

15 novembre 2024

Lettura

Obesità e diabete
dalla fisiopatologia alla clinica

Salvatore Corrao

Dipartimento di Medicina Clinica
U.O.C. Medicina Interna

A.R.N.A.S. Civico - Di Cristina - Benfratelli
Palermo



Ai sensi dell'art. 4.5 su "Docenti e moderatori dell'evento", pag. 8 del Manuale Nazionale di Accreditamento per l'erogazione di eventi ECM del 06/12/2018, dichiaro che nell'ultimo biennio ho avuto fonti di finanziamento e rapporti con i seguenti soggetti portatori di interessi commerciali in ambito sanitario:

- Abbvie
- Amgen
- Astra Zeneca
- Eli Lilly
- Novo Nordisk
- Sanofi

Agenda

Obesità Malattia Cronica

Il Diabete Mellito e il Core Fisiopatologico

Approccio Terapeutico-Fisiopatologico

Riflessioni Conclusive

Obesity
is a chronic, relapsing, progressive disease process...
...progressive multifactorial process

Modified from a position statement of the World Obesity Federation 2017

WHO Classification

Body mass index (kg/m ²)	Class	Body mass index (kg/m ²)	Class
25–29.9	Overweight	25–29.9	Overweight
30–34.9	Class I obesity	≥30	Obese
35–39.9	Class II obesity	35–39.9	Severe obesity
≥40	Class III obesity	40–49.9	Morbid obesity
		≥50	Super obesity

Curr Atheroscler Rep (2014) 16:409

DOI 10.1007/s11883-014-0409-1

CARDIOVASCULAR DISEASE AND STROKE (P PERRONE-FILARDI AND S. AGEWALL, SECTION EDITORS)

Adiposopathy, “Sick Fat,” Ockham’s Razor, and Resolution of the Obesity Paradox

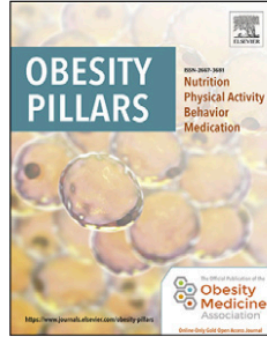
Harold Bays



Contents lists available at [ScienceDirect](#)

Obesity Pillars

journal homepage: www.journals.elsevier.com/obesity-pillars



Review

Obesity definition, diagnosis, bias, standard operating procedures (SOPs), and telehealth: An Obesity Medicine Association (OMA) Clinical Practice Statement (CPS) 2022

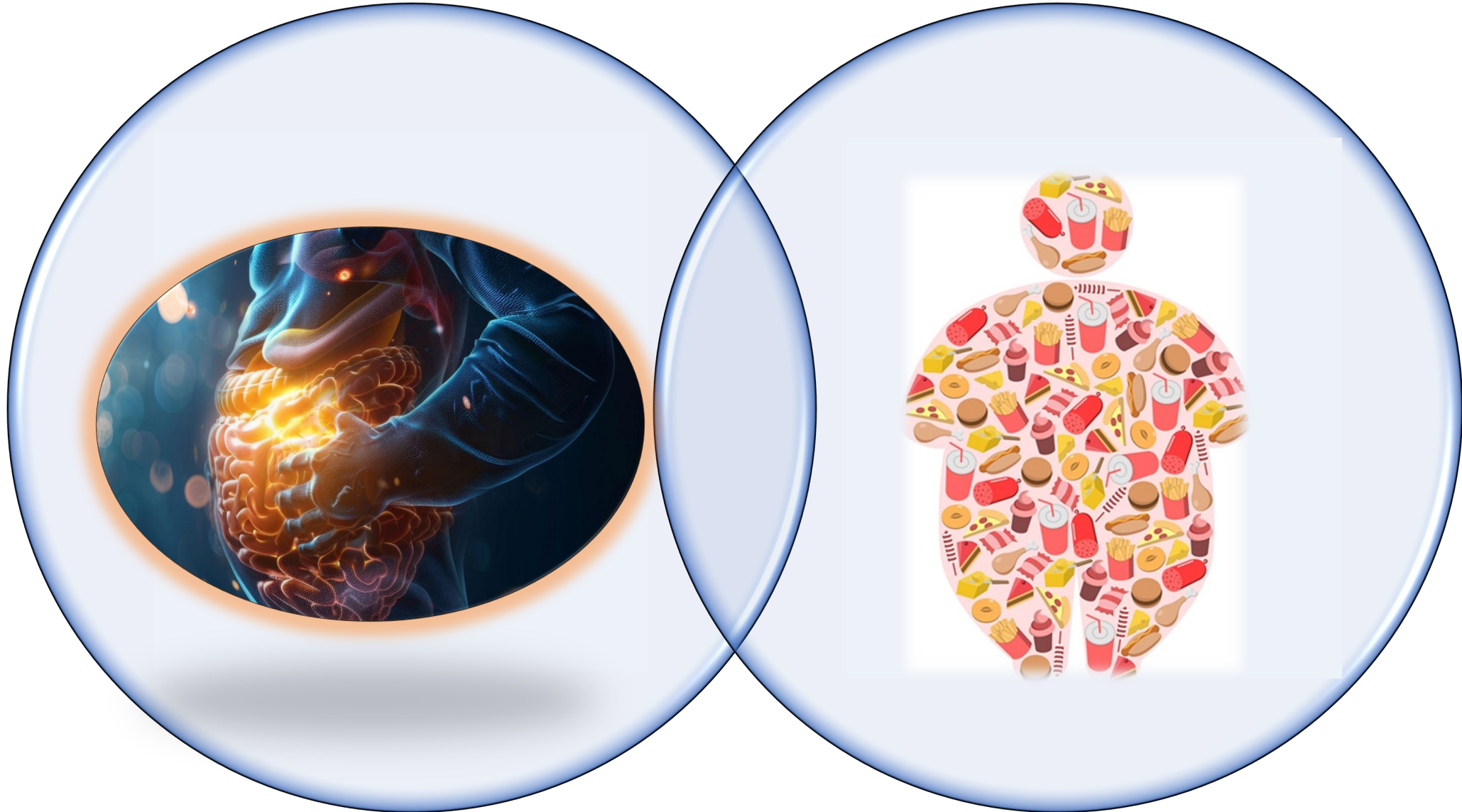


Angela K. Fitch^a, Harold E. Bays^{b,*}

^a Massachusetts General Hospital Weight Center, Harvard Medical School, 50 Staniford Street Suite 430, Boston, MA, 02114, USA

^b Louisville Metabolic and Atherosclerosis Research Center, University of Louisville School of Medicine, 3288 Illinois Avenue, Louisville, KY, 40213, USA

Metabolic and Fat Complications of Obesity



FRANCO CRISTALDI PRESENTA

FEDERICO FELLINI

AMARCORD



SOGGETTO E
SCENEGGIATURA DI

FEDERICO FELLINI

UNA COPRODUZIONE ITALO-FRANCESE

F.C. (ROMA) P.E.C.F. (PARIGI)

E

TONINO GUERRA

PRODOTTO DA

FRANCO CRISTALDI

IL LIBRO OMONIMO È
EDITO IN ITALIA DA

RIZZOLI

REGIA DI

FEDERICO FELLINI

TECHNICOLOR[®]

UNA ESCLUSIVITA' P.I.C. 

Salerno L, Corrao S, Curiale B, Salvato F, Salli L. [Different prevalence of some indices of cardiac and vascular impairment in normal weight and obese patients with essential arterial hypertension]. **Minerva Cardioangiol.** 1989

Licata G, Corrao S, Parrinello G, Scaglione R. Obesity and cardiovascular diseases. **Ann Ital Med Int.** 1994

Merlino G, Scaglione R, Paterna S, Corrao S, Parrinello G, Licata A, D'Amico C, Ganguzza A, Licata G. Lymphocyte beta-adrenergic receptors in young subjects with peripheral or central obesity: relationship with central haemodynamics and left ventricular function. **Eur Heart J.** 1994

Parrinello G, Merlino G, Dichiara MA, Arnone S, D'Aubert MD, Licata G. Central obesity and hypertension: pathophysiologic role of renal haemodynamics and function. **Int J Obes Relat Metab Disord.** 1995

Ganguzza A, Corrao S, Arnone S, Di Chiara T. Hemostatic function in young subjects with central obesity: relationship with left ventricular function. **Metabolism.** 1995

Licata G, Scaglione R, Avellone G, Parrinello G, Merlino G, Corrao S. Obesity, hypertension and atherosclerosis. **Int Angiol.** 1993

Licata G, Scaglione R, Ganguzza A, Corrao S, Donatelli M, Parrinello G, Dichiara MA, Merlino G, Cecala MG. Central obesity and hypertension. Relationship between fasting serum insulin, plasma renin activity, and diastolic blood pressure in young obese subjects. **Am J Hypertens.** 1994

Merlino G, Scaglione R, Corrao S, D'Amico C, Paterna S, Licata A, Parrinello G, Ganguzza A, Licata G. Association between reduced lymphocyte beta-adrenergic receptors and left ventricular dysfunction in young obese subjects. **Int J Obes Relat Metab Disord.** 1994

Licata G, Scaglione R, Corrao S, Ganguzza A, Mazzola G, Arnone S, Dichiara MA, Licata A, Merlino G, Di Chiara T. Heredity and obesity-associated hypertension: impact of hormonal characteristics and left ventricular mass. **J Hypertens.** 1995

Parrinello G, Scaglione R, Pinto A, Corrao S, Cecala M, Di Silvestre G, Amato P, Licata A, Licata G. Central obesity and hypertension: the role of plasma endothelin. **Am J Hypertens.** 1996

Scaglione R, Parrinello G, Corrao S, Ganguzza A, Di Chiara T, Arnone S, Mazzola G, Matita MC, D'Aubert MD, Licata G. Prevalence of obesity and ischaemic heart disease in hypertensive subjects. **Eur Rev Med Pharmacol Sci.** 1997

Corrao S, Arnone S, Scaglione R, Amato V, Amico G, Licata A, Licata G. Effects of a short-term hypoenergetic diet on morphofunctional left ventricular parameters in centrally obese subjects. An echocardiographic study. **Panminerva Med.** 2000

Scaglione R, Argano C, di Chiara T, Colomba D, Parrinello G, Corrao S, Avellone G, Licata G. Central obesity and hypertensive renal disease: association between higher levels of BMI, circulating transforming growth factor beta1 and urinary albumin excretion. **Blood Press.** 2003

Di Chiara T, Licata A, Argano C, Duro G, Corrao S, Scaglione R. Plasma adiponectin: a contributing factor for cardiac changes in visceral obesity-associated hypertension. **Blood Press.** 2014

Chiara TD, Argano C, Scaglione A, Corrao S, Pinto A, Scaglione R. Circulating adiponectin: a cardiometabolic marker associated with global cardiovascular risk. **Acta Cardiol.** 2015

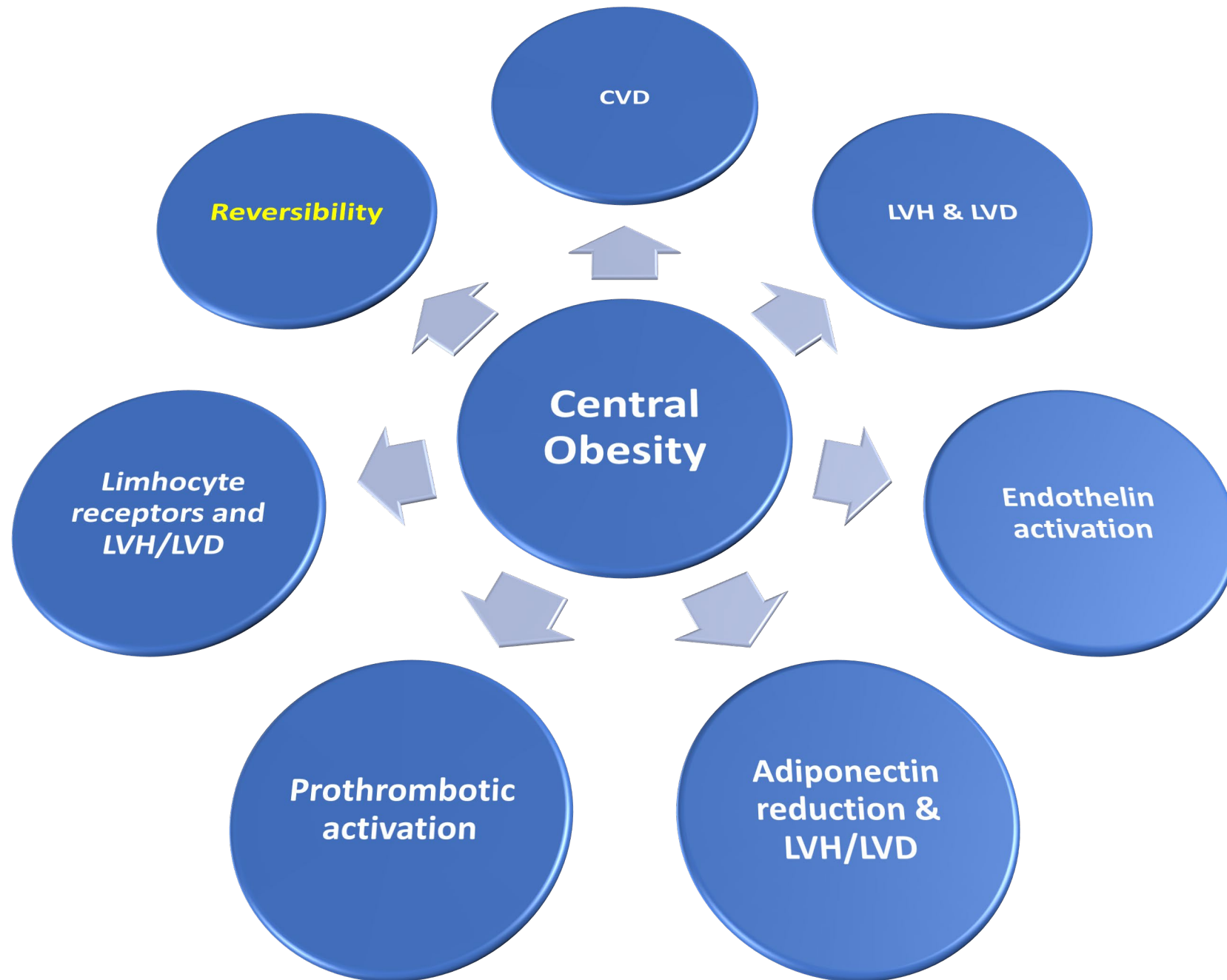
Licata G, Corrao S, Ganguzza A, Pinto A, Arnone S, Di Chiara T, Licata A, Salerno L, Scaglione R. Micro-albuminuria in obese subjects: relationship among body fat distribution, blood pressure and left ventricular structure and function. **Blood Press Monit.** 1998

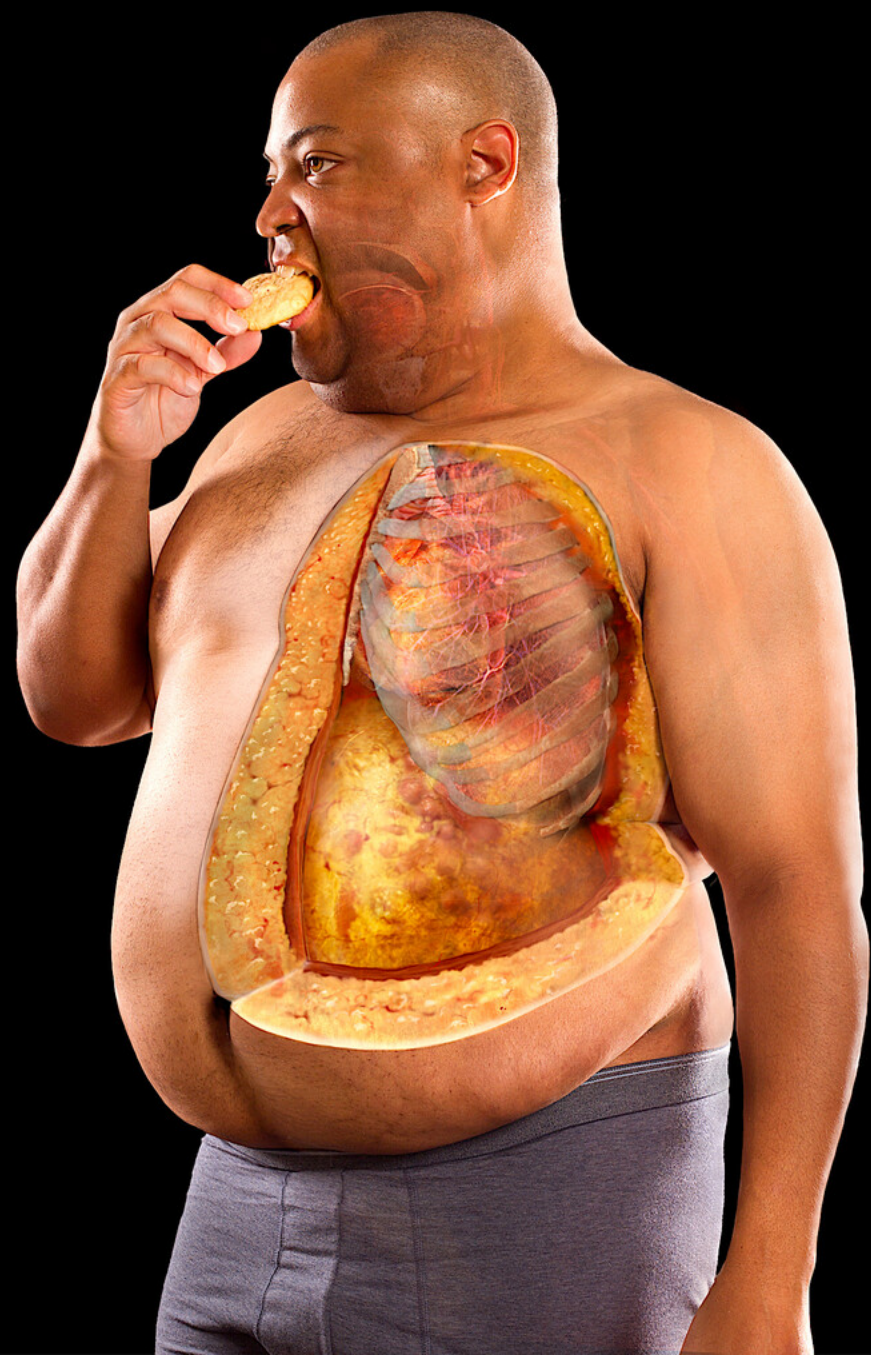
Argano C, Pinto A, Parrinello G, Corrao S, Duro G, Scaglione R. Relationship between circulating E-selectin, DD genotype of angiotensin-converting-enzyme, and cardiovascular damage in central obese subjects. **Metabolism.** 2003

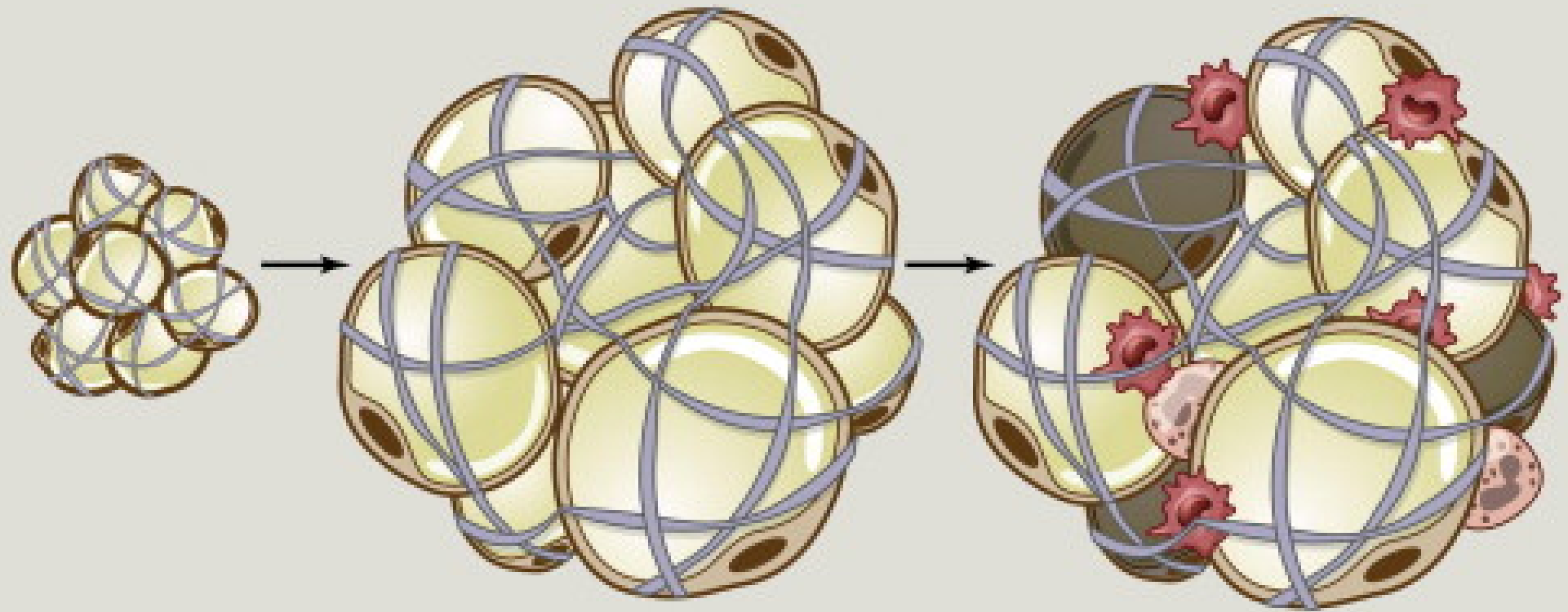
Parrinello G, Licata A, Colomba D, Di Chiara T, Argano C, Bologna P, Corrao S, Avellone G, Scaglione R, Licata G. Left ventricular filling abnormalities and obesity-associated hypertension: relationship with overproduction of circulating transforming growth factor beta1. **J Hum Hypertens.** 2005

Di Chiara T, Argano C, Scaglione A, Duro G, Corrao S, Scaglione R, Licata G. Hypoadiponectinemia, cardiometabolic comorbidities and left ventricular hypertrophy. **Intern Emerg Med.** 2015

Lo Coco D, Lopez G, Corrao S. Cognitive impairment and stroke in elderly patients. **Vasc Health Risk Manag.** 2016







Hypertrophy

Adipocyte death
Hypoxia
Inflammation
Insulin resistance



Adipocyte

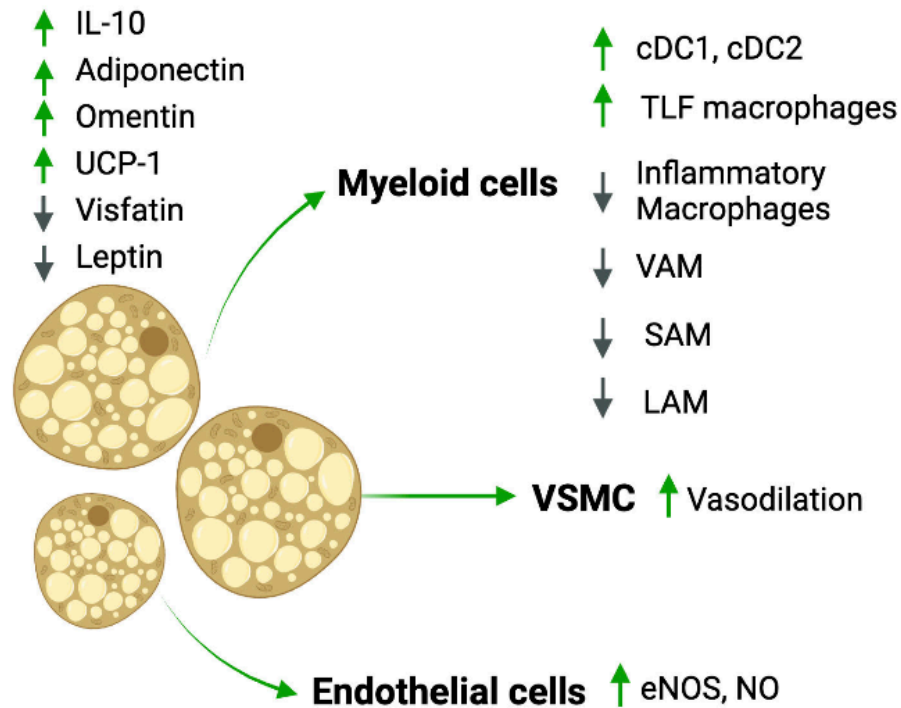


Macrophages, other inflammatory immune cells

Fat and inflammation: adipocyte-myeloid cell crosstalk in atherosclerosis

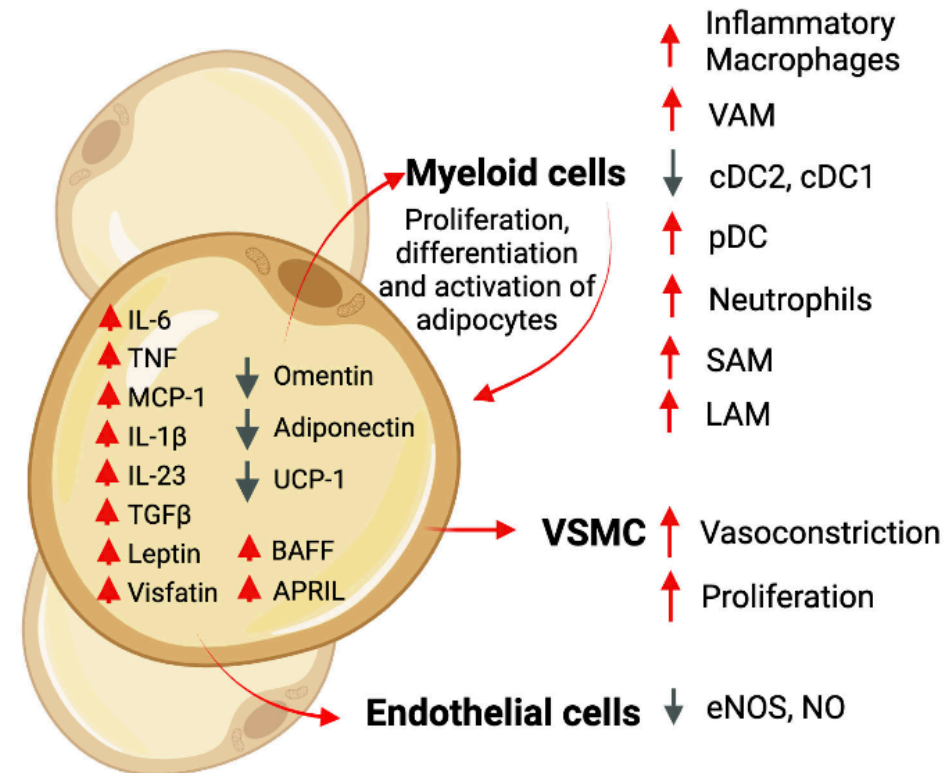
A

Healthy PVAT

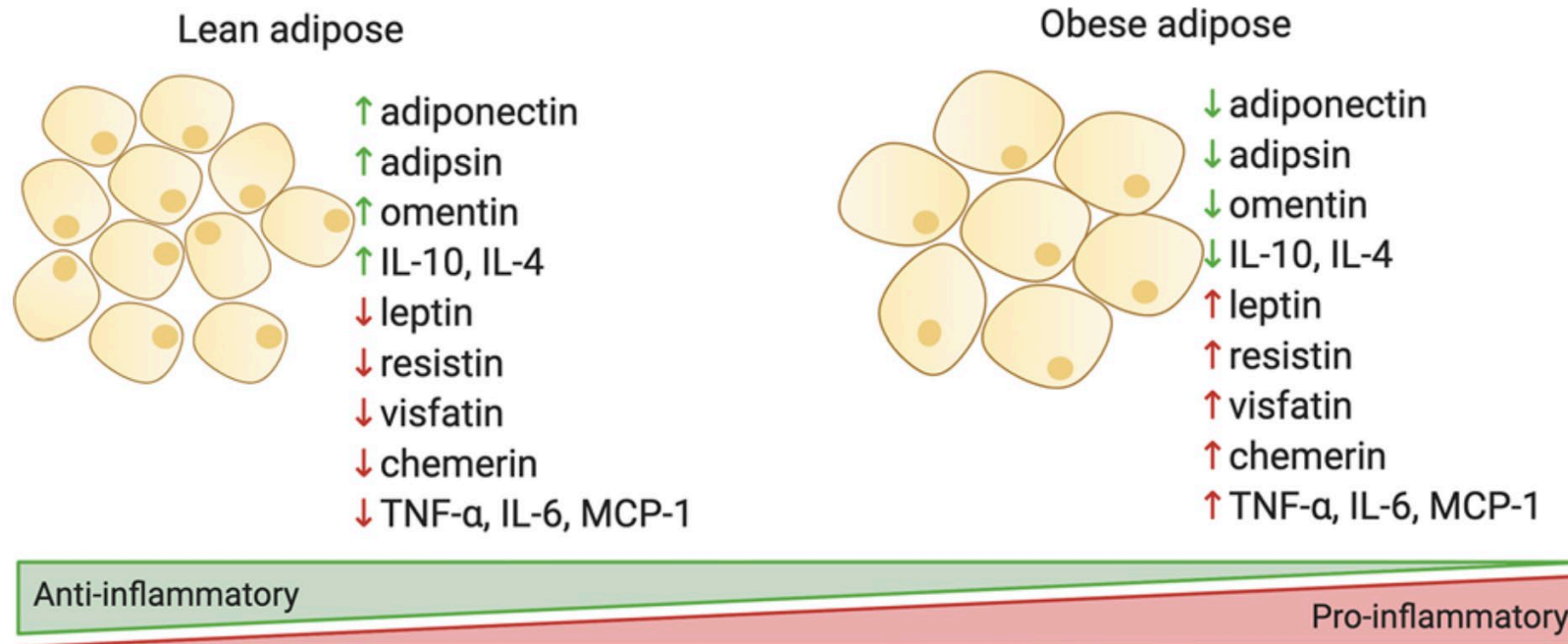


B

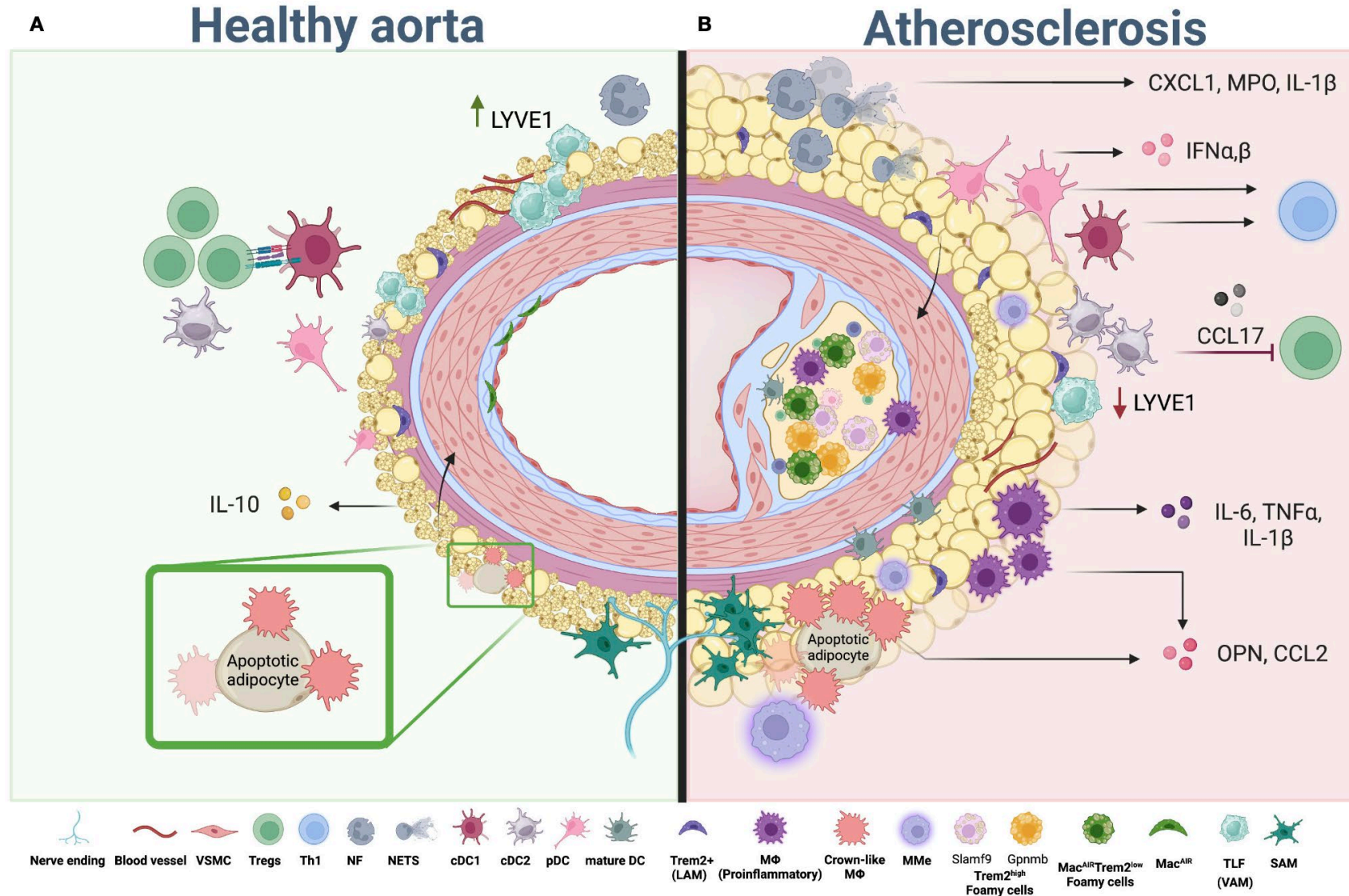
PVAT in Atherosclerosis

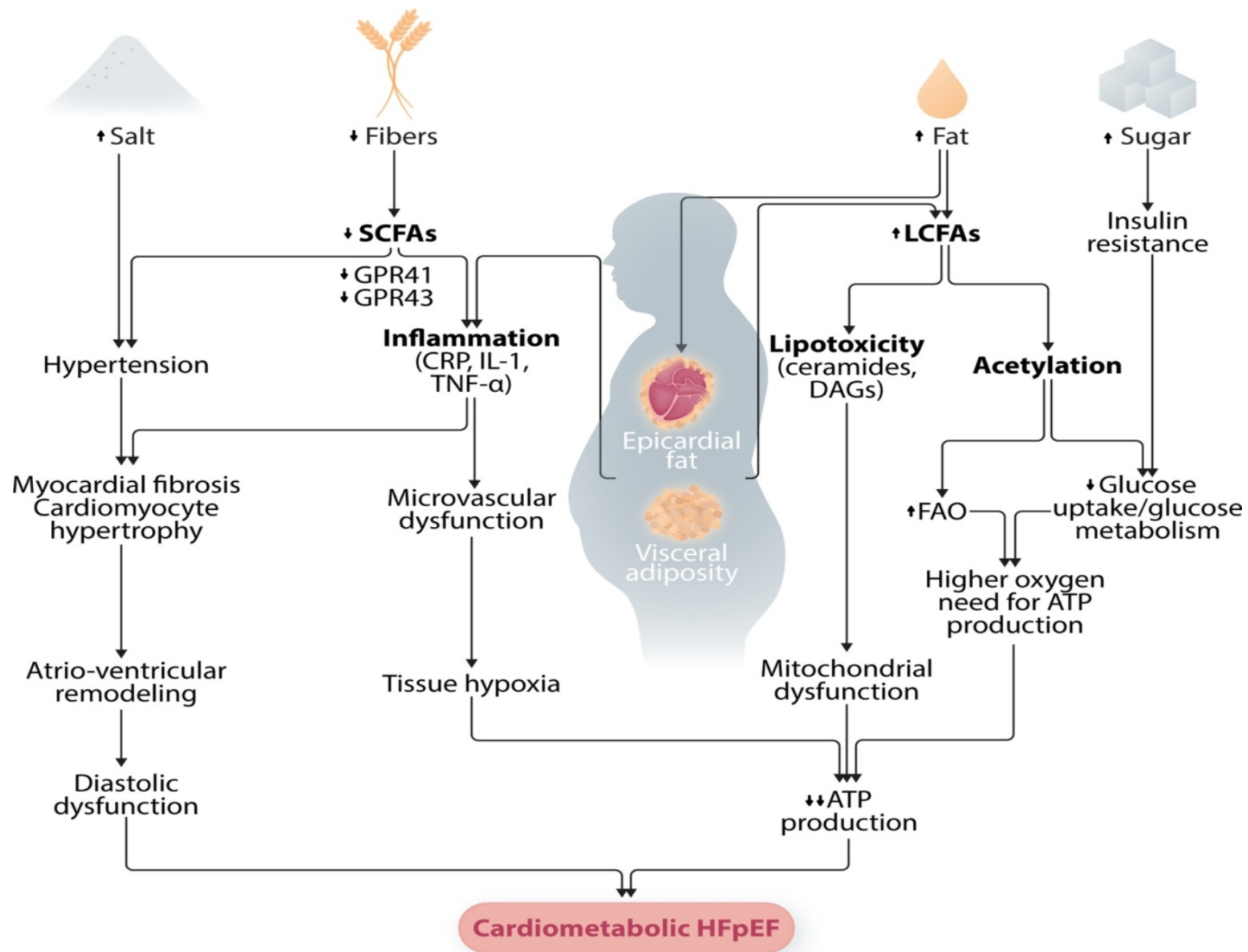


Adipokines in lean and obese states



Fat and inflammation: adipocyte-myeloid cell crosstalk in atherosclerosis





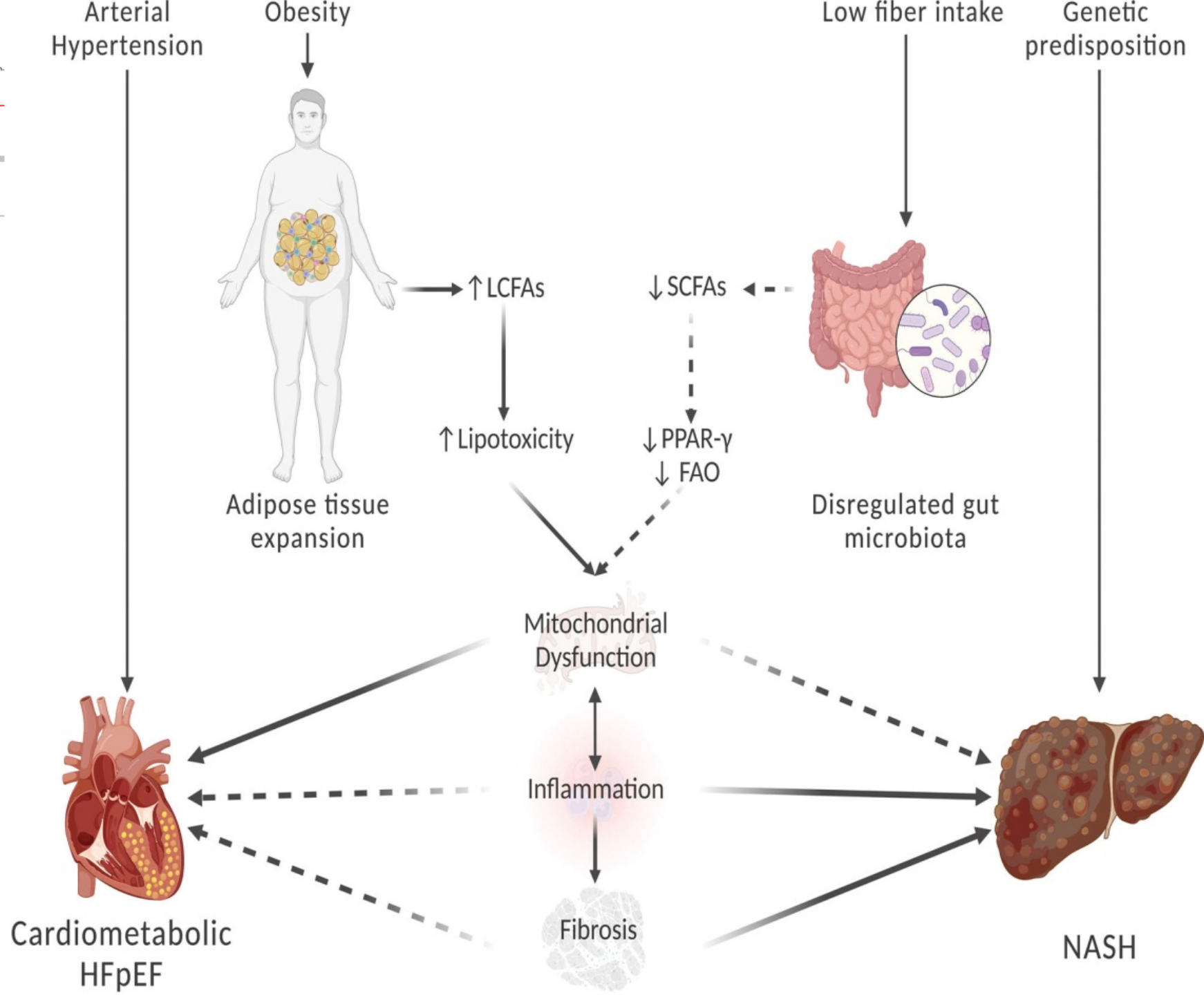


ON MY MIND

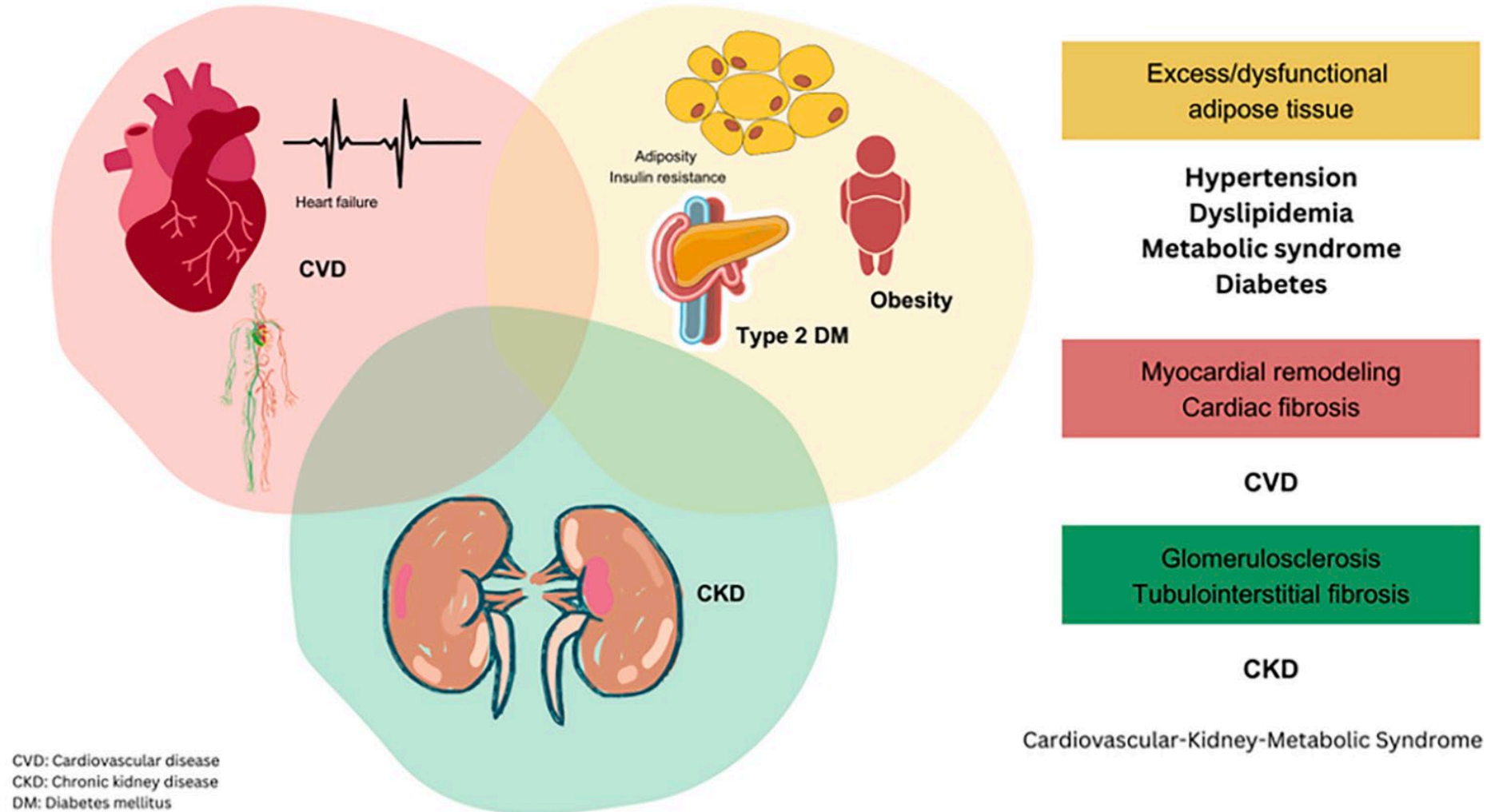
Cardiometabolic HFpEF: NASH of the Heart

Federico Capone, MD, Roberto Vettor, MD, and Gabriele G. Schiattarella, MD, PhD

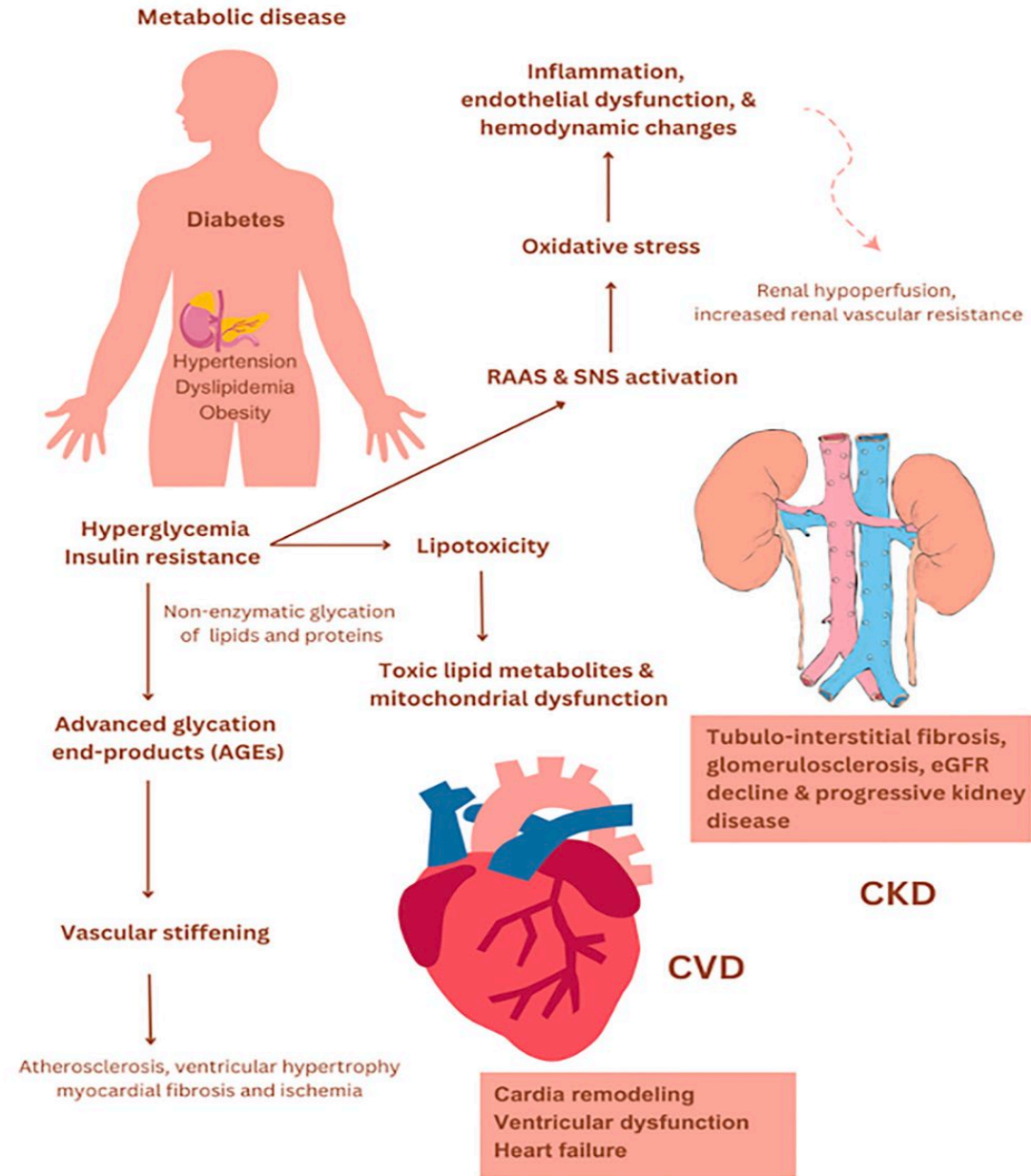
Heart Failure With Preserved Ejection Fraction: Time To Change Perspective?



Cardiovascular-Kidney-Metabolic Syndrome

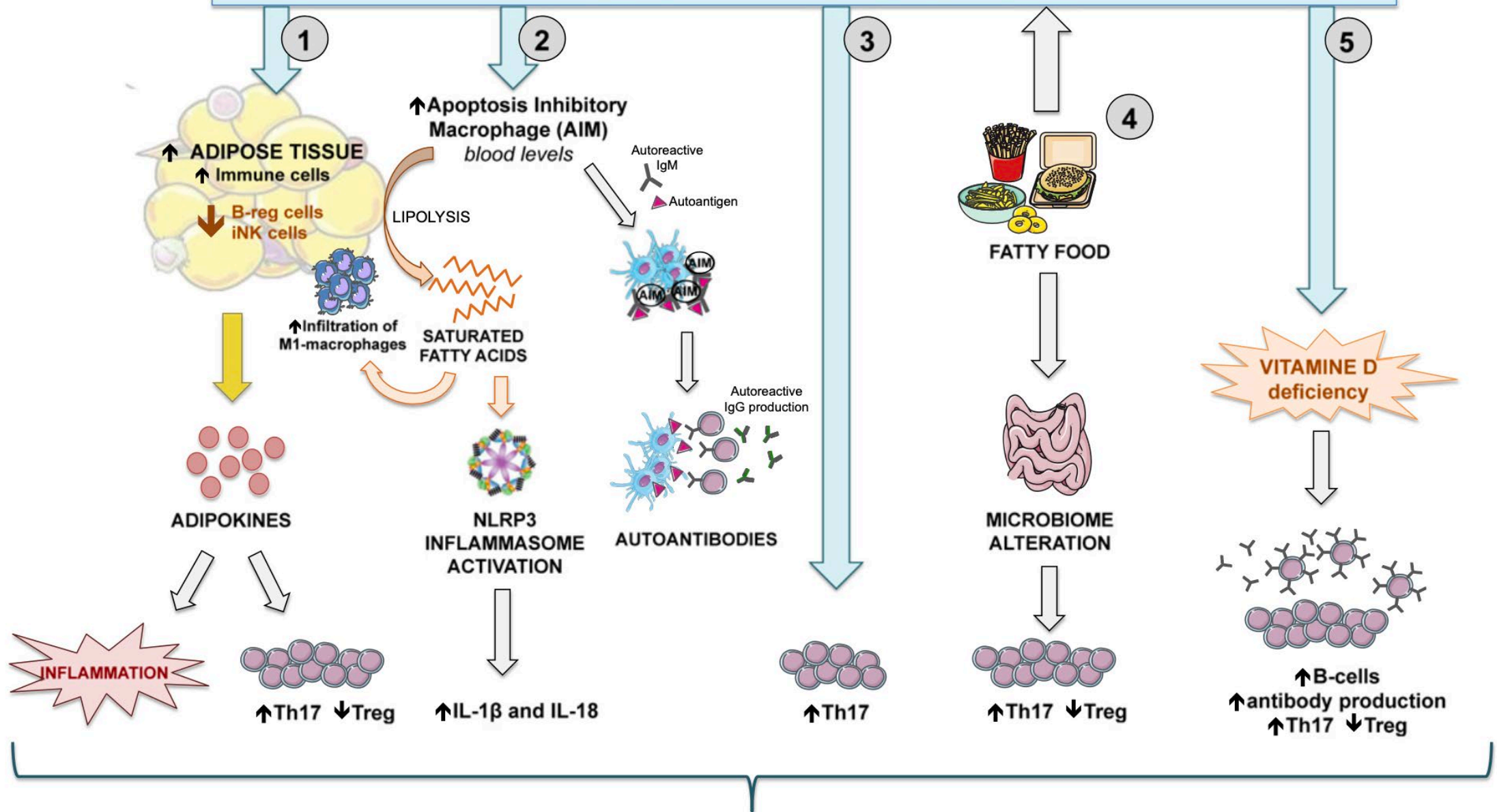


Cardiovascular-Kidney-Metabolic Syndrome

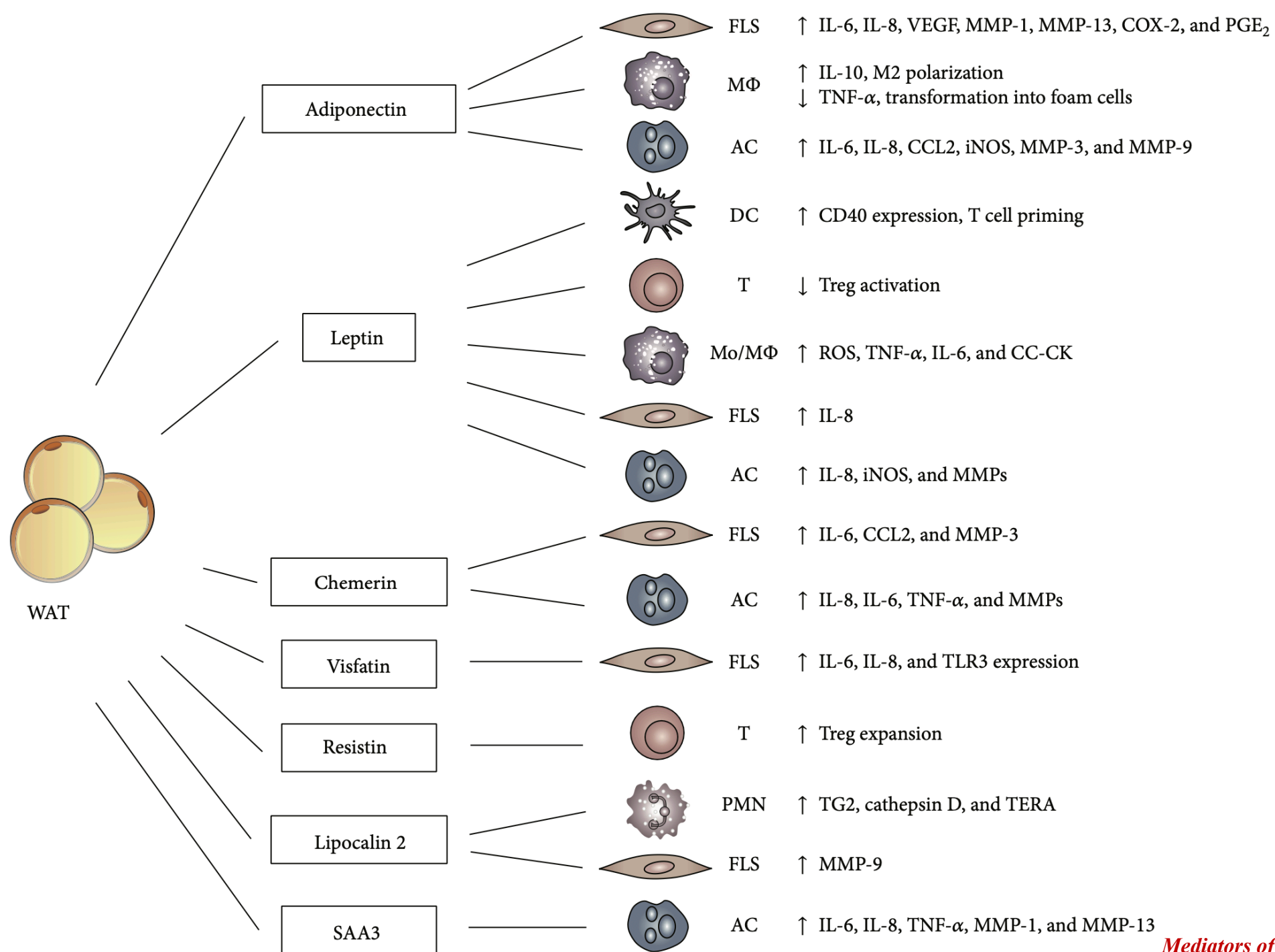


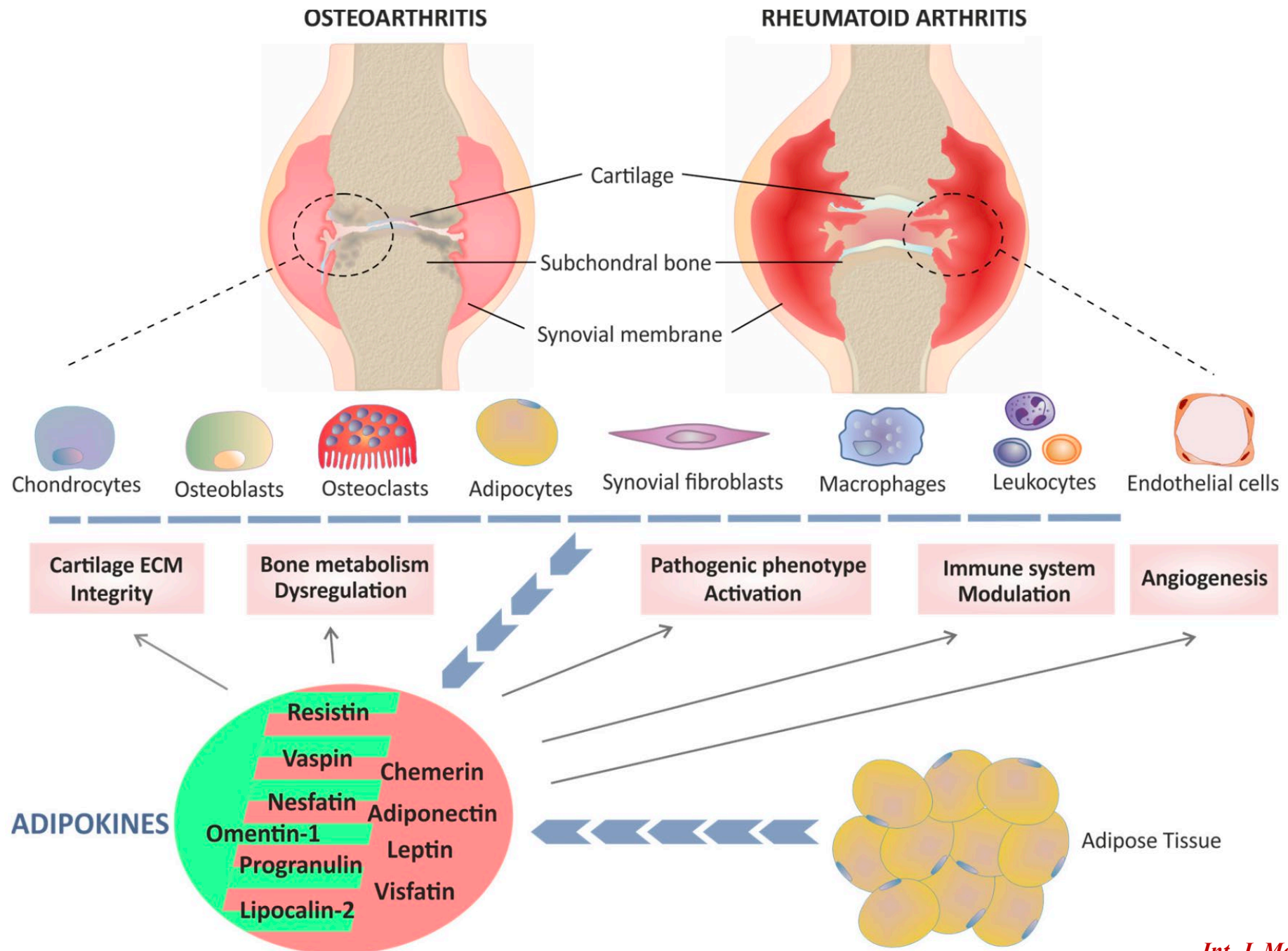
RAAS: Renin-angiotensin-aldosterone system; SNS: Sympathetic nervous system; eGFR: Estimated glomerular filtration rate; CVD: Cardiovascular disease; CKD: Chronic kidney disease

O B E S I T Y



PROMOTE AUTOIMMUNE DISEASES





Results: DAPSA

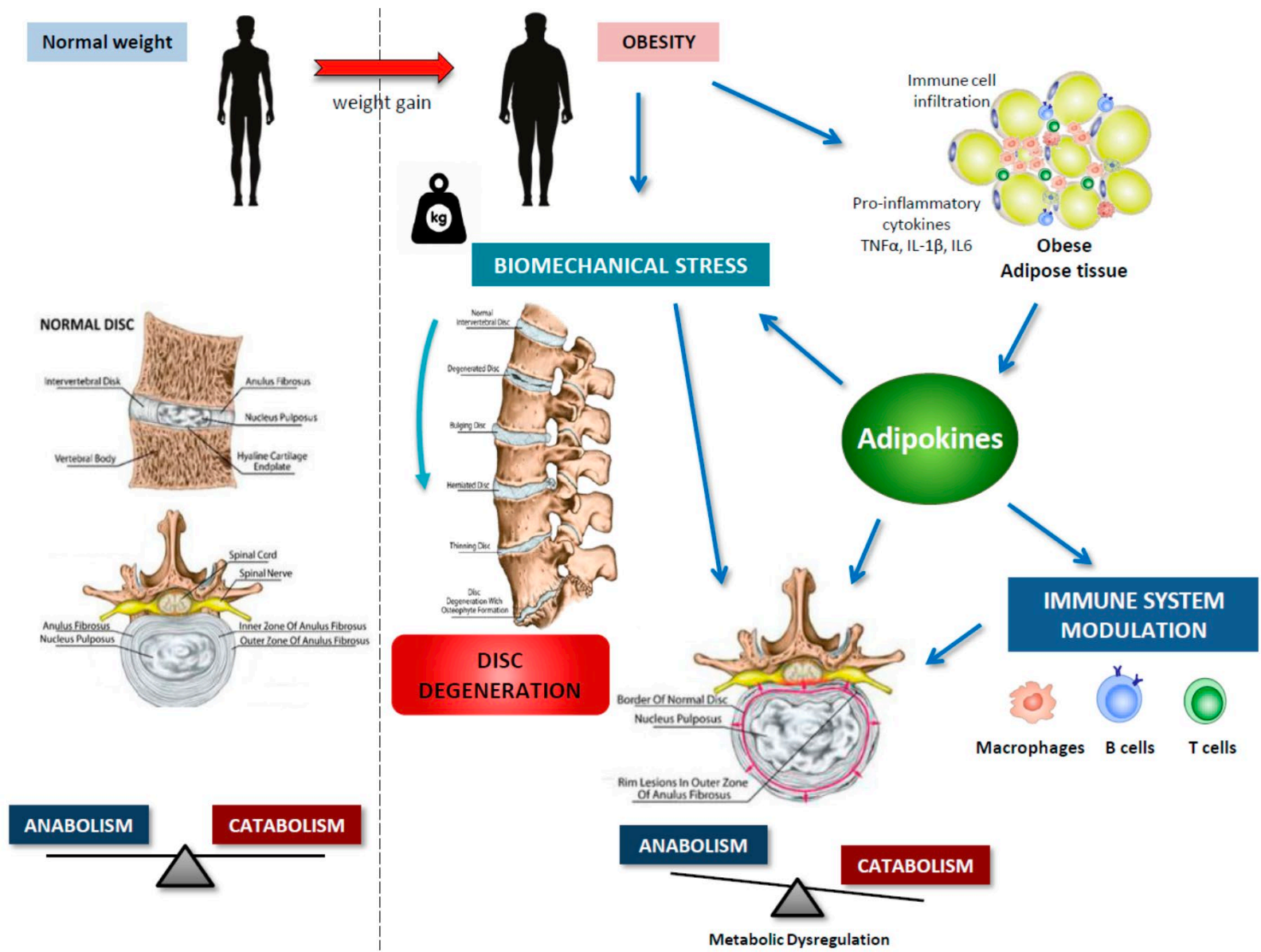
Multivariable regression model

OUTCOME: DAPSA

Variables	Coef. (95% CI)	P=
Age	0.0056 (0.0024 – 0.0088)	0.001
Gender	-0.2059 (-0.2814 - -0.1303)	0.000
Disease duration	-0.0127 (-0.0176 - -0.0077)	0.000
C-DMARD	0.0120 (-0.0618 – 0.0859)	0.750
B-DMARD	-0.1031 (-0.1924 - -0.0137)	0.024
Central obesity	0.3624 (0.2730 – 0.4519)	0.000

The higher the DAPSA score the worst the Outcome

Adipokines as molecular linkers between obesity, immune system and intervertebral disc disease



Agenda

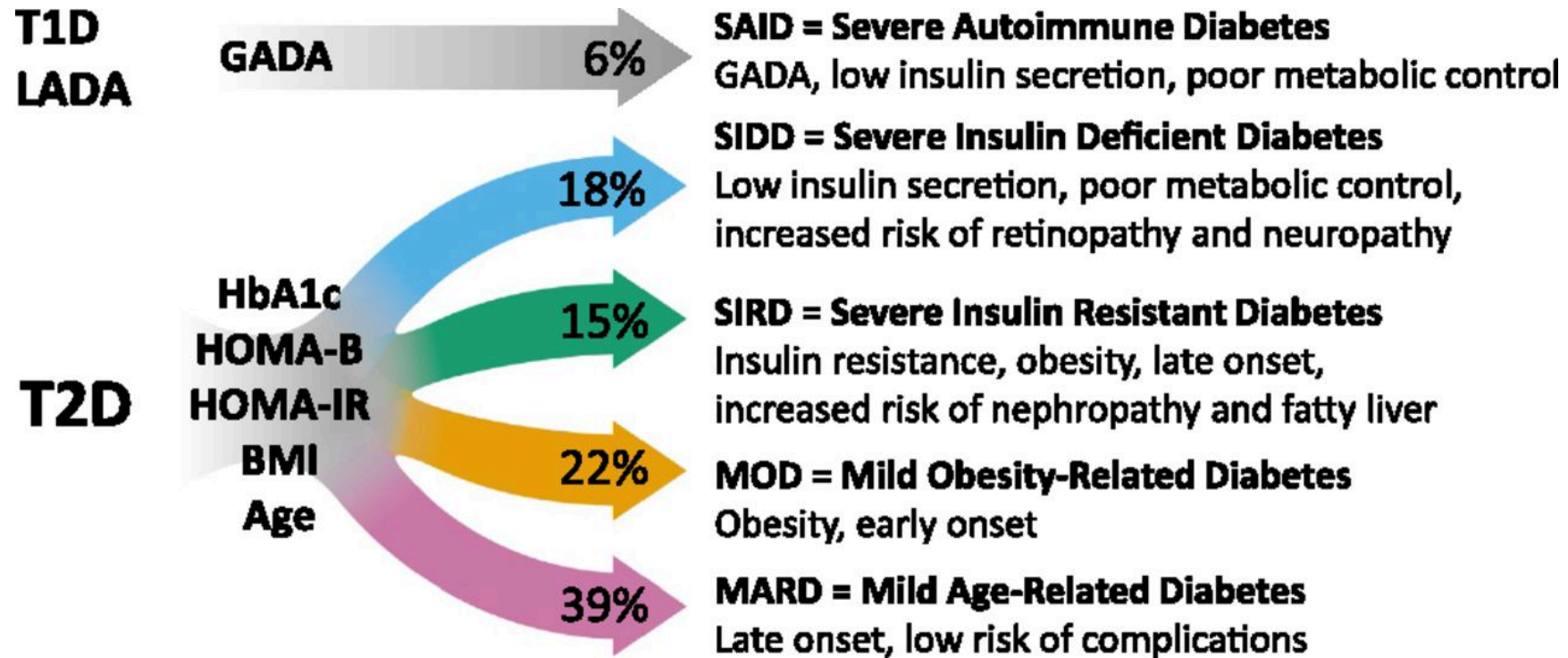
Obesità Malattia Cronica

Il Diabete Mellito e il Core Fisiopatologico

Approccio Terapeutico-Fisiopatologico

Riflessioni Conclusive

Diabetes. 2020;69(10):2086-2093. doi:10.2337/dbi20-0001

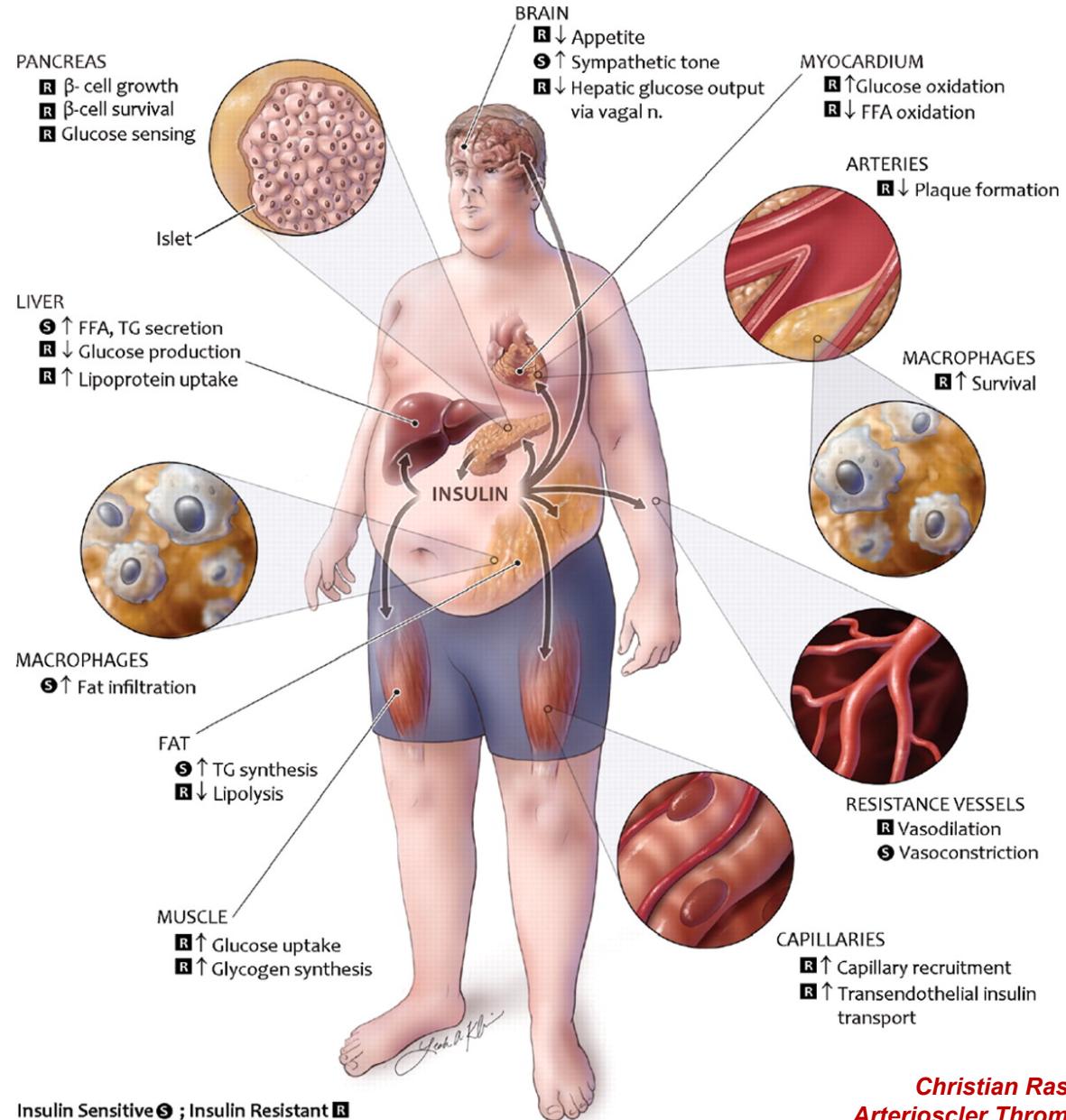
**Figure Legend:**

Novel diabetes subtype characteristics. Overview of distribution and characteristics of subtypes generated by clustering based on clinical parameters in the Swedish ANDIS cohort.

Physiology of insulin signaling in metabolic syndrome.

High Food intake

Metabolic Stress

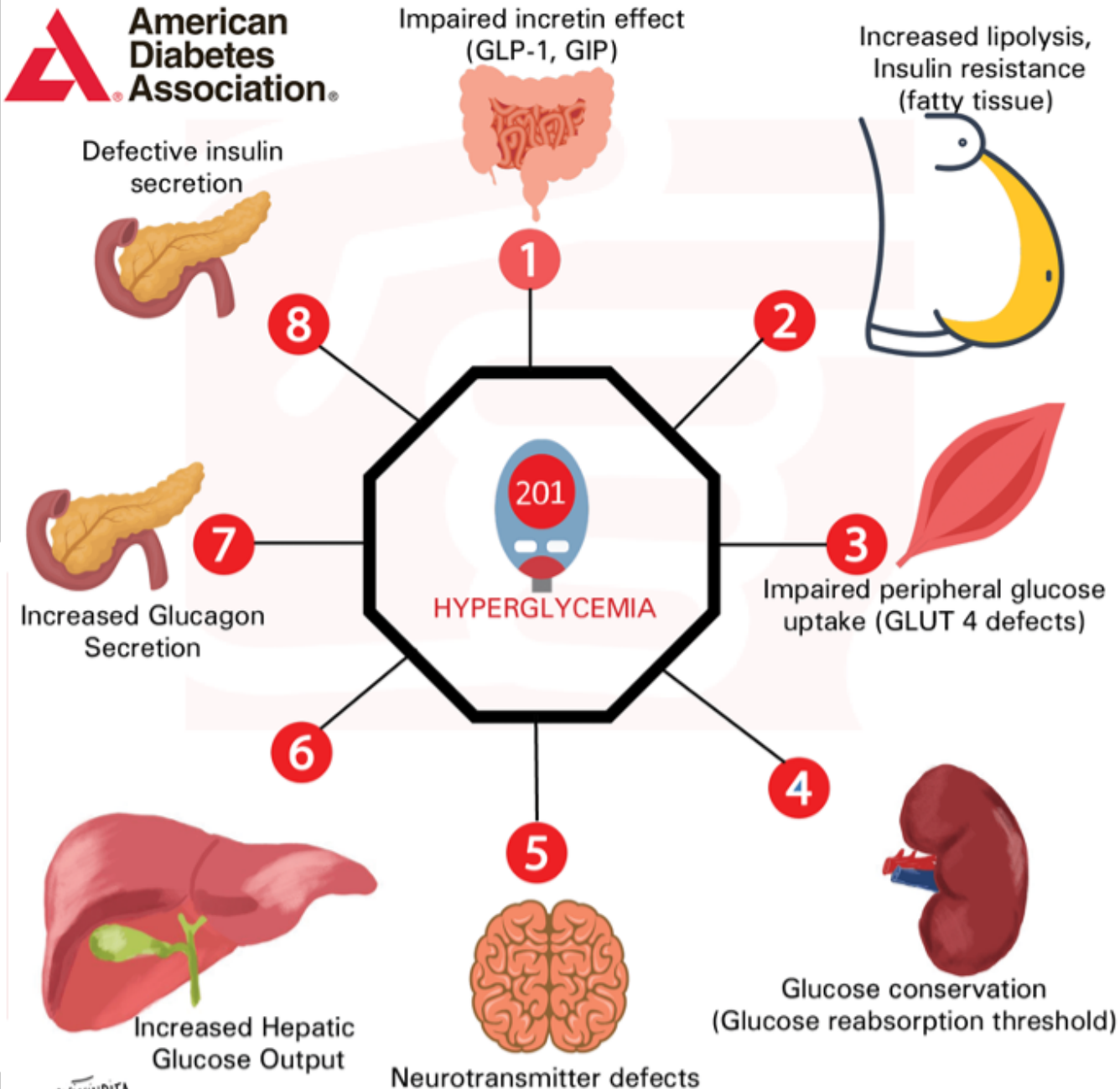


Energy expenditure unbalance

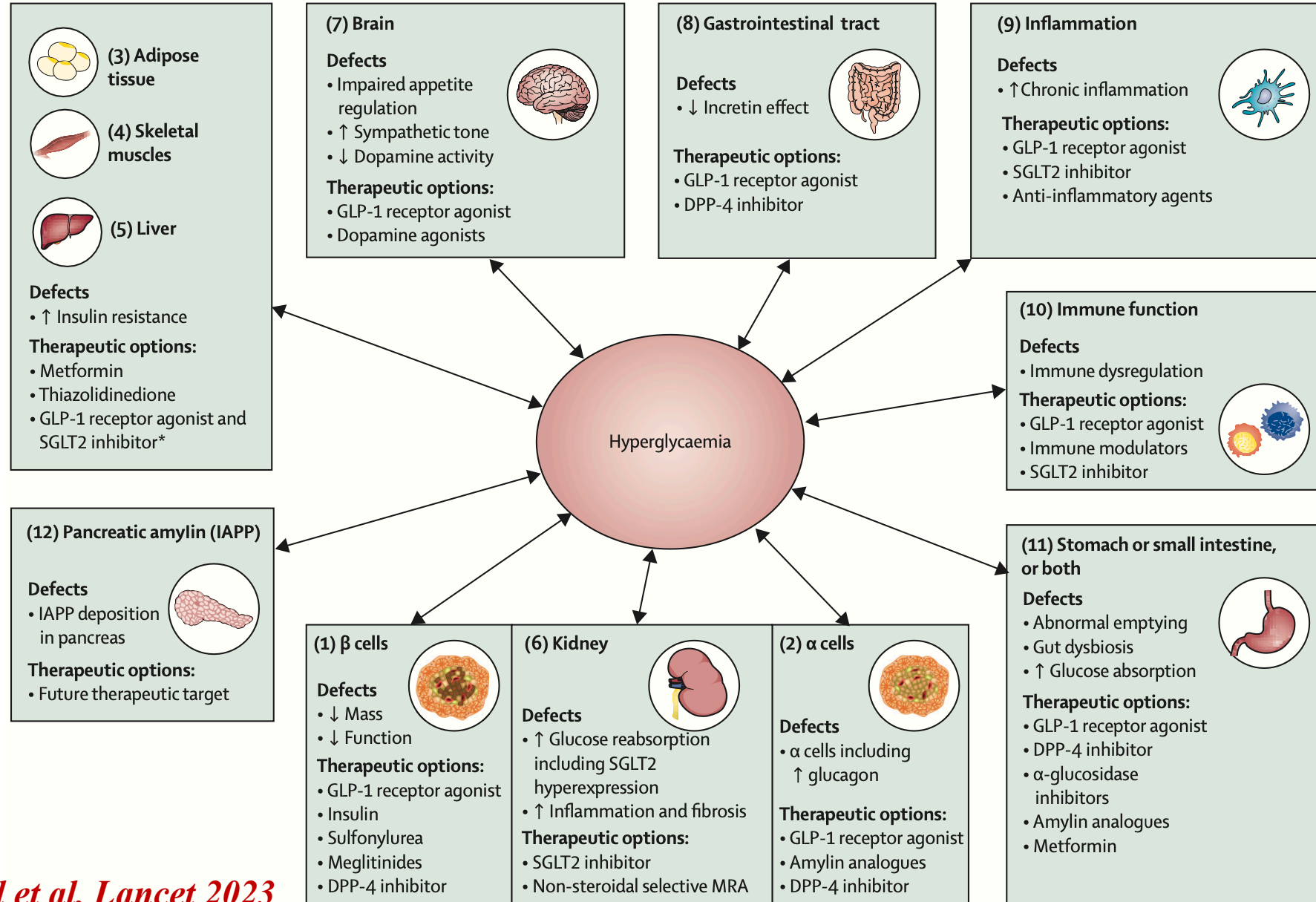
DIABETES MELLITUS : THE OMINOUS OCTET

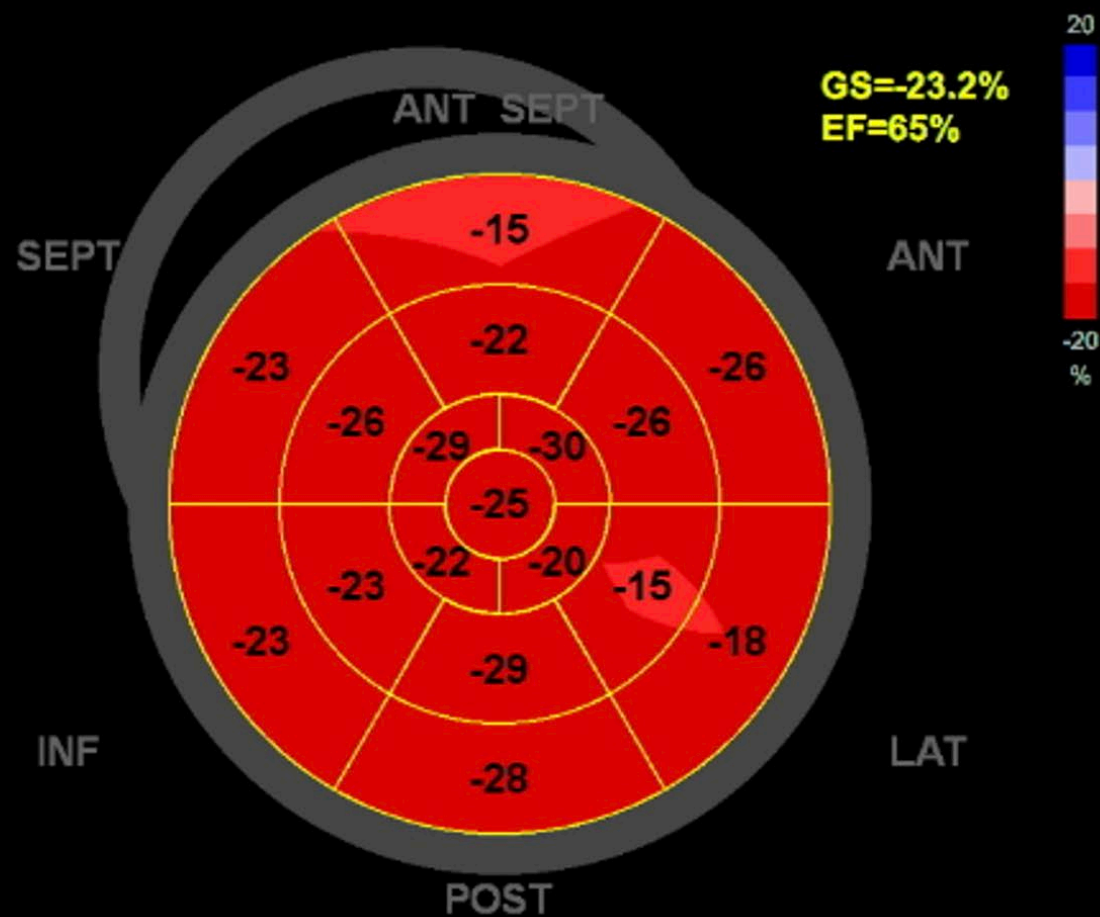
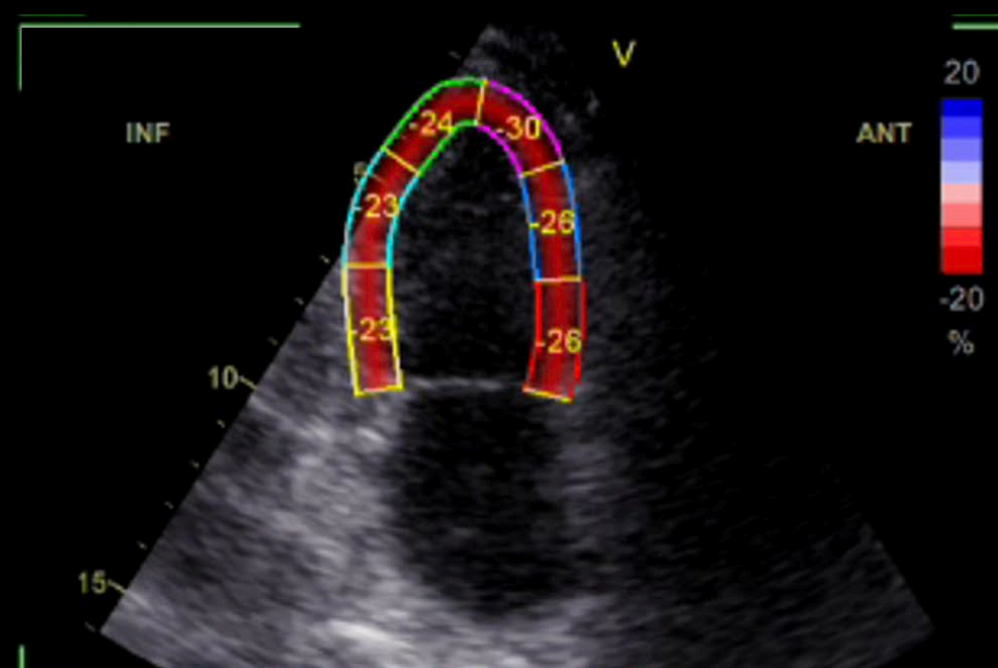
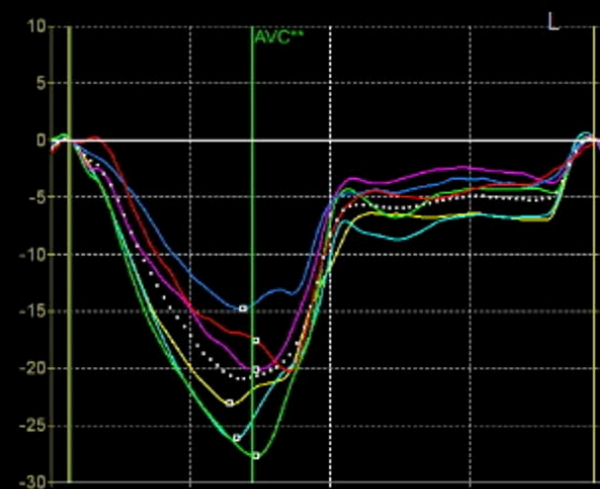
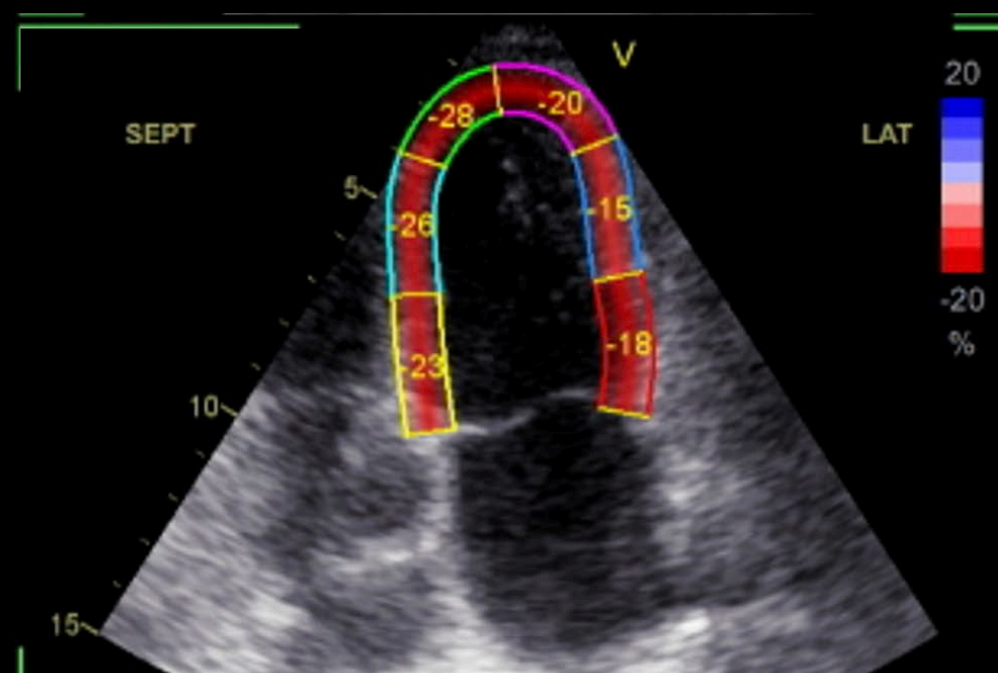


**American
Diabetes
Association®**

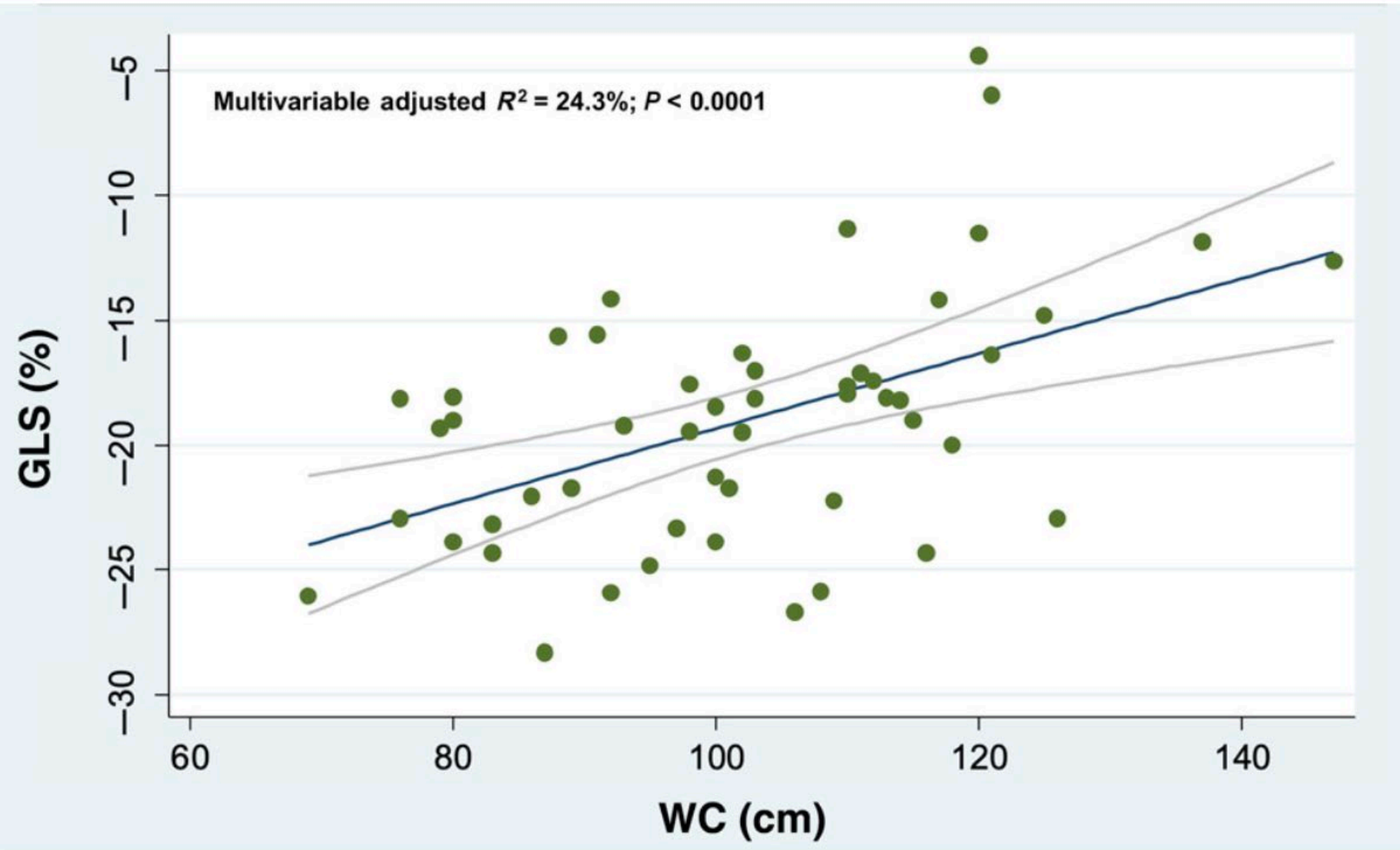


The deleterious dozen: 12 pathophysiological defects contributing to β -cell failure in type 2 diabetes with therapeutic options for individual pathways





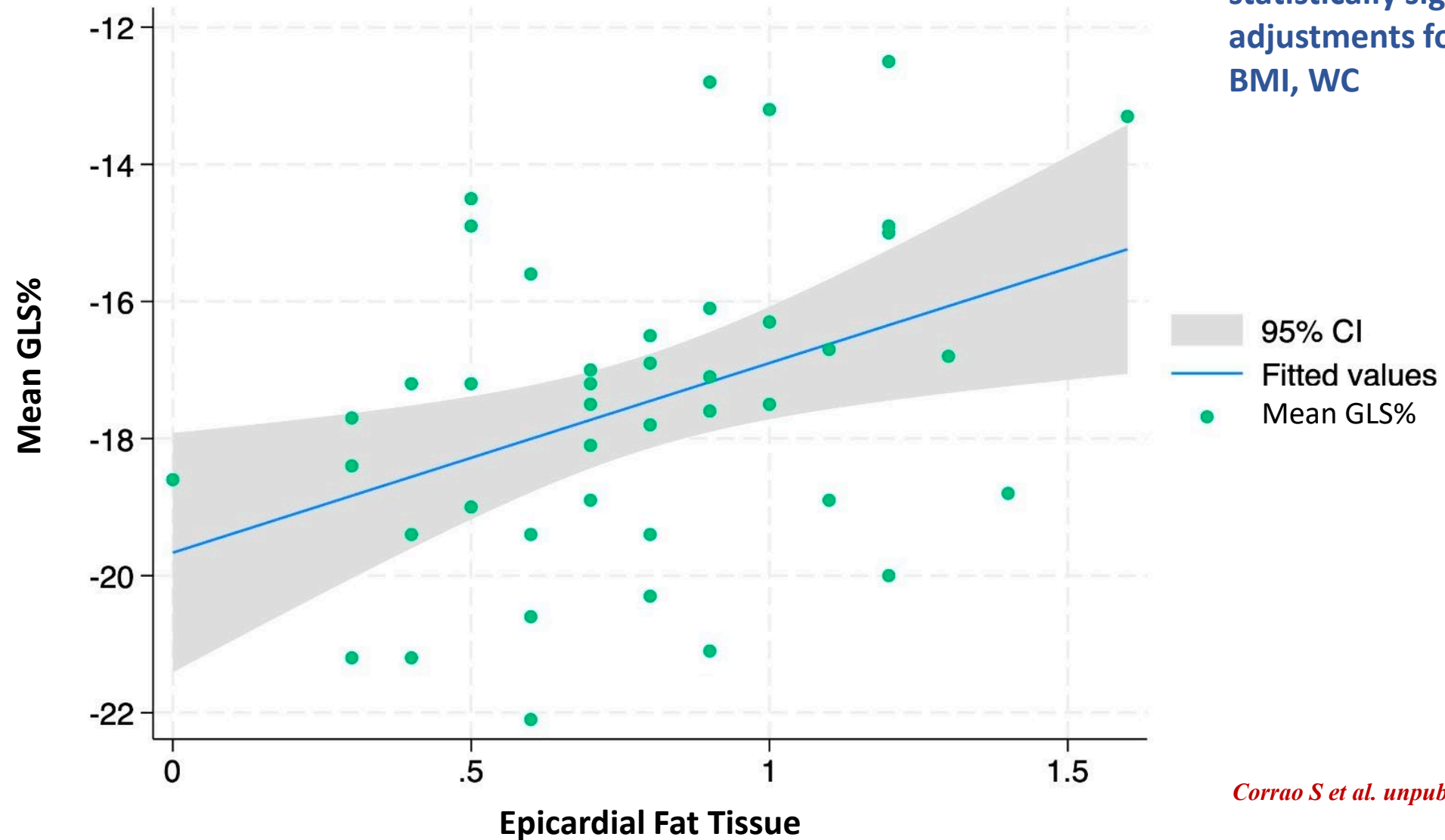
Relazione lineare tra la circonferenza vita (WC) e il global longitudinal strain (GLS)



La relazione è stata corretta, nell'analisi multivariabile, per età, sesso, HbA1c o HOMA-IR e Sindrome Metabolica secondo i criteri ATPIII

Il Global Longitudinal Strain rappresenta un indice precoce di performance del ventricolo sinistro e rappresenta un forte predittore di Scompenso Cardiaco.

T2DM patients



Corrao S et al. unpublished data

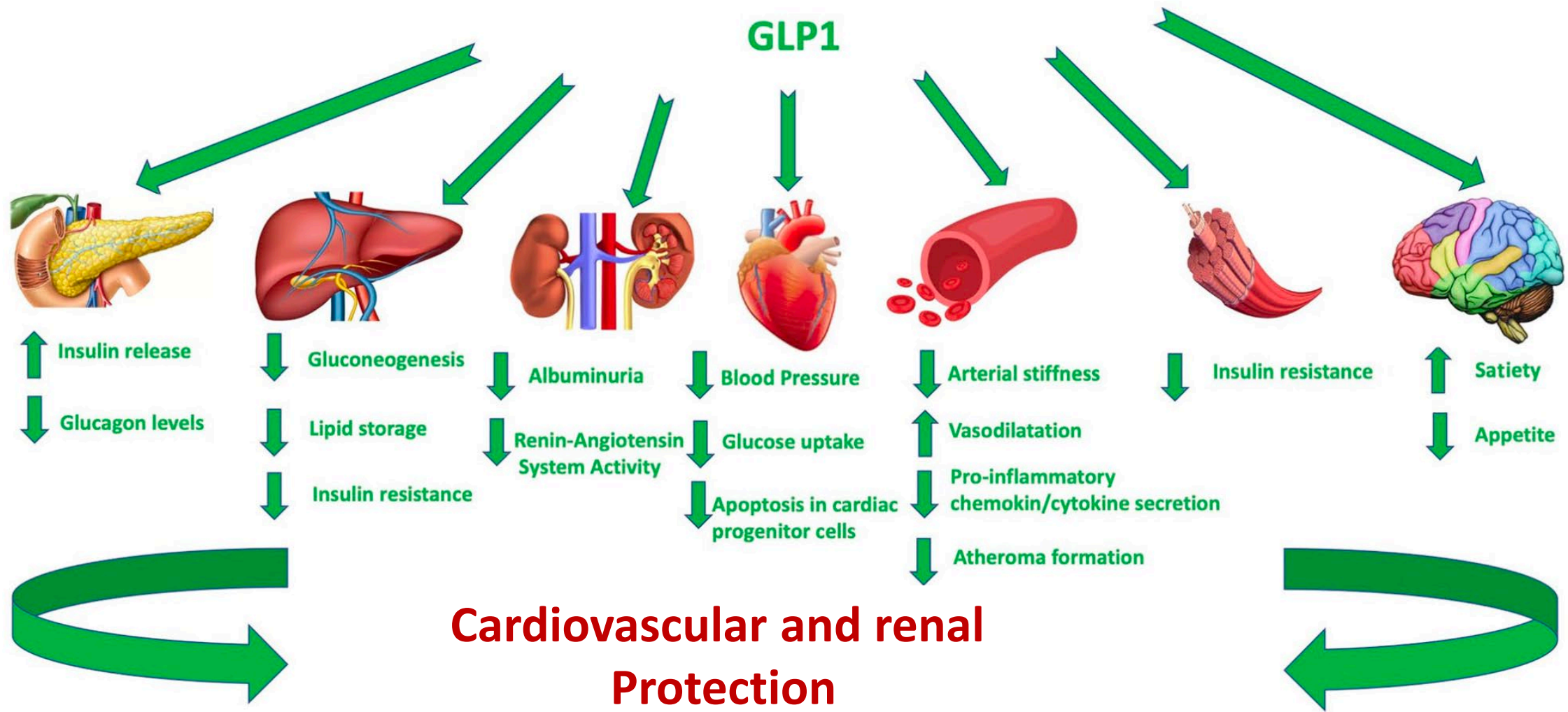
Agenda

Obesità Malattia Cronica

Il Diabete Mellito e il Core Fisiopatologico

Approccio Terapeutico-Fisiopatologico

Riflessioni Conclusive



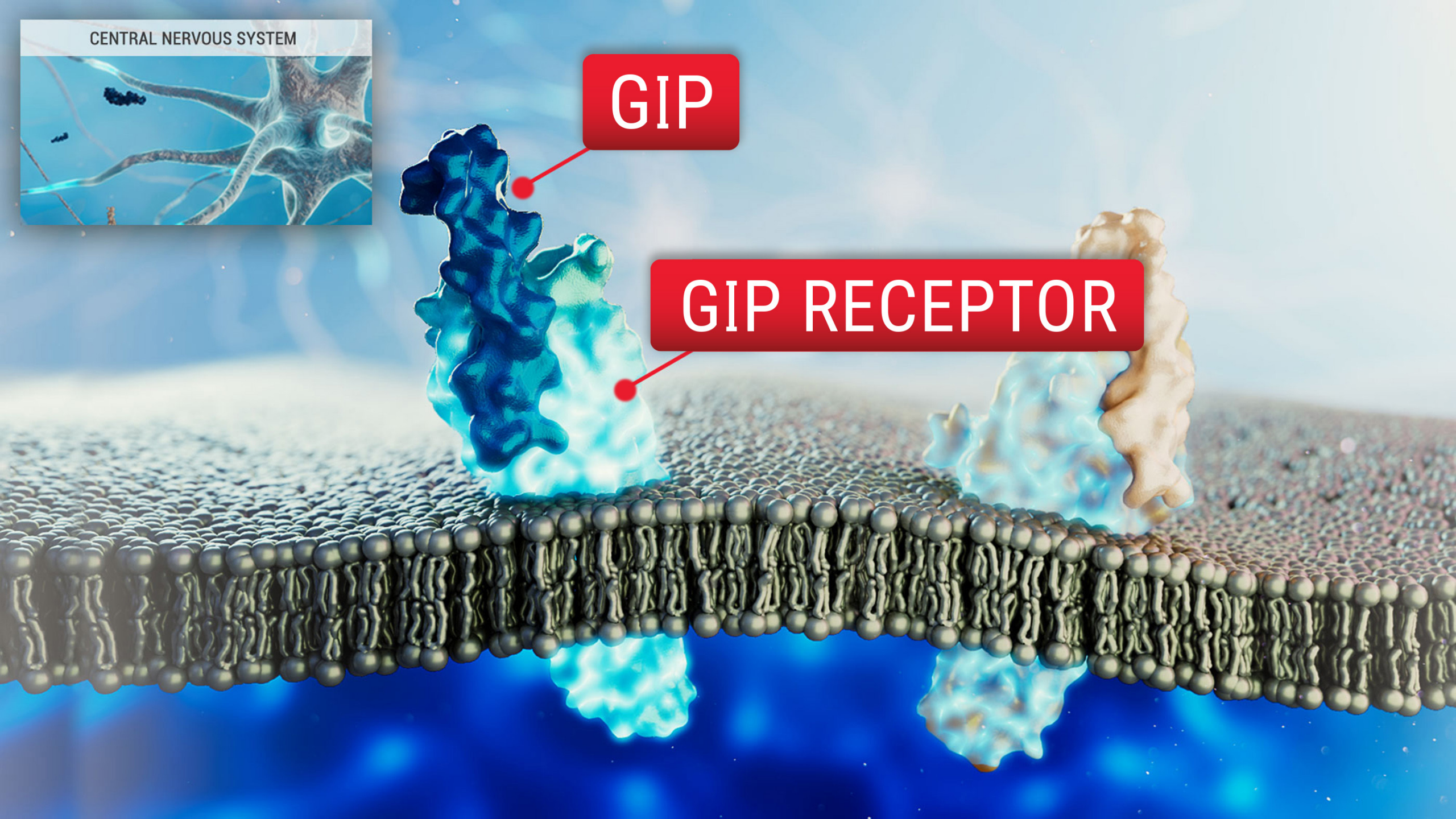
Modified from Heart Failure Reviews (2023)

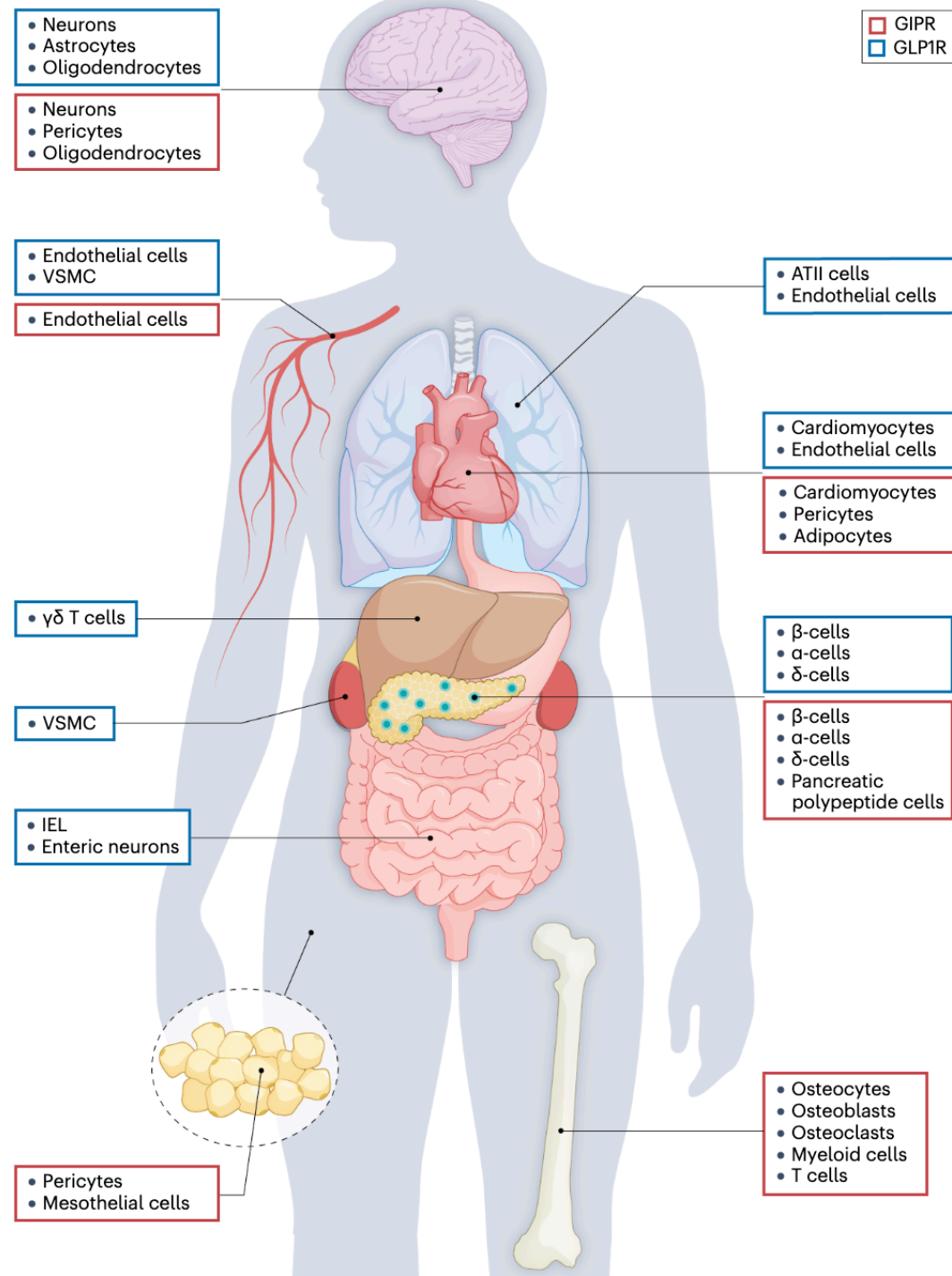
CENTRAL NERVOUS SYSTEM



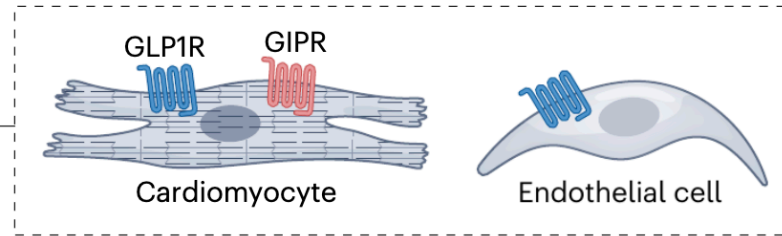
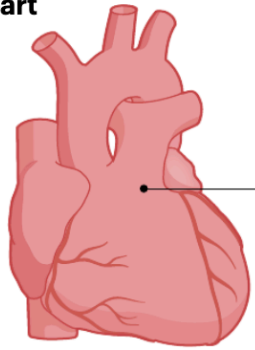
GIP

GIP RECEPTOR



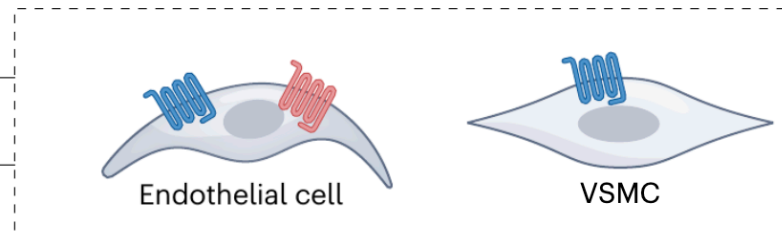
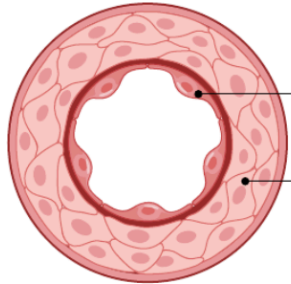


Heart



- ↑ Cardioprotection
- ↑ Myocardial contractility
- ↑ Heart rate
- ↑ Glucose uptake

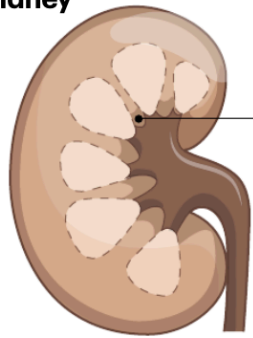
Blood vessel



- ↑ Vasodilation and NO production
- ↓ Systemic inflammation
- ↓ Foam cell formation

- ↓ Macrophage-driven inflammation
- ↓ Foam cell formation
- ↓ VSMC proliferation
- ↓ Arterial remodelling

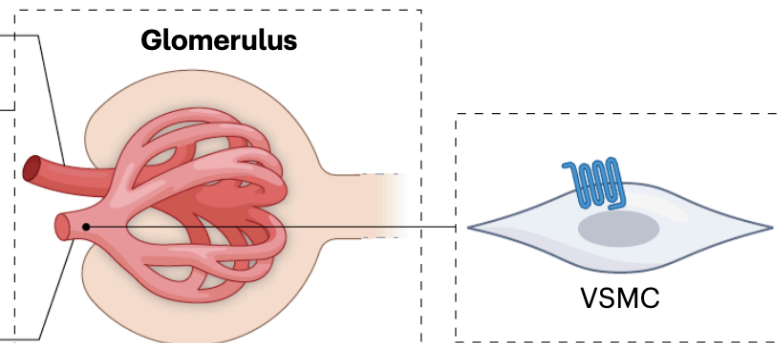
Kidney



Efferent arteriole

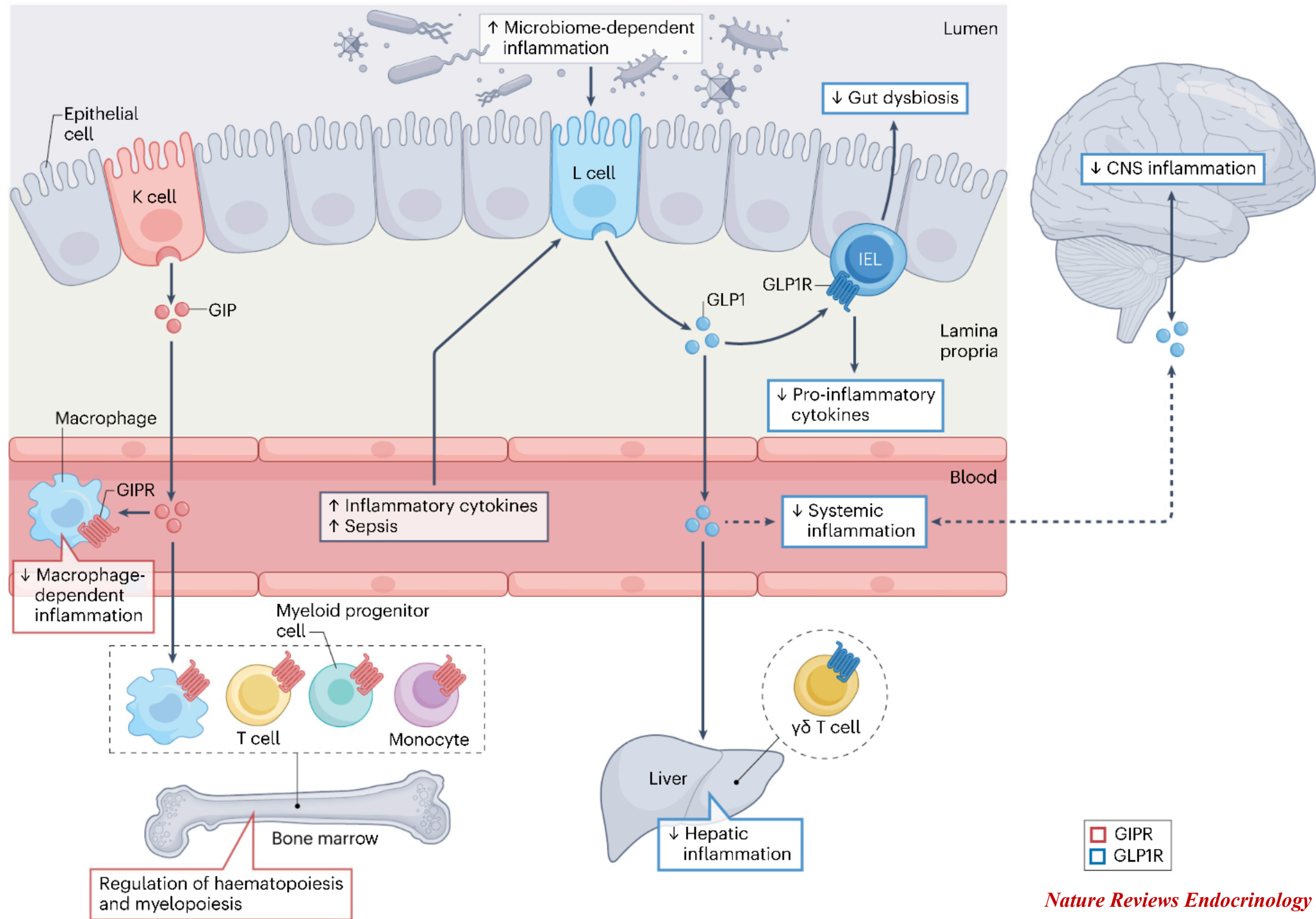
Glomerulus

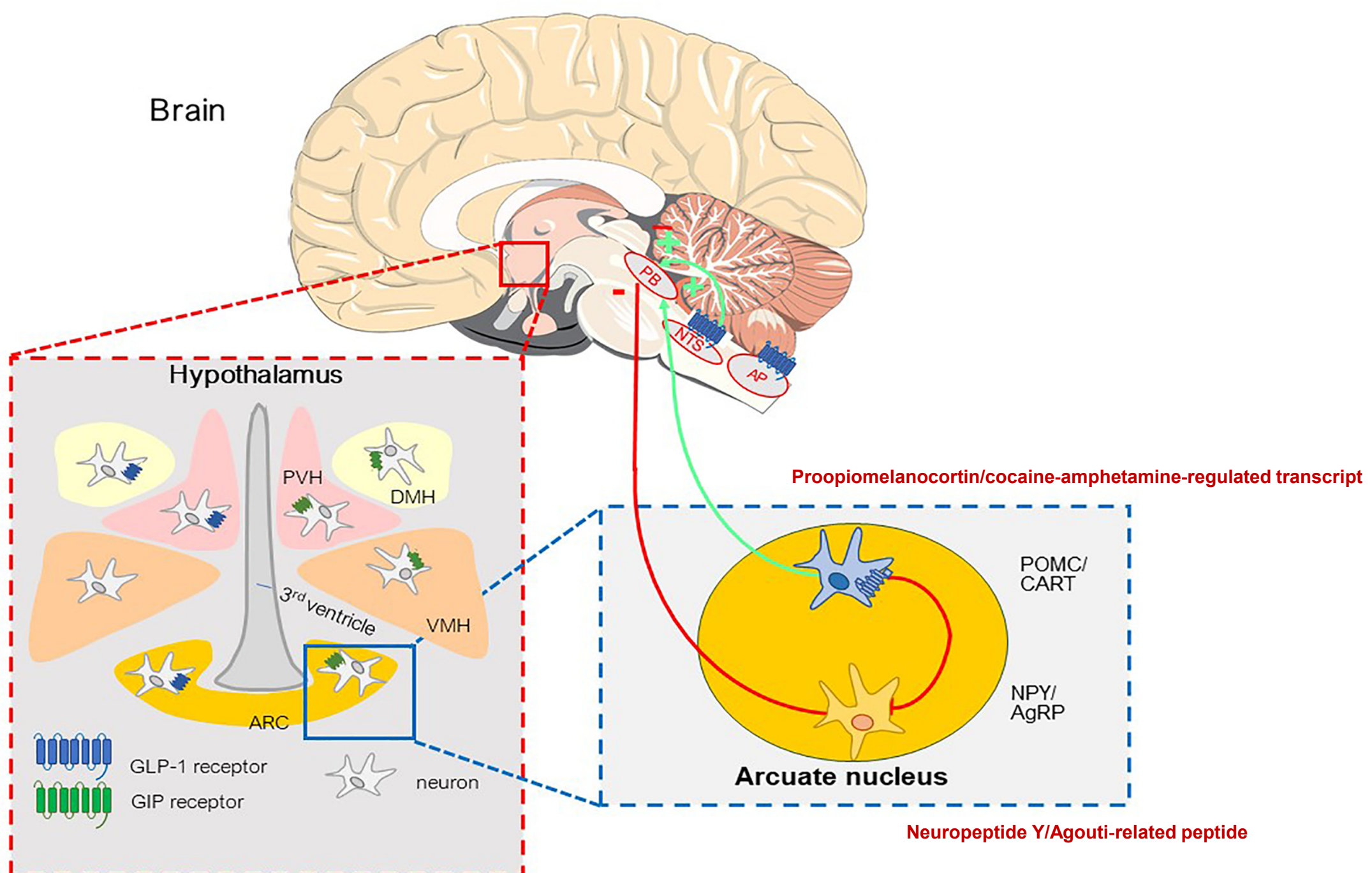
Afferent arteriole



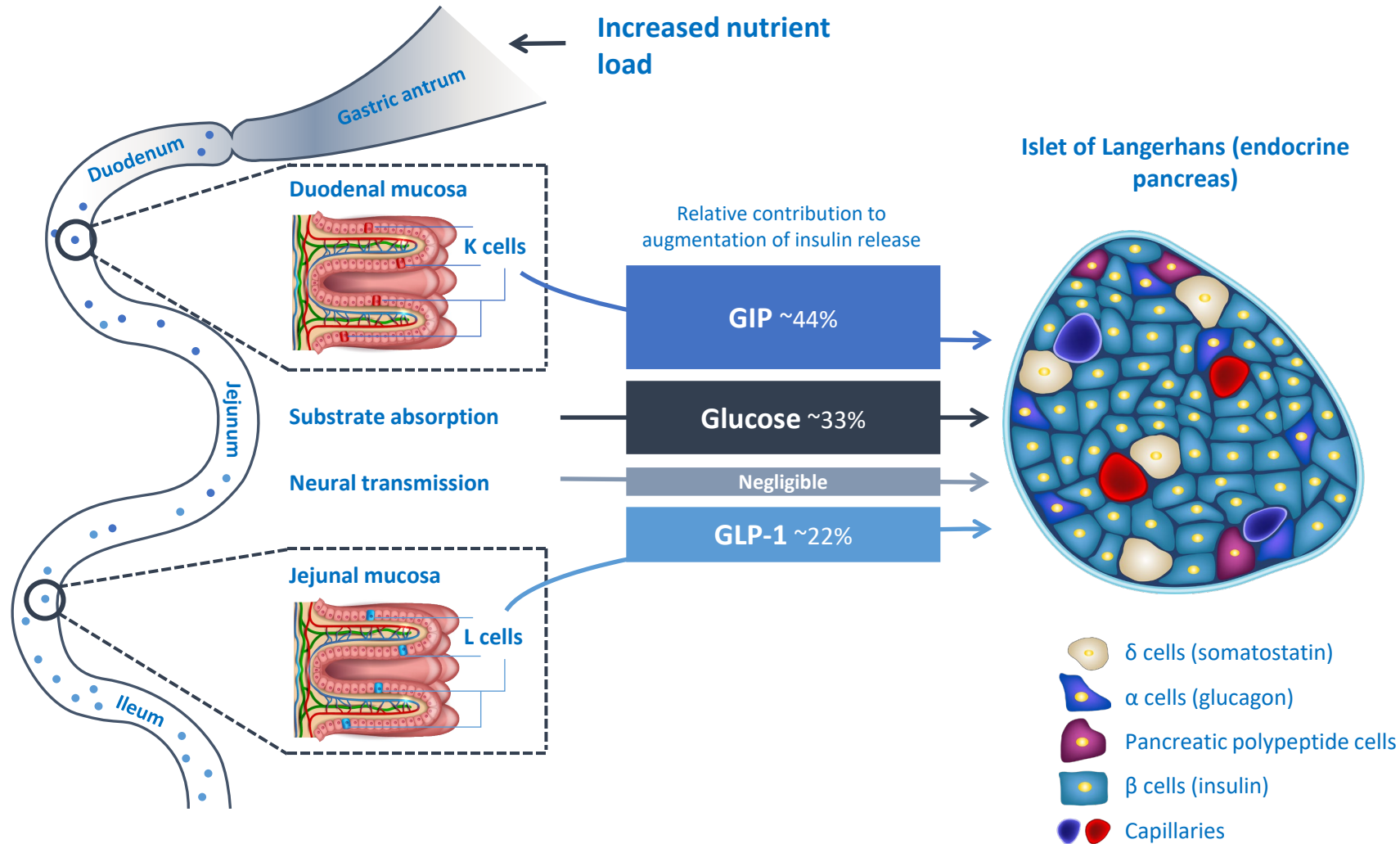
- ↑ Nephroprotection
- ↑ Sodium and water excretion
- ↓ Blood pressure
- ↓ Albumin excretion







The Incretin Hormones GIP and GLP-1 Signal to the Pancreas

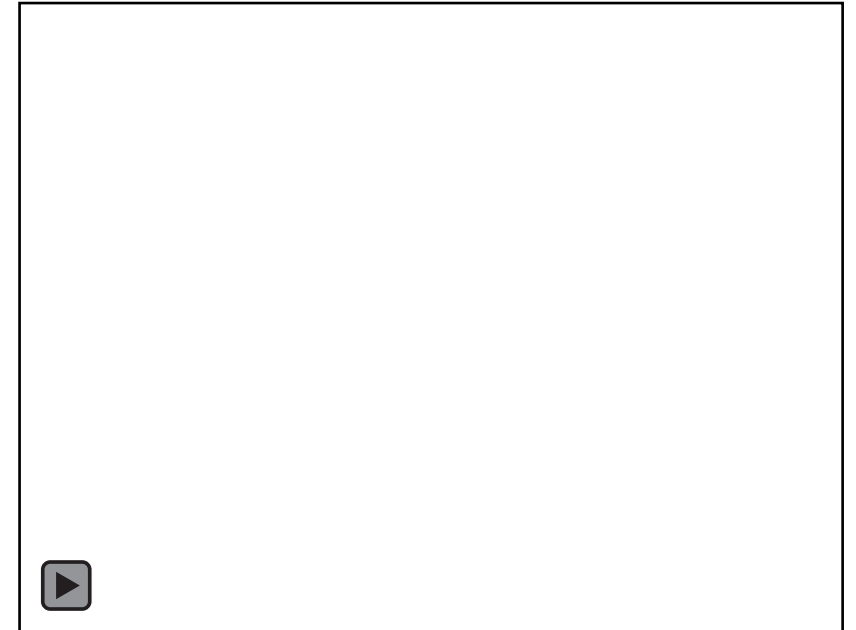


- Nutrient load in the gut stimulates release of the incretin hormones GIP and GLP-1
- GIP and GLP-1 signal to pancreatic islets to enhance glucose-dependent insulin secretion and subsequent PPG clearance in healthy people

GIP = gastric inhibitory polypeptide; GLP-1 = glucagon-like peptide-1; PPG = postprandial glucose. Nauck MA, Meier JJ. Diabetes. 2019;68(5):897-900.

Tirzepatide

- **Structure: linear peptide, 39 amino acids based on the GIP sequence¹**
 - Binds to both GIPR and GLP-1R
 - Includes a C20 fatty diacid moiety
- **Mean half-life: approximately 5 days¹**
- **Plasma concentrations in people with renal impairment do not differ vs healthy people²**



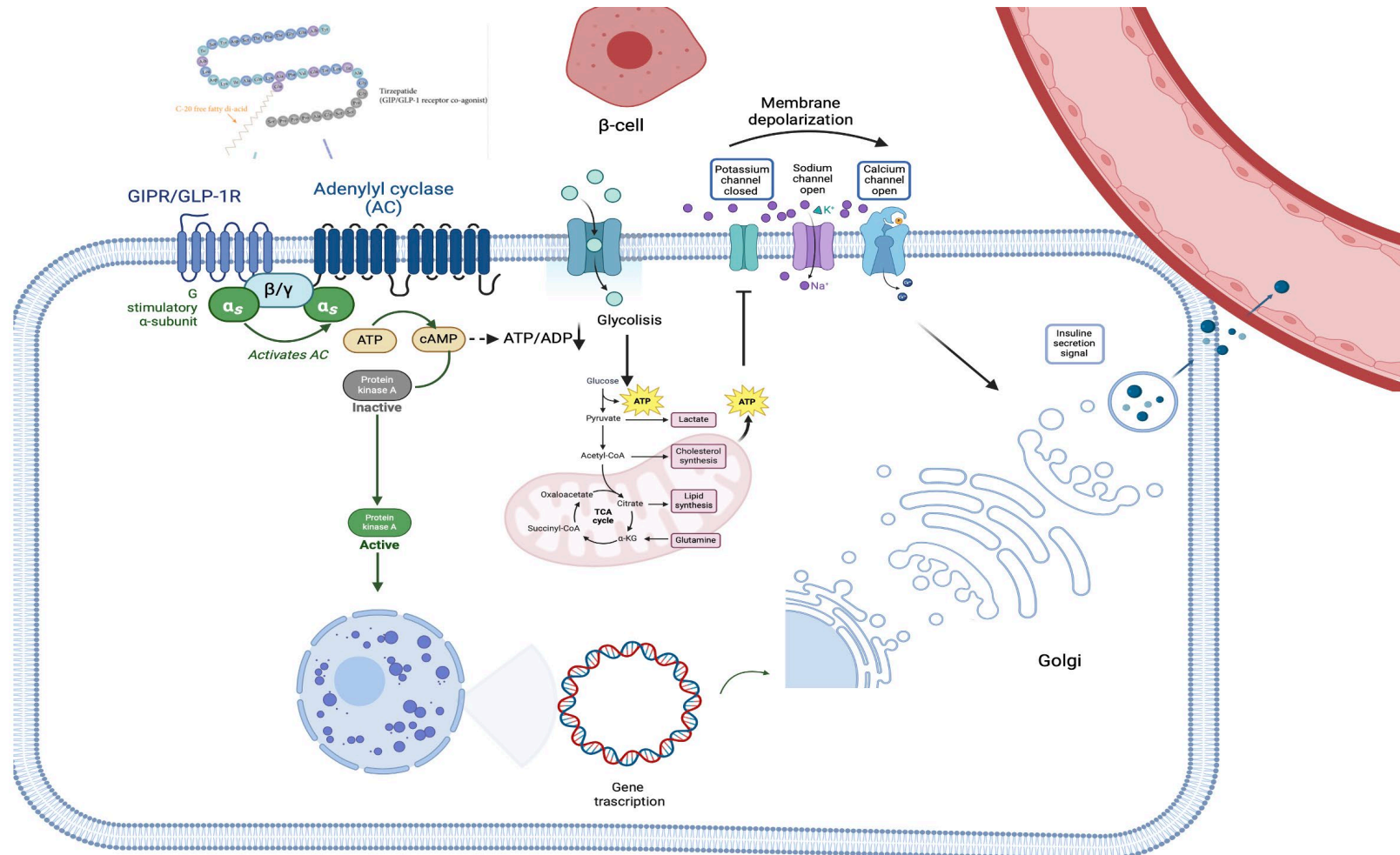
This 3-dimensional rendering of tirzepatide is not an exact reproduction of the molecule and should be used for representative purposes only.

GIP = glucose-dependent insulinotropic polypeptide; GIPR = glucose-dependent insulinotropic polypeptide receptor; GLP-1R = glucagon-like peptide-1 receptor.

1. Coskun T, et al. *Mol Metab.* 2018;18:3-14. 2. Urva S, et al. *Diabetes.* 2020;69(suppl 1):Abstract 971-P.

2. Informazioni come da RCP di Prodotto

Tirzepatide's pathway signalling



Programma di sviluppo SURPASS

Obiettivo primario: variazione della HbA1c

Obiettivi secondari: variazione del peso corporeo, della glicemia a digiuno e % di pazienti che raggiungevano il target di HbA1c.

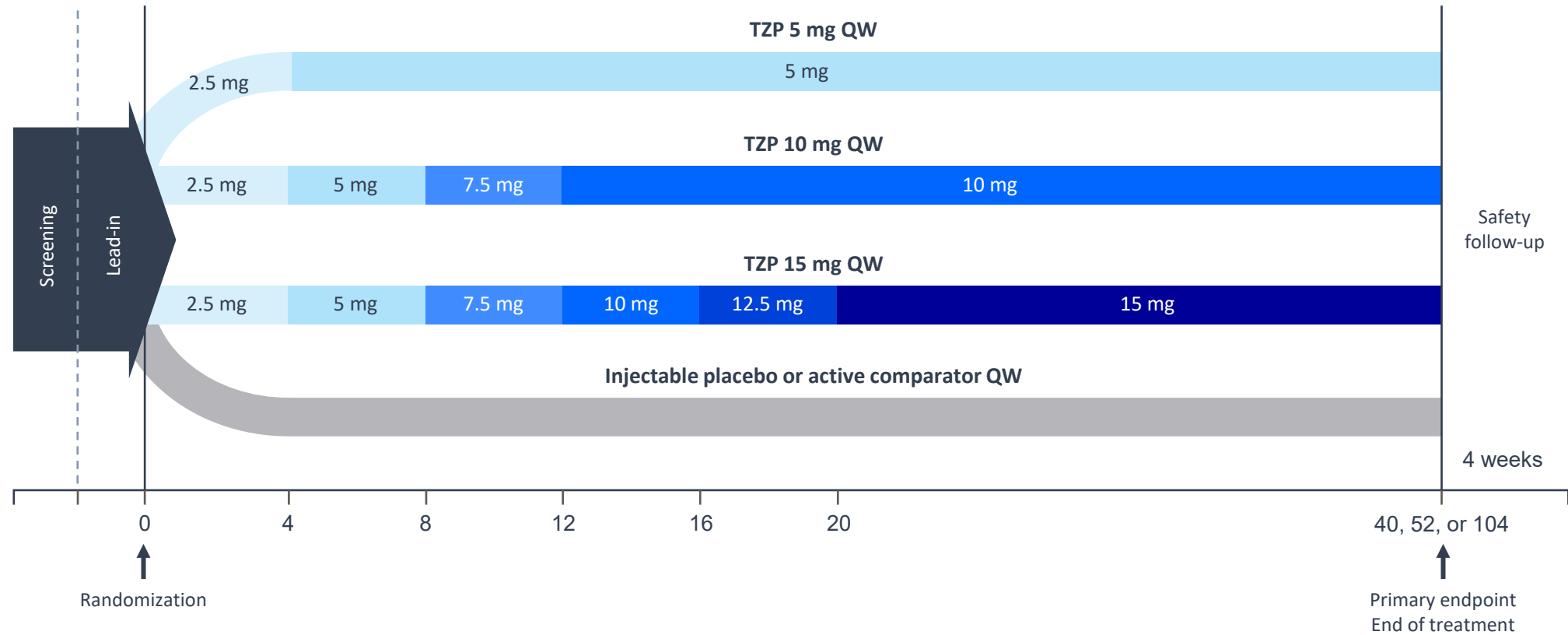
6 263 pazienti con diabete di tipo 2 (di cui 4 199 trattati con tirzepatide)

Monotherapy	2-Drug Combination	2-3 Drug Combinations	2-4 Drug Combinations	Combination With Insulin
SURPASS-1 vs. placebo¹ Drug-naïve or washout from any OAM	SURPASS-2 vs. semaglutide² Add-on to metformin	SURPASS-3 vs. insulin degludec³ Add-on to metformin with or without SGLT-2i	SURPASS-4 vs. insulin glargine⁴ Add-on to ≥ 1 and ≤ 3 OAMs (metformin, SGLT-2i, or SU)	SURPASS-5 vs. placebo⁵ Both with insulin glargine with or without metformin

1. Rosenstock J, et al. *Lancet*. 2021;398(10295):143-155. 2. Frias JP, et al. *N Eng J Med*. 2021;385(6):503-515. 3. Ludvik B, et al. *Lancet*. 2021;398(10300):583-598. 4. Del Prato S, et al. *Lancet*. 2021;398(10313):1811-1824. 5. Dahl D, et al. *JAMA*. 2022;327(6):534-545

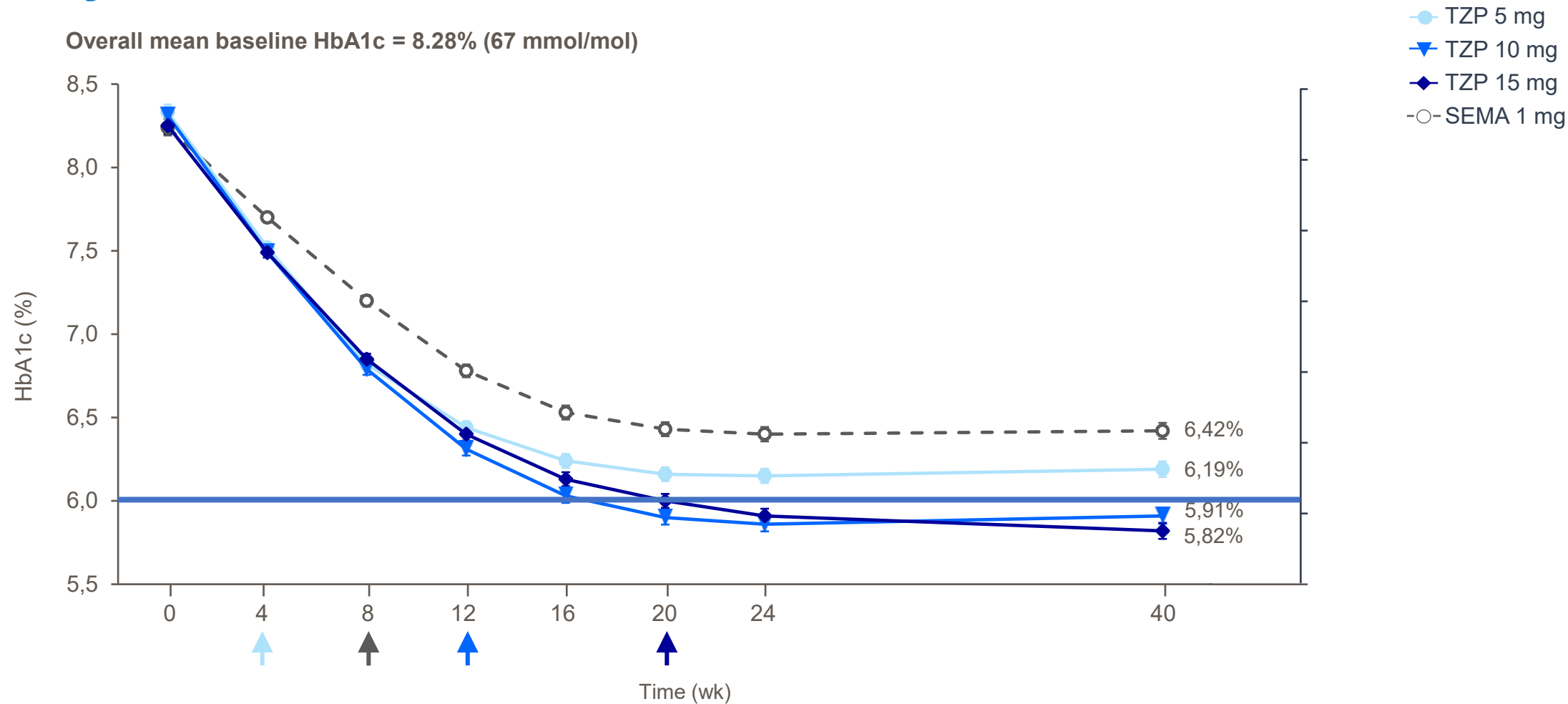
Rielaborazione grafica di informazioni contenute nel RCP Tirzepatide

Disegno generale degli studi SURPASS



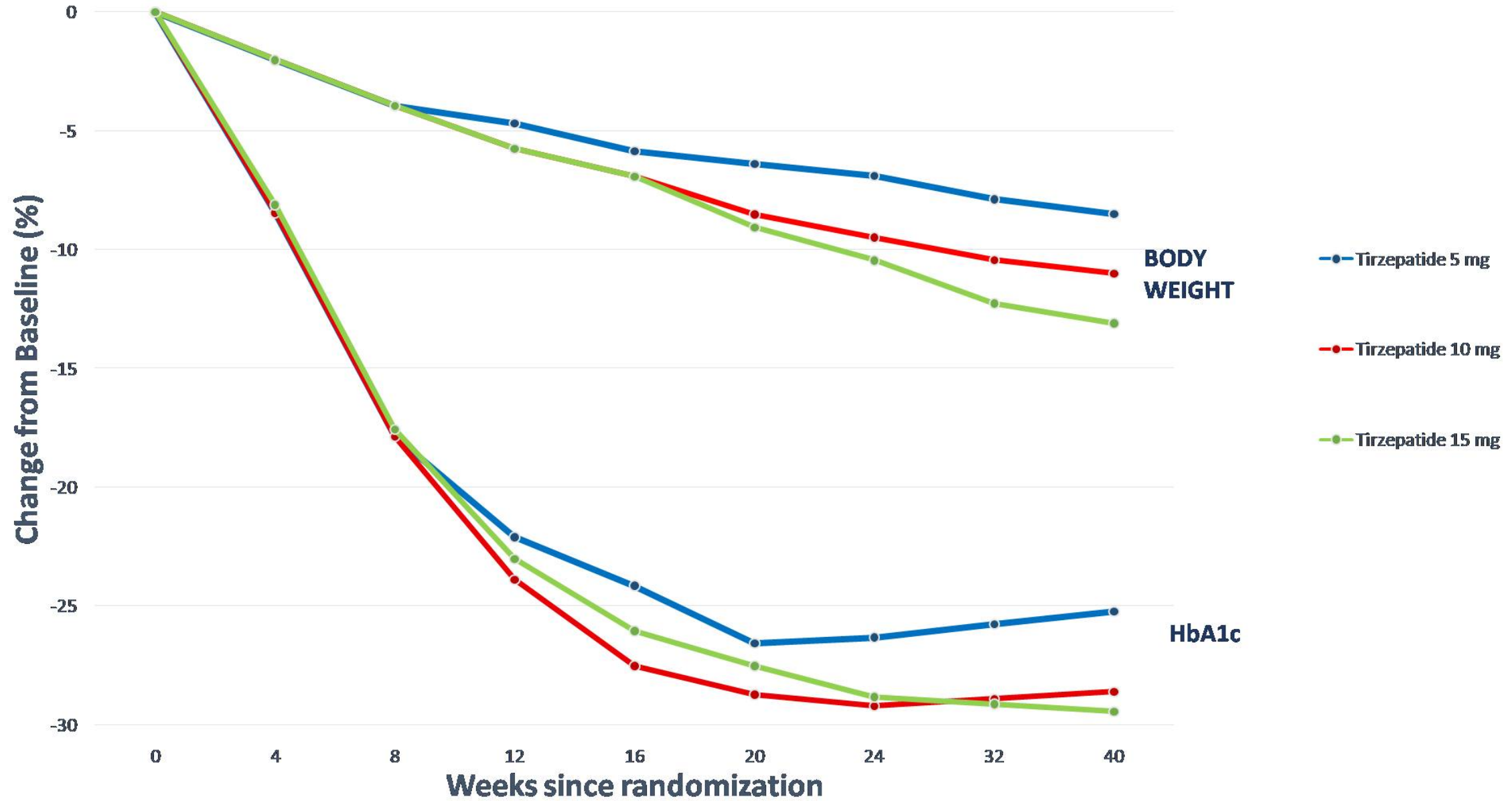
HbA1c Over Time (SURPASS-2)

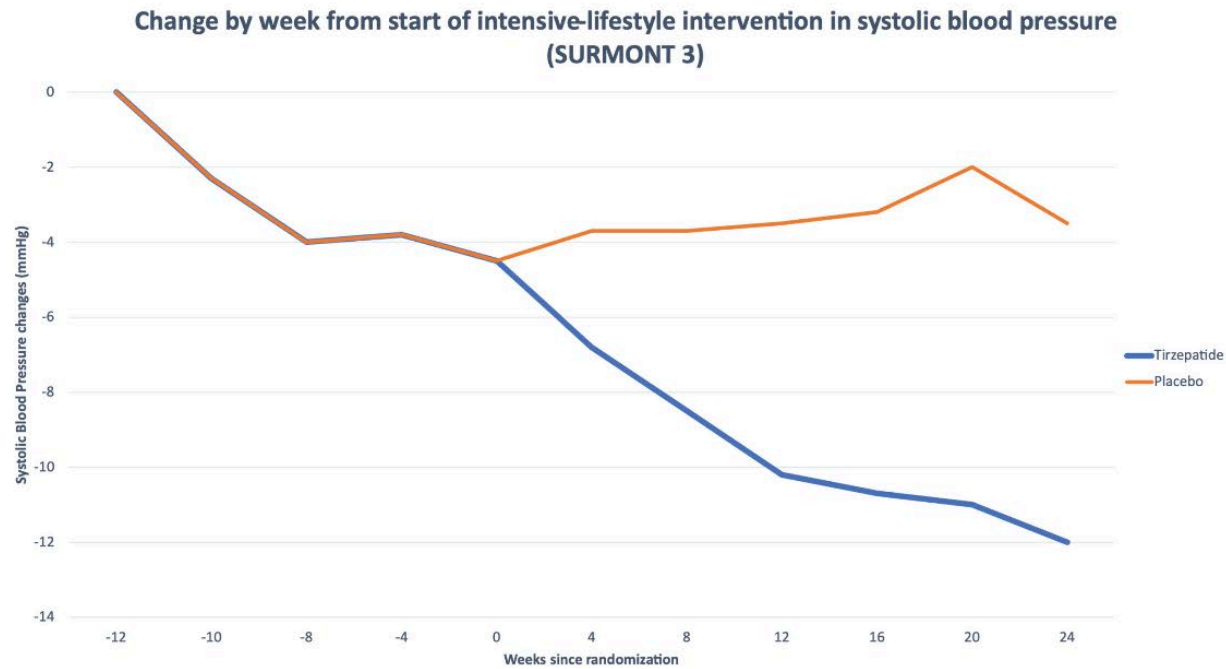
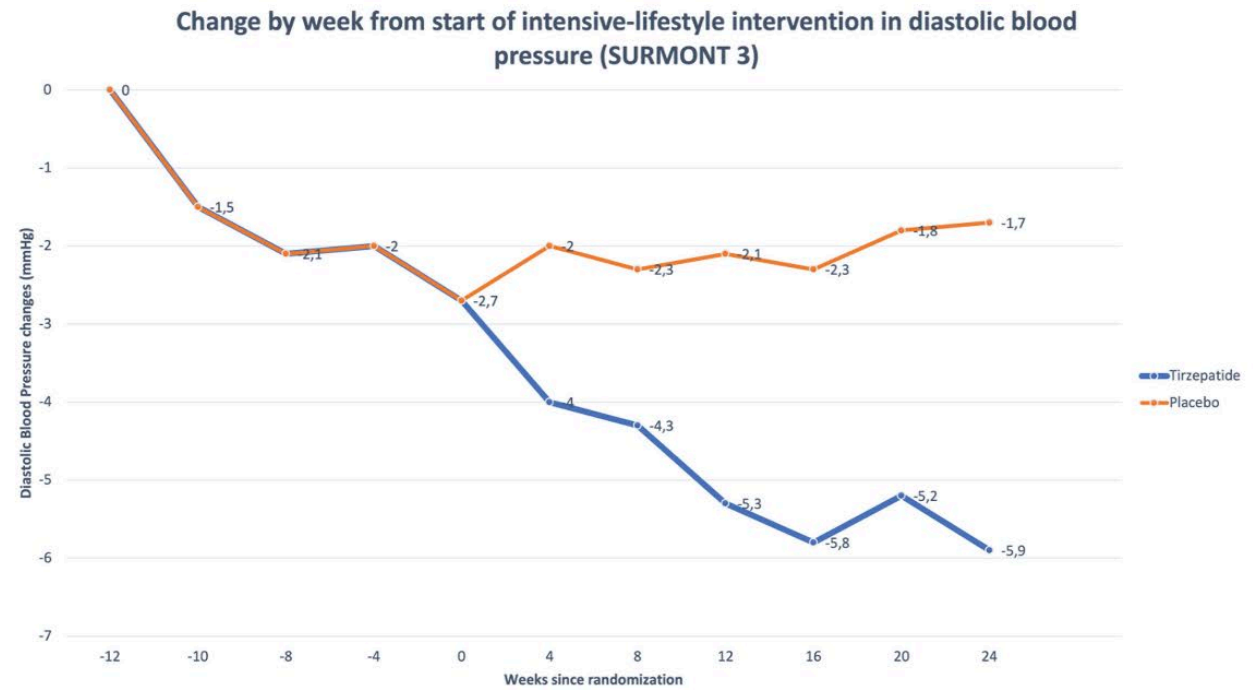
Efficacy Estimand



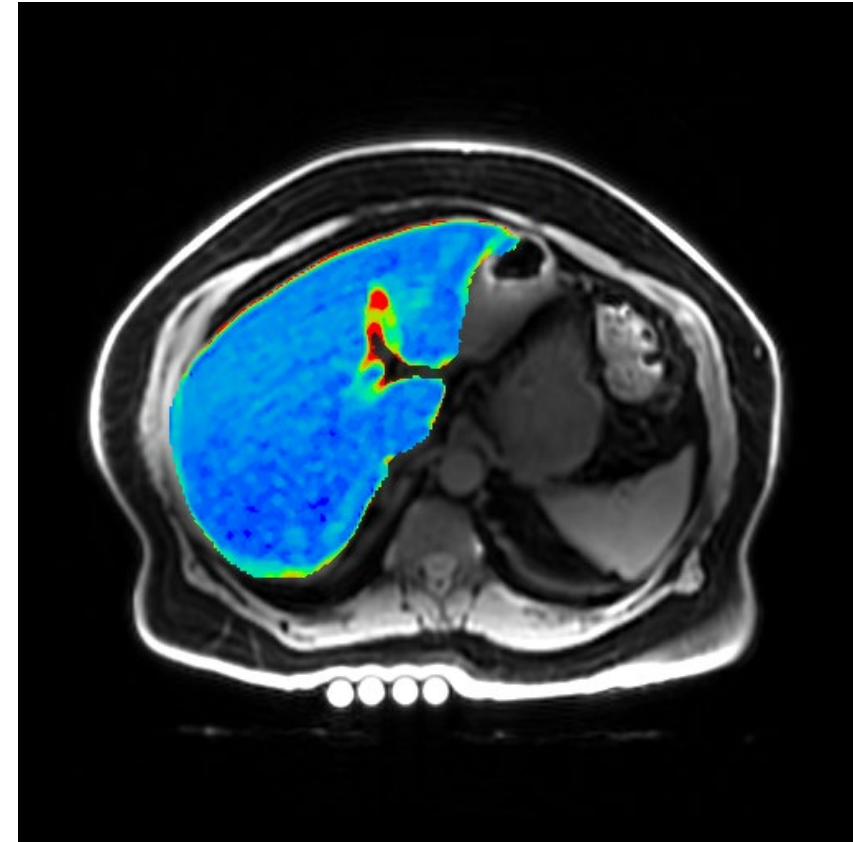
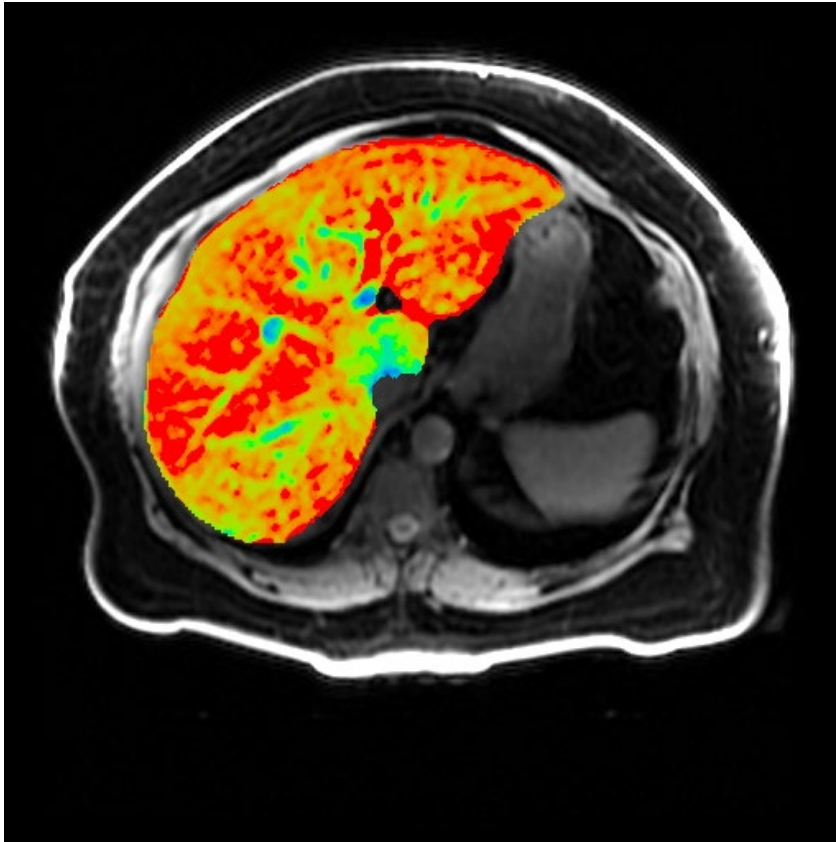
Data are LSM (SE); mITT population (efficacy analysis set). ANOVA analysis (week 0) and MMRM analysis (week 40). Arrows indicate when the dose of TZP 5 mg, 10 mg, and 15 mg and SEMA 1 mg were achieved. Data labels are % HbA1c. ANOVA = analysis of variance; HbA1c = glycated haemoglobin; LSM = least squares mean; mITT = modified intent-to-treat; MMRM = mixed model repeated measures; SEMA = semaglutide; TZP = tirzepatide. Frias JP, et al. *N Engl J Med*. Published online June 25, 2021.

Tirzepatide's effects on body weight and in HbA_{1c} (SURPASS 2)



A**B**

MRI Scans Showing LFC (%) at Baseline and At Week 52a SURPASS-3 MRI



LFC at 52 Weeks: 2.6%

^aMRI scans from one participant randomised to tirzepatide 5 mg: 59-year old male on metformin with an SGLT-2i.
LFC=Liver Fat Content; MRI=Magnetic Resonance Imaging; SGLT-2i=Sodium-Glucose Cotransporter-2 Inhibitor.
Gastaldelli A, et al. *Lancet Diabetes Endocrinol.* 2022;doi: 10.1016/S2213-8587(22)00070-5

ORIGINAL ARTICLE

Tirzepatide for Metabolic Dysfunction–Associated Steatohepatitis with Liver Fibrosis

R. Loomba, M.L. Hartman, E.J. Lawitz, R. Vuppalanchi, J. Boursier, E. Bugianesi, M. Yoneda, C. Behling, O.W. Cummings, Y. Tang, B. Brouwers, D.A. Robins, A. Nikoole, M.C. Bunck, A. Haupt, and A.J. Sanyal, for the SYNERGY-NASH Investigators*

ABSTRACT

BACKGROUND

Metabolic dysfunction–associated steatohepatitis (MASH) is a progressive liver disease associated with liver-related complications and death. The efficacy and safety of tirzepatide, an agonist of the glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptors, in patients with MASH and moderate or severe fibrosis is unclear.

METHODS

We conducted a phase 2, dose-finding, multicenter, double-blind, randomized, placebo-controlled trial involving participants with biopsy-confirmed MASH and stage F2 or F3 (moderate or severe) fibrosis. Participants were randomly assigned to receive once-weekly subcutaneous tirzepatide (5 mg, 10 mg, or 15 mg) or placebo for 52 weeks. The primary end point was resolution of MASH without worsening of fibrosis at 52 weeks. A key secondary end point was an improvement (decrease) of at least one fibrosis stage without worsening of MASH.

RESULTS

Among 190 participants who had undergone randomization, 157 had liver-biopsy results at week 52 that could be evaluated, with missing values imputed under the assumption that they would follow the pattern of results in the placebo group. The percentage of participants who met the criteria for resolution of MASH without worsening of fibrosis was 10% in the placebo group, 44% in the 5-mg tirzepatide group (difference vs. placebo, 34 percentage points; 95% confidence interval [CI], 17 to 50), 56% in the 10-mg tirzepatide group (difference, 46 percentage points; 95% CI, 29 to 62), and 62% in the 15-mg tirzepatide group (difference, 53 percentage points; 95% CI, 37 to 69) ($P < 0.001$ for all three comparisons). The percentage of participants who had an improvement of at least one fibrosis stage without worsening of MASH was 30% in the placebo group, 55% in the 5-mg tirzepatide group (difference vs. placebo, 25 percentage points; 95% CI, 5 to 46), 51% in the 10-mg tirzepatide group (difference, 22 percentage points; 95% CI, 1 to 42), and 51% in the 15-mg tirzepatide group (difference, 21 percentage points; 95% CI, 1 to 42). The most common adverse events in the tirzepatide groups were gastrointestinal events, and most were mild or moderate in severity.

CONCLUSIONS

In this phase 2 trial involving participants with MASH and moderate or severe fibrosis, treatment with tirzepatide for 52 weeks was more effective than placebo with respect to resolution of MASH without worsening of fibrosis. Larger and longer trials are needed to further assess the efficacy and safety of tirzepatide for the treatment of MASH. (Funded by Eli Lilly; SYNERGY-NASH ClinicalTrials.gov number, NCT04166773.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Loomba can be contacted at roloomba@health.ucsd.edu or at the Metabolic Dysfunction–Associated Steatotic Liver Disease Research Center, Division of Gastroenterology and Hepatology, Department of Medicine, University of California at San Diego, La Jolla, CA 92037.

*A complete list of the investigators in this trial is provided in the Supplementary Appendix, available at [NEJM.org](https://www.nejm.org).

Drs. Loomba and Hartman contributed equally to this article.

This article was published on June 8, 2024, at [NEJM.org](https://www.nejm.org).

DOI: 10.1056/NEJMoa2401943
Copyright © 2024 Massachusetts Medical Society.

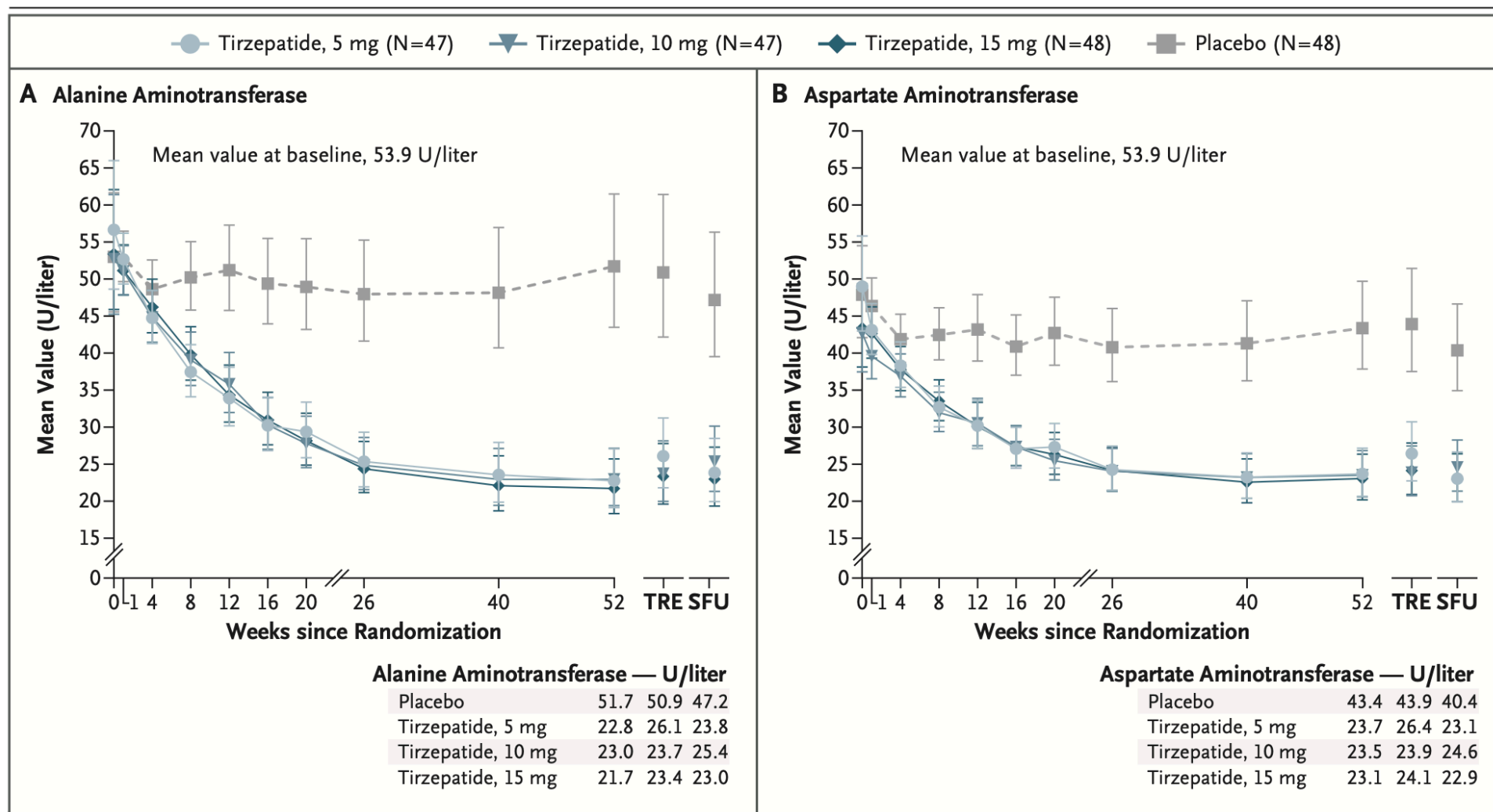


Figure 2. Mean Liver-Enzyme Levels over Time.

Shown are the mean alanine aminotransferase and aspartate aminotransferase levels from baseline through week 52 and during the subsequent 4-week safety follow-up period (SFU). Values were estimated with the use of a mixed model for repeated measures with log transformation, and the analysis included data for all the participants who had undergone randomization. Week 52 estimates for the treatment-regimen estimand (TRE) are also shown (see the Supplementary Appendix for details). The TRE included data obtained during the treatment period for all the randomly assigned participants who received at least one dose of tirzepatide or placebo, regardless of adherence to the trial drug. The mean values at baseline (top left of each graph) are geometric means from actual measurements at baseline. I bars indicate 95% confidence intervals.

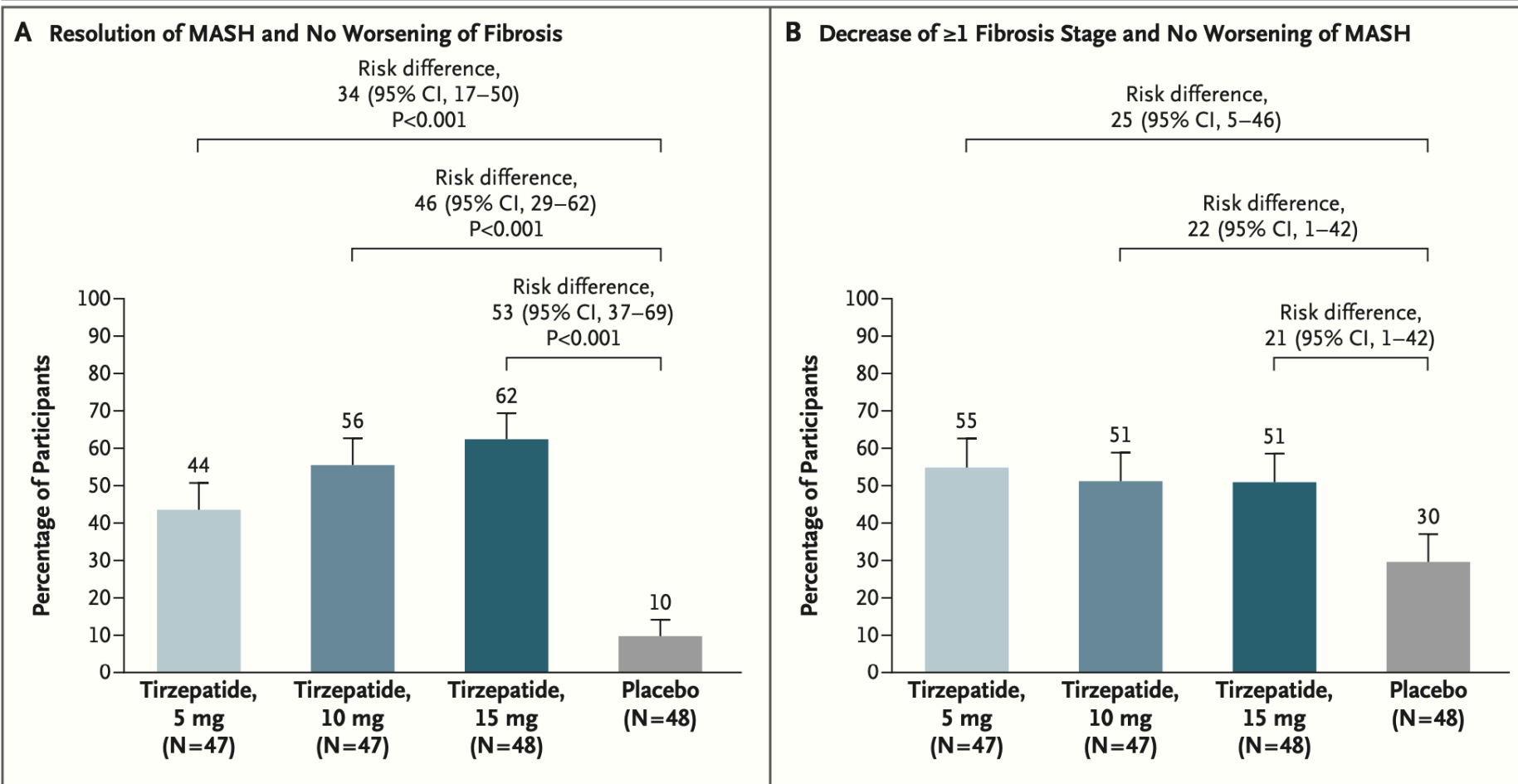


Figure 1. Primary and Key Secondary End Points.

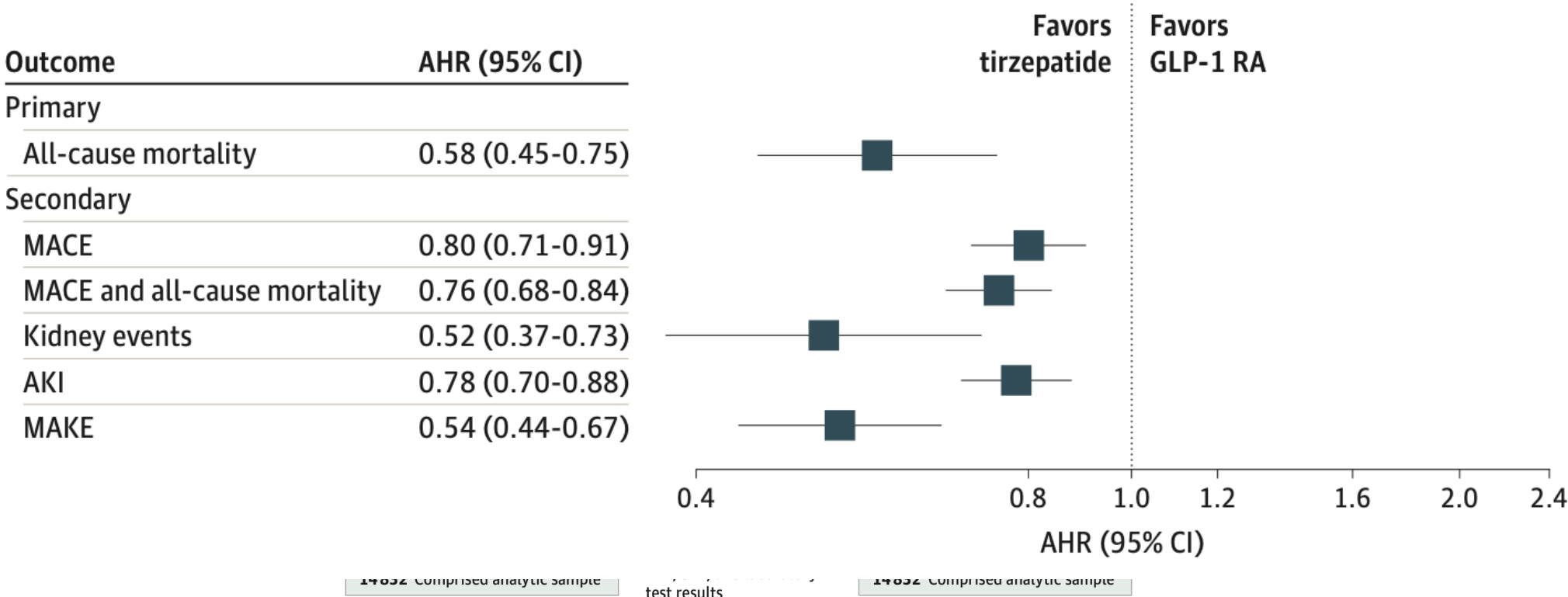
Panel A shows the percentage of participants with resolution of metabolic dysfunction–associated steatohepatitis (MASH) and no worsening of fibrosis (defined as no increase in the fibrosis stage) at week 52 (primary end point). MASH resolution was defined as no steatotic liver disease (steatosis score of 0 [on a scale of 0 to 3]) or simple steatosis (a steatosis score of 1, 2, or 3) without steatohepatitis and an inflammation score of 0 or 1 (on a scale of 0 to 2) and a hepatocellular ballooning score of 0 (on a scale of 0 to 2); higher scores indicate more severe disease. Panel B shows the percentage of participants with an improvement (decrease) of at least one fibrosis stage and no worsening of MASH (defined as no increase in the nonalcoholic fatty liver disease activity score) at week 52 (key secondary end point). Risk differences indicate percentage-point differences between the groups. The confidence intervals have not been adjusted for multiple comparisons and should not be used to infer definitive effects of tirzepatide. The percentage estimates and risk differences were calculated with the use of a logistic-regression model.²³ I bars indicate standard errors.

Clinical Outcomes of Tirzepatide or GLP-1 Receptor Agonists in Individuals With Type 2 Diabetes

Min-Hsiang Chuang, MD; Jui-Yi Chen, MD; Hsien-Yi Wang, MD; Zheng-Hong Jiang, MD; Vin-Cent Wu, MD, PhD

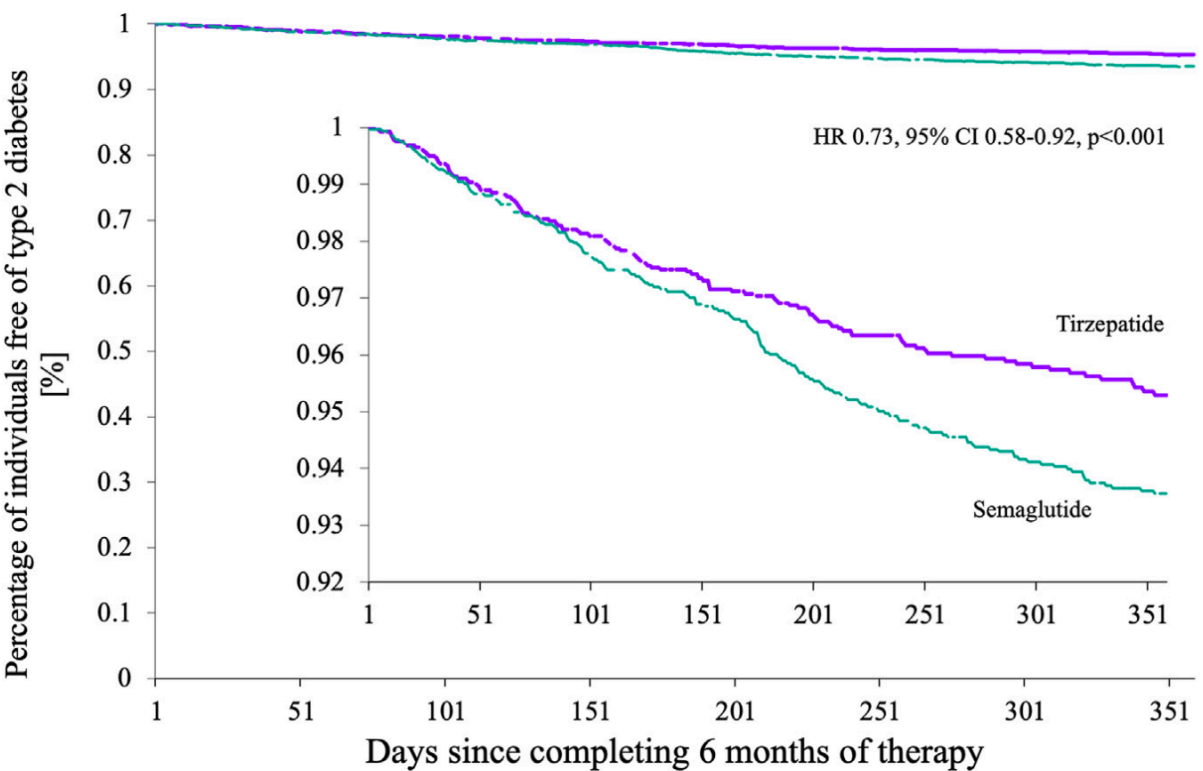
Figure 1. Flow Diagram of Cohort Construction

Figure 2. Forest Plot of Primary and Secondary Outcomes



Incidence of new onset type 2 diabetes in adults living with obesity treated with tirzepatide or semaglutide: real world evidence from an international retrospective cohort study

Matthew Anson,^a Alex E. Henney,^a Nicholas Broadwell,^b Sizheng S. Zhao,^c Gema H. Ibarburu,^d Gregory Y. H. Lip,^{e,f} John P. H. Wilding,^a Daniel J. Cuthbertson,^{a,*} and Uazman Alam^{a,g,**}



Number at risk	Day 0	Day 90	Day 180	Day 270	Day 365
Tirzepatide group	6923	6806	6718	6645	6597
Semaglutide group	6923	6800	6673	6546	6477

Fig. 3: Kaplan–Meier estimates of event free rate between tirzepatide and semaglutide groups.

Agenda

Obesità Malattia Cronica

Il Diabete Mellito e il Core Fisiopatologico

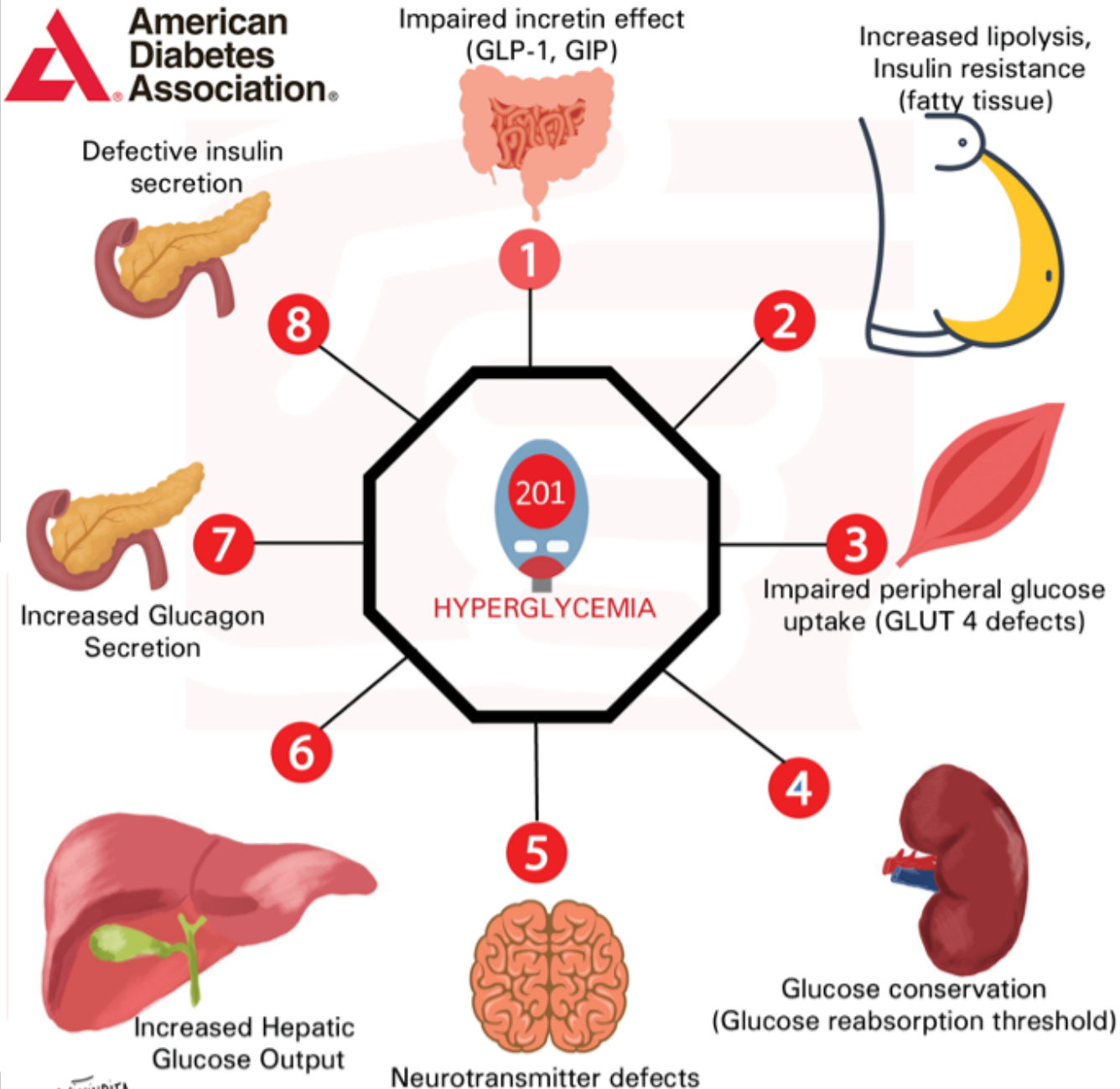
Approccio Terapeutico-Fisiopatologico

Riflessioni Conclusive

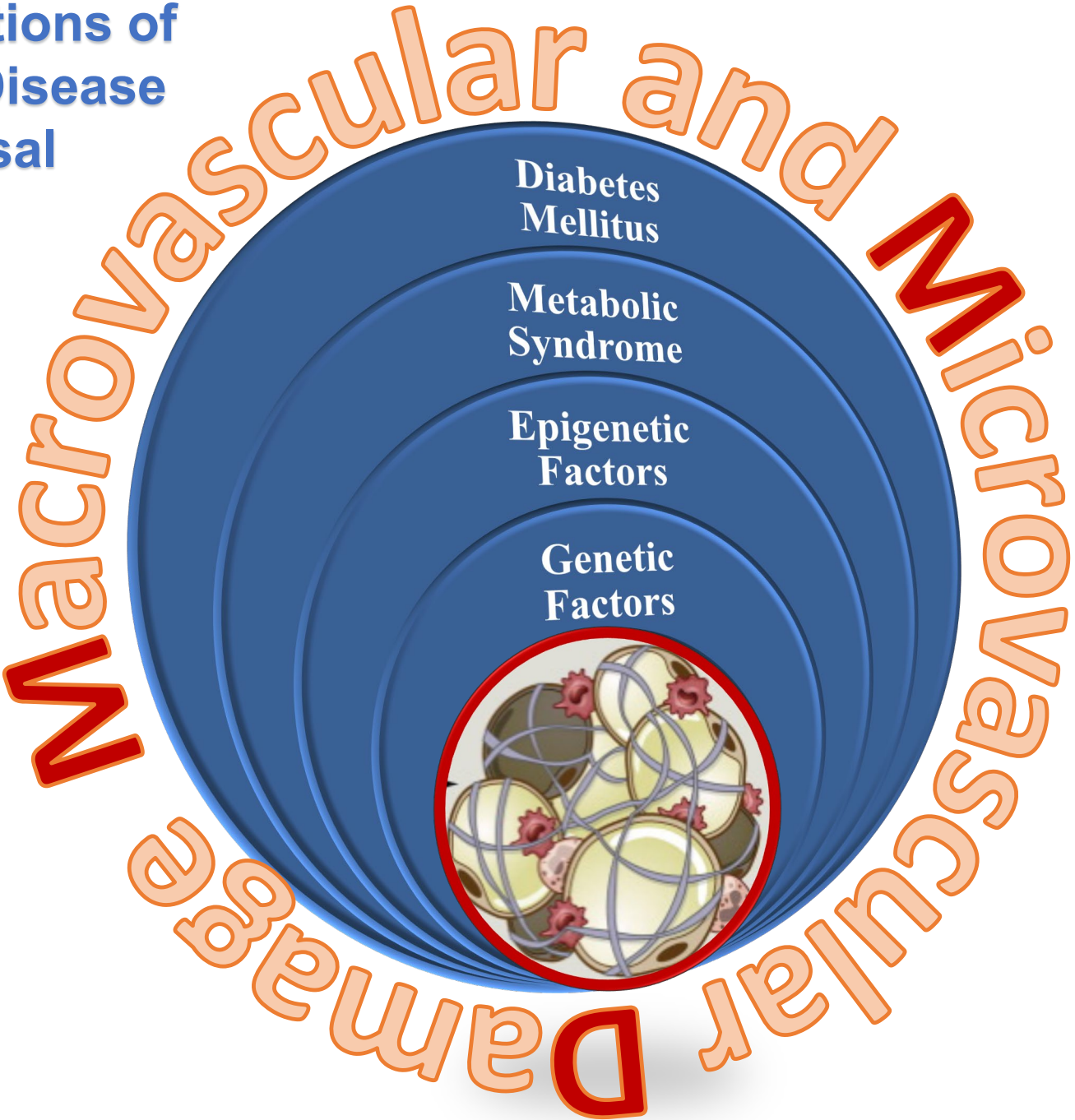
DIABETES MELLITUS : THE OMINOUS OCTET



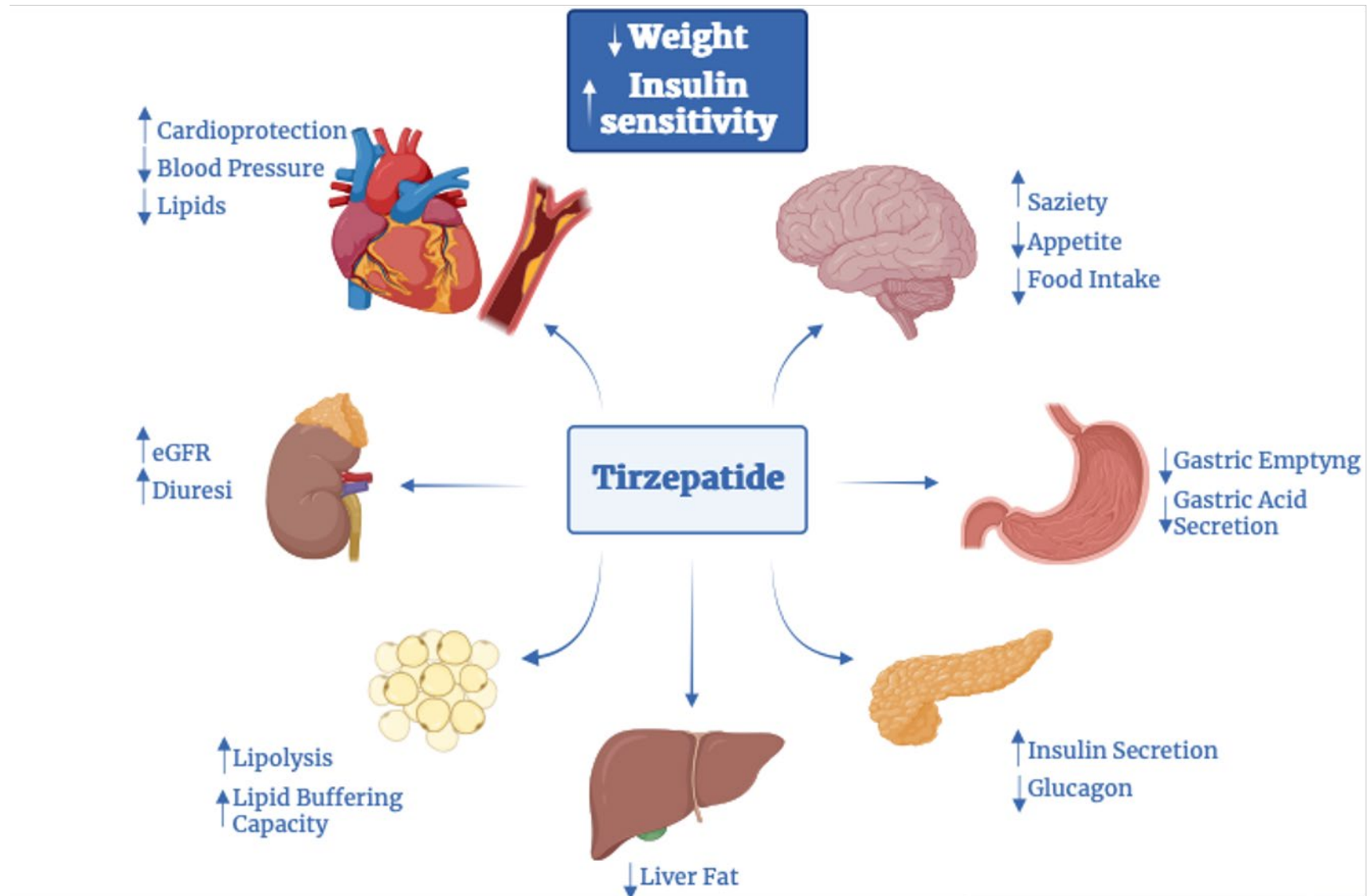
**American
Diabetes
Association®**



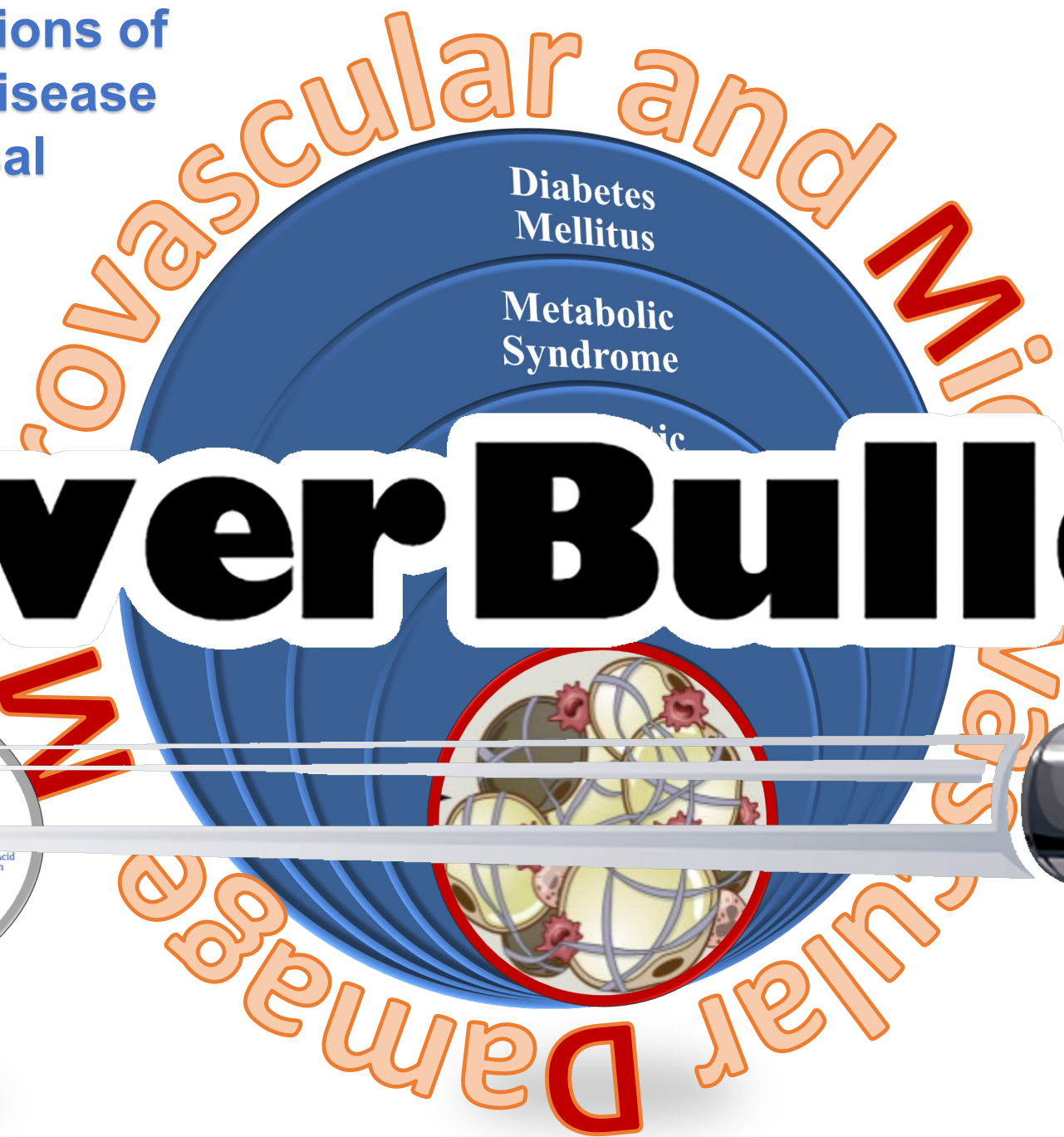
**Pathological directions of
Disfuncional Fat Disease
and its Reversal**



“Tirzepatide promotes the reversal of adiposopathy”



Pathological directions of
Disfuncional Fat Disease
and its Reversal



SilverBullet

