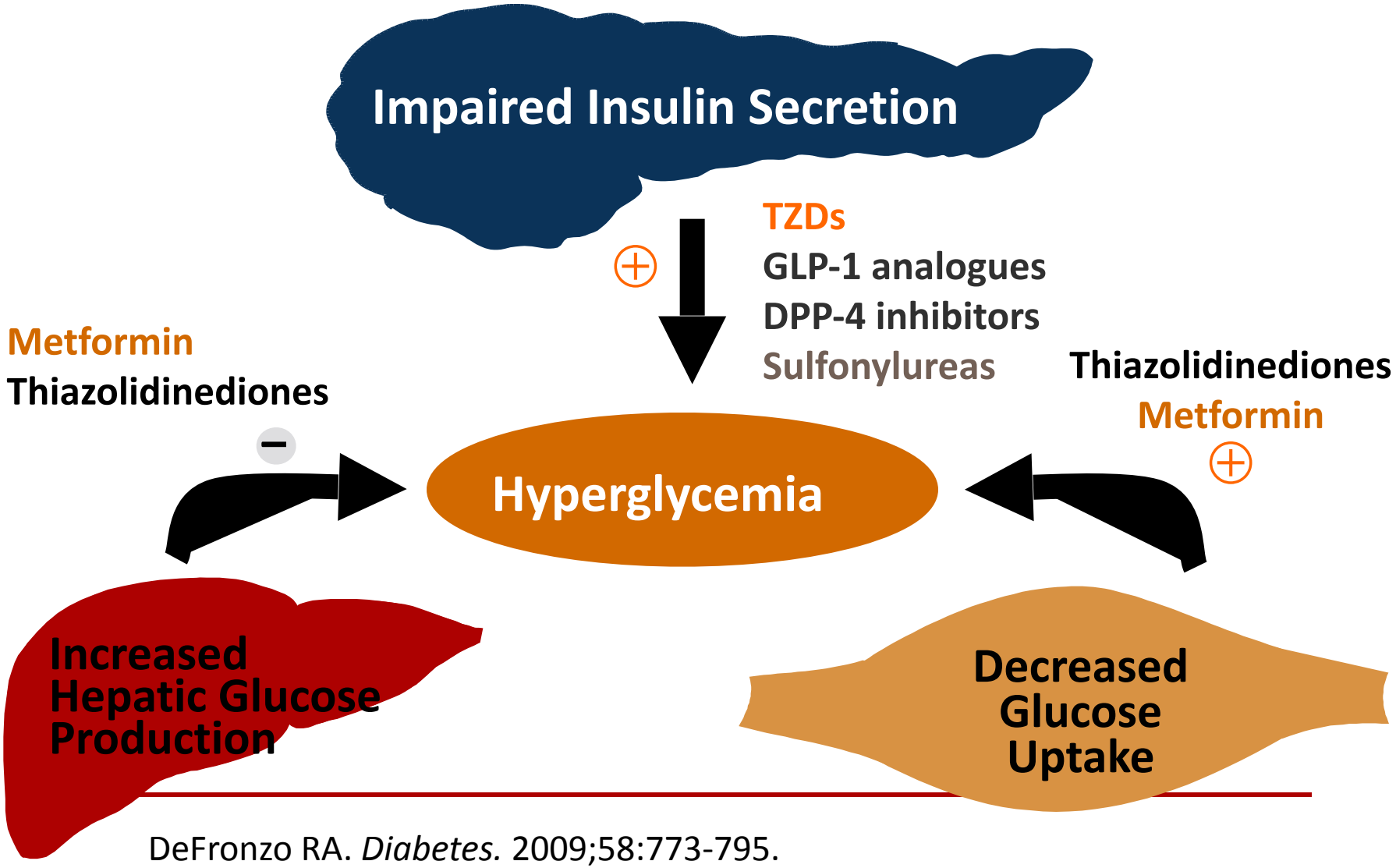
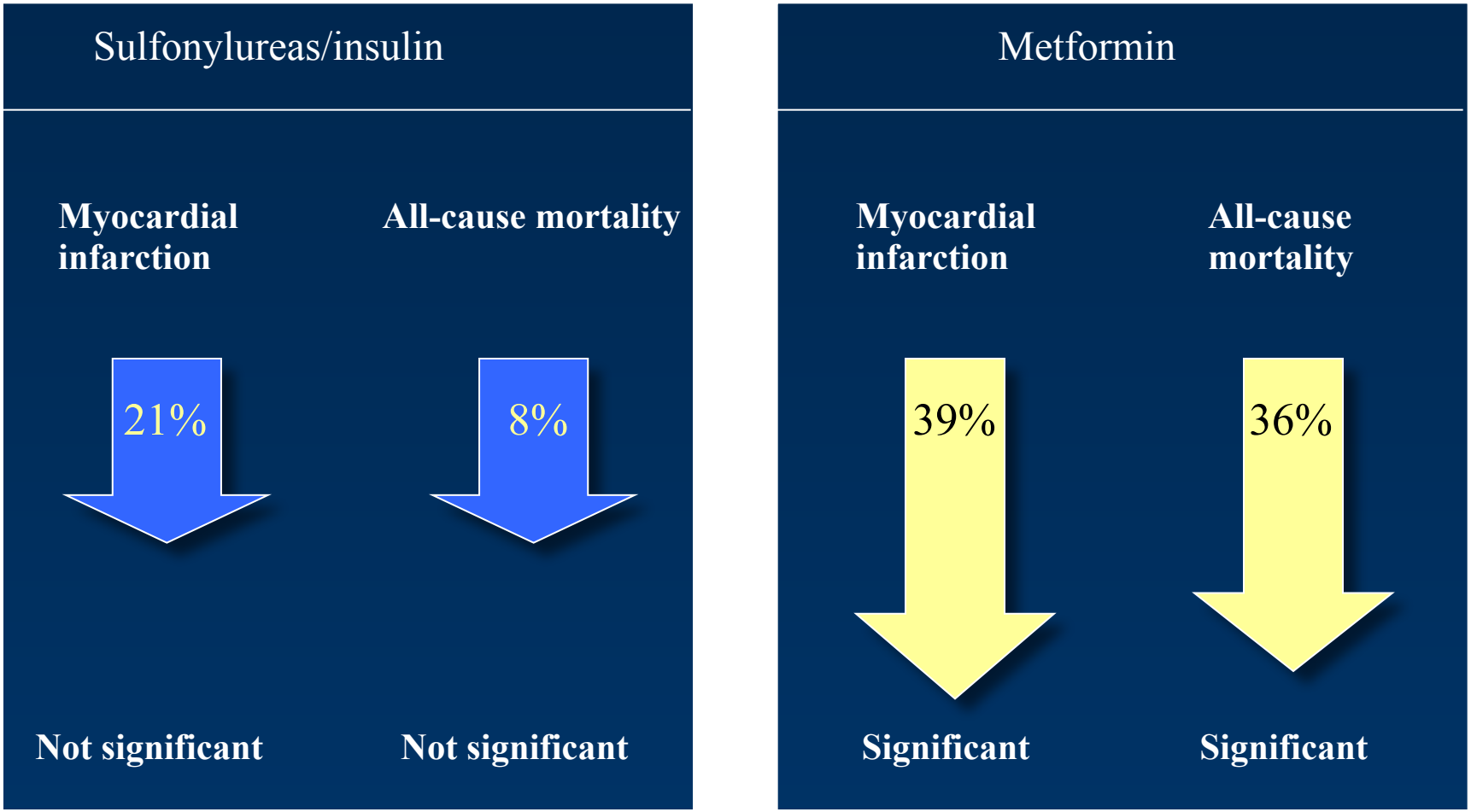
UKPDS 35. BMJ 2000; 321: 405-12

Pathophysiologic Approach to Treatment of T2DM

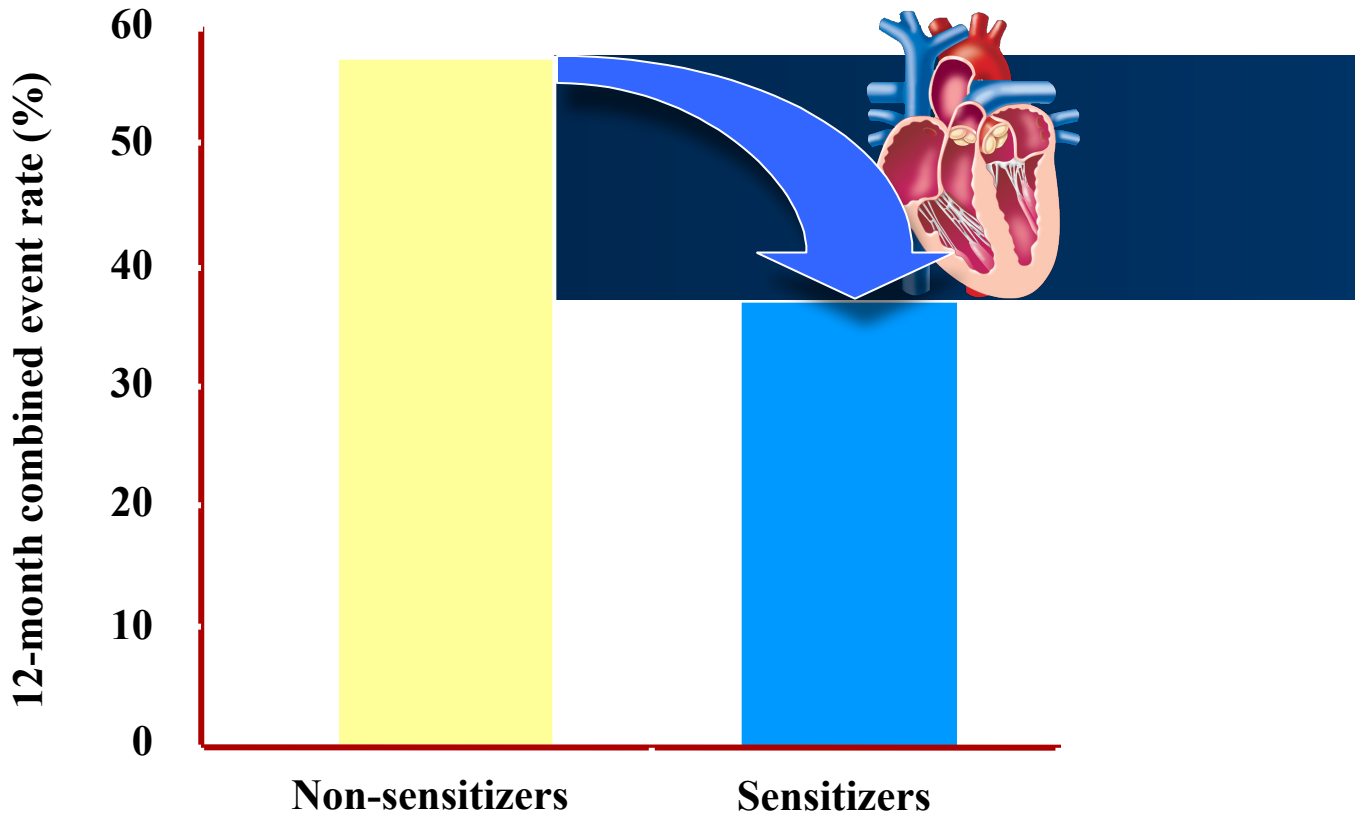


DeFronzo RA. *Diabetes.* 2009;58:773-795.

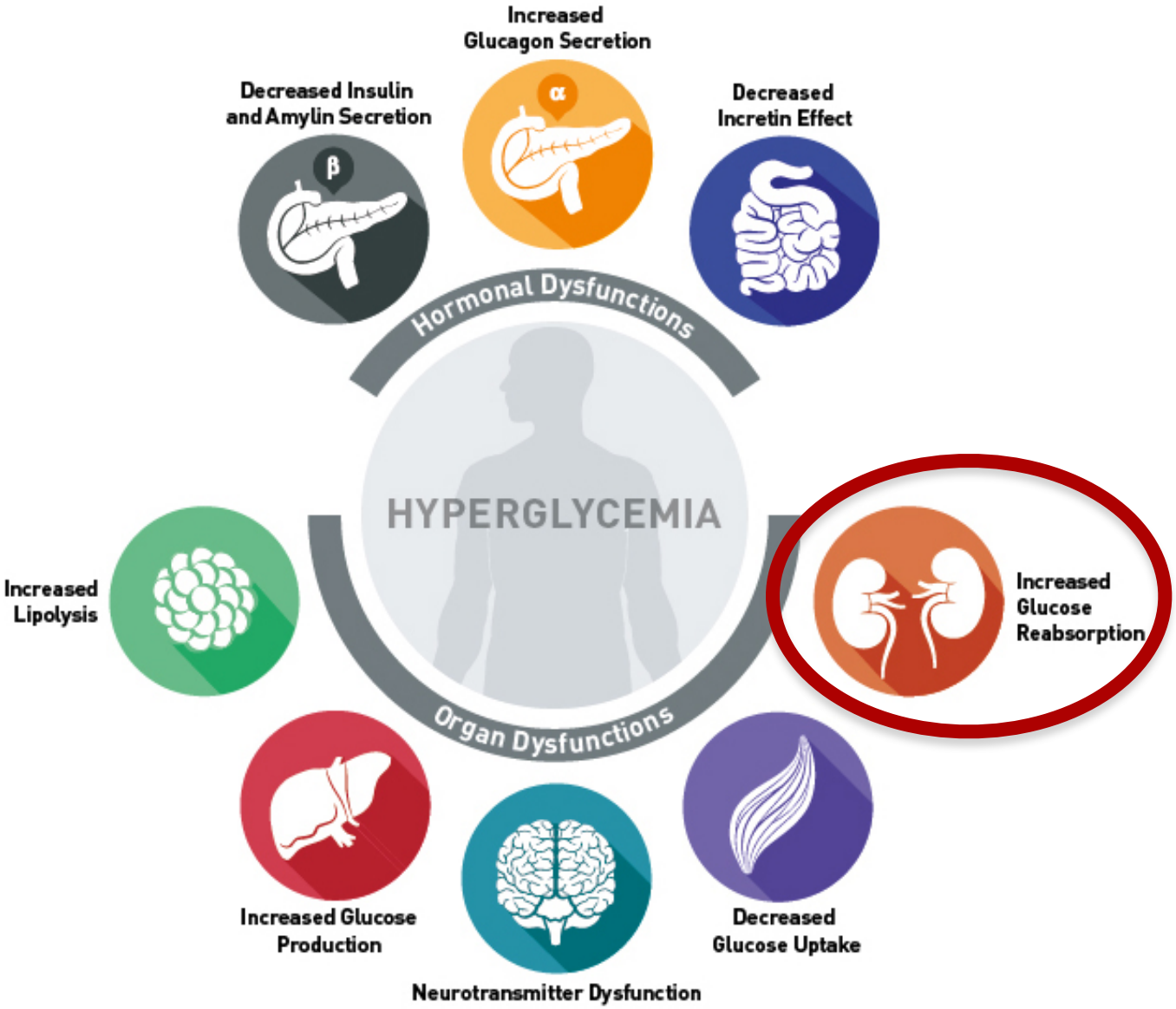
Does decreasing insulin resistance decrease macrovascular complications?



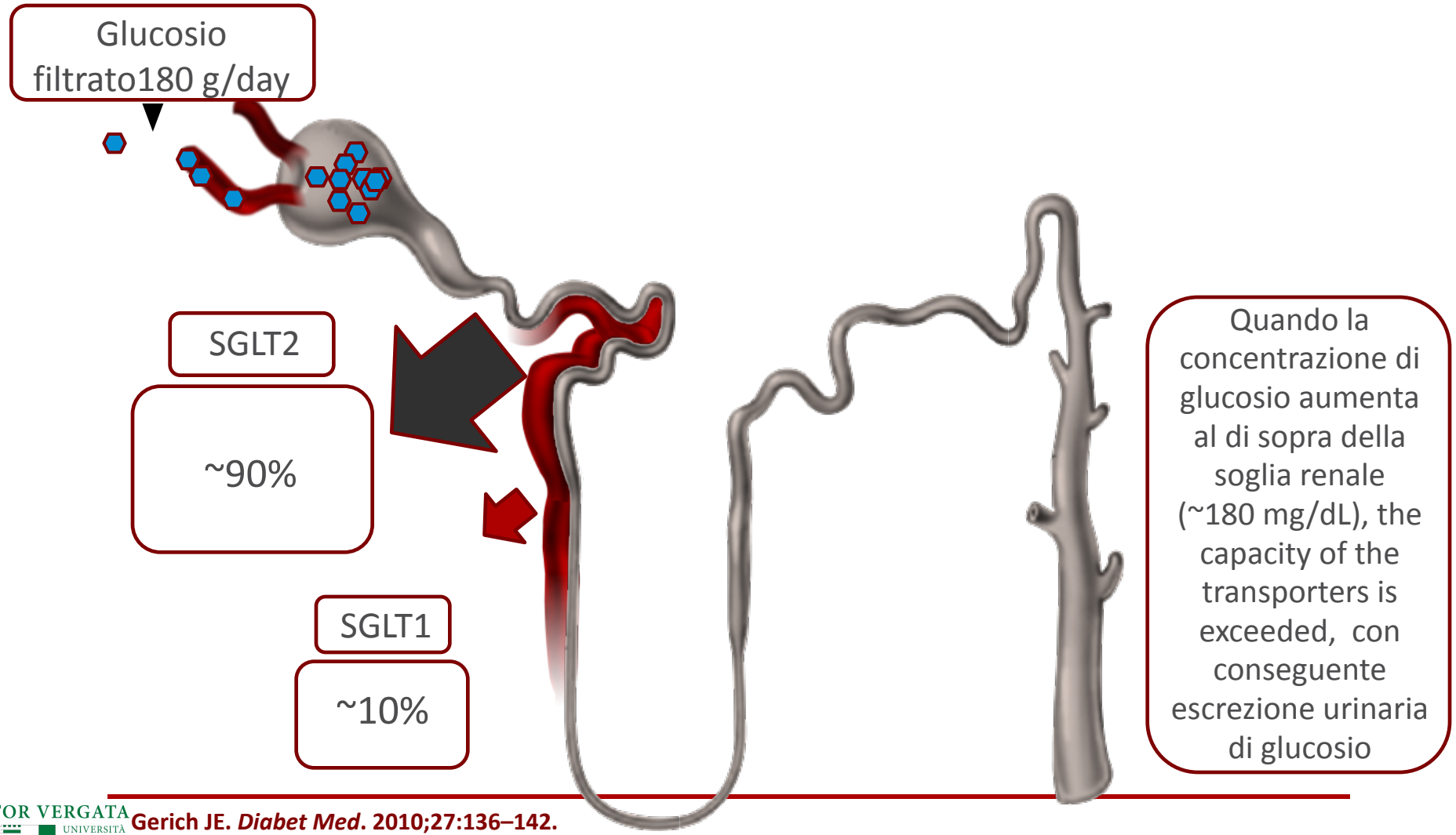
Insulin sensitizers reduce cardiovascular events in type 2 diabetes



Kao JA, *et al. J Am Coll Cardiol* 2004; 43:37A.

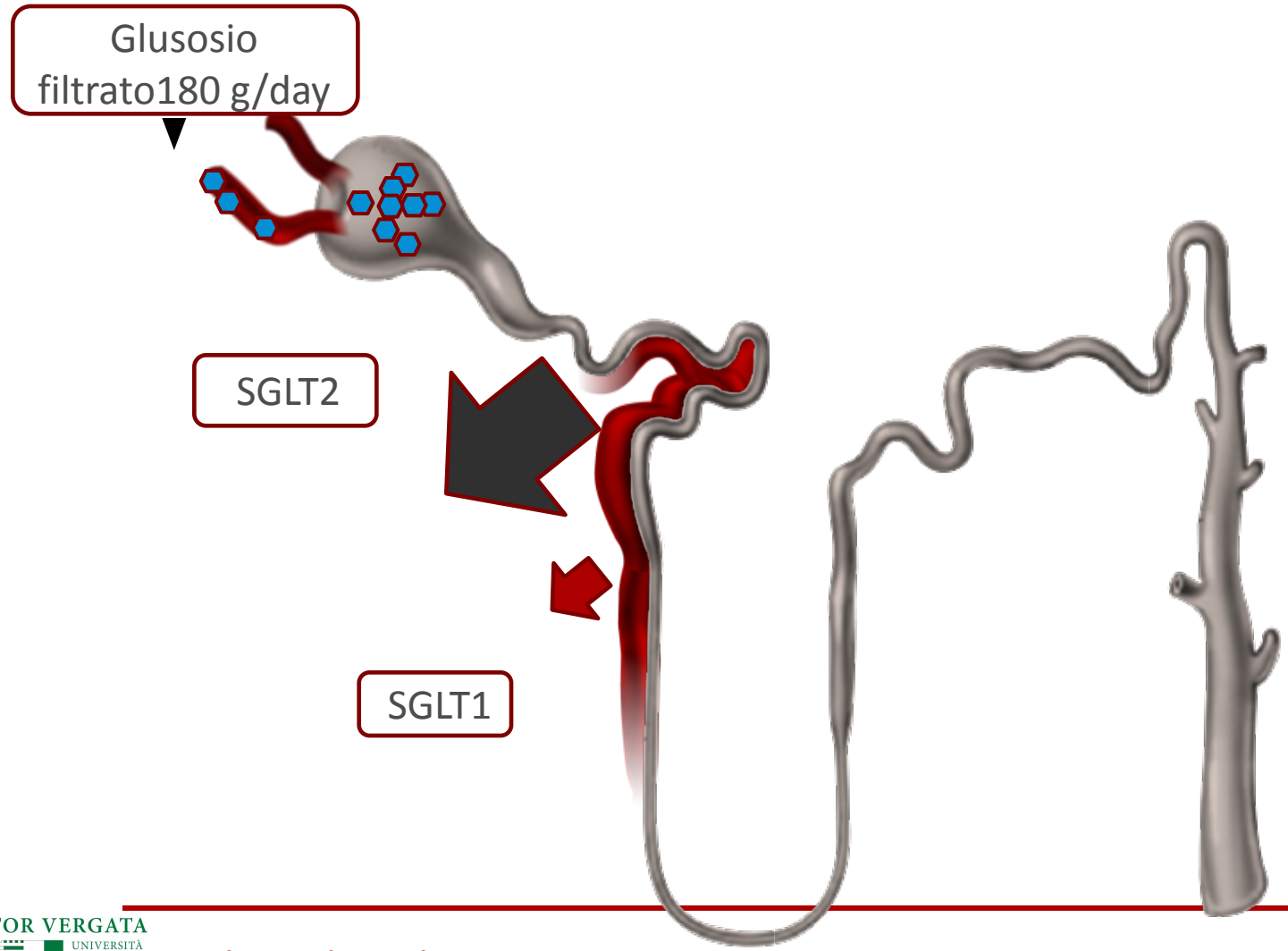


Riassrbomineto del glucosio a livello renale in pazienti con iperglicemia



Gerich JE. *Diabet Med*. 2010;27:136–142.

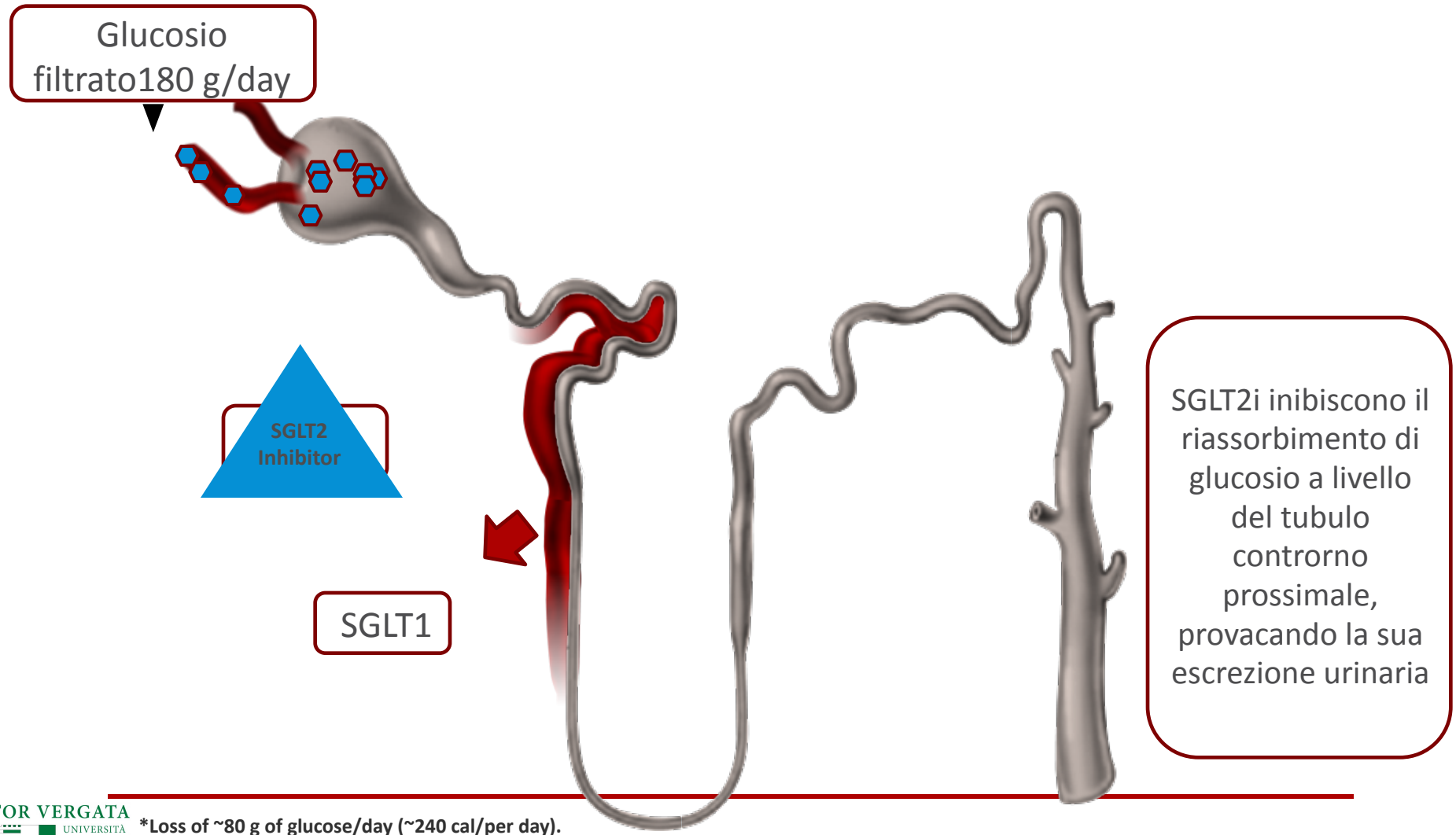
Upregulation del SGLT2 in pazienti diabetici con iperglicemia



Nel diabete di tipo 2, il SGLT2 è upregulated, incrementando cosi l'assorbimento di glucosio a livello del tubulo renale e diminuendo la sua escrezione urinaria

Gerich JE. *Diabet Med*. 2010;27:136–142.

Urinary glucose excretion via SGLT2 inhibition



*Loss of ~80 g of glucose/day (~240 cal/per day).

Gerich JE. *Diabet Med*. 2010;27:136–142.

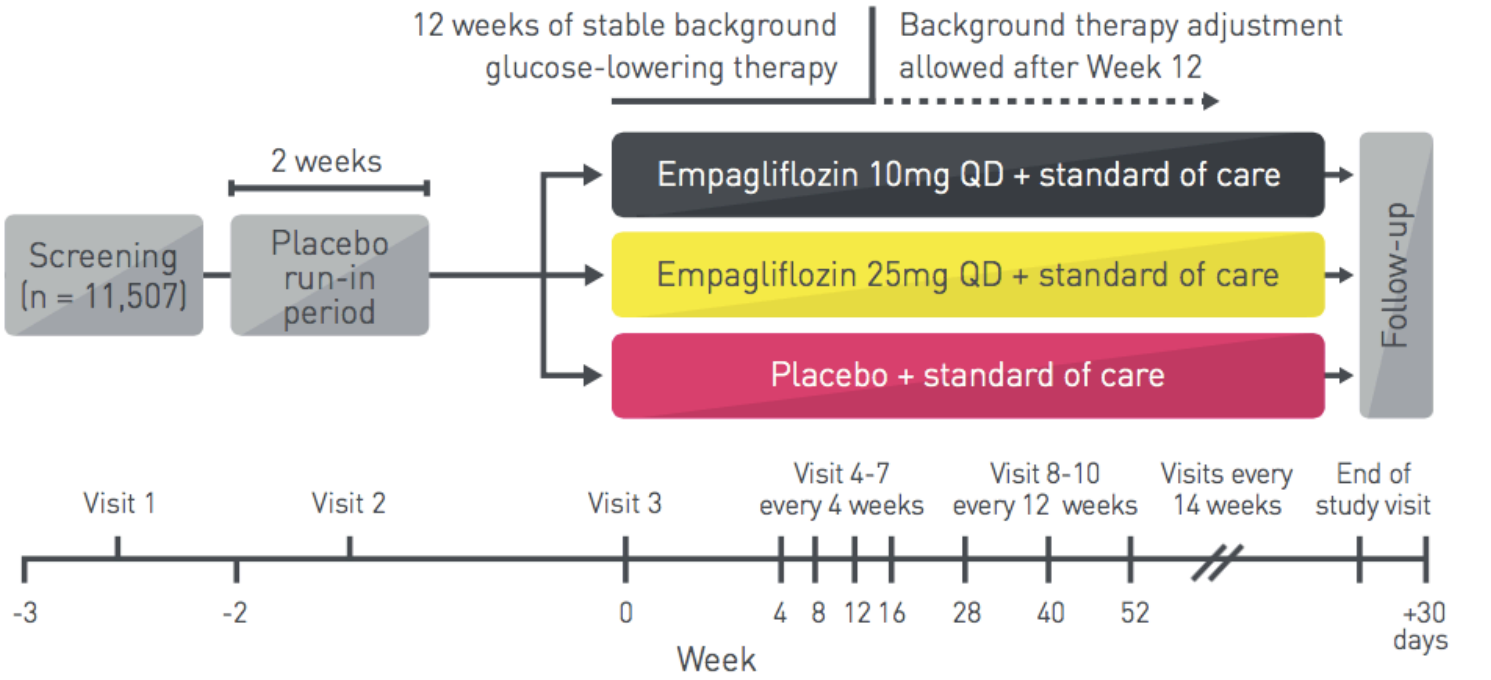
The NEW ENGLAND JOURNAL of MEDICINE

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

EMPA-REG OUTCOME® Trial Design

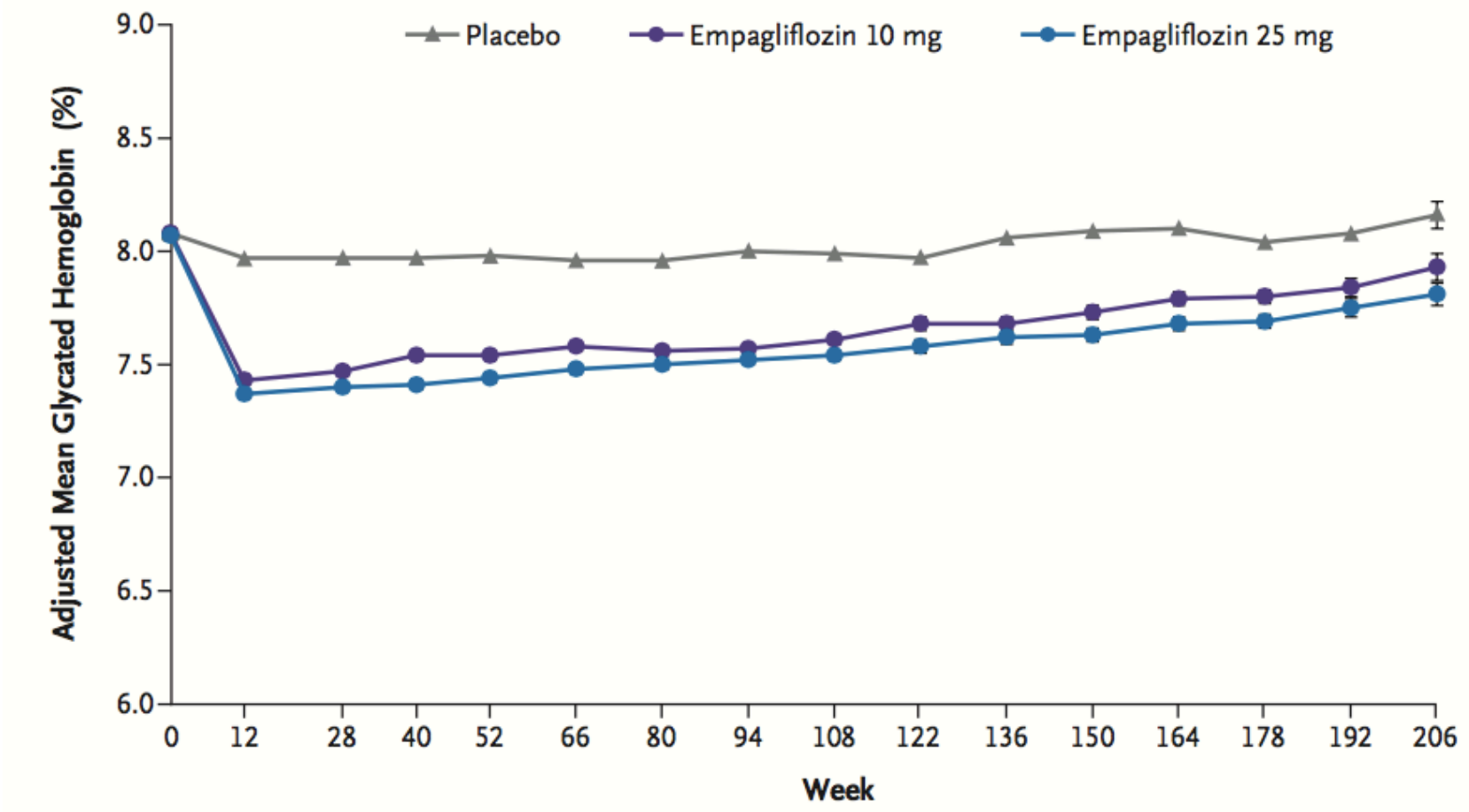


Key inclusion criteria[3]

- High risk of CV events due to previous CV event or established CVD
- Insufficient glycemic control

Zinman B et al, NEJM, 17 September 2015

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes



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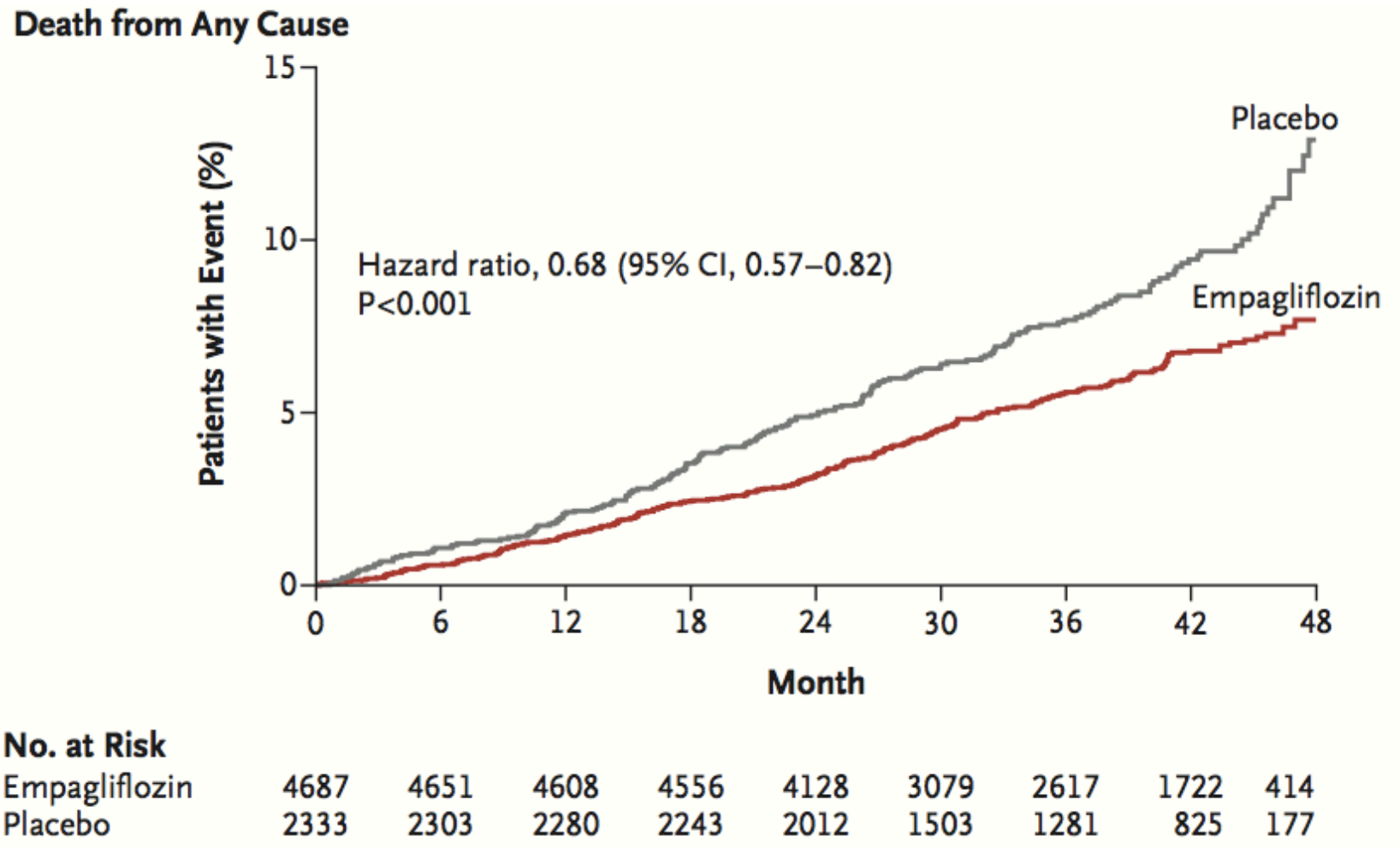

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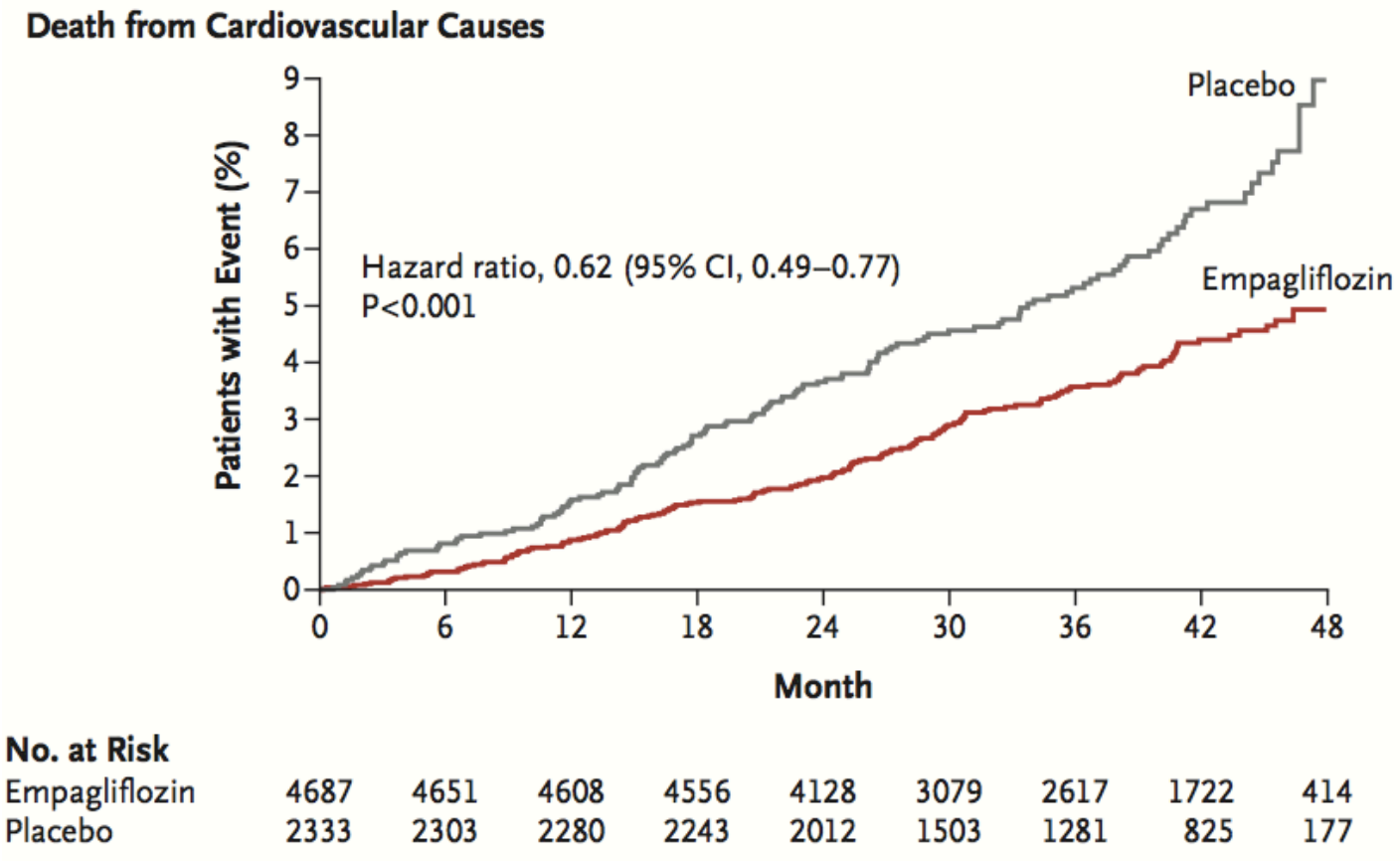
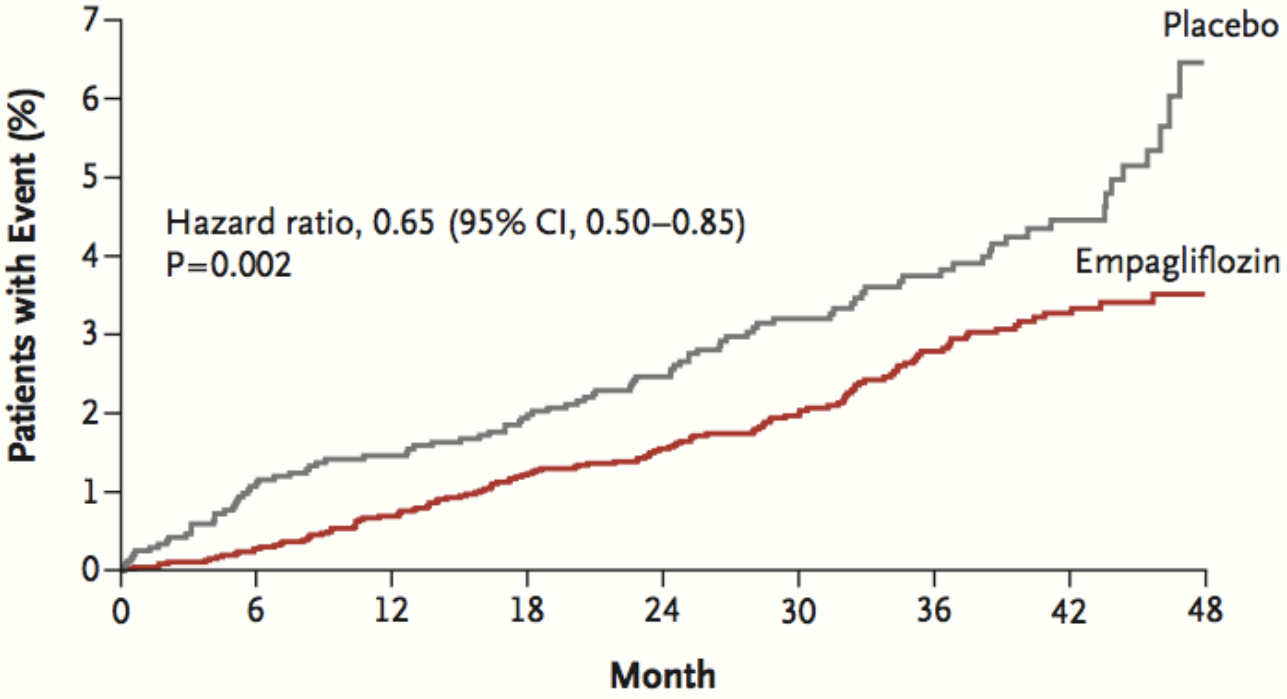


Zinman B et al, NEJM, 17 September 2015

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Hospitalization for Heart Failure



No. at Risk

Empagliflozin	4687	4614	4523	4427	3988	2950	2487	1634	395
Placebo	2333	2271	2226	2173	1932	1424	1202	775	168

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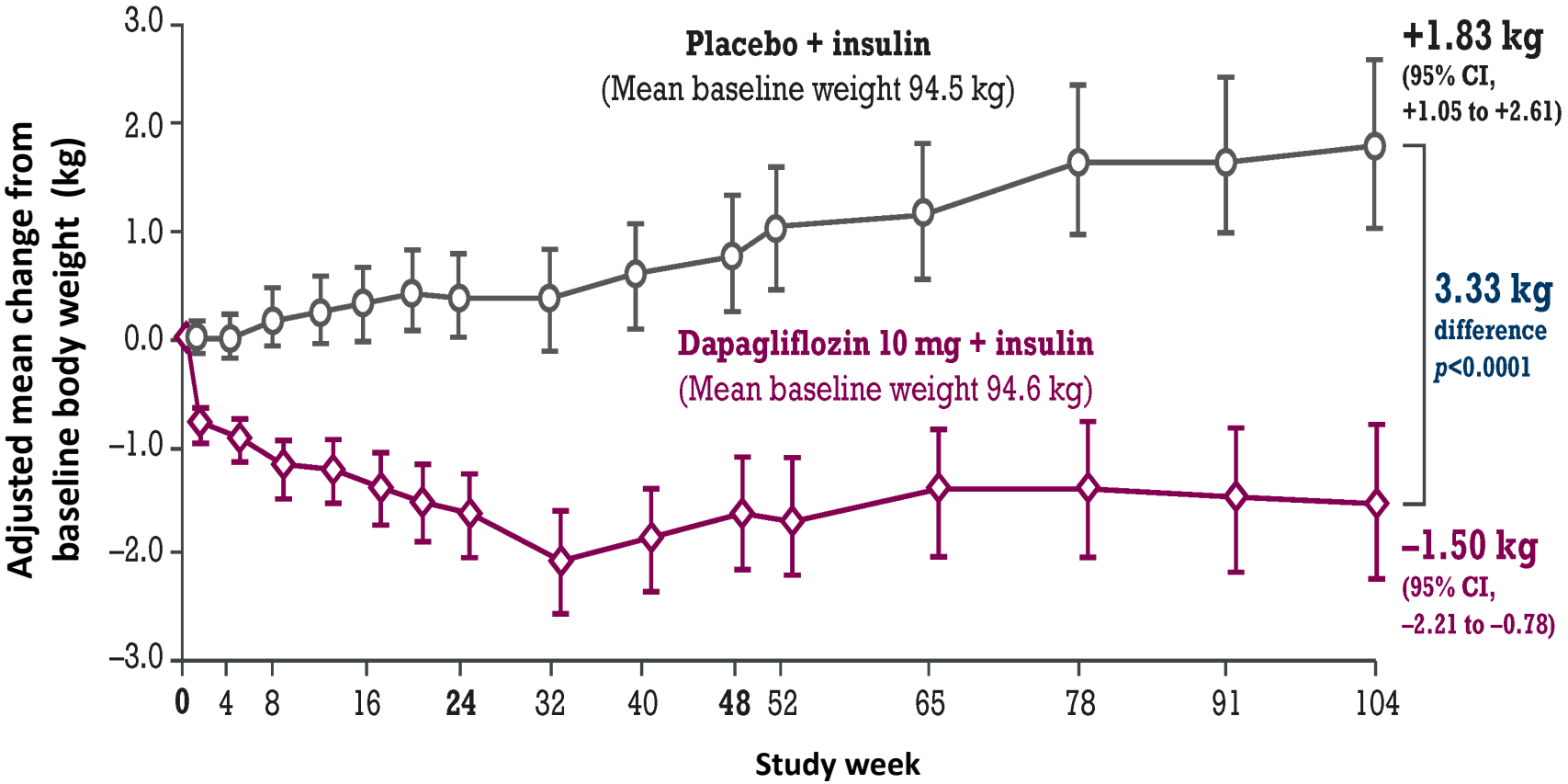
Zinman B et al, NEJM, 17 September 2015

Dapagliflozin in patients with type 2 diabetes receiving high doses of insulin: efficacy and safety over 2 years

J. P. H. Wilding[1], V. Woo[2], K. Rohwedder[3], J. Sugg[4] & S. Parikh[4] for the Dapagliflozin 006 Study Group[†]



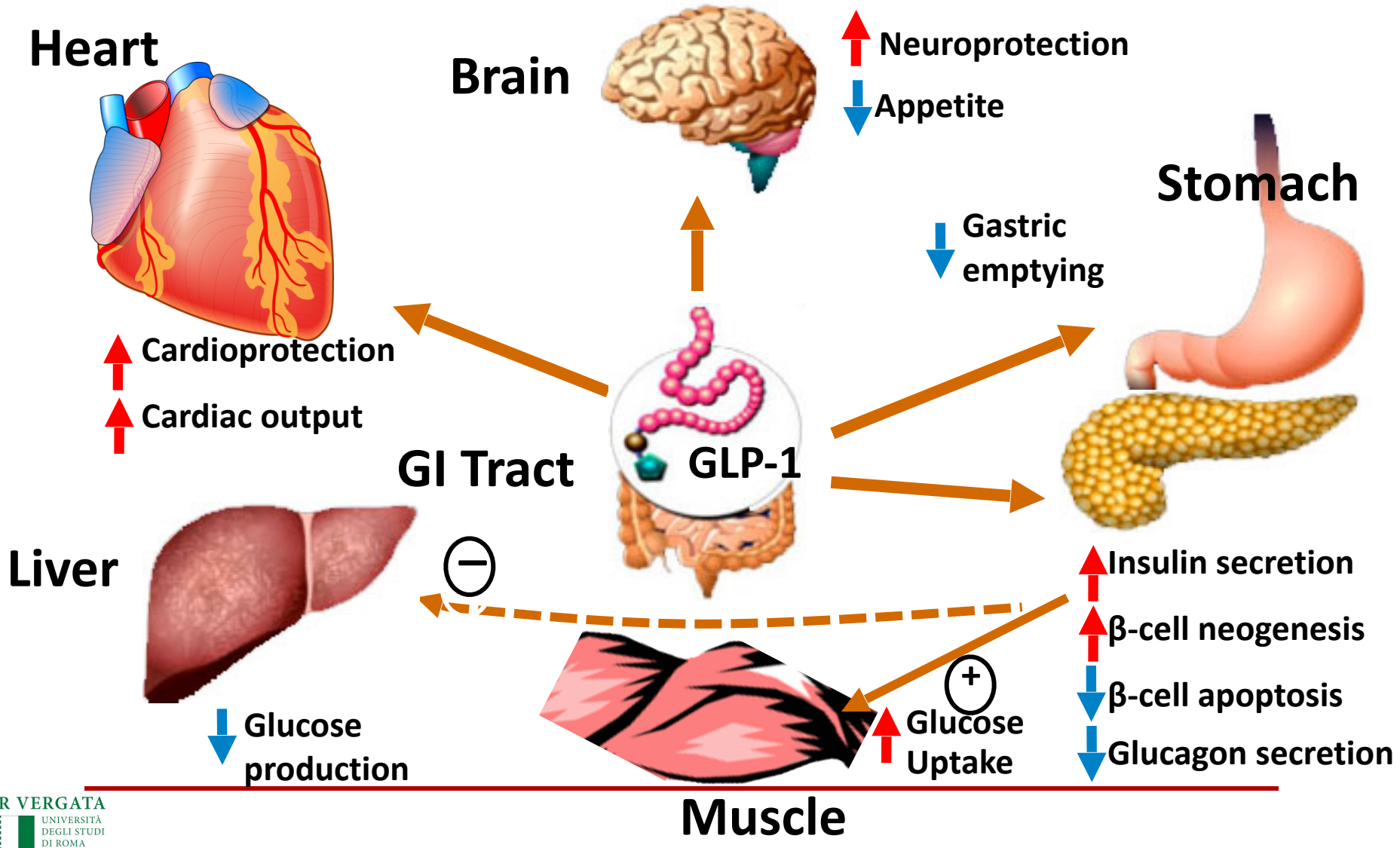
Wilding JP, *et al. Diabetes Obes Metab* 2014;16:124–136

GLP-1 Receptor Agonists

- First-in-class exenatide approved in 2005
- Augment insulin secretion
- Inhibit glucagon secretion
- Lower fasting glucose and improve postprandial glucose profile

Schnabel CA, et al. *Vasc Health Risk Manag*. 2006;2:69-77.

GLP-1 Actions in Peripheral Tissue



Drucker DJ. *Cell Metab*. 2006;3:153-165.

Side Effects: GLP-1 Receptor Agonists and DPP-4 Inhibitors

	GLP-1 Receptor Agonists	DPP-4 Inhibitors
Side effects	Gastrointestinal	Well tolerated
Weight	> 85% patients lose weight	Weight neutral
Administration	Once, twice-daily or weekly injection	Oral, once daily
Other cardiac risk factors	↓ Triglycerides ↑ HDL ↓ Blood pressure	Unknown

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Davidson JA. *Cleve Clin J Med*. 2009;76(suppl5):S28-S38.

Side Effects: Metformin and Thiazolidinediones

	Metformin	Thiazolidinediones
Side effects	Gastrointestinal	Fluid retention, congestive heart failure, bone fractures
Weight	Weight neutral	Weight gain
Renal impairment	Restricted > 1.4 mg/dL	

Seufert J, et al. *Clin Ther*. 2004;26:805-818.

How much exercise?

Exercises should be done according to FITT principle.

- **FREQUENCY:** Exercising 4 to 6 times a week.
- **INTENSITY:** 30-40 min of exercise at 50- 60 % of target heart rate.
- **TYPE:** SAFE exercises are recommended.
- **TIME:** Morning is ideal

Peripheral and autonomic neuropathy

Recommended:

- non-weight-bearing activities
- swimming
- bicycling
- chair and arm exercises

Contraindicated:

- treadmill
- prolonged walking
- jogging
- step exercises

Nephropathy

Recommended

- Low to moderate intensity forms of exercise

Contraindicated

- High intensity forms of exercise

Diabetic retinopathy

Recommended

- Low-impact cardiovascular conditioning, such as swimming, walking, low-impact aerobics, stationary cycling, endurance exercises

Contraindicated

- Strenuous activities, pounding or jarring, such as weight lifting, jogging, high-impact aerobics, racquet sports.

Summary

- Physical activity should be encouraged in all people with diabetes
- People need to be educated about prevention and treatment of hypoglycaemia
- People should be taught to plan for periods of physical activity

"Exercise is the best insulin sensitizer on the market; better than any medication we currently have available"