

Obésité et syndrome métabolique

«le point de vue de l'endocrinologue»

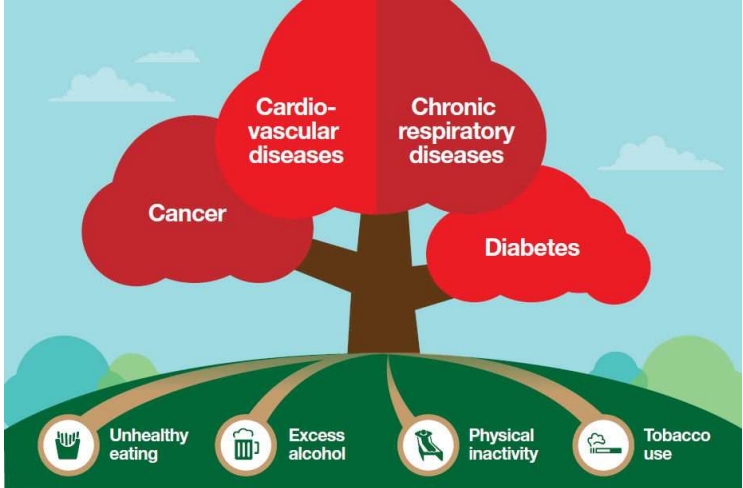
PD Dr. med. Giacomo Gastaldi

DiaCenTRE – Maison du Diabète – Hirslanden Grangettes SA

1224 Chêne-Bougeries



Mortality and Non Communicable Diseases (NCDs)



WHO report 2022

6x6	Oral diseases and conditions	Sugars
5x5	Mental disorders and conditions	Air pollution
4x4	Cardiovascular diseases	Tobacco
	Diabetes	Alcohol
	Cancers	Unhealthy diet
	Chronic respiratory diseases	Physical inactivity

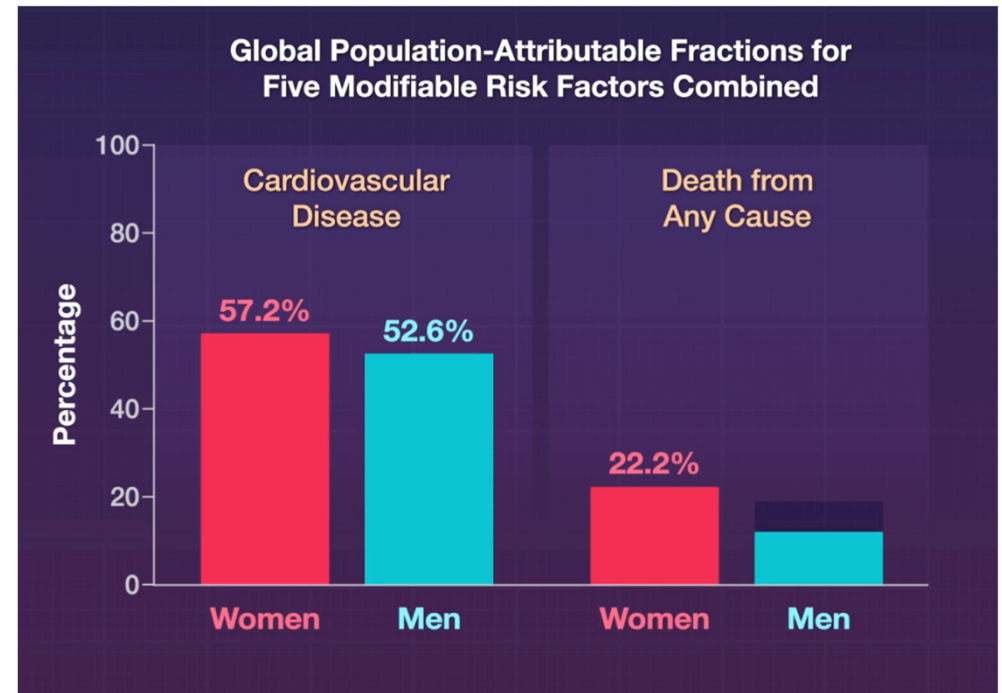
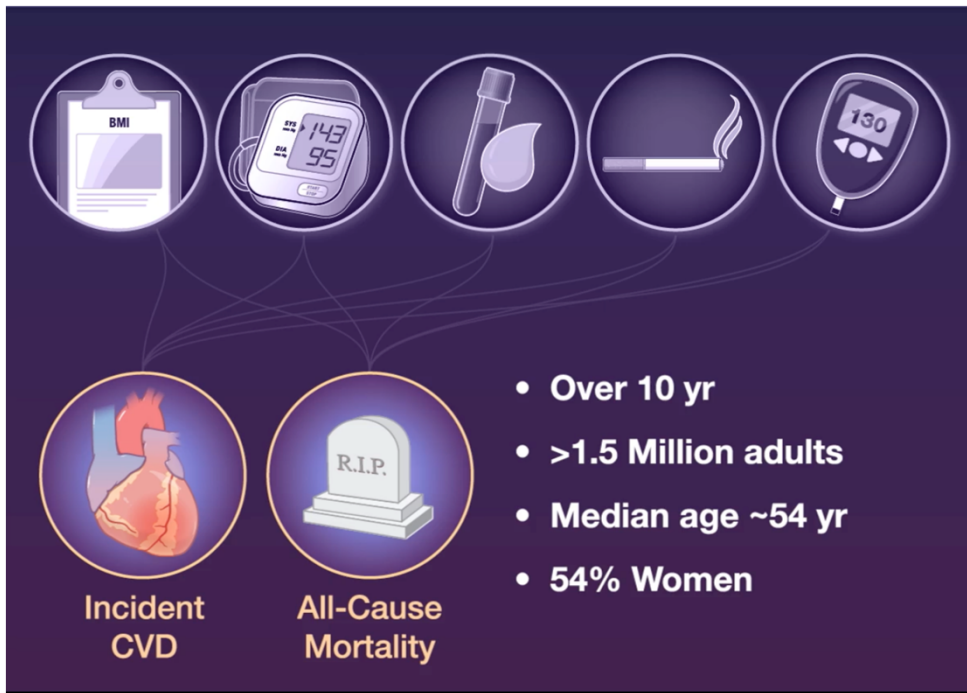
Benzian H et al. Lancet Public Health 2023

NCDs kill 41 million people each year, equivalent to 74% of all deaths globally

- **Cardiovascular diseases** (17,9 mio)
- **Cancers** (9,3 millions)
- **Chronic respiratory diseases** (4,1 millions)
- **Diabetes Mellitus** (2,0 millions)

NCD countdown Lancet 2022; 399: 1266–78

Global population



Cardiovascular diseases (CVDs)

- Out of the 17 million premature deaths (under the age of 70) due to noncommunicable diseases in 2019, 38% were caused by CVDs.
- **It is important to detect cardiovascular disease as early as possible so that management with counselling and medicines can begin.**
- Most cardiovascular diseases can be prevented by addressing **behavioural risk factors** such as tobacco use, unhealthy diet and obesity, physical inactivity and harmful use of alcohol.

Metabolic syndrome

▪ High waist circumference (WC), whose thresholds depend on populations and country-specific definitions (≥ 102 cm and ≥ 88 cm for European men and women respectively) [9];

▪ Blood TG $\geq 1,7$ mmol/L;

▪ Blood HDL cholesterol $< 1,0$ mmol/L in men and $< 1,3$ mmol/L in women;

▪ Blood pressure (BP) $\geq 130/85$ mmHg;

▪ Blood fasting glucose ≥ 5.6 mmol/L.

Measure	Categorical Cut Points
Elevated waist circumference*	Population- and country-specific definitions
Elevated triglycerides (drug treatment for elevated triglycerides is an alternate indicator [†])	≥ 150 mg/dL (1.7 mmol/L)
Reduced HDL-C (drug treatment for reduced HDL-C is an alternate indicator [†])	< 40 mg/dL (1.0 mmol/L) in males; < 50 mg/dL (1.3 mmol/L) in females
Elevated blood pressure (antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator)	Systolic ≥ 130 and/or diastolic ≥ 85 mm Hg
Elevated fasting glucose [‡] (drug treatment of elevated glucose is an alternate indicator)	≥ 100 mg/dL
HDL-C indicates high-density lipoprotein cholesterol.	
[*] It is recommended that the IDF cut points be used for non-Europeans and either the IDF or AHA/NHLBI cut points used for people of European origin until more data are available.	
[†] The most commonly used drugs for elevated triglycerides and reduced HDL-C are fibrates and nicotinic acid. A patient taking 1 of these drugs can be presumed to have high triglycerides and low HDL-C. High-dose ω -3 fatty acids presumes high triglycerides.	
[‡] Most patients with type 2 diabetes mellitus will have the metabolic syndrome by the proposed criteria.	

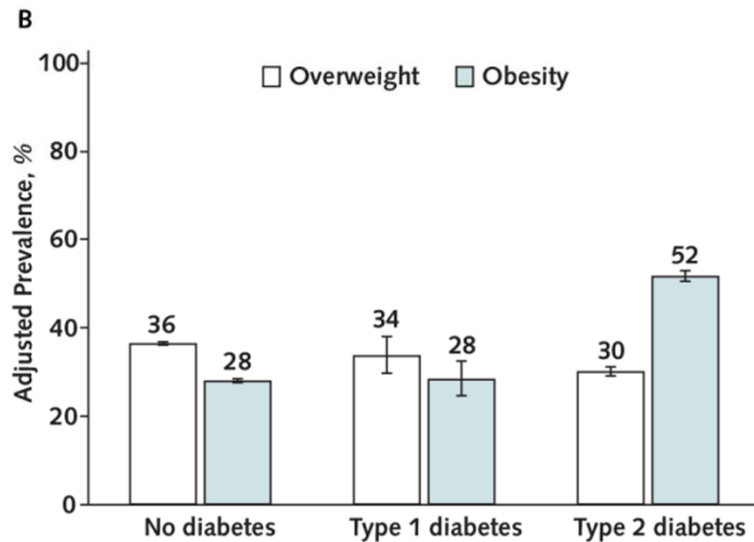
3 sur 5 critères



Circulation. 2009;120(16):1640-1645.

Obesity and DM

Page 4



Characteristics of U.S. Adults, by Diabetes Status: NHIS, 2016 to 2021 *

Characteristic	No Diabetes (Unweighted <i>n</i> = 115 441)	Type 1 Diabetes (Unweighted <i>n</i> = 733)	Type 2 Diabetes (Unweighted <i>n</i> = 12 397)
Mean age, y	46.6 ± 0.1	49.2 ± 0.9	62.8 ± 0.2
Age category, %			
18-44 y	48.6 ± 0.3	42.1 ± 2.4	9.3 ± 0.4
45-64 y	32.6 ± 0.2	34.3 ± 2.1	43.2 ± 0.6
≥65 y	18.8 ± 0.2	23.6 ± 1.8	47.5 ± 0.6

Percentage of adults with overweight or obesity:

- 64% of adults without diabetes
- 62% of adults with type 1 diabetes
- 82% of adults with type 2 diabetes

Risk factors for T2D

Categories	14 Risks factors for T2D	Amount
Environmental or occupational	Ambient particulate matter pollution, household air pollution from solid fuels (PM _{2.5} and 10)	Incidence and prevalence of DM OR 1.2-1.4
Tobaco use	Smoking, second-hand smoke	> 20 cig/day OR 1.55-1.9 (men) OR 1.47 (women)
Alcool use	High alcohol use	60g/day (men) 50g/day (women)
Body fat	BMI (body-mass index)	OR 1.5 (BMI 24kg/m²) (men) OR 2.9 (BMI 23kg/m²) (women)
Dietary risk	Diet low in fruits, diet low in vegetables, diet low in whole grains, diet high in red meat, diet high in processed meat, diet high in sugar-sweetened beverages, diet low in fibre	
Physical activity	low physical activity (< 1.5 METs)	150 minutes; 75 min (high intensity)

Yang B, et al. *Environ Res* (2020)

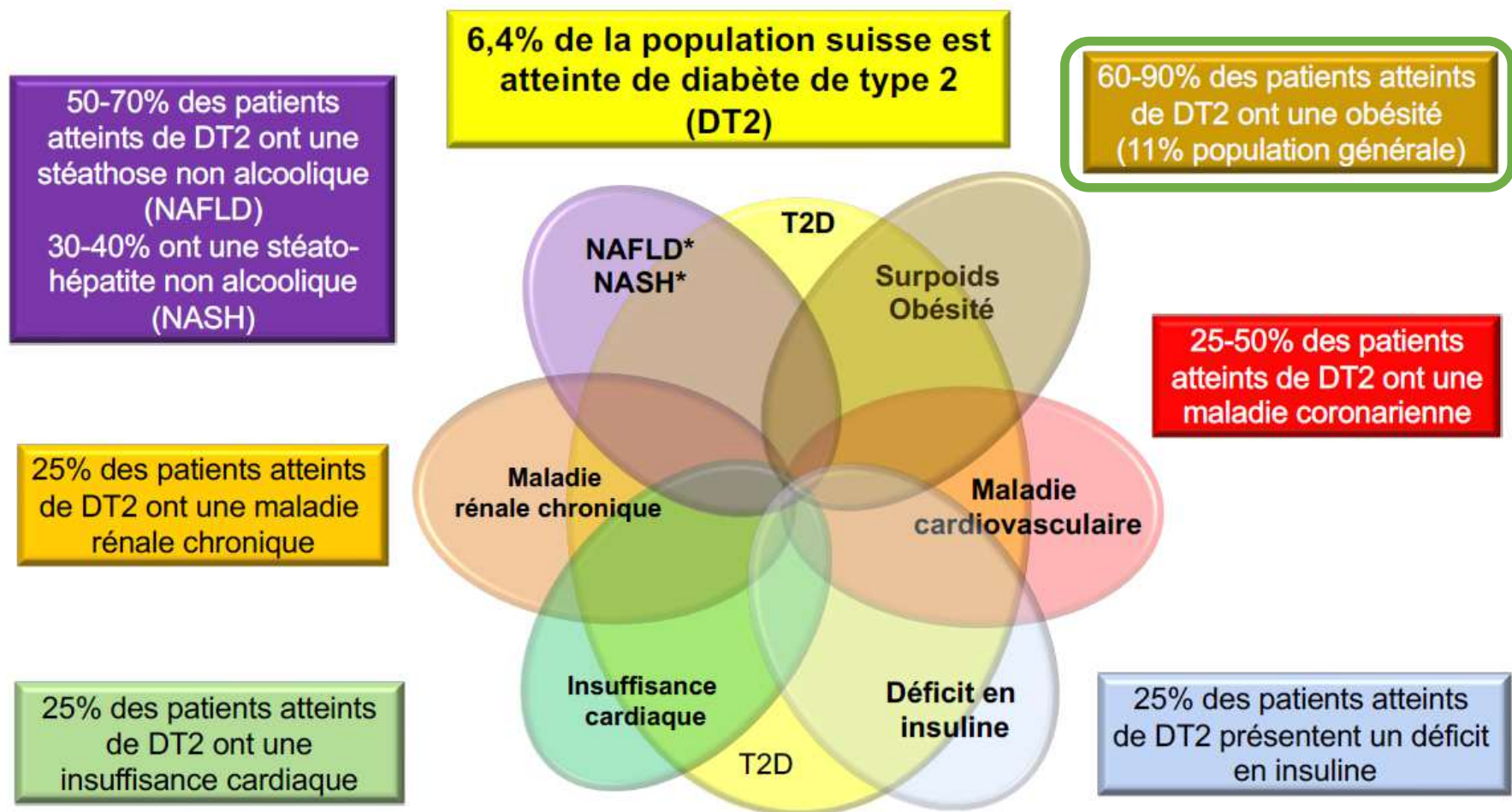
Chang S et al. *Diabetes Metab J*. 2012 Dec; 36(6): 399–403.

Baliunas et al. *Diabetes Care*. 2009 Nov; 32(11): 2123–2132.

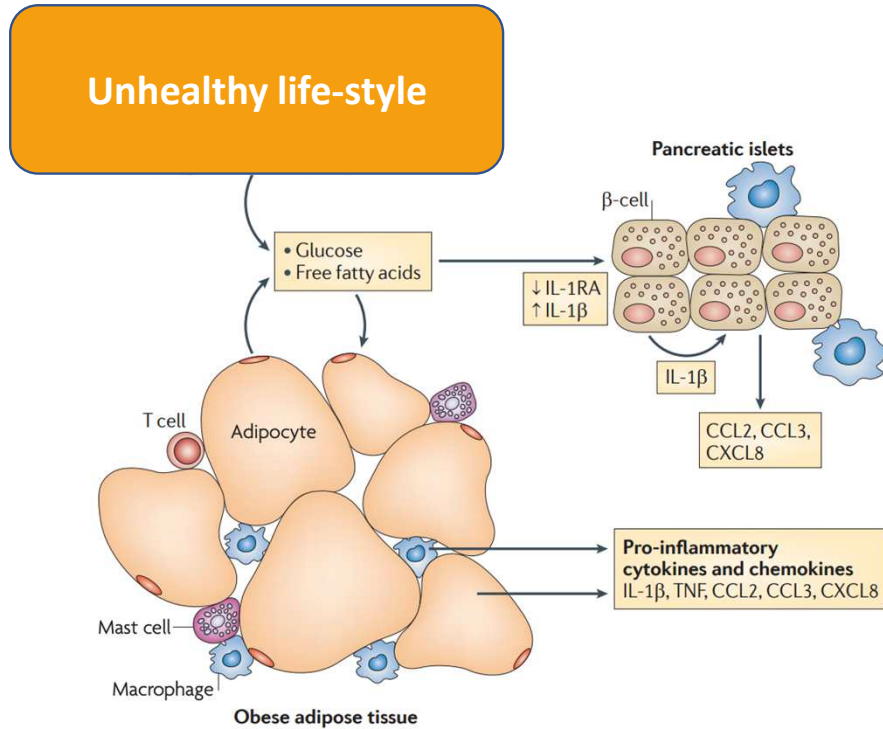
Chan J, et al. *Diabetes Care*. 1994;17:961-969 (hommes)

Colditz G, et al. *Ann Intern Med*. 1995;122:481-486 8 (femmes)

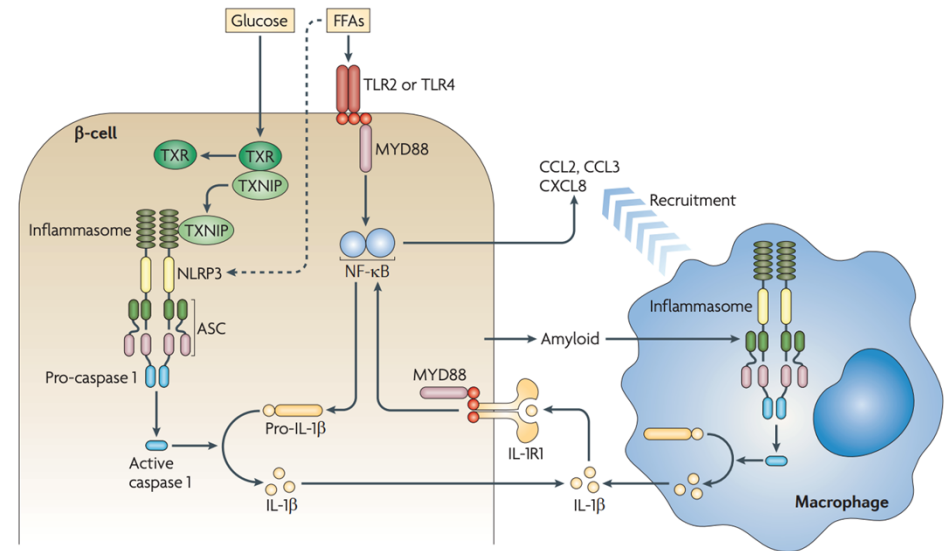
Type 2 diabetes and many others



Inflammation and insulin resistance

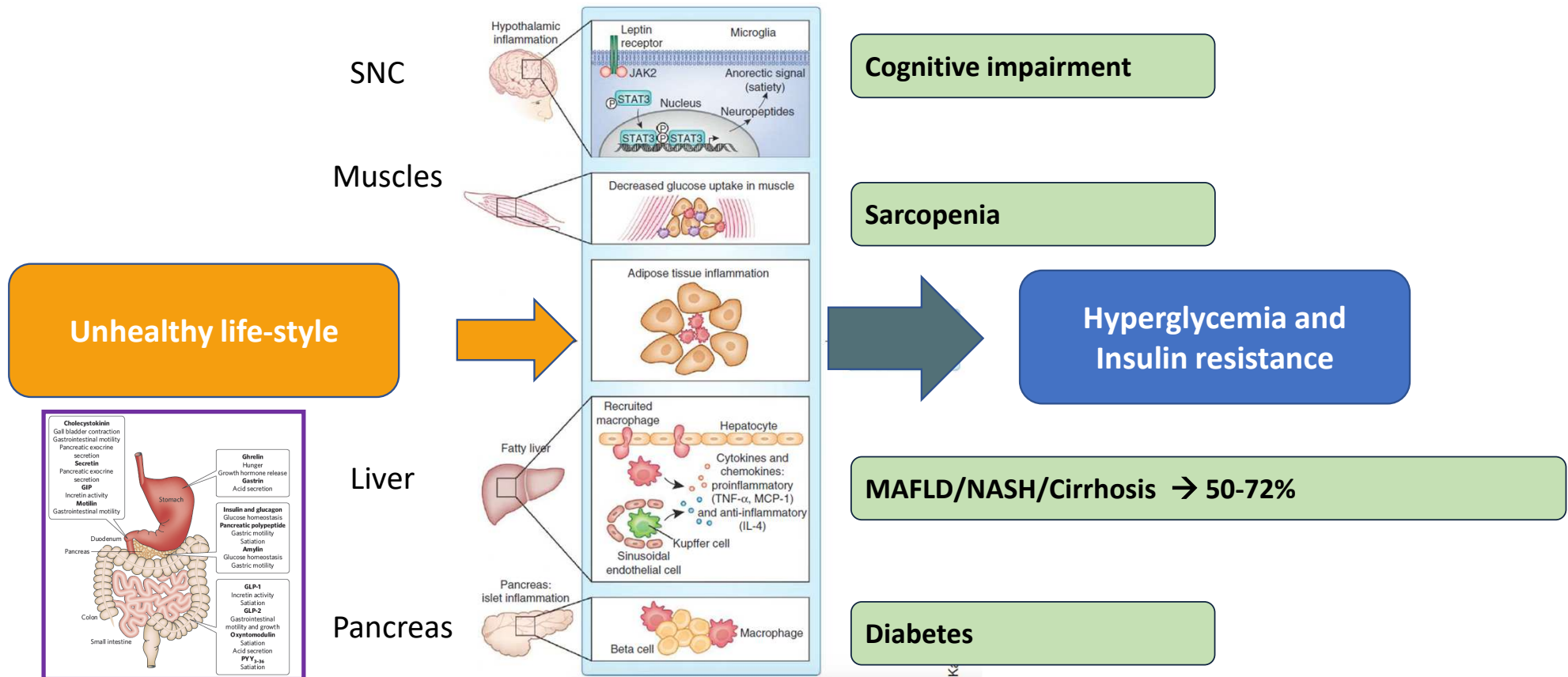


Development of inflammation in T2D

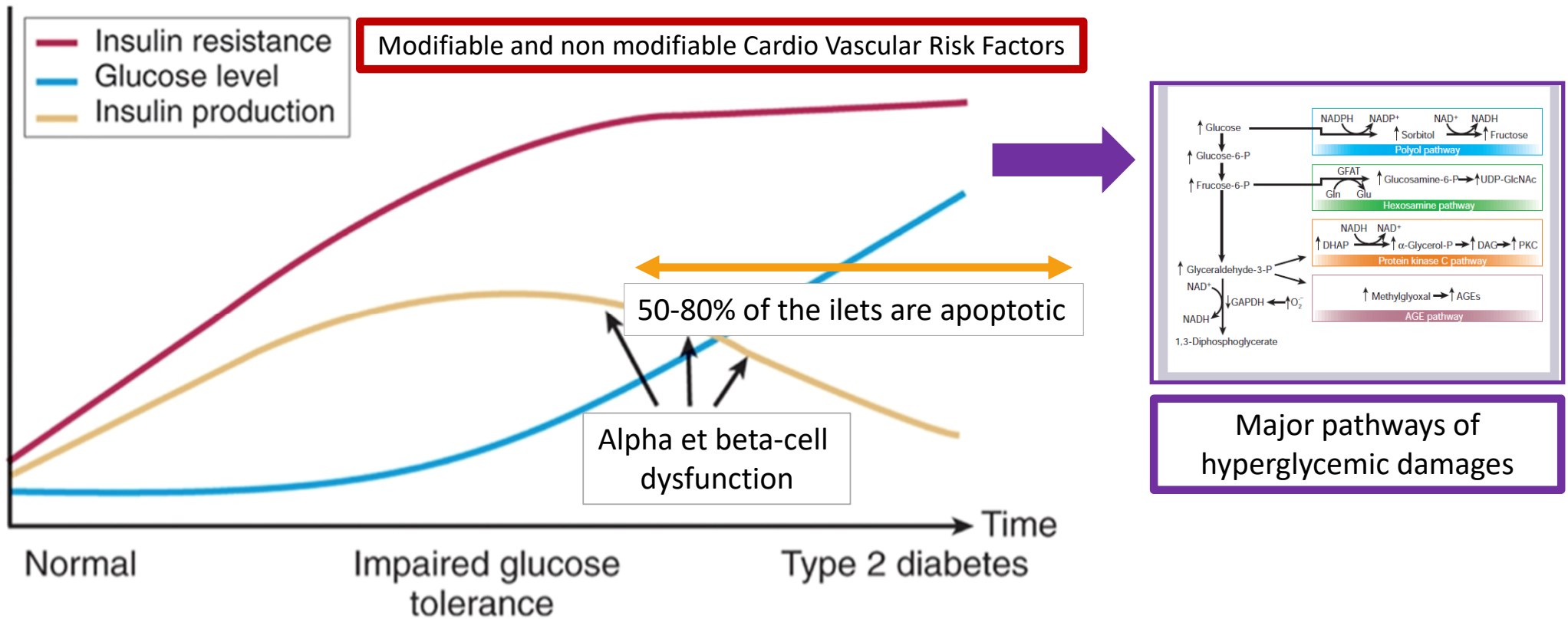


Interleukin-1β-induced inflammation in islets of patients with T2D

Overview of T2D complexity



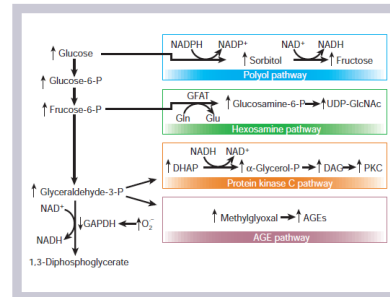
Type 2 diabetes is an evolutive disease



Brownlee M. et al Nature. 2001 Dec 13;414(6865):813-20.
Henry RR. Am J Med. 1998 Jul 6;105(1A):20S-26S

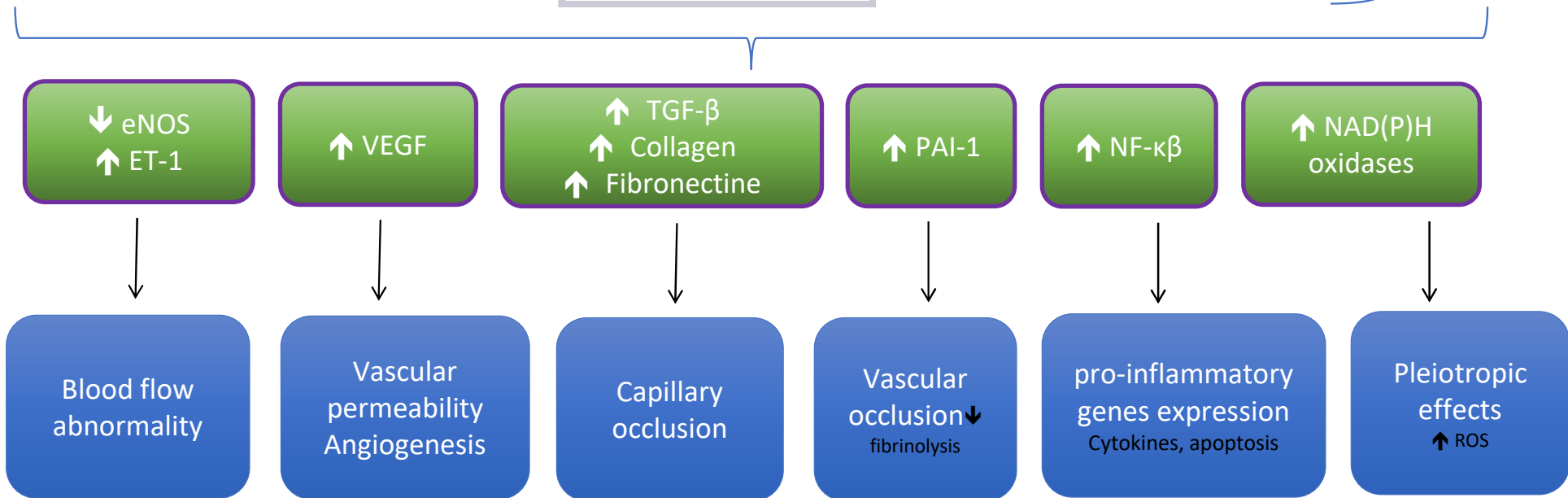
4 major pathways of hyperglycemic damages

Hyperglycemia



1. Polyol pathway
2. Hexosamine pathway
3. Protein kinase C pathway
4. AGE pathway

Damage to the Endothelial Glycocalyx

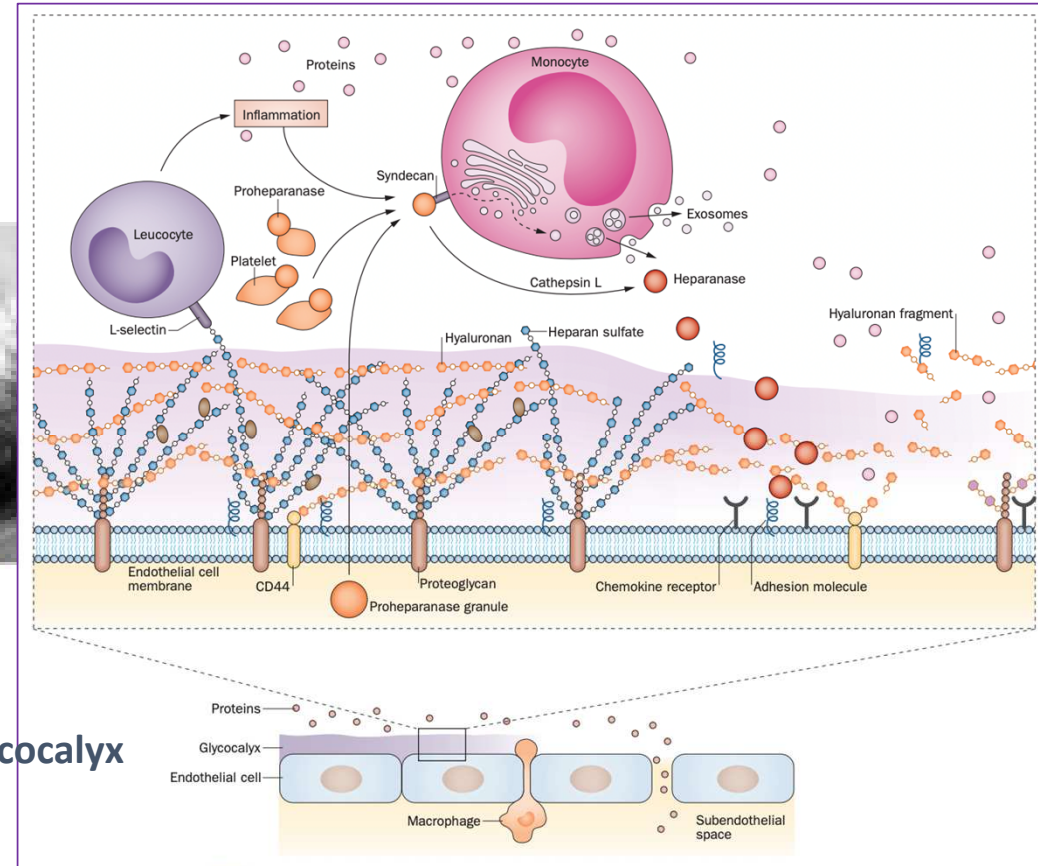


AGE, advanced glycation end-product; eNOS, endothelial nitric oxide synthetase; Et-1, endothelin-1; VEGF, vascular endothelial growth factor; TGF-β, transforming growth factor-β; PAI-1, plasminogen activator inhibitor-1 (PAI-1), ROS, reactive oxygen species.
Adapted from Brownlee M. Biochemistry and molecular cell biology of diabetic complications. Nature. 2001 Dec 13;414(6865):813-20.

Circulatory system



arteries, veins and lymphatics

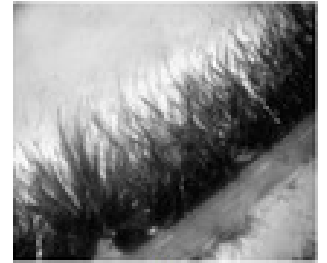


Endothelial Glycocalyx

Dogné S. et al. 2018 Arteriosclerosis, Thrombosis, and Vascular Biology

Rabelink, T., de Zeeuw, D. *Nat Rev Nephrol* **11**, 667–676 (2015)

Diabetes is associated with endothelial glycocalyx damages



Acute hyperglycemia reduce the glycolayx volume

Niewdorp M et al. Diabetes. 2006;55:480–486.

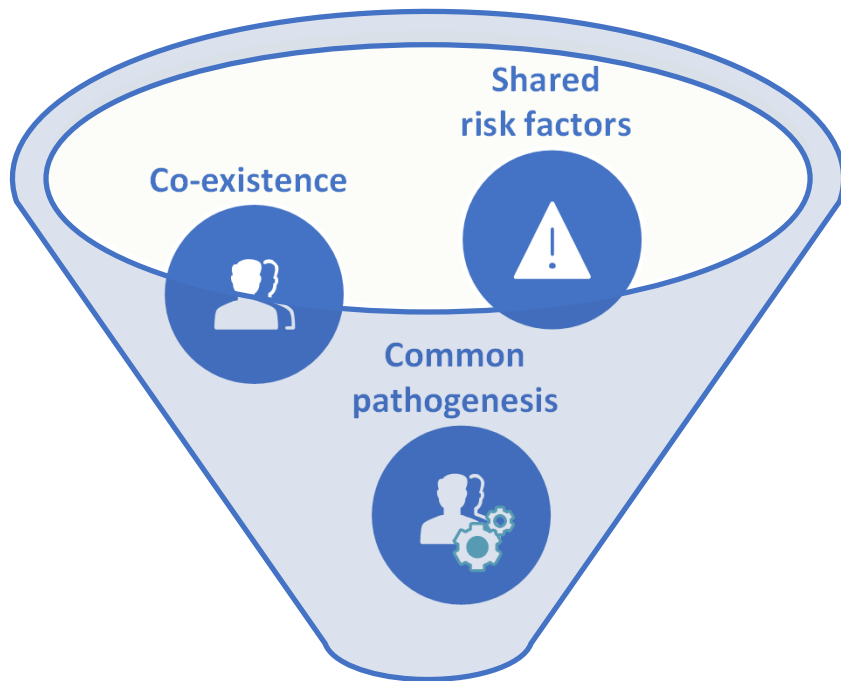
Patients with T2D have decreased endothelial glycocalyx dimensions compared with healthy controls (sublingual and retinal microcirculation; erythrocyte–endothelium gap)

Broekhuizen L.N et al. Diabetologia. 2010; 53(12): 2646–2655.

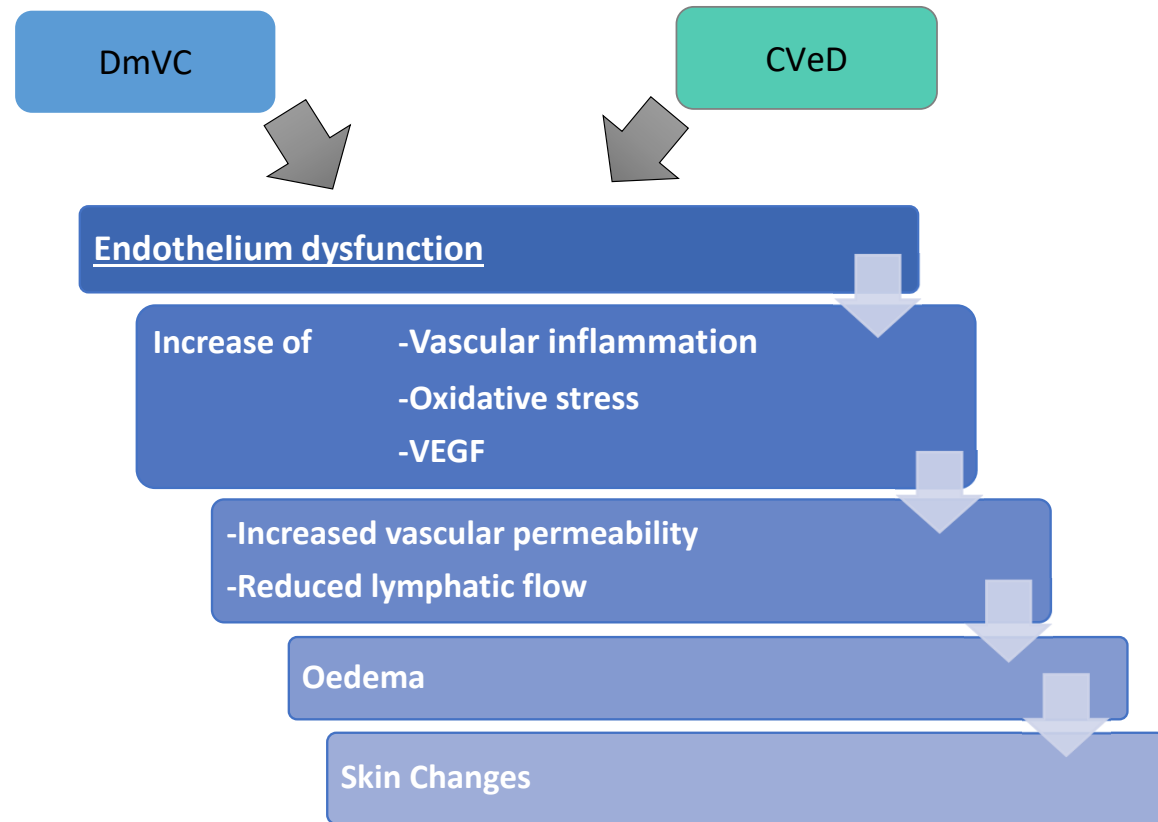
Endothelial glycocalyx : a **shield against** diabetes related vascular complications !

Sophie Dogné et al. 2018 Arteriosclerosis, Thrombosis, and Vascular Biology.

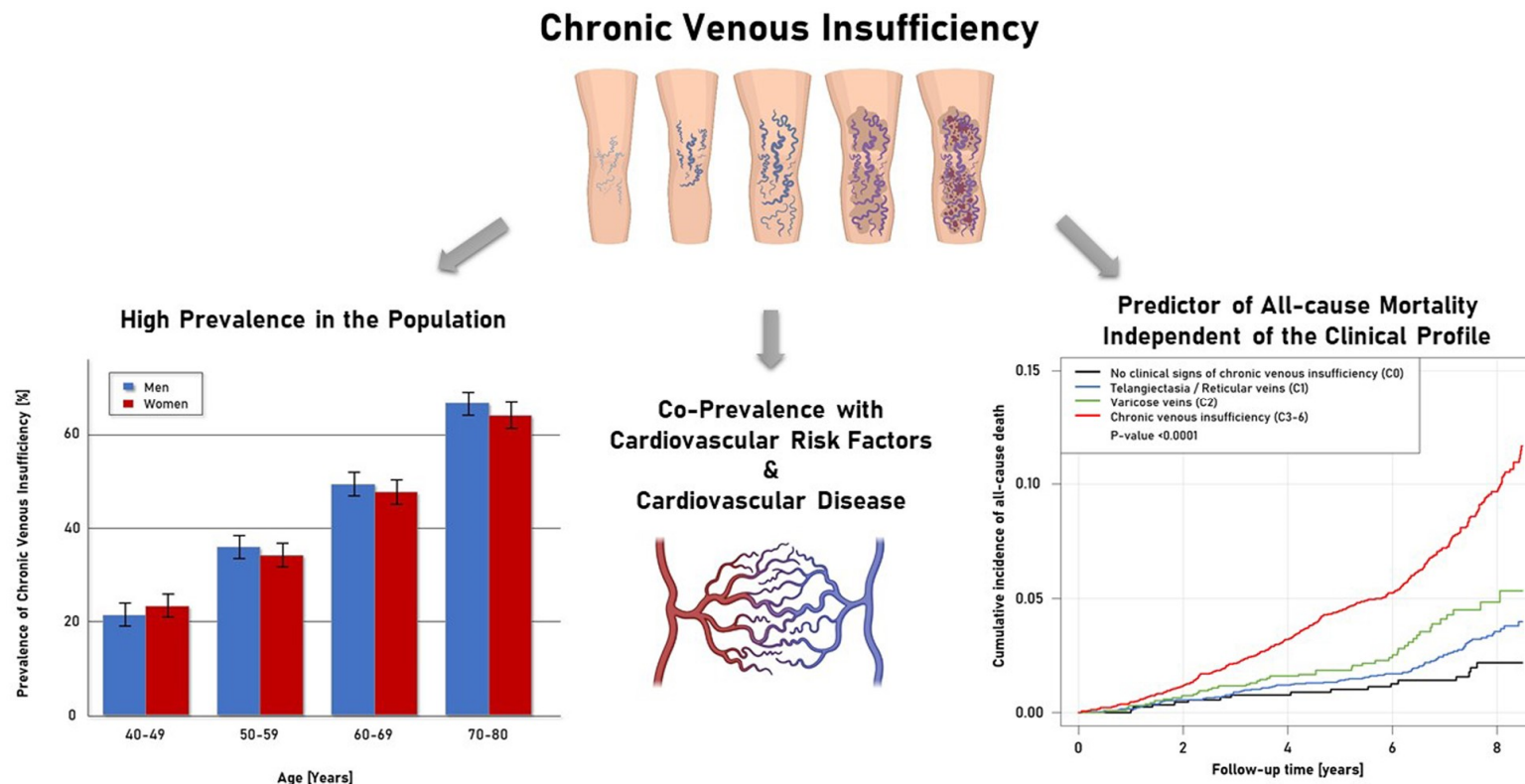
DmVC and Chronic Venous Disease (CVeD) have common risk factors and pathophysiology



CVeD, chronic venous disease; DmVC, Diabetic microvascular Complications; VEGF, vascular endothelial growth factor.



CVeD (CVI) is associated with arterial cardiovascular disease and an increased risk of all-cause mortality



Int J Colorectal Dis (2012) 27:215–220
DOI 10.1007/s00384-011-1316-3

976 participants

ORIGINAL ARTICLE

The prevalence of hemorrhoids in adults

Stefan Riss · Friedrich Anton Weiser ·
Katrin Schwameis · Thomas Riss · Martina Mittlböck ·
Gottfried Steiner · Anton Stift

Prevalence 38.93%

(18.42%) as grade II
(8.16%)
(0.53%)

Accepted: 5 September 2011 / Published online: 20 September 2011
© Springer-Verlag 2011

Older age, female sex, smoking, overweight, and being hypertensive were independently associated with the presence of hemorrhoidal disease.

www.nature.com/scientificreports

scientific reports

 Check for updates

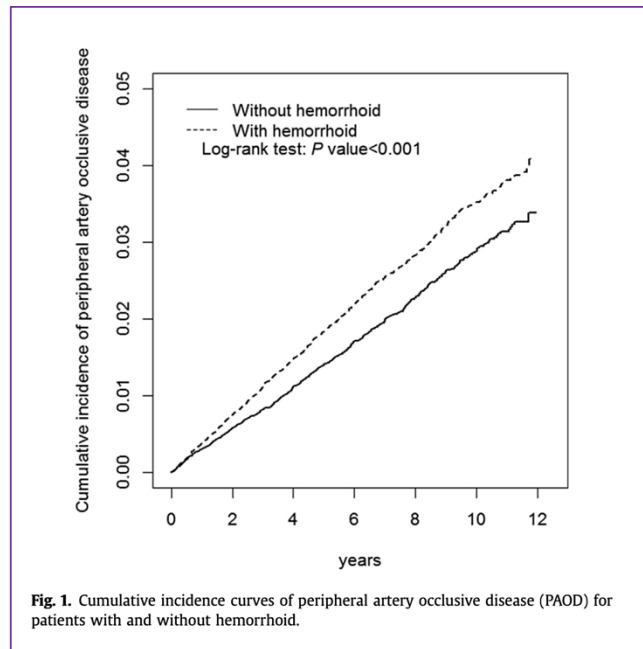
OPEN **Risk factors for hemorrhoidal disease among healthy young and middle-aged Korean adults**

Yun Soo Hong^{1,10}, Kyung Uk Jung^{2,10}, Sanjay Rampal³, Di Zhao¹, Eliseo Guallar^{1,4},
Seungho Ryu^{4,5,6}, Yoosoo Chang^{4,5,6}, Hyung Ook Kim², Hungdai Kim², Ho-Kyung Chun²,
Chong Il Sohn^{5,7}, Hocheol Shin^{5,8} & Juhee Cho^{1,4,5,9}✉

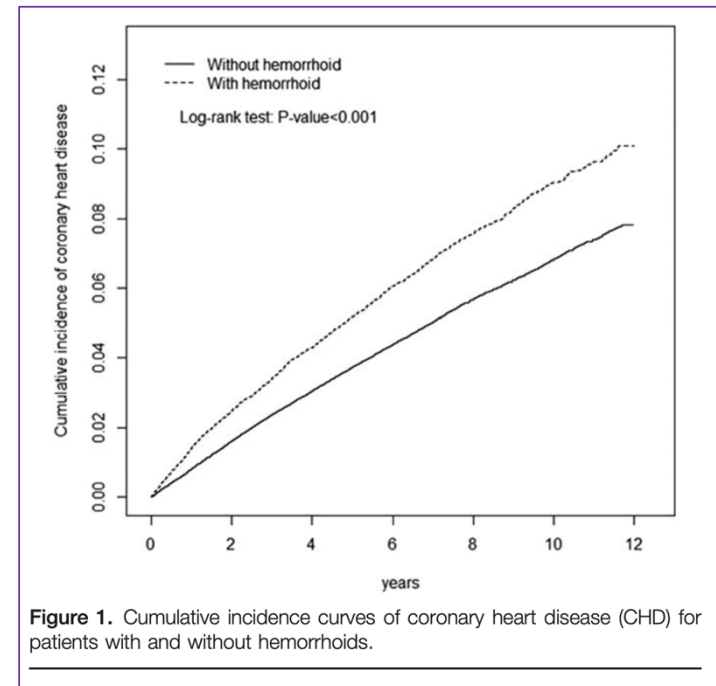
Scientific Reports volume 12, Article number: 129 (2022)

The Taiwanese Longitudinal Health Insurance Database 2000

No, N=132,136 Yes, N=33,034

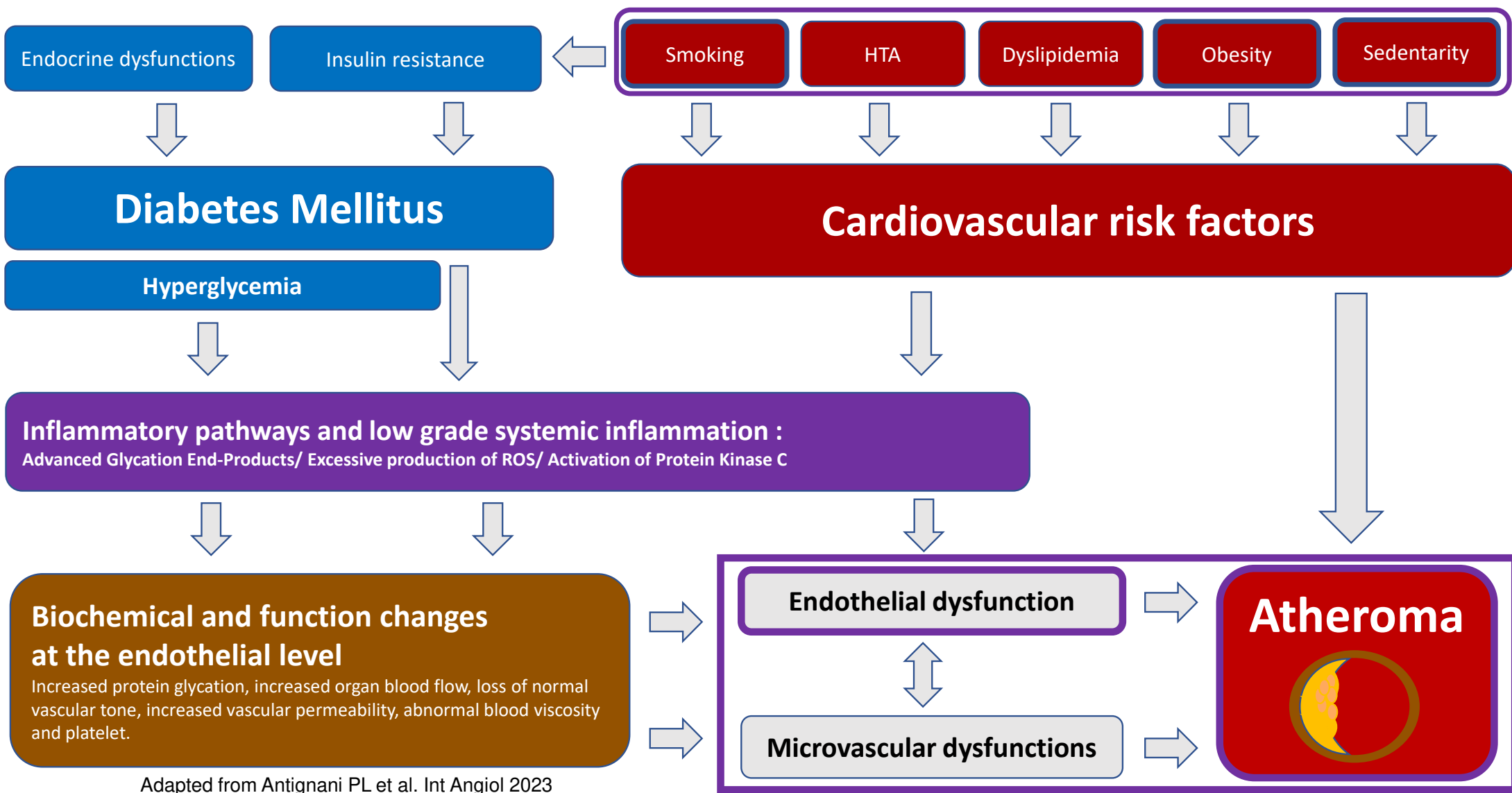


Conclusions: A significantly increased PAOD risk in patients with hemorrhoids was found in this nationwide cohort study.



Hemorrhoid patients have a 1.27-fold higher risk of CHD compared with those without hemorrhoids after adjusting for the potential confounding factors

Pathophysiology of complications related to DM



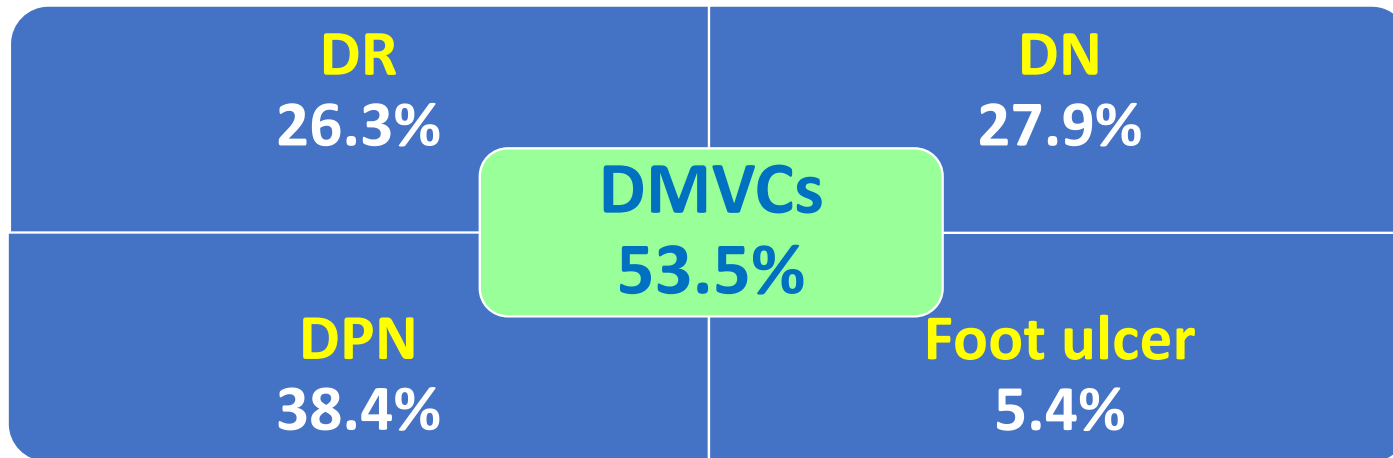
Adapted from Antignani PL et al. Int Angiol 2023

~50% of T2DM patients are developing microvascular complications (DMVCs)

6.7
Million
Deaths due to
DM in 2021

10th IDF atlas

Prevalence rates for DMVCs in T2DM patients

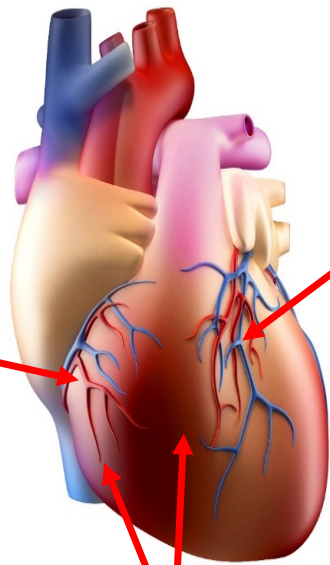


DMVC, diabetic microvascular complication; DN, diabetic nephropathy; DPN, diabetic peripheral neuropathy; DR, diabetic retinopathy

Litwak L, et al. Diabetol Metab Syndr 2013;5(1):57

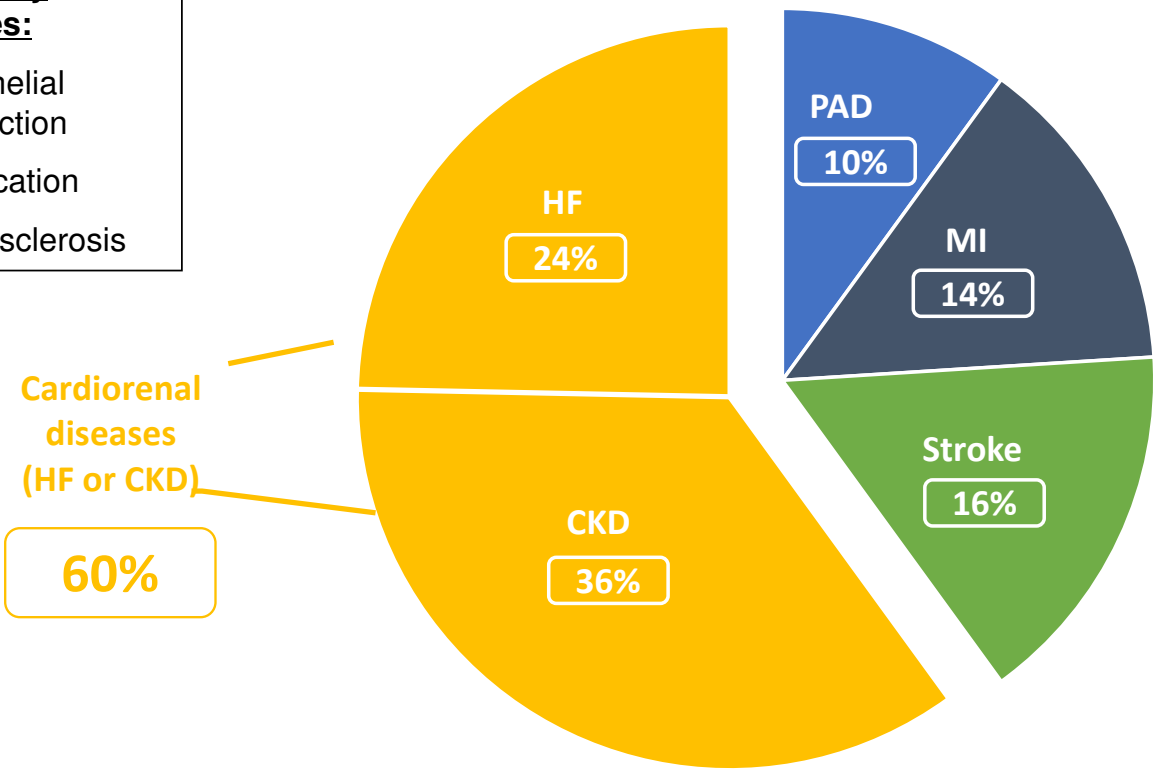
T2D and Cardiorenal complications

Cardiac muscle:
Specific heart disease (cardiomyopathy)
Diastolic and systolic dysfunction



Coronary arteries:
Endothelial dysfunction
Calcification
Atherosclerosis

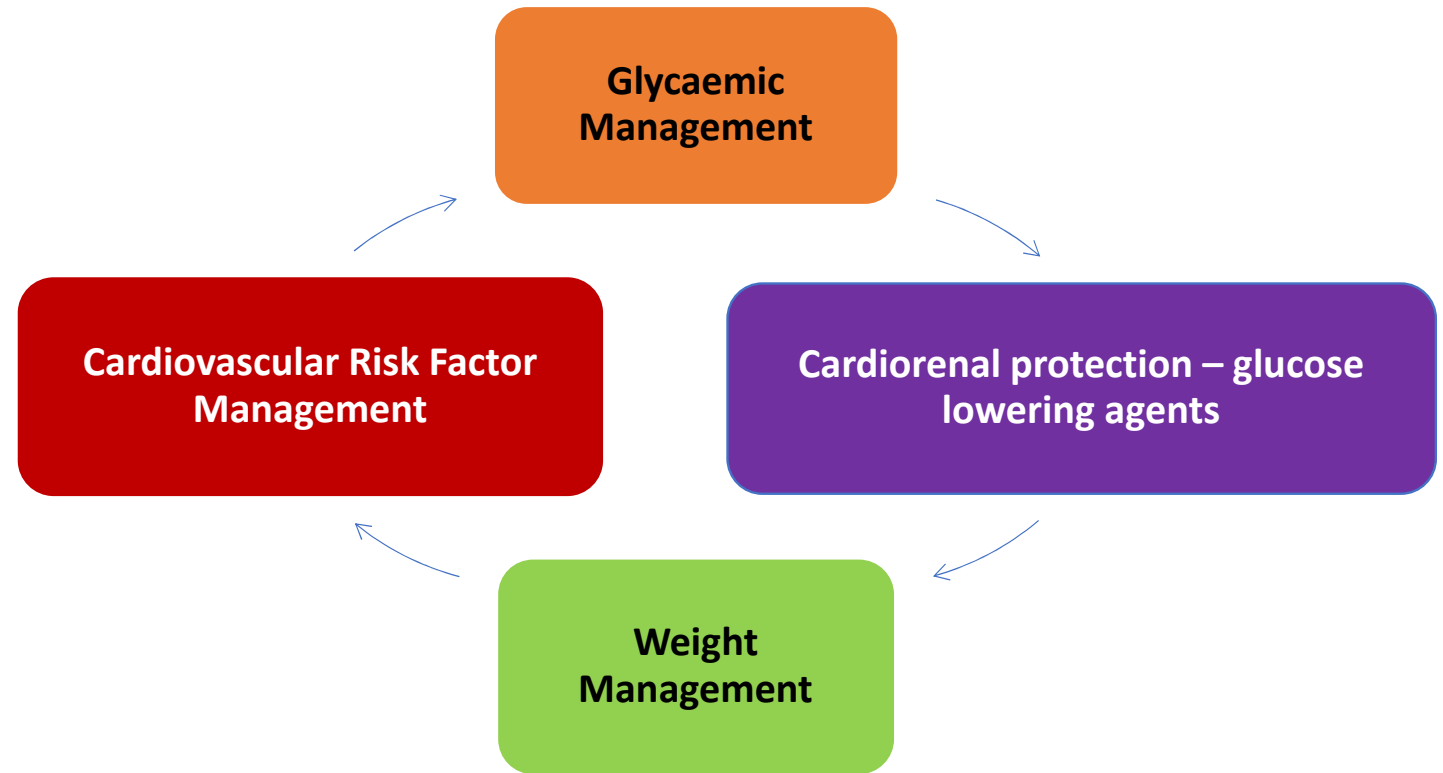
Autonomic nerves:
Neuropathy
Impaired coronary vasomotor capacity



In the comorbidity-free population from 6 countries 18% (137,081) had a first event during a mean follow-up of 4.5 years.^{1,}

T2D Management → preventing complications

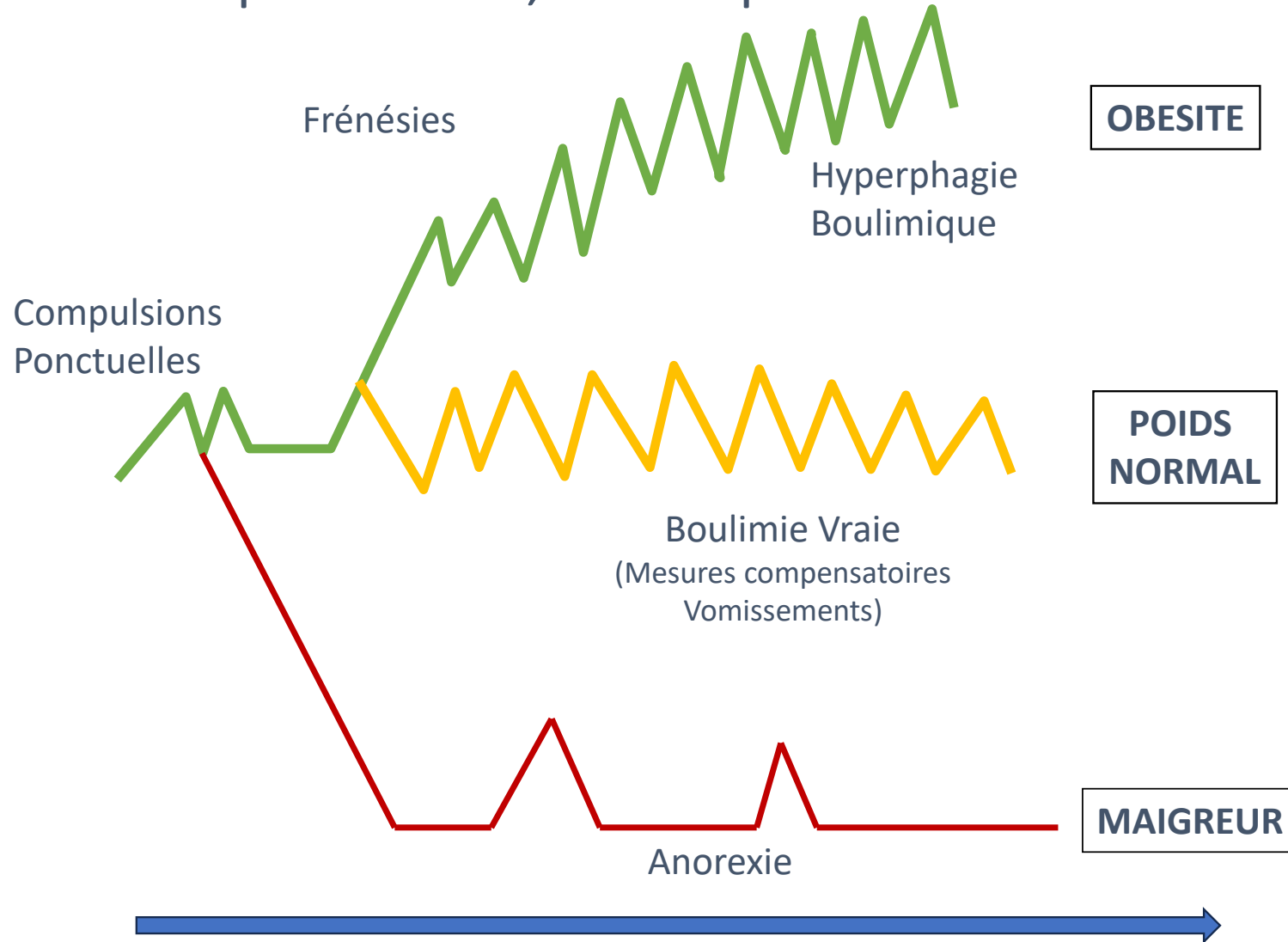
Early T2D screening
Early detection



Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, Rosas SE, Del Prato S, Mathieu C, Mingrone G, Rossing P, Tankova T, Tsapas A, Buse JB

Diabetes Care 2022; <https://doi.org/10.2337/dci22-0034>. *Diabetologia* 2022; <https://doi.org/10.1007/s00125-022-05787-2>.

Courbe pondérale, cinétique et TCA



Mode de vie

Foods play a key role in the prevention of Mets

cluster of health conditions:

- VISCERAL OBESITY
- INSULIN RESISTANCE
- LOW HDL-CHOLESTEROL
- HYPERTENSION
- HIGH TRIGLYCERIDES

- Olive oil
- Olive and fish oil
- Legumes - Black bean
- Fruits - Walnuts
- Fruits - Bergamots
- Fruits - Bilberries and blackcurrants
- Nervine plants - Green and roasted coffee
- Plants - Ginger
- Plants - Artichoke
- Curcumin

- Cereals
- Legumes - Soy
- Fruits - Cranberry juice
- Seeds - Pumpkin seeds

- Nervine plants - Yellow tea
- Plants - Garlic
- Seeds - Flaxseed



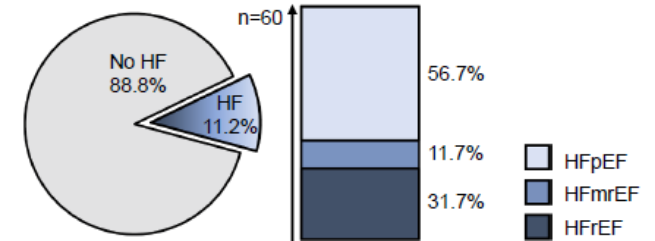
150 min

Among patients with diabetes, there is a high rate of undiagnosed HF and sub-optimal GDMT

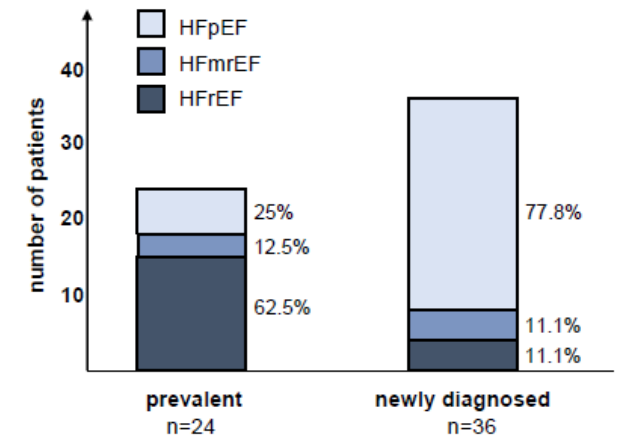
534 patients enrolled in the SwissDiab Registry at KSSG were screened for HF based on the ESC recommendations between 28.09.2020 and 31.03.2022.

Results:

- HF was identified in **16%** of patients with T2D.
- Of the identified cases of HF, **3 out of 5 were previously undiagnosed**, the majority **HFpEF**.
- Of the 60 patients that were identified with HF, n=19 (**31.7%**) were prescribed SGLT2i (HFpEF, n=7 [20.6 %]; HFmrEF, n=2 [28.6 %]; HFrEF, n=10 [52.6 %]).



Proportion of identified case with HF, stratified by LVEF



Proportion of HFrEF, HFmrEF and HFpEF among previously and newly diagnosed cases of HF.

Physiological effects of New pharmacologic options for DM

Benefits of early tight glycemic control in reducing the occurrence of micro- and macrovascular disease

Blood pressure control and lipid-lowering therapy outweigh glycemic control for cardiovascular prevention

Cardiorenal outcome benefits with the use of new glucose-lowering d 3 years intervals, starting at age 45 yrs

BW

GLP-1 (glucagon-like peptide-1)¹

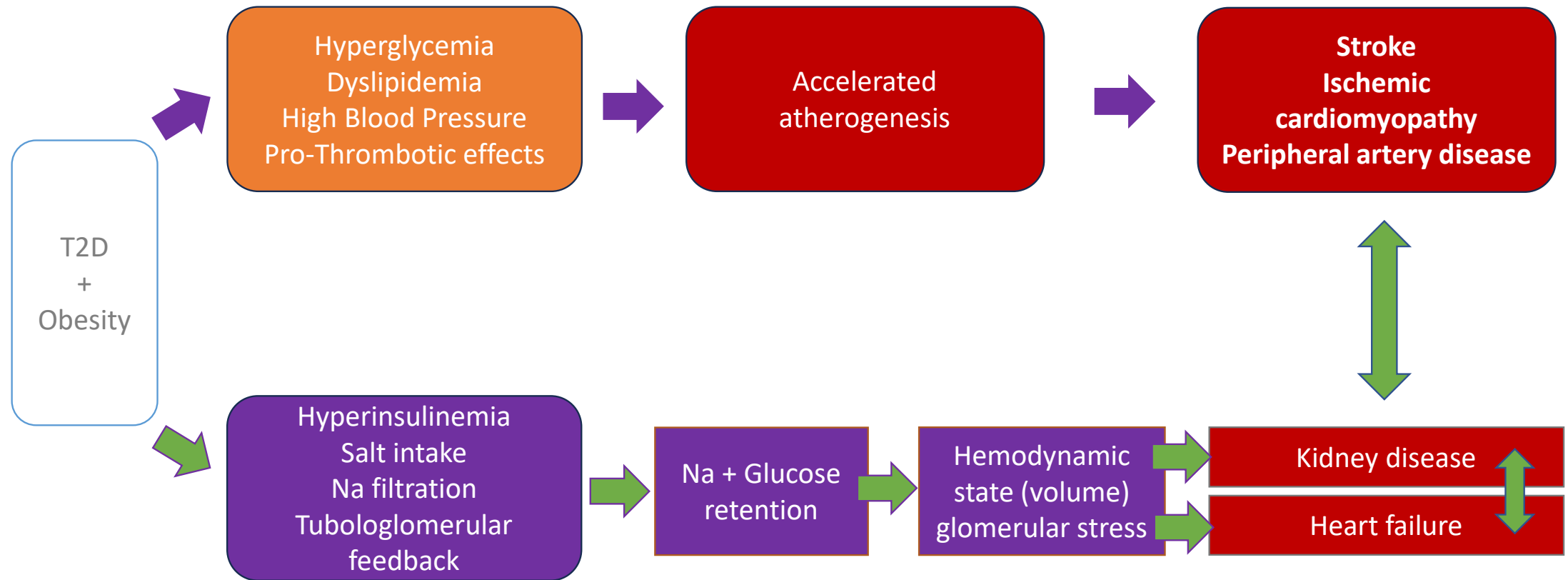
- ↓ Appetite (body weight)
- ↓ Glycemia
- ↑ Heart rate
- ↑ ↑ Insulin secretion
- ↓ ↓ Glucagon secretion
- ↓ ↓ Gastric emptying
- ↓ **Chylomicron production**
- ↓ Na excretion (transient)
- ↑ Meal-associated bone remodelling

iSGLT2 (Sodium-Glucose Co-transporter 2 Inhibitor)²

- ↓ Body weight (visceral fat)
- ↓ Blood pressure
- ↓ Glycemia
- ↑ Glucagon secretion
- ↑ ↑ **Na excretion**
- ↓ **Circulating volume**

- 1. Nauk MA et al. Diabetes Obes Metab. 2021 Sep;23 Suppl 3:5-29
- 2. Yang Y et al. Front Endocrinol (Lausanne). 2020 Apr 15;11:190.

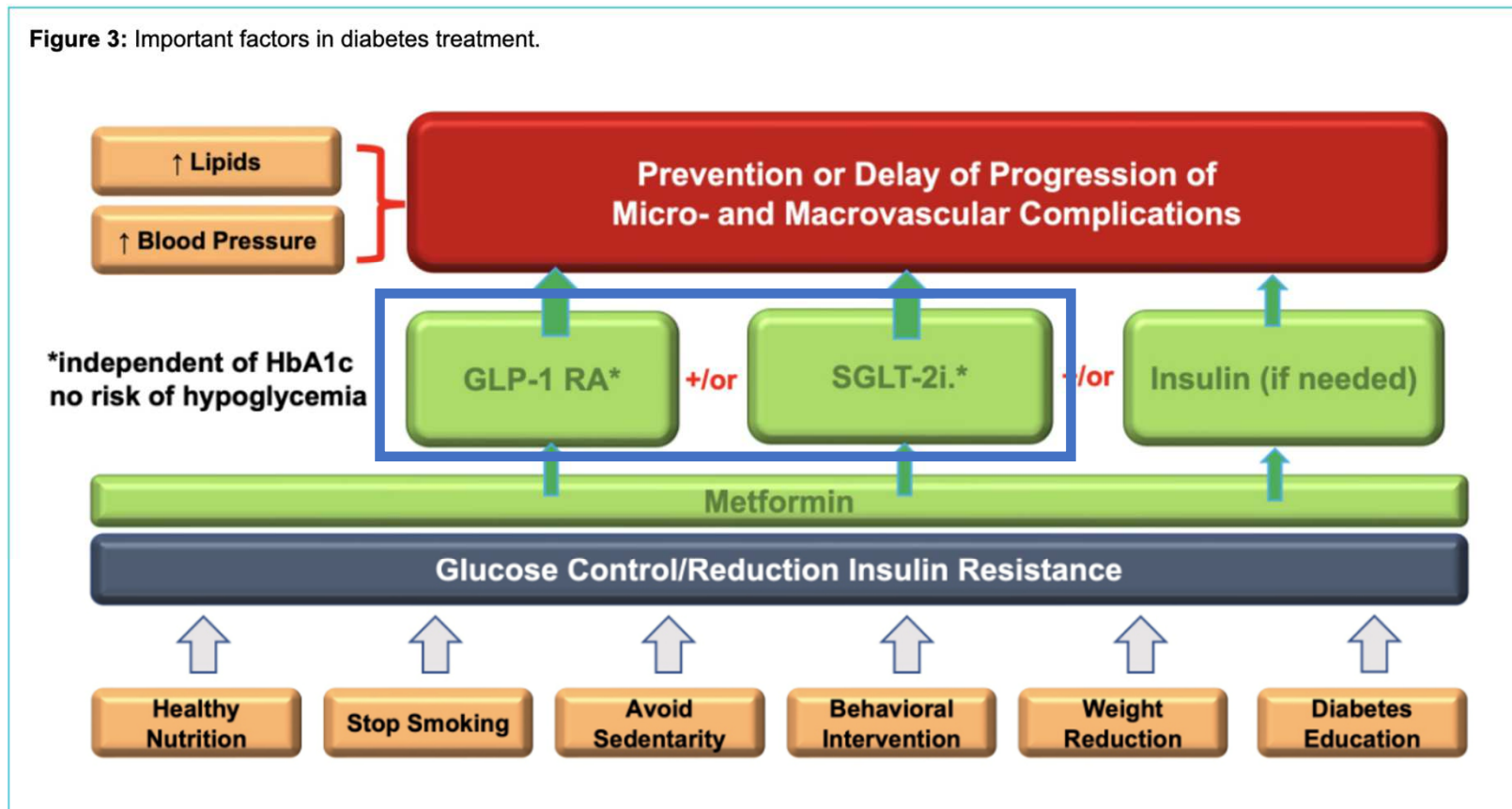
Atherogenic and cardiorenal risk pathways in DM



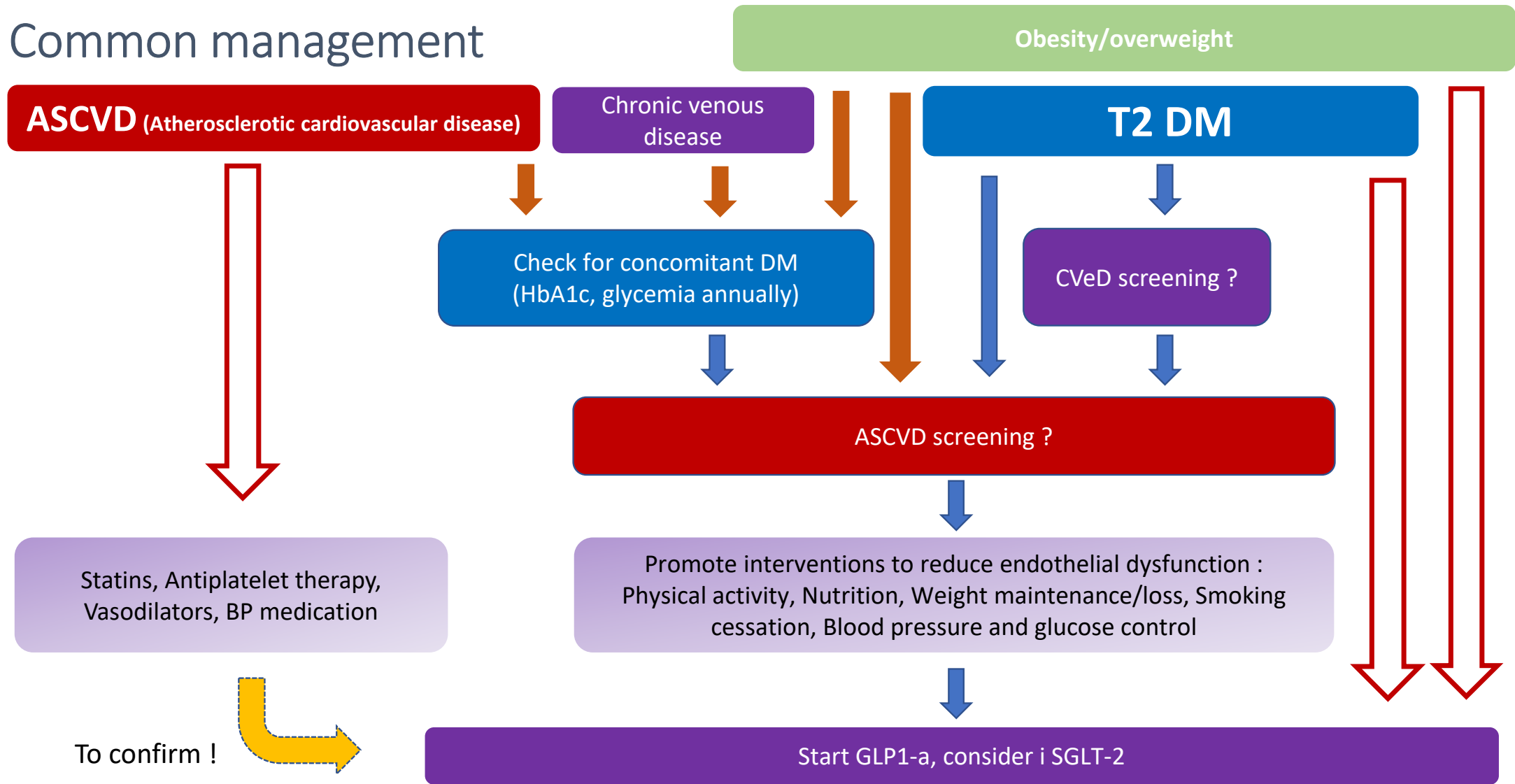
Adapted from Sattar N. et al. Circulation 2018;138:(7-9)

T2D management: disease-modifying drugs

Figure 3: Important factors in diabetes treatment.



Common management



CVeD, chronic venous disease; DmVC, Diabetic microvascular Complications; GLP-1, glucagon-like peptide-1; iSGLT2, Sodium-Glucose Co-transporter 2 Inhibitor.

Take home messages

Cardiovascular diseases (CVDs) are the leading cause of death globally.

People living with Type 1 and type 2 diabetes are 2 times more likely to develop and die from **cardiovascular disease** (heart attacks, strokes, heart failure)

Risk of **DmVC and Atheromatosis** after intensified therapy is still present in people with diabetes

DM related complications and pathophysiology of hemorrhoidal disease, and chronic venous disease **are** driven by **endothelial dysfunction due to increase of vascular inflammation, oxidative stress and VEGF²**.

Drugs targeting the glycocalyx and indicated for the treatment of HD, as well as both **CVI** and **DmVC** should be considered for patients with co-existing conditions.

Patients with circulatory system diseases may benefit from **new glucose lowering drugs (iSGLT2 and GLP-1a)^{8,9}** as well as from **drugs targeting the glycocalyx matrix**.

*Based on brands from the Swiss market (<https://compendium.ch/product/19768-doxium-caps-500-mg/product>)
CvED, chronic venous disease; CVI, chronic venous insufficiency, DmVC, Diabetic microvascular Complications; GLP-1, glucagon-like peptide-1; iSGLT2, Sodium-Glucose Co-transporter 2 Inhibitor; VEGF, vascular endothelial growth factor.
References : see note section



Thank you for your attention!

Questions?