Μακροαγγειοπάθεια

Δημήτριος Σκούτας

Ειδικός Παθολόγος-Διαβητολόγος

Διδάκτωρ Ιατρικής Σχολής ΔΠΘ

Highlights

In 2021, IDF estimates show that:

1 in 10

Adults (20-79 years) has diabetes
537 million people

1 in 18

Adults (20-79 years) has impaired fasting glucose
319 million people

3 in 4

People with diabetes live in low and middle-income countries

1 in 2

Adults is undiagnosed
240 million people

1 in 6

Live births (21 million) affected by hyperglycaemia in pregnancy, 80% have mothers with GDM

11.5%

Of global health expenditure spent on diabetes (USD 966 billion)

1 in 9

Adults (20-79 years) has impaired glucose tolerance
541 million people

1.2 million

Children and adolescents below 20 years have type 1 diabetes

6.7 million

Deaths attributed to diabetes

Highlights

In 2021, IDF estimates show that:

1.67 million

More adults with impaired glucose tolerance

US$206 billion

More USD spent on diabetes

700,000

More pregnancies affected by hyperglycaemia

7.8 million

More adults with diabetes undiagnosed

149,500

More children and adolescents with type 1 diabetes

2.5 million

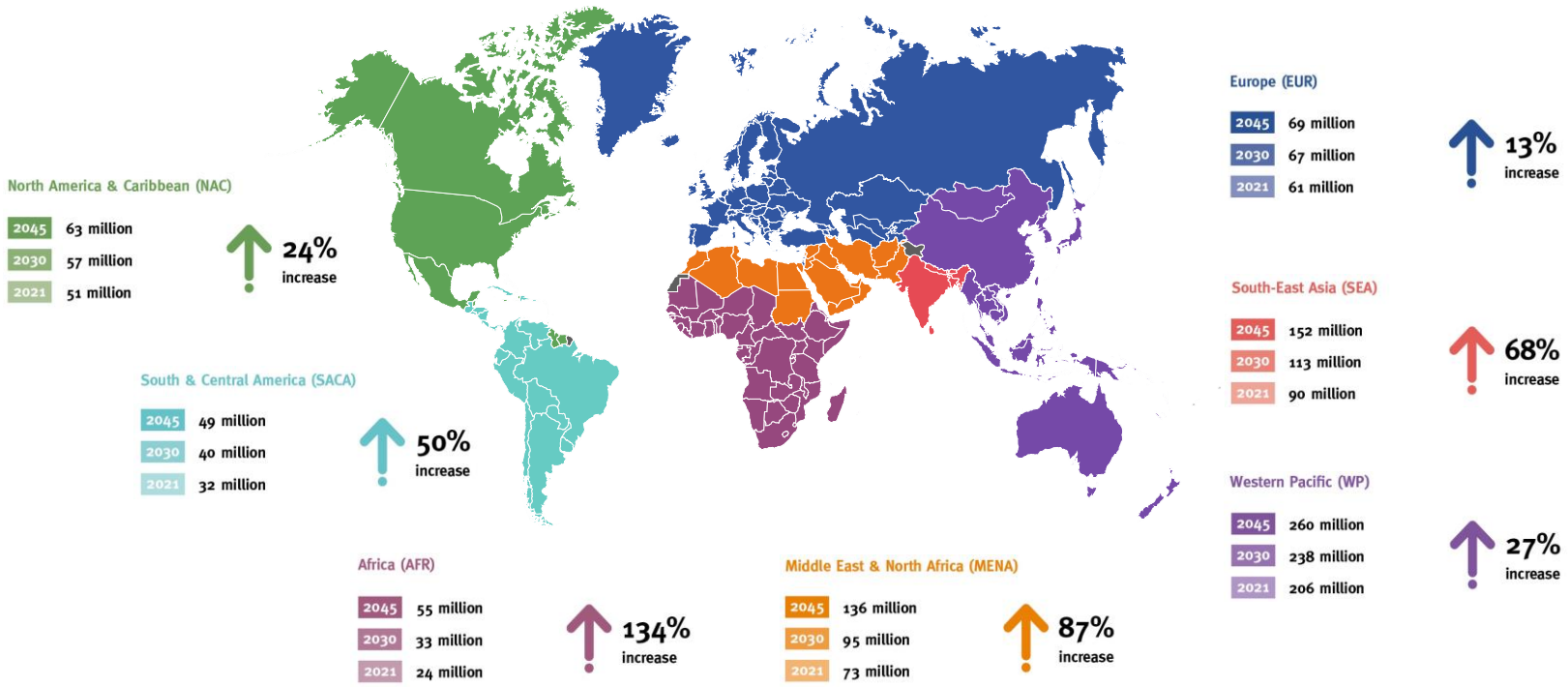
More deaths caused by diabetes

73.6 million

More adults with diabetes

Number of people with diabetes

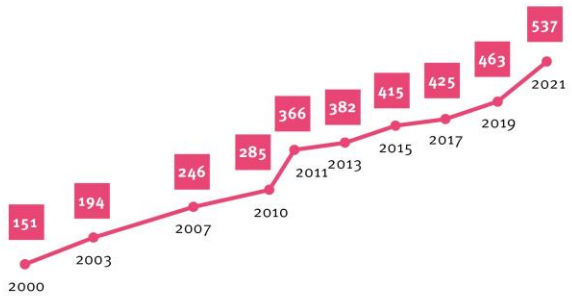
Aged 20–79 years globally and by IDF region



Estimates and projections

Global number of adults (20–79 years) in millions

Estimates of the global prevalence of diabetes in the 20–79 year age group (millions)



Key

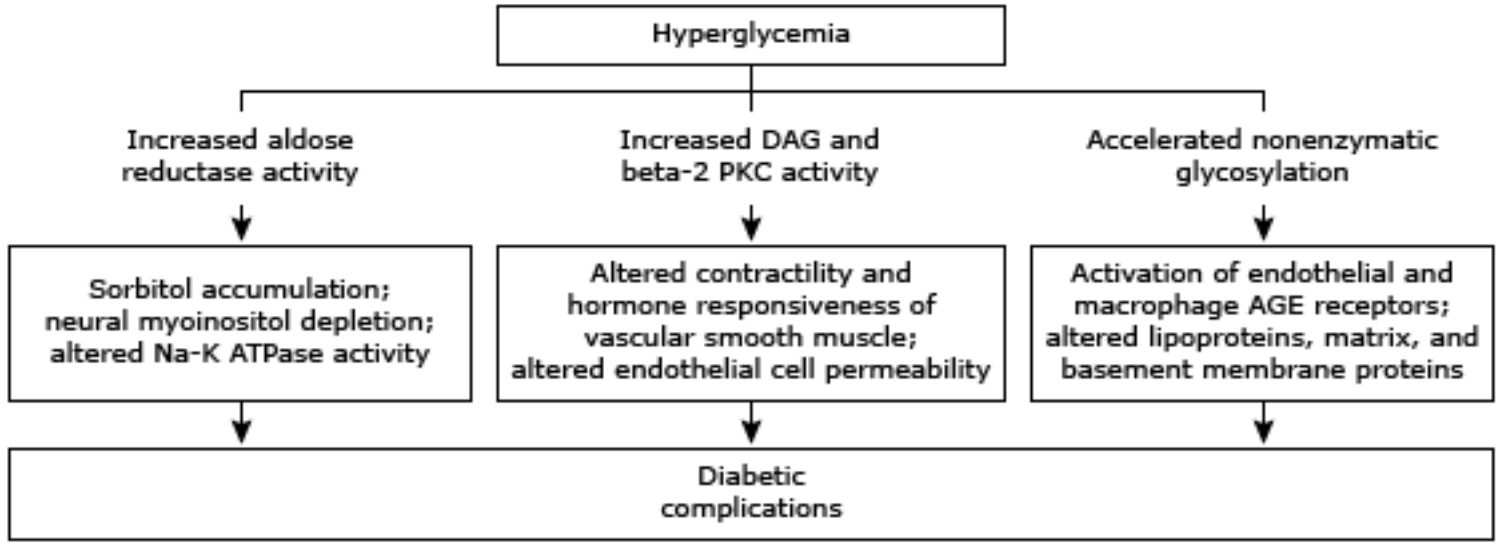
151 Number of people with diabetes in millions

Projections of the global prevalence of diabetes in the 20–79 year age group (millions)

Key

333 2003 Projection in millions, Year projection made

Mechanisms of hyperglycemia-induced vascular complications



Flow diagram showing how too much glucose may lead to the long-term complications of diabetes.

DAG: diacylglycerol; PKC: protein kinase C; AGE: advanced glycosylation end products.

UpToDate®

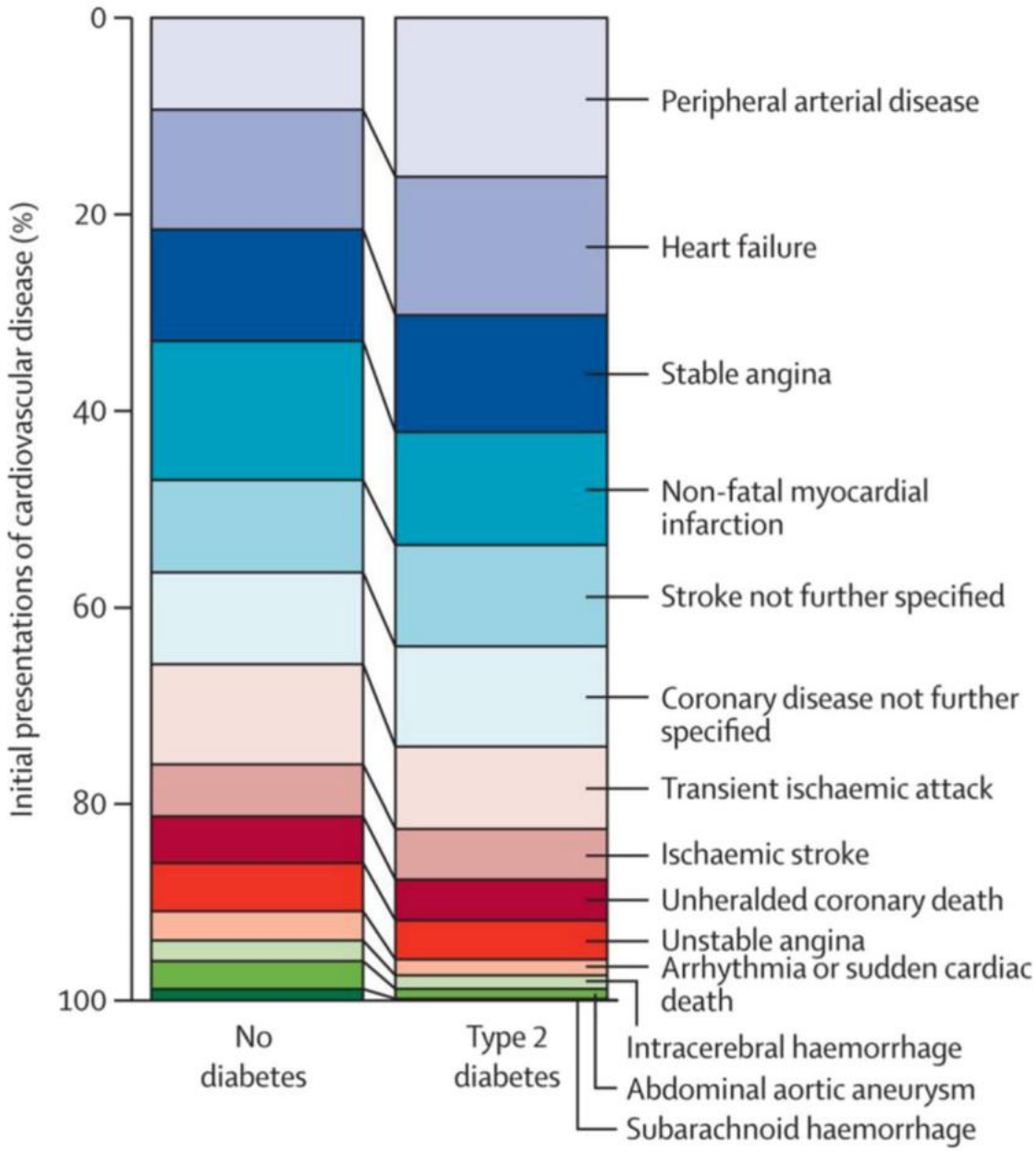


Fig. 2 Distribution of initial presentations of cardiovascular disease in participants with and without type 2 diabetes and no history of cardiovascular disease. (with permission from Shah et al. Lancet Diabetes Endocrinol. 2015;3:105–13) [47]

Prevalence of cardiovascular disease in younger people with type 1 diabetes

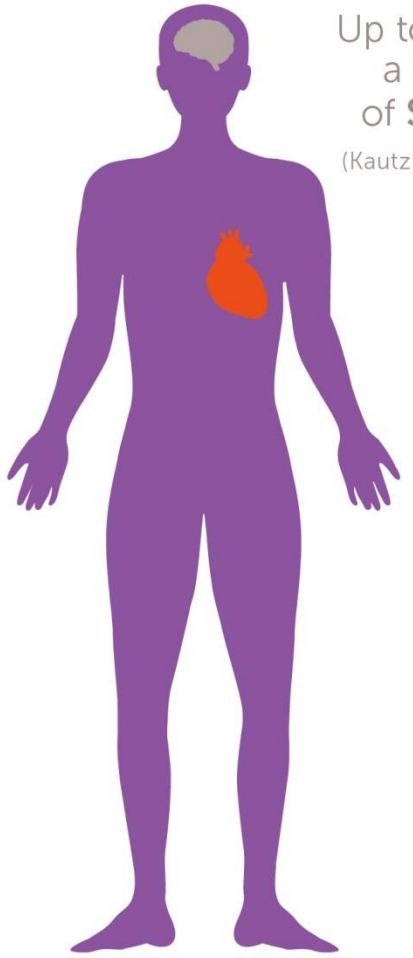
International Diabetes Federation

In studies of younger people with type 1 diabetes living in high- and middle-income countries:

Up to **16%** had a history of **CVD**

includes stroke, coronary artery disease, and peripheral artery disease

(David, 2010)



Up to **2%** had a history of **STROKE**

(Kautzy-Willer, 2013)

Up to **1%** had a history of **HEART ATTACK**

(Koivisto, 1996)

Mean age of study population: 25 to 44 years

www.idf.org/cvd

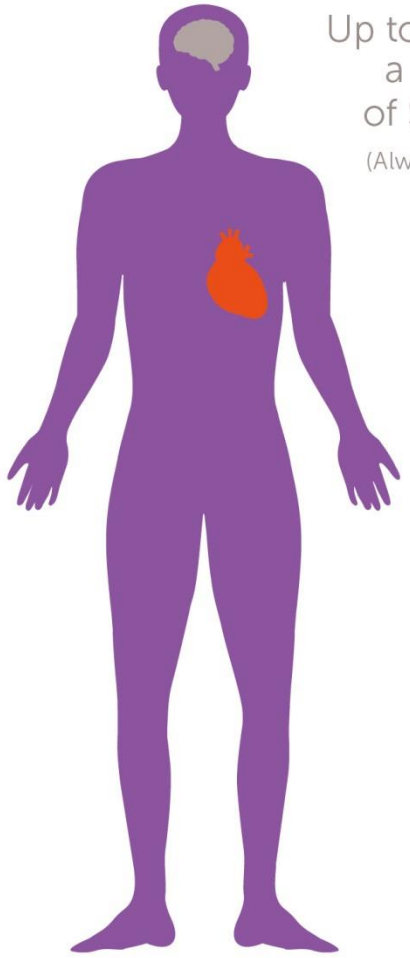
Prevalence of cardiovascular disease in middle-aged people with diabetes

In studies of middle-aged people with diabetes living in high- and middle-income countries:

Up to **41%** had a history of **CVD**

includes stroke, coronary artery disease, and peripheral artery disease

(van Hateren, 2009)



Up to **10%** had a history of **STROKE**

(Alwakeel, 2008)

Up to **14%** had a history of **HEART ATTACK**

(Alwakeel, 2008)

Mean age of study population: 50 to 69 years

www.idf.org/cvd

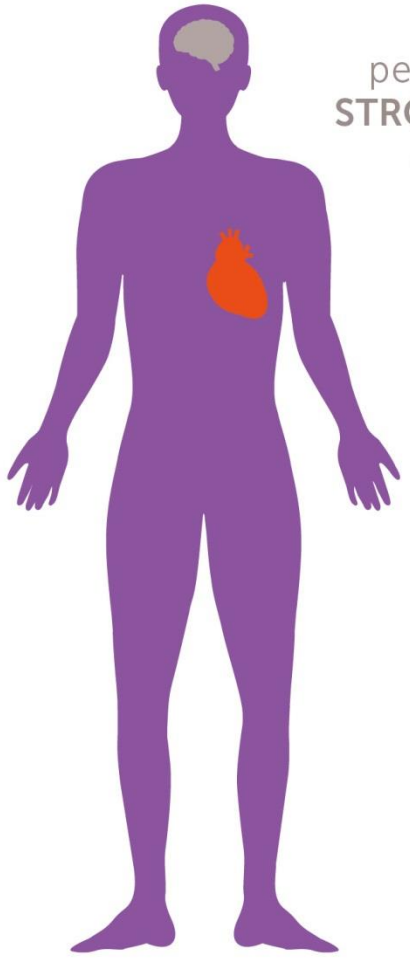
Cardiovascular disease mortality in middle-aged people with diabetes

International Diabetes Federation

In studies of middle-aged people with diabetes living in high- and middle-income countries:

Up to **27** per 1,000 died from **CVD** each year

(Miot, 2012)



Up to **9** per 1,000 died **STROKE** each year

(Mlacak, 1999)

Up to **7** per 1,000 died from **CORONARY ARTERY DISEASE** each year

(Bidel, 2006)

Mean age of study population: 49 to 69 years

www.idf.org/cvd

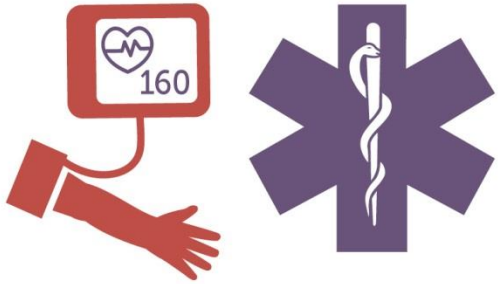
Strategies to decrease the impact of diabetes and cardiovascular diseases

International Diabetes Federation

Increase **HEALTHY EATING** and **PHYSICAL ACTIVITY**

Implement non-communicable disease **MONITORING SYSTEMS** and **SCREENING** plans for diabetes in high-risk populations

Decrease **TOBACCO** use



Improve **BLOOD PRESSURE** control and access to essential **MEDICINES**

TOGETHER
LET'S BEAT NCDS

www.idf.org/cvd

Η ΚΔ νόσος σε ασθενείς με ΣΔτ2 είναι υπεύθυνη για περισσότερους θανάτους από τον καρκίνο

2.5 φορές περισσότεροι θάνατοι από ό,τι ο καρκίνος

Θάνατοι που οφείλονται στη ΚΔ νόσο σε ασθενείς με ΣΔτ2

Θάνατοι εξαιτίας καρκίνου* σε ασθενείς Με ΣΔτ2

24ετή παρακολούθηση 7461 ασθενών με ΣΔτ2 και 37.271 στην ομάδα ελέγχου από το Skaraborg Diabetes Register
*Solid tumour cancers only, ΚΔ: Καρδιαγγειακή, ΣΔτ2 Σακχαρώδης Διαβήτης τύπου 2,

Diabetes and CVD Risk

Patients with T2D are more likely to experience CVD and CV death

Increased risk of CVD

Patients with T2D have an
increased risk of CVD

CV, cardiovascular; CVD, cardiovascular disease; T2D, type 2 diabetes.
Cordero A, et al. Am J Cardiol. 2016;117:1088-1094.

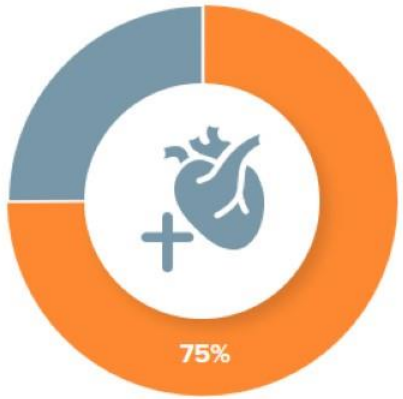
Diabetes and CVD Risk

Patients with T2D are more likely to experience CVD and CV death

Increased risk of CVD

Patients with T2D have an **increased risk of CVD**

Deaths caused by CVD



75% of all deaths among patients with T2D are caused by CVD

CV, cardiovascular; CVD, cardiovascular disease; T2D, type 2 diabetes.

Cordero A, et al. Am J Cardiol. 2016;117:1088-1094.

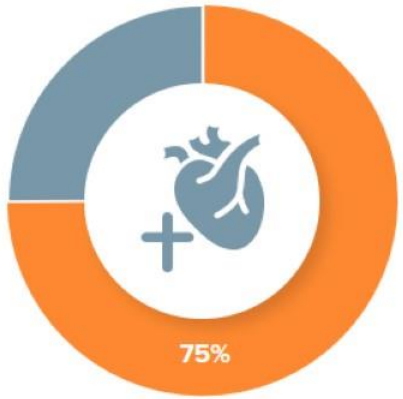
Diabetes and CVD Risk

Patients with T2D are more likely to experience CVD and CV death

Increased risk of CVD

Patients with T2D have an **increased risk of CVD**

Deaths caused by CVD



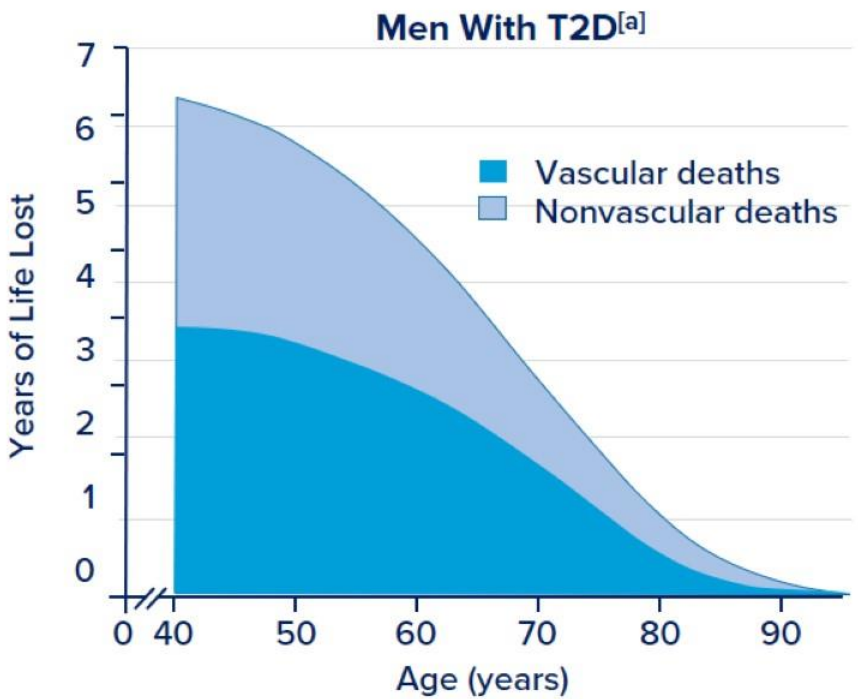
75% of all deaths among patients with T2D are caused by CVD

CV mortality

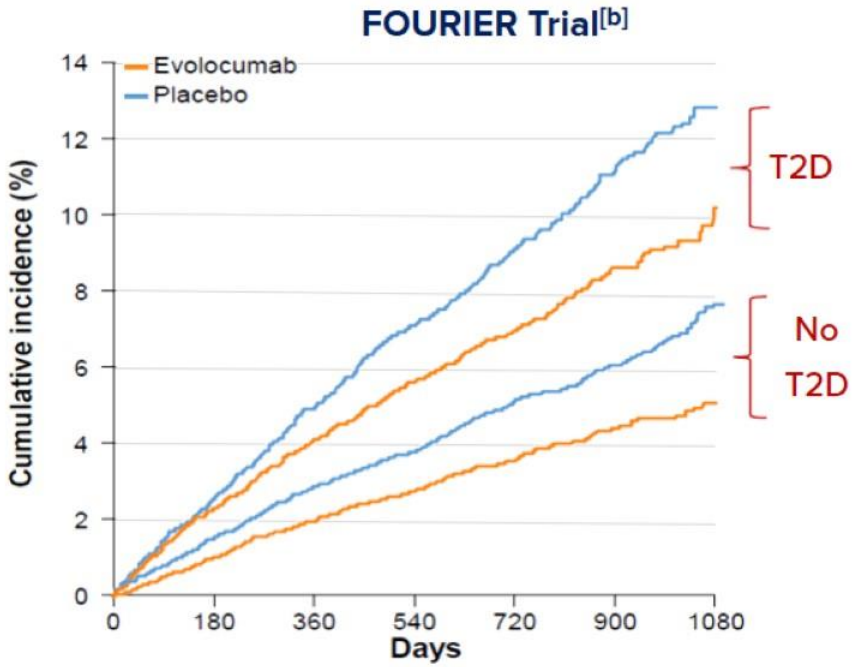
CV mortality is **higher among patients with T2D** than in patients without diabetes

CV, cardiovascular; CVD, cardiovascular disease; T2D, type 2 diabetes.
Cordero A, et al. Am J Cardiol. 2016;117:1088-1094.

CV Consequences of T2D



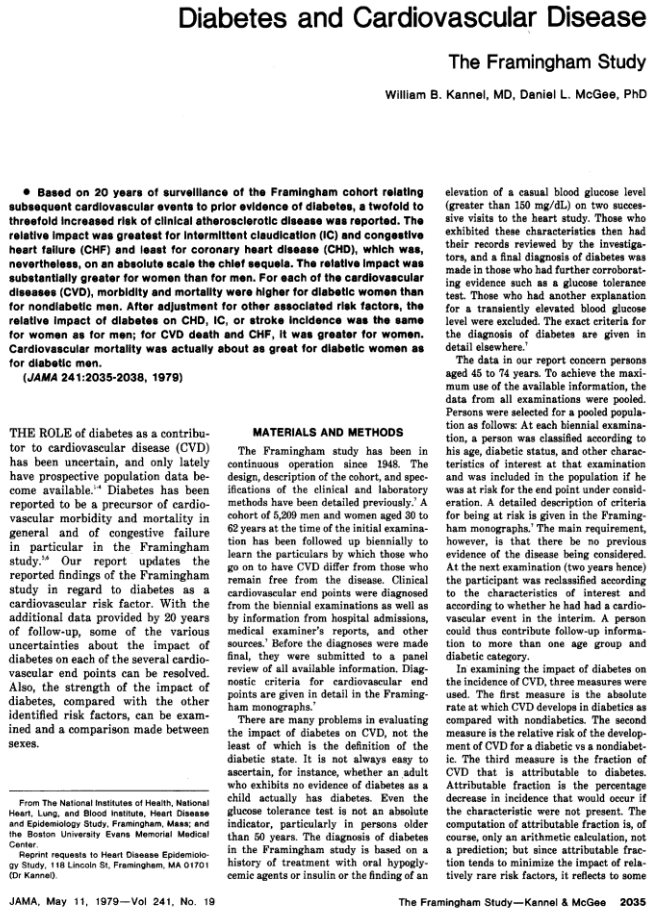
A 50-y-old with T2D but no CVD is ≈ 6 y younger at time of death



T2D doubles the risk for CV events

CV, cardiovascular.

a. Seshasai RK, et al. N Engl J Med. 2011;364:829-841; b. Sabatine MS, et al. Lancet Diab Endocrinol. 2017;5:941-950.



Diabetes and Cardiovascular Disease

The Framingham Study

William B. Kannel, MD, Daniel L. McGee, PhD

• **Based on 20 years of surveillance of the Framingham cohort relating subsequent cardiovascular events to prior evidence of diabetes, a twofold to threefold increased risk of clinical atherosclerotic disease was reported. The relative impact was greatest for intermittent claudication (IC) and congestive heart failure (CHF) and least for coronary heart disease (CHD), which was, nevertheless, on an absolute scale the chief sequela. The relative impact was substantially greater for women than for men. For each of the cardiovascular diseases (CVD), morbidity and mortality were higher for diabetic women than for nondiabetic men. After adjustment for other associated risk factors, the relative impact of diabetes on CHD, IC, or stroke incidence was the same for women as for men; for CVD death and CHF, it was greater for women. Cardiovascular mortality was actually about as great for diabetic women as for diabetic men.**

(*JAMA* 241:2035-2038, 1979)

THE ROLE of diabetes as a contributor to cardiovascular disease (CVD) has been uncertain, and only lately have prospective population data become available.[1-4] Diabetes has been reported to be a precursor of cardiovascular morbidity and mortality in general and of congestive failure in particular in the Framingham study.[1-6] Our report updates the reported findings of the Framingham study in regard to diabetes as a cardiovascular risk factor. With the additional data provided by 20 years of follow-up, some of the various uncertainties about the impact of diabetes on each of the several cardiovascular end points can be resolved. Also, the strength of the impact of diabetes, compared with the other identified risk factors, can be examined and a comparison made between sexes.

From The National Institutes of Health, National Heart, Lung, and Blood Institute, Heart Disease and Epidemiology Study, Framingham, Mass; and the Boston University Evans Memorial Medical Center.

Reprint requests to Heart Disease Epidemiology Study, 118 Lincoln St, Framingham, MA 01701 (Dr Kannel).

MATERIALS AND METHODS

The Framingham study has been in continuous operation since 1948. The design, description of the cohort, and specifications of the clinical and laboratory methods have been detailed previously.[7] A cohort of 5,209 men and women aged 30 to 62 years at the time of the initial examination has been followed up biennially to learn the particulars by which those who go on to have CVD differ from those who remain free from the disease. Clinical cardiovascular end points were diagnosed from the biennial examinations as well as by information from hospital admissions, medical examiner's reports, and other sources.[7] Before the diagnoses were made final, they were submitted to a panel review of all available information. Diagnostic criteria for cardiovascular end points are given in detail in the Framingham monographs.[7]

There are many problems in evaluating the impact of diabetes on CVD, not the least of which is the definition of the diabetic state. It is not always easy to ascertain, for instance, whether an adult who exhibits no evidence of diabetes as a child actually has diabetes. Even the glucose tolerance test is not an absolute indicator, particularly in persons older than 50 years. The diagnosis of diabetes in the Framingham study is based on a history of treatment with oral hypoglycemic agents or insulin or the finding of an elevation of a casual blood glucose level (greater than 150 mg/dL) on two successive visits to the heart study. Those who exhibited these characteristics then had their records reviewed by the investigators, and a final diagnosis of diabetes was made in those who had further corroborating evidence such as a glucose tolerance test. Those who had another explanation for a transiently elevated blood glucose level were excluded. The exact criteria for the diagnosis of diabetes are given in detail elsewhere.[7]

The data in our report concern persons aged 45 to 74 years. To achieve the maximum use of the available information, the data from all examinations were pooled. Persons were selected for a pooled population as follows: At each biennial examination, a person was classified according to his age, diabetic status, and other characteristics of interest at that examination and was included in the population if he was at risk for the end point under consideration. A detailed description of criteria for being at risk is given in the Framingham monographs.[7] The main requirement, however, is that there be no previous evidence of the disease being considered. At the next examination (two years hence) the participant was reclassified according to the characteristics of interest and according to whether he had had a cardiovascular event in the interim. A person could thus contribute follow-up information to more than one age group and diabetic category.

In examining the impact of diabetes on the incidence of CVD, three measures were used. The first measure is the absolute rate at which CVD develops in diabetics as compared with nondiabetics. The second measure is the relative risk of the development of CVD for a diabetic vs a nondiabetic. The third measure is the fraction of CVD that is attributable to diabetes. Attributable fraction is the percentage decrease in incidence that would occur if the characteristic were not present. The computation of attributable fraction is, of course, only an arithmetic calculation, not a prediction; but since attributable fraction tends to minimize the impact of relatively rare risk factors, it reflects to some

Η μελέτη Framingham Heart Study, που δημοσιεύθηκε το 1979, κατέδειξε για πρώτη φορά μια υψηλότερη επίπτωση καρδιαγγειακής νόσου σε όλες τις ηλικιακές ομάδες για άτομα με ΣΔ (που ορίστηκε εκείνη τη στιγμή από τυχαία γλυκόζη αίματος ≥150 mg/dL) σε σύγκριση με άτομα χωρίς ΣΔ.[1]

Η επίδραση του ΣΔ στην καρδιαγγειακή νοσηρότητα και θνησιμότητα ήταν εντονότερη για τις γυναίκες παρά για τους άνδρες.[1]

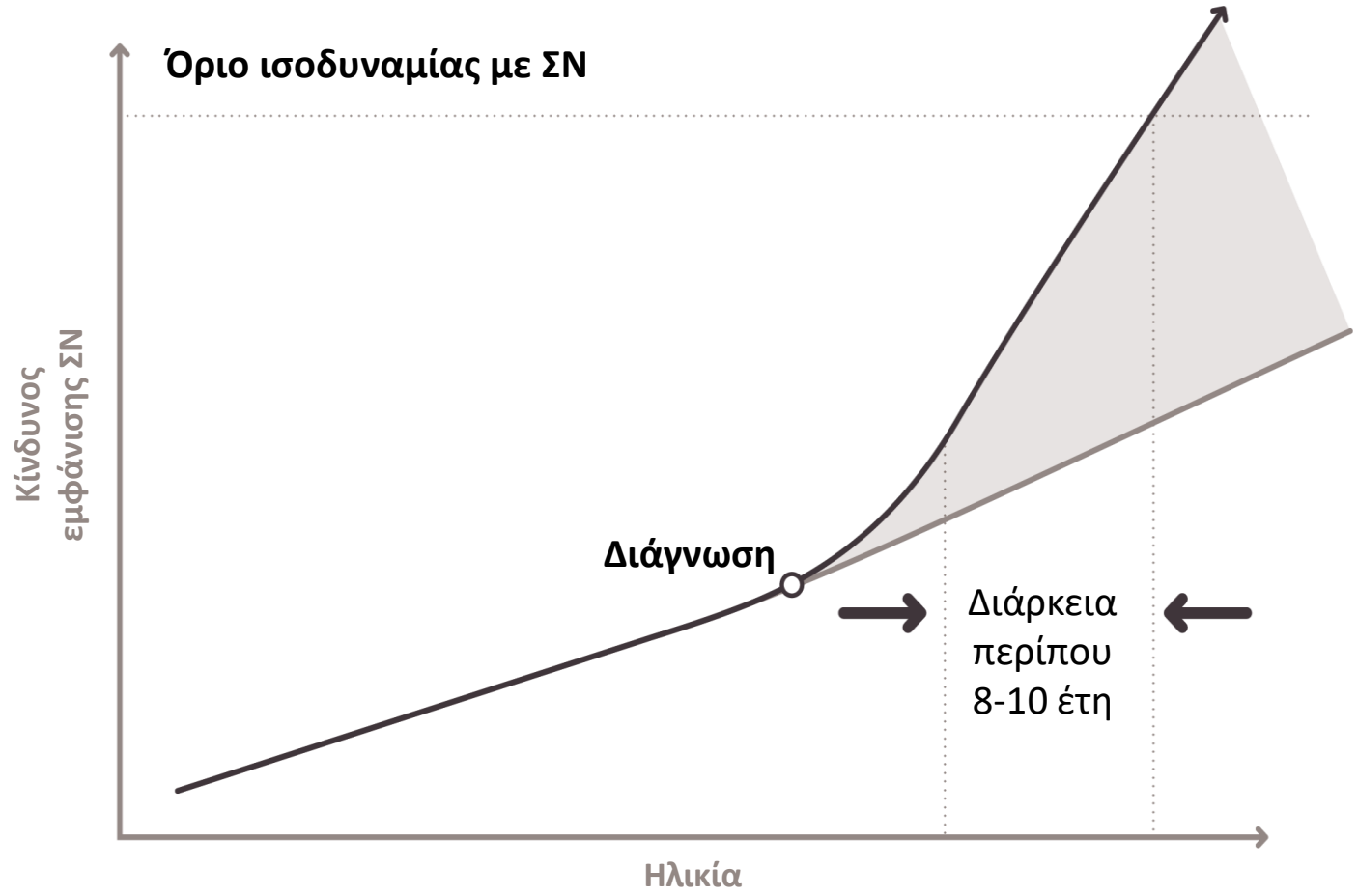
Ακολούθησαν πολλές μελέτες σε διαφορετικούς πληθυσμούς που επιβεβαίωναν τον αυξημένο κίνδυνο ASCVD στους ασθενείς με ΣΔΤ2.

Ο κίνδυνος ΟΕΜ σε άτομα με ΣΔΤ2 χωρίς προηγούμενο ΟΕΜ είναι παρόμοιος με τον κίνδυνο νέου ΟΕΜ σε άτομα με προηγούμενο ΟΕΜ χωρίς ΣΔ. [2]

Diabetes mellitus as a risk equivalent for established coronary heart disease.[3]

[1]Kannel WB, McGee DL. Diabetes and glucose tolerance as risk factors for cardiovascular disease: the Framingham study. Diabetes Care. 1979; *2*:120–6. [2]Haffner SM et al. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med. 1998; 339:229–34.
[3]Bulugahapitiya U et al. Is diabetes a coronary risk equivalent? Systematic review and meta-analysis. Diabet Med. 2009; *26*:142–8.

Ο κίνδυνος εμφάνισης ΚΑΝ ξεκινά πριν από τη διάγνωση του διαβήτη τύπου 2 αλλά αυξάνεται στη συνέχεια[1]



ΚΑΝ = Καρδιαγγειακή νόσος ΣΝ = στεφανιαία νόσος

Βιβλιογραφική Αναφορά: 1. Sattar N. *Diabetologia*. 2013;53:686-695.

ΣΔ και καρδιαγγειακός θάνατος

Risk of Cause-Specific Death in Individuals With Diabetes: A Competing Risks Analysis

Diabetes Care 2016;39:1987–1995 | DOI: 10.2337/dc16-0614

OBJECTIVE

Diabetes is a common cause of shortened life expectancy. We aimed to assess the association between diabetes and cause-specific death.

RESEARCH DESIGN AND METHODS

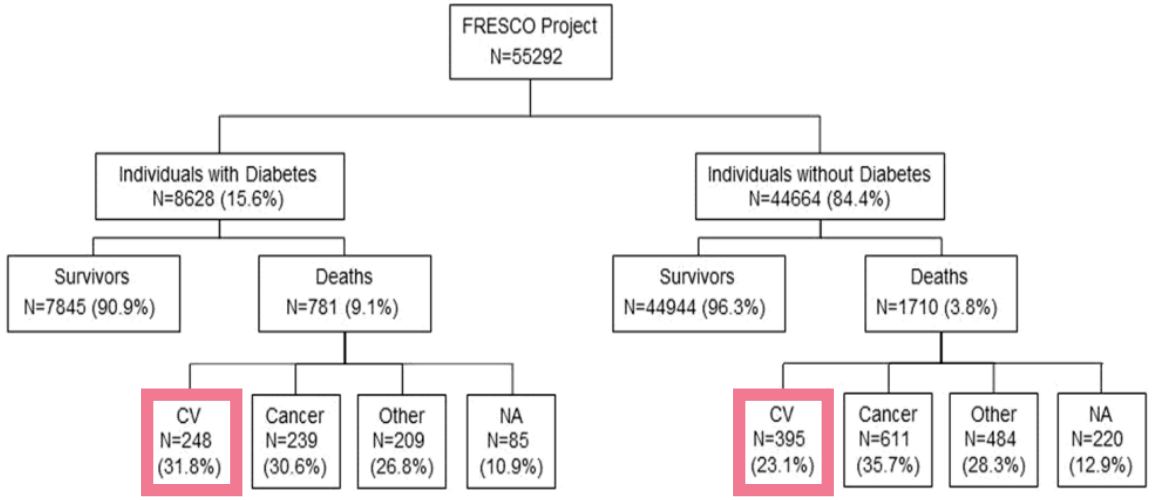
We used the pooled analysis of individual data from 12 Spanish population cohorts with 10-year follow-up. Participants had no previous history of cardiovascular diseases and were 35–79 years old. Diabetes status was self-reported or defined as glycemia >125 mg/dL at baseline. Vital status and causes of death were ascertained by medical records review and linkage with the official death registry. The hazard ratios and cumulative mortality function were assessed with two approaches, with and without competing risks: proportional subdistribution hazard (PSH) and cause-specific hazard (CSH), respectively. Multivariate analyses were fitted for cardiovascular, cancer, and noncardiovascular noncancer deaths.

RESULTS

We included 55,292 individuals (15.6% with diabetes and overall mortality of 9.1%). The adjusted hazard ratios showed that diabetes increased mortality risk: *1*) cardiovascular death, CSH = 2.03 (95% CI 1.63–2.52) and PSH = 1.99 (1.60–2.49) in men; and CSH = 2.28 (1.75–2.97) and PSH = 2.23 (1.70–2.91) in women; *2*) cancer death, CSH = 1.37 (1.13–1.67) and PSH = 1.35 (1.10–1.65) in men; and CSH = 1.68 (1.29–2.20) and PSH = 1.66 (1.25–2.19) in women; and *3*) noncardiovascular noncancer death, CSH = 1.53 (1.23–1.91) and PSH = 1.50 (1.20–1.89) in men; and CSH = 1.89 (1.43–2.48) and PSH = 1.84 (1.39–2.45) in women. In all instances, the cumulative mortality function was significantly higher in individuals with diabetes.

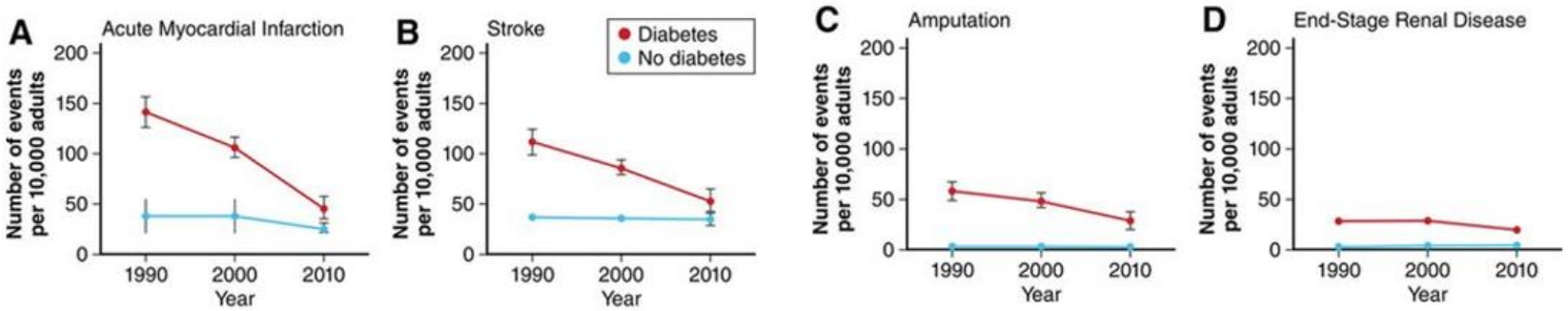
CONCLUSIONS

Diabetes is associated with premature death from cardiovascular disease, cancer, and noncardiovascular noncancer causes. The use of CSH and PSH provides a comprehensive view of mortality dynamics in a population with diabetes.



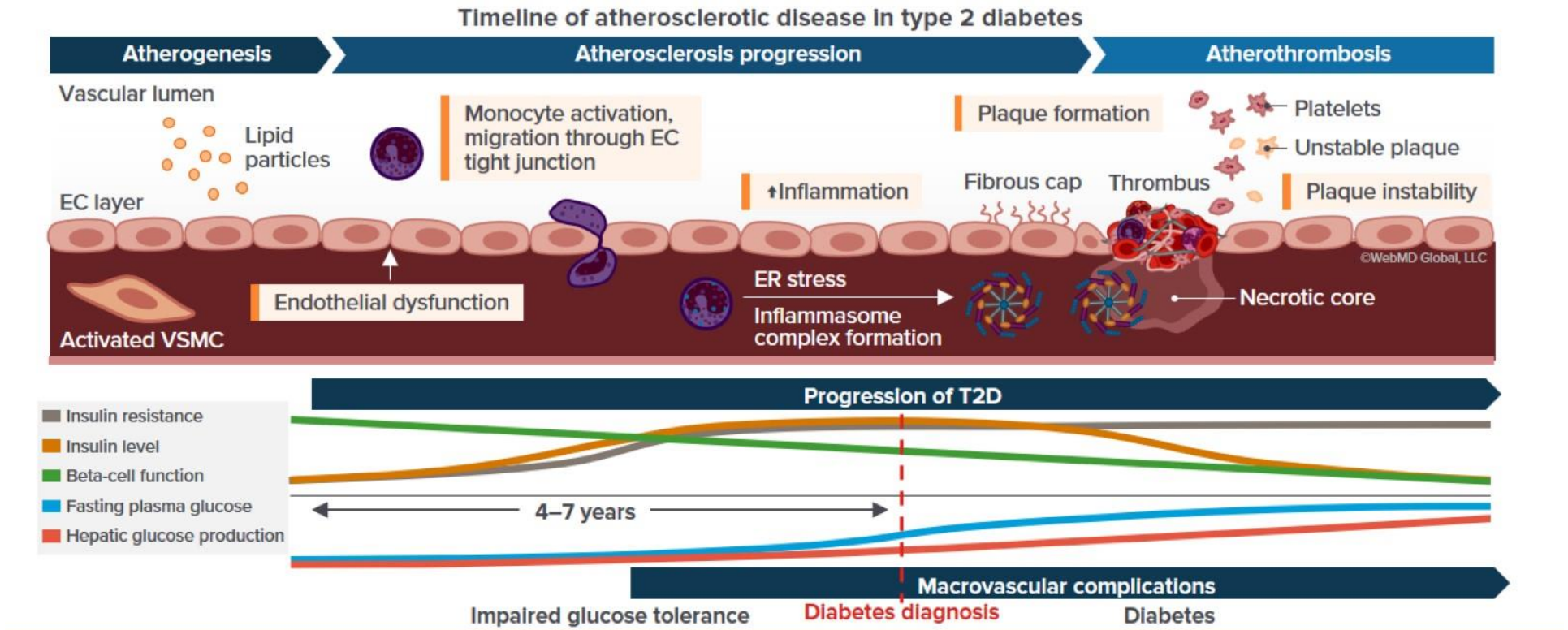
Οι ασθενείς με ΣΔ έχουν πολλαπλάσιο κίνδυνο θανάτου από **Στεφανιαία νόσο, Καρδιακή ανεπάρκεια, Αγγειακό Εγκεφαλικό** επεισόδιο σε σχέση με μη διαβητικούς.

- Η αθηροσκληρωτική καρδιαγγειακή νόσος (atherosclerotic cardiovascular disease - ASCVD) παραμένει η κύρια αιτία θανάτου και αναπηρίας μεταξύ των ασθενών με ΣΔ.
- Οι ασθενείς με ΣΔΤ2 εμφανίζουν νωρίτερα (14,6 χρόνια) και πιο βαριά ASCVD από ό,τι άτομα χωρίς ΣΔ.
- Μεταξύ των ατόμων με σακχαρώδη διαβήτη, ο κίνδυνος θανάτου από οποιαδήποτε αιτία και από ASCVD είναι ιδιαίτερα εμφανής σε άτομα με μικρότερη ηλικία, υψηλότερη γλυκαιμική επιβάρυνση και νεφρικές επιπλοκές.
- Παρά την προσπάθεια των τελευταίαων δεκαετίων για μείωση των μικρο- και μακρο-αγγειακών επιπλοκών του ΣΔ, οι ασθενείς με ΣΔΤ2 συνεχίζουν ακόμη και σήμερα να έχουν σημαντικά αυξημένο κίνδυνο για αγγειακές επιπλοκές σε σχέση με τα άτομα χωρίς ΣΔ.



Cecilia C. Low Wang. Circulation. Clinical Update: Cardiovascular Disease in Diabetes Mellitus, Volume: 133, Issue: 24, Pages: 2459-502.

Macrovascular Complications of T2D



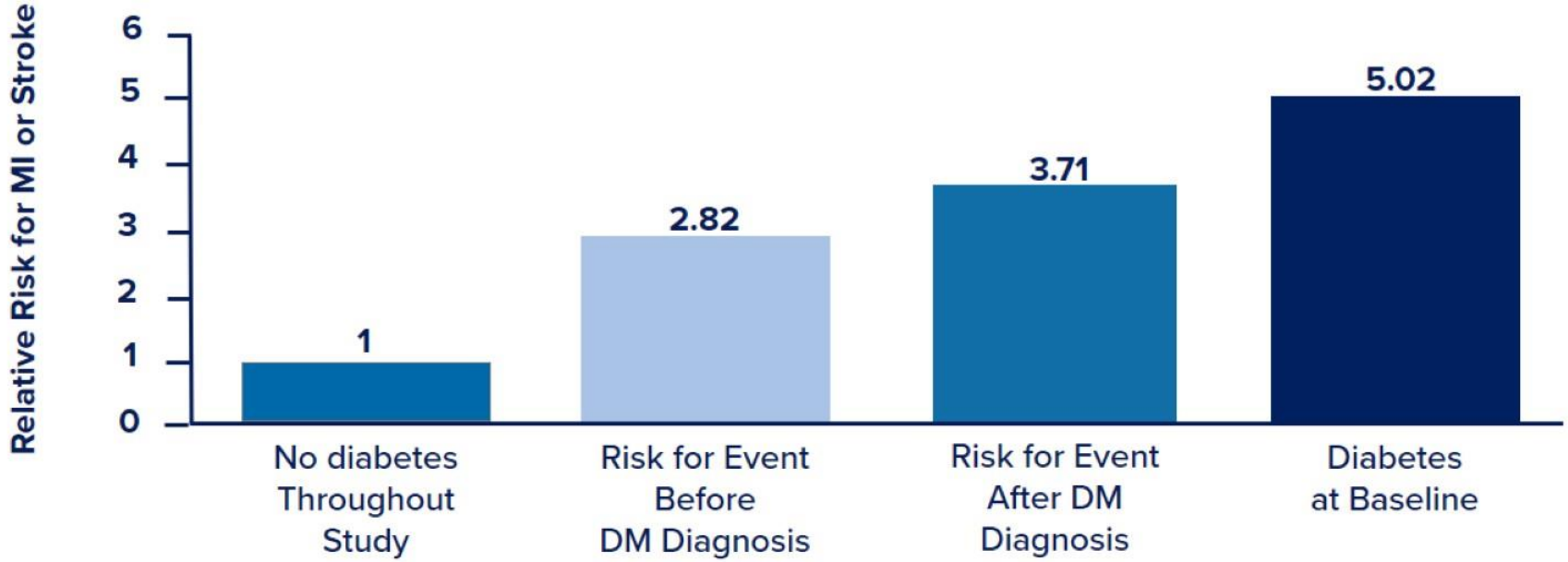
Macrovascular complications may precede type 2 diabetes diagnosis

EC, epicardium; ER, endoplasmic reticulum; VSMC, vascular smooth muscle cell.

a. Low Wang CC, et al. Circulation. 2016;133:2459-2502; b. Adapted from Kendall DM, et al. Am J Med. 2009:122(Suppl 6):S37-S50.

The Ticking Clock — ↑ CV Risk Before ↑ Glucose

Nurses' Health Study

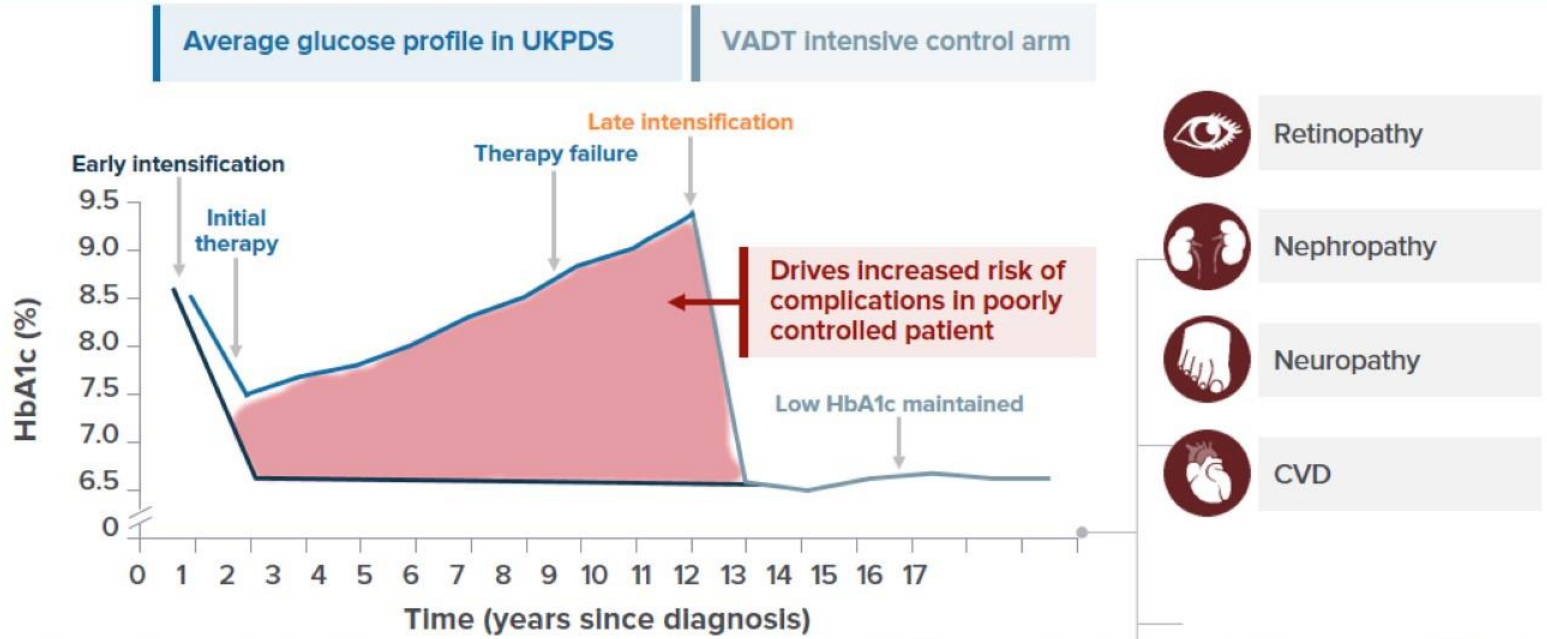


20-y follow-up of 117,629 women: n = 1508 have diabetes at baseline; n = 5894 developed diabetes; n = 110,227 free from diabetes

Hu FB, et al. Diabetes Care. 2002;25:1129-1134.

Early Glycemic Control
Reduces Risk of Complications

Failure to intensify treatment and reach HbA1c target in a timely manner increases the risk of long-term complications related to sustained hyperglycemia[a,b]

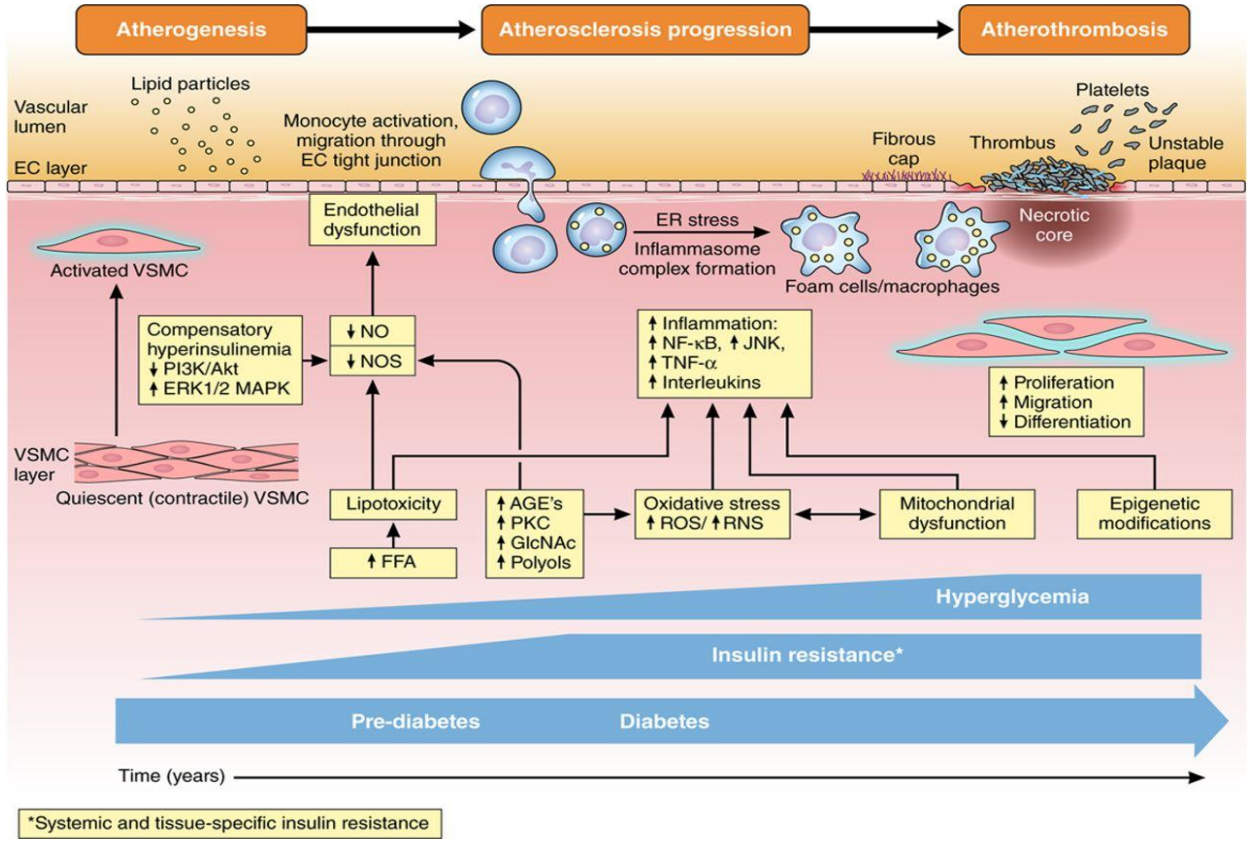


Hypothetical representation of the natural history of the patients with diabetes who were recruited in the VADT.[b] The upper blue line represents the time course of HbA1c estimated based on the average glucose profile described in the UKPDS. The green line represents the time course of HbA1c in the VADT. The lower gray line represents the ideal time course of glycemic control. CVD, cardiovascular disease; HbA1c, glycated hemoglobin; UKPDS, United Kingdom Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.

a. Okemah J, et al. Adv Ther. 2018;35:1735-1745; b. Del Prato S. Diabetologia. 2009;52:1219-1226.

Καρδιαγγειακή Νόσος και ΣΔ
Key manifestations

- Στεφανιαία Νόσος
- Ισχαιμικό ΑΕΕ
- Περιφερική Αρτηριακή Νόσος
- Διαβητική Καρδιομυοπάθεια (διαστολική δυσλειτουργία ή υπερτροφία αριστερής κοιλίας)
- Καρδιακή Ανεπάρκεια



- Υπεργλυκαιμία
- Αντίσταση στην Ινσουλίνη
- Ενδοθηλιακή Δυσλειτουργία
- Οξειδωτικό stress
- Φλεγμονή
- Υπερπηκτικότητα
- Δυσλιπιδαιμία
- Επασβεστώσεις αγγείων

Cecilia C. Low Wang. Circulation. Clinical Update: Cardiovascular Disease in Diabetes Mellitus, Volume: 133, Issue: 24, Pages: 2459-502.

Υπεργλυκαιμία

Table 2.2—Criteria for the diagnosis of diabetes

FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
OR
2-h PG ≥200 mg/dL (11.1 mmol/L) during OGTT. The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
OR
A1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

DCCT, Diabetes Control and Complications Trial; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; WHO, World Health Organization; 2-h PG, 2-h plasma glucose. *In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples.

American Diabetes Association Professional Practice Committee; 2. Classification and Diagnosis of Diabetes: *Standards of Medical Care in Diabetes—2022*. *Diabetes Care* 1 January 2022; 45 (Supplement_1): S17–S38.

- Η HbA_1c είναι ισχυρός προγνωστικός δείκτης θανατηφόρου και μη θανατηφόρου ΣΝ, θανατηφόρου και μη θανατηφόρου ΑΕΕ, θανατηφόρου και μη θανατηφόρου CVD, και συνολικής θνησιμότητας, στους ασθενείς με ΣΔΤ2. (>18000 ασθενείς, follow up 5,6 έτη).[1]
- 11%-16% αύξηση καρδιαγγειακών επεισοδίων για κάθε 1% αύξηση στην HbA_1c.[2,3]
- 12% αύξηση του ASCVD κινδύνου για κάθε 18 mg/dl αύξηση της γλυκόζης νηστείας >105mg/dl.[2,3]
- 13% αύξηση του κινδύνου για αγγειακό θάνατο για κάθε 18 mg/dl αύξηση της γλυκόζης νηστείας >100mg/dl.[2,3]

[1]Eeg-Olofsson K et all. New aspects of HbA1c as a risk factor for cardiovascular diseases in type 2 diabetes: an observational study from the Swedish National Diabetes Register (NDR) *J Intern Med.* 2010;268:471–82. [2]Sarwar N et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet.* 2010;375:2215–22. [3]Seshasai SR et al. Diabetes mellitus, fasting glucose, and risk of cause-specific death. *N Engl J Med.* 2011;364:829–41.

Αντίσταση στην Ινσουλίνη/Υπερινσουλιναιμία

- Η αντίσταση στην ινσουλίνη (IR) είναι χαρακτηριστικό γνώρισμα του ΣΔΤ2.
- Η IR σχετίζεται με μια ομάδα καρδιομεταβολικών παραγόντων κινδύνου που συμβάλλουν στον αυξημένο κίνδυνο ASCVD στους ασθενείς με ΣΔΤ2.[1]
- Επιδημιολογικές μελέτες έχουν αναδείξει αυτή τη σχέση και έχουν τονίσει τον αυξημένο κίνδυνο υπέρτασης, δυσλιπιδαιμίας και IGT στα άτομα με IR. [1]
- Οι κλασσικοί παράγοντες κινδύνου για ASCVD μπόρεσαν να εξηγήσουν μόνο το 69% των παρατηρούμενων καρδιαγγειακών συμβαμάτων αφήνοντας το 31% ανεξήγητο.[2]
- Έχει διατυπωθεί η υπόθεση ότι η αντίσταση στην ινσουλίνη (βασικά μοριακά μονοπάτια) και η υπερινσουλιναιμία ευθύνονται για το μεγαλύτερο μέρος αυτού του υπολειπόμενου καρδιαγγειακού κινδύνου.[3]

[1]Cecilia C. Low Wang. Circulation. Clinical Update: Cardiovascular Disease in Diabetes Mellitus. 2016;133(24): 2459-502.
[2]D'Agostino RB et al. CHD Risk Prediction Group. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. JAMA. 2001;286:180–7.
[3]Di Pino A. et al. Insulin Resistance and Atherosclerosis: Implications for Insulin-Sensitizing Agents, Endocrine Reviews. 2019;40(6):1447–67.

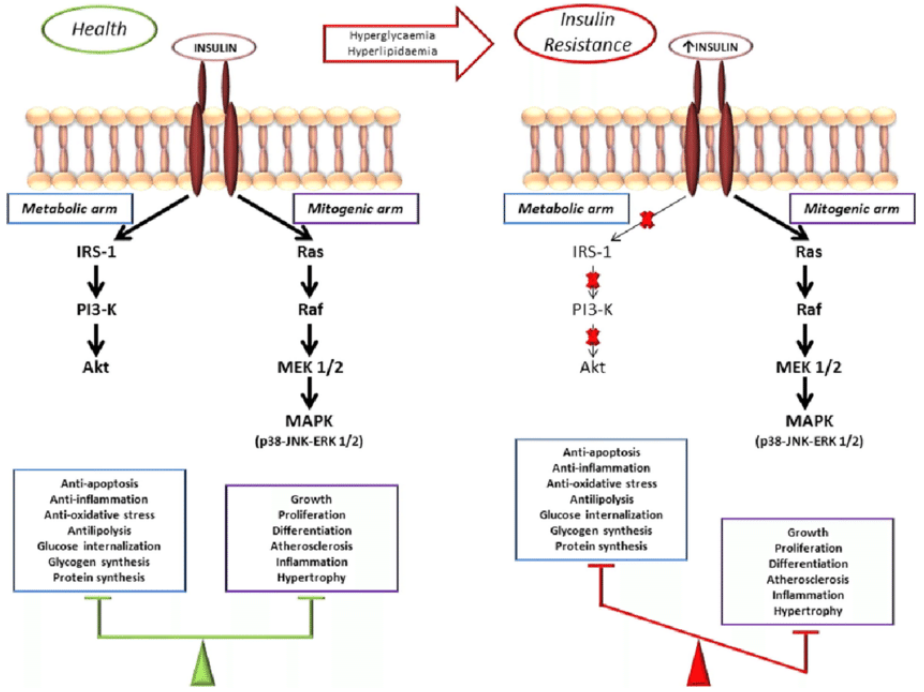
Αντίσταση στην Ινσουλίνη/Υπερινσουλιναιμία

Η ενεργοποίηση του υποδοχέα ινσουλίνης έχει ως αποτέλεσμα την παράλληλη και ισορροπημένη σηματοδότηση της ινσουλίνης μέσω των του PI 3-Kinase-Akt και Ras-MAP-kinase σηματοδοτικών μονοπατιών.

Στις αντιαθηρογόνες δράσεις συγκαταλέγονται η διέγερση της παραγωγής του NO, η διατήρηση σε διαφοροποιημένη κατάσταση των VSMCs, και η αντιμετώπιση των επιδράσεων του VEGF και του PDGF.

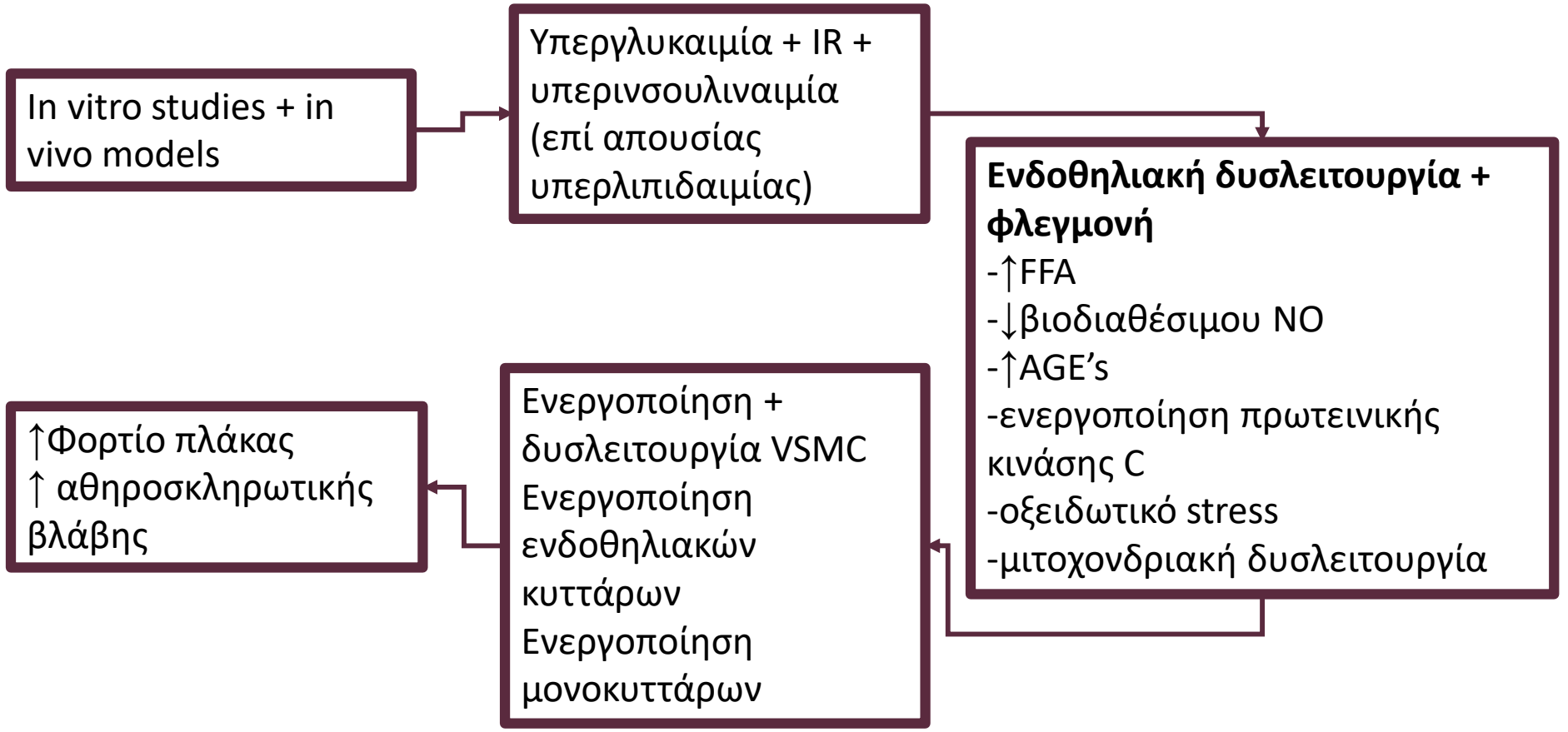
Οι μη μεταβολικές δράσεις είναι πολλαπλασιαστικές, μιτογόνες, προφλεγμονώδεις και προ-αθηρογόνες.

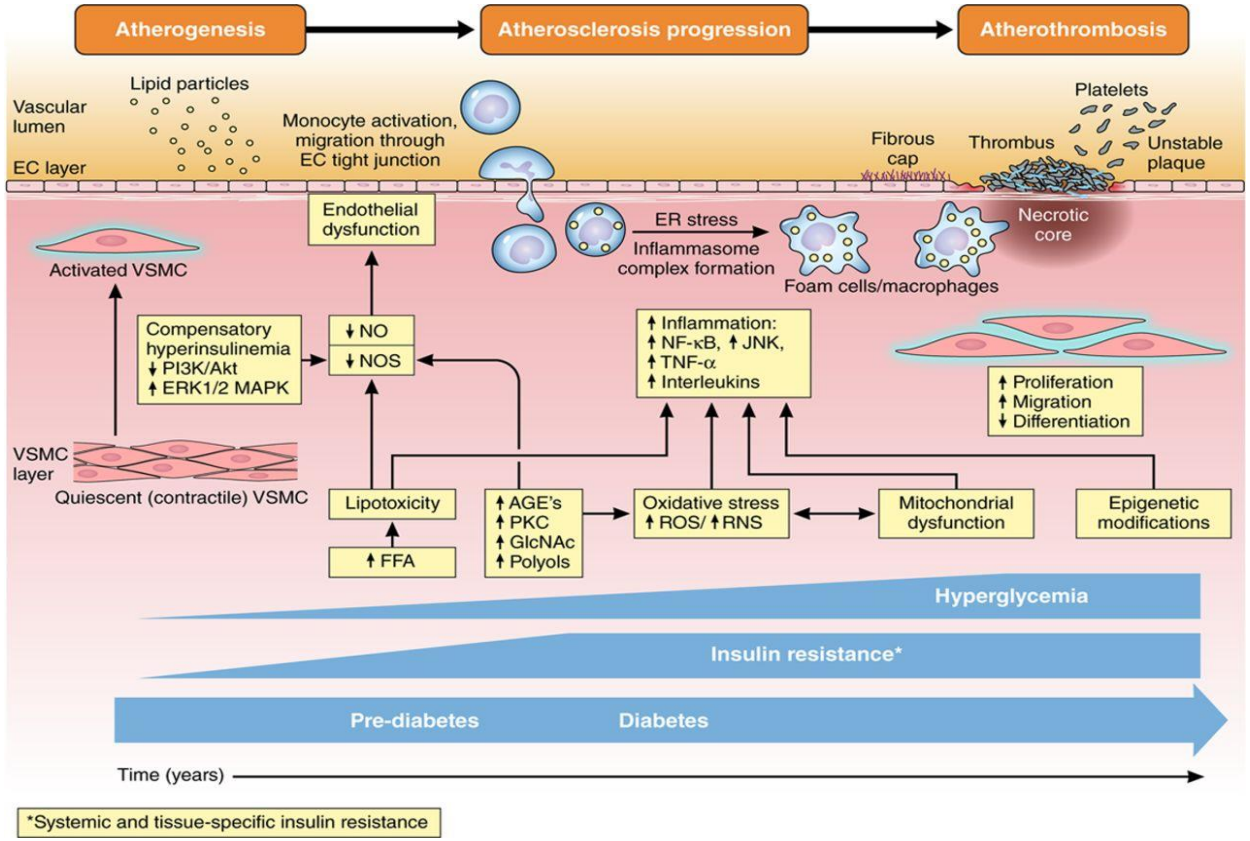
Στο ΣΔΤ2, υπάρχει επιλεκτική εξασθένηση της σηματοδότησης της ινσουλίνης μέσω μέσω του PI 3-Kinase-Akt σηματοδοτικού μονοπατιού ενώ η σηματοδότηση μέσω του Ras-MAP-kinase μονοπατιού παραμένει ανέπαφη.



Cecilia C et al. Molecular Mechanisms of Insulin Resistance That Impact Cardiovascular Biology. *Diabetes* 1 November 2004; 53 (11): 2735–2740.

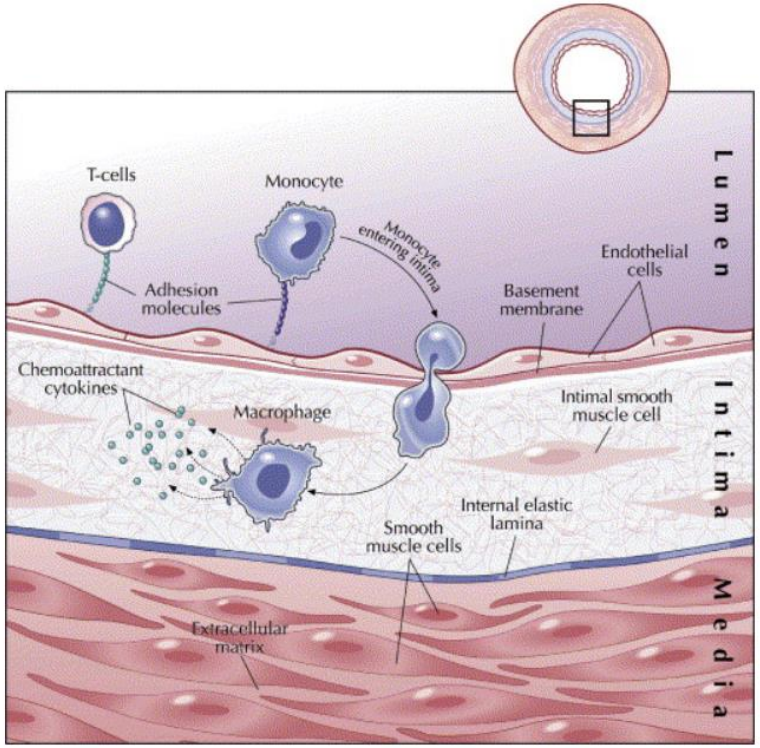
Υπεργλυκαιμία/IR/Υπερινσουλιναιμία





Cecilia C. Low Wang. Circulation. Clinical Update: Cardiovascular Disease in Diabetes Mellitus, Volume: 133, Issue: 24, Pages: 2459-502.

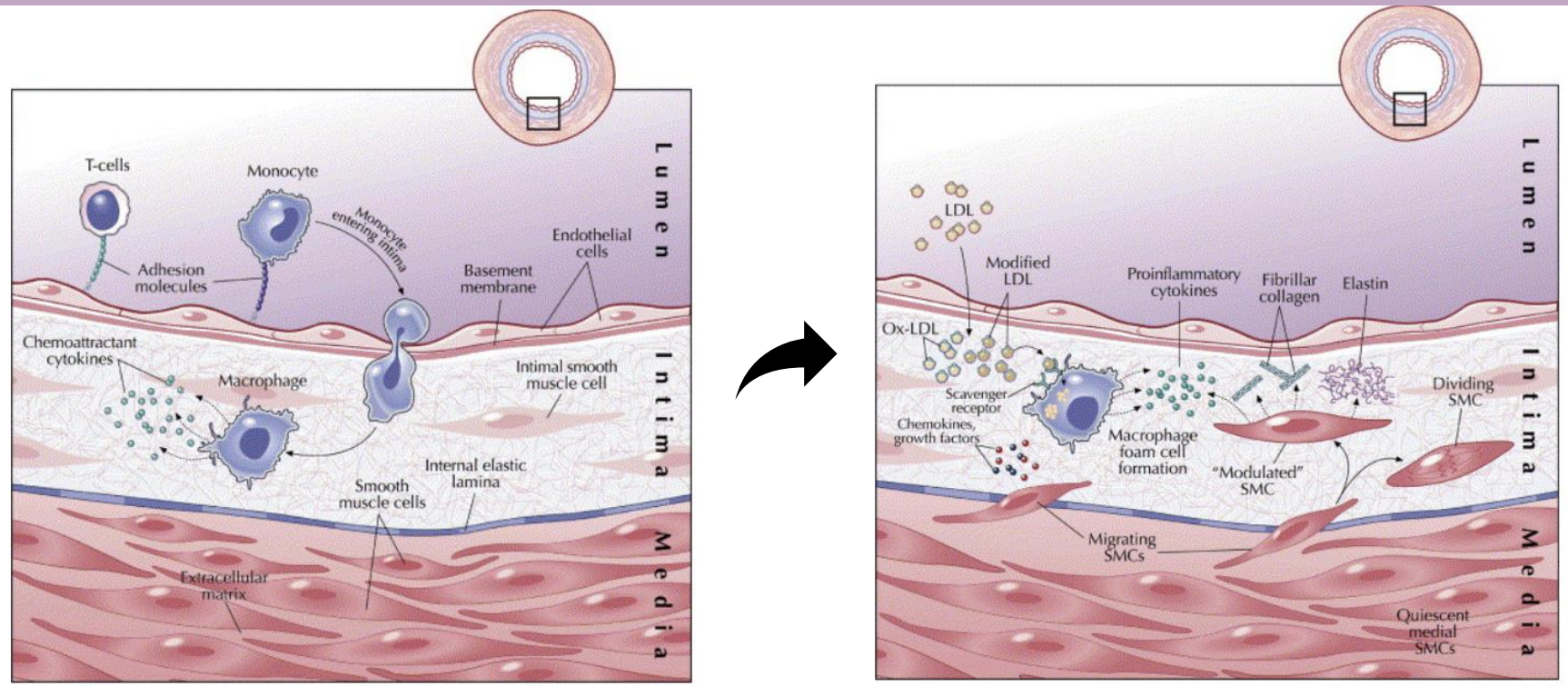
ΣΔ – Φλεγμονή - Αθηροσκλήρωση



- Ο ΣΔ, η αντίσταση στην ινσουλίνη και η παχυσαρκία χαρακτηρίζονται από χρόνια υποκλινική συστηματική και αγγειακή φλεγμονή.
- Η hsCRP είναι ένας αναγνωρισμένος δείκτης φλεγμονής, ο οποίος θεωρείται επιπρόσθετος (στους ήδη παραδοσιακούς) προγνωστικός δείκτης καρδιαγγειακού κινδύνου.
- Αναμενόμενα, η φλεγμονή διαδραματίζει βασικό ρόλο στη διαδικασία της αθηρογένεσης και της αθηροσκλήρωσης.

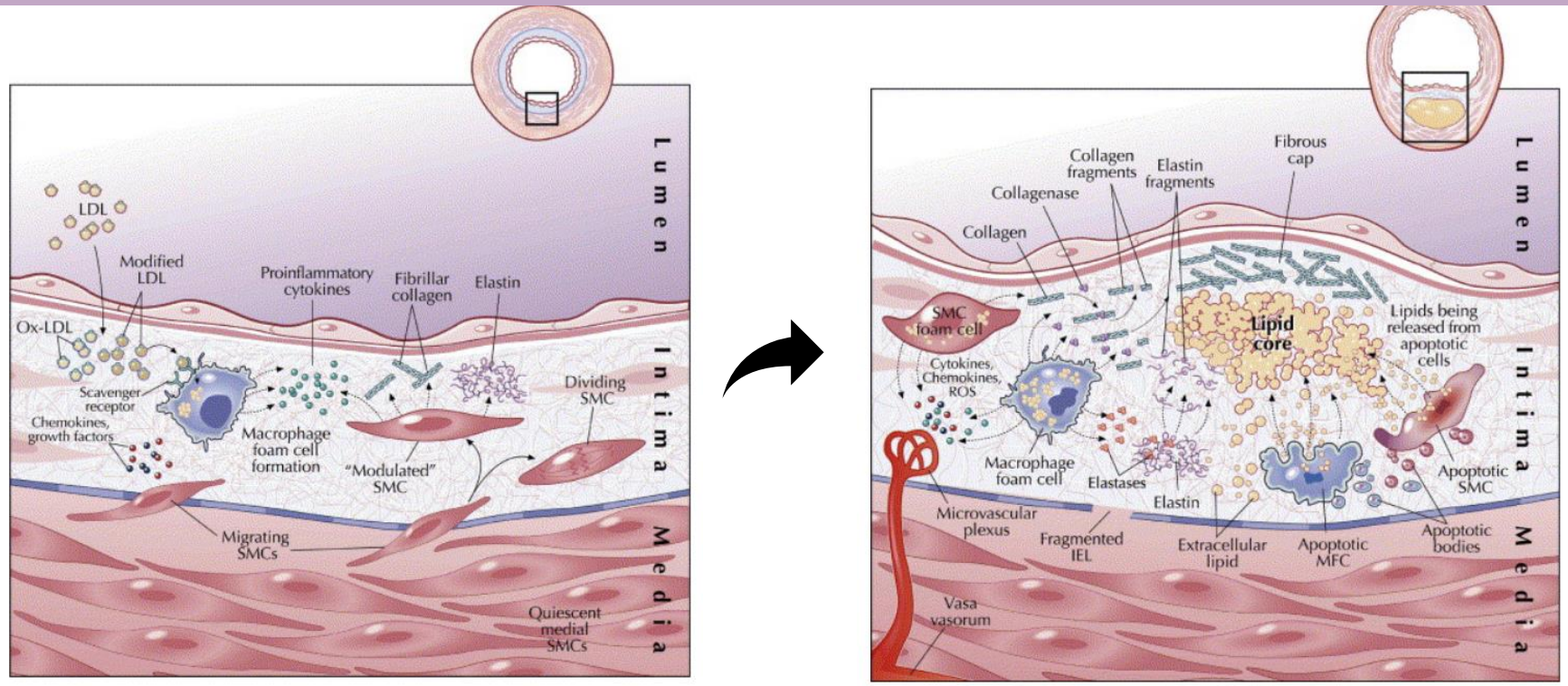
Libby P et al. Inflammation and Atherothrombosis: From Population Biology and Bench Research to Clinical Practice. Journal of the American College of Cardiology, 2006.

ΣΔ – Φλεγμονή - Αθηροσκλήρωση



Libby P et al. Inflammation and Atherothrombosis: From Population Biology and Bench Research to Clinical Practice. Journal of the American College of Cardiology, 2006.

ΣΔ – Φλεγμονή - Αθηροσκλήρωση



Libby P et al. Inflammation and Atherothrombosis: From Population Biology and Bench Research to Clinical Practice. Journal of the American College of Cardiology, 2006.

Κατάσταση Υπερπηκτικότητας

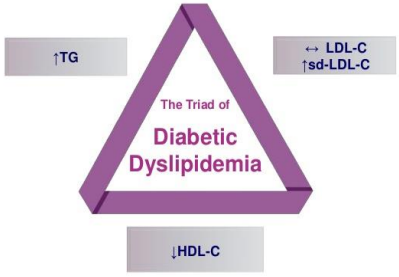
- Οι ασθενείς θεωρείται ότι βρίσκονται σε κατάσταση υπερπηκτικότητας εάν έχουν εργαστηριακές ευρήματα ή κλινικές καταστάσεις που σχετίζονται με αυξημένο κίνδυνο θρόμβωσης (Schafer, 1985).

Διαταραχές δεικτών πήξης σε ασθενείς με ΣΔ
Ενδοθηλιακή δυσλειτουργία
Αυξημένα επίπεδα δεικτών ενεργοποίησης της πήξης
Thrombin – antithrombin complexes, prothrombin activation fragment 1+2
Αυξημένα επίπεδα παραγόντων πήξης
fibrinogen, παράγοντες VII, VIII, XI, XII, καλλικρεΐνη και παράγοντας von Willebrand
Μειωμένα επίπεδα αντιπηκτικής πρωτεΐνης C.
Αναστολή λειτουργίας του συστήματος ινωδόλυσης.
Διαφορετική δομή θρόμβων (ανθεκτικοί στην αποδόμηση)
↑ plasminogen activator inhibitor type 1 (PAI-1).
Αυξημένη δραστηριότητα αιμοπεταλίων
↑Συσσώρευση αιμοπεταλίων.
↑ Κυκλοφορούντα συσσωματώματα αιμοπεταλίων.
↑ Επίπεδα προϊόντων απελευθέρωσης των αιμοπεταλίων (β-θρομβοσφαιρίνη, ο παράγοντας αιμοπεταλίων 4 και η θρομβοξάνη Β2).

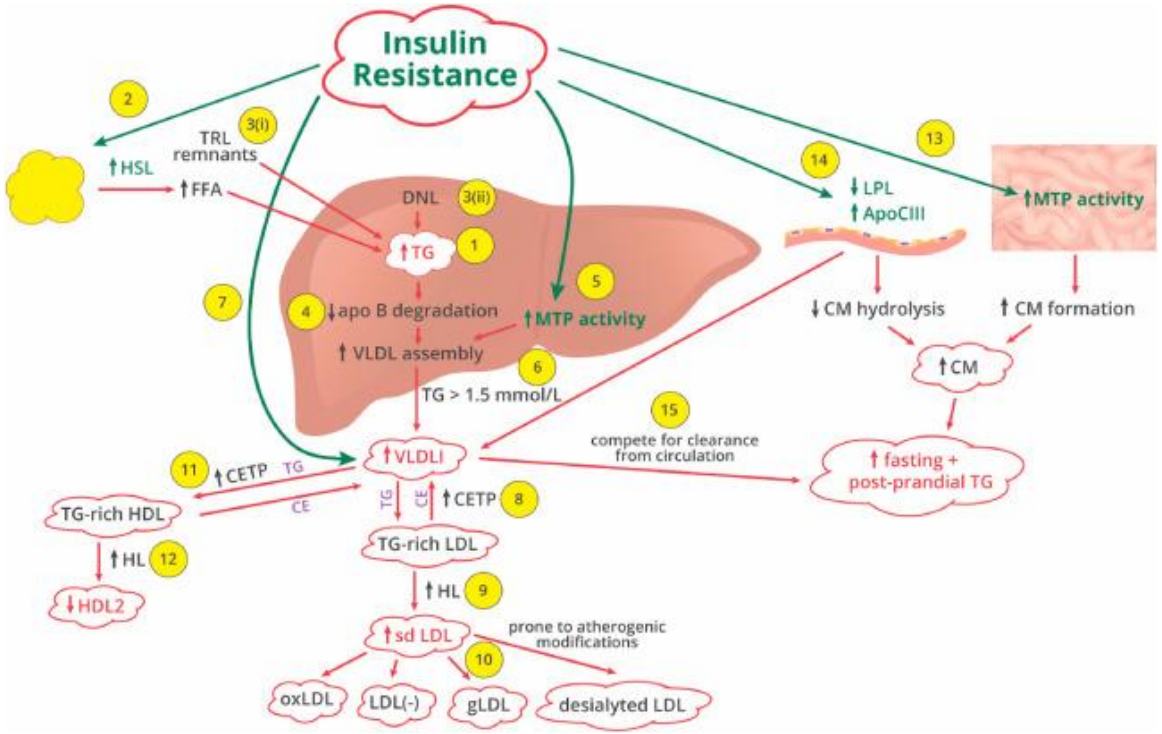
Carr ME. Diabetes mellitus: a hypercoagulable state. Review J Diabetes Complications. 2001;15(1):44-54.

Διαβητική Δυσλιπιδαιμία

- 60% -70% των ασθενών με ΣΔΤ2 εμφανίζουν διαταραχή στο λιπιδαιμικό προφίλ τους.
- Η LDL-C των ασθενών με ΣΔΤ2 είναι ιδιαίτερα αθηρογόνος, ακόμη και αν ο απόλυτος αριθμός της δεν είναι αυξημένος.
- Οι παθοφυσιολογικοί μηχανισμοί πίσω από διαβητική δυσλιπιδαιμία ακόμη και σήμερα δεν είναι πλήρως κατανοητοί.
- Διαταραχές στο λιπιδαιμικό προφίλ παρατηρούνται από το στάδιο της αντίστασης στην ινσουλίνη, πριν την εμφάνιση διαταραχής στο μεταβολισμό της γλυκόζης.



Διαβητική Δυσλιπιδαιμία



Subashini C et al. Diabetic dyslipidaemia. Practical Laboratory Medicine, 2021.

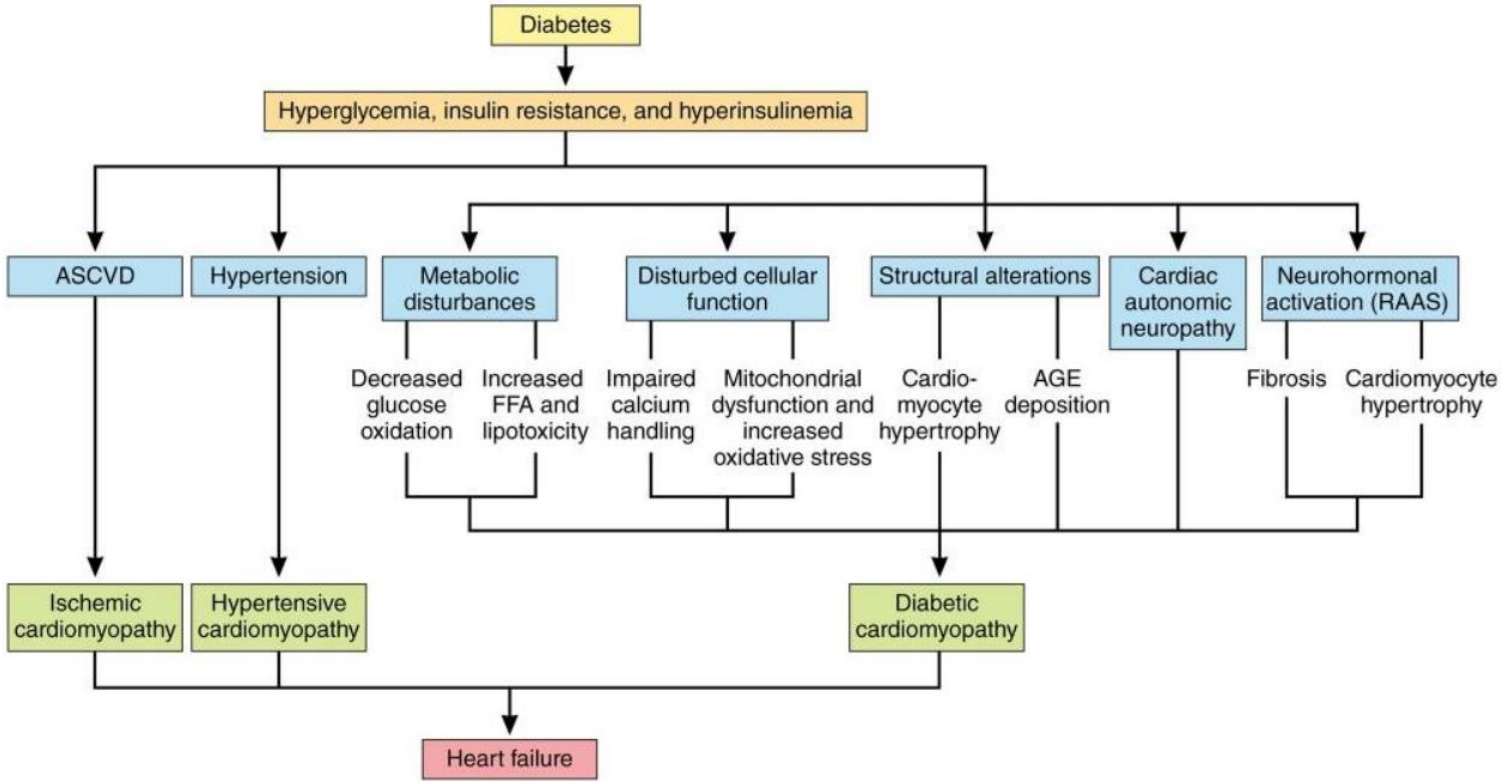
Επασβεστώσεις των αγγείων

- Coronary Calcium Score = δείκτης επασβέστωσης των αγγείων – εκτιμάται με τη χρήση αξονικής τομογραφίας. Αποτελεί ανεξάρτητο παράγοντα κινδύνου για καρδιαγγειακή νόσο και θάνατο από οποιαδήποτε αιτία, τόσο σε άτομα με ΣΔ όσο και σε άτομα σχωρίς ΣΔ.
- Τα άτομα με ΣΔ έχουν ↑ Coronary Calcium Score σε σχέση με τα άτομα χωρίς διαβλητη.
- Διατρέχουν ↑ κίνδυνο να αναπτύξουν περιφερική αρτηριακή νόσο (άπω κνημιαίας αρτηρίας). Η επασβέστωση της κνημιαίας αρτηρίας σχετίζεται με αυξημένο κίνδυνο ακρωτηριασμού άκρων και θνησιμότητα από κάθε αιτία.

Υπεργλυκαιμία→ AGEs →επιταχύνουν την αγγειακή επασβέστωση.

Υπεργλυκαιμία → αρτηριακής φλεγμονής → TNFα → μεσολαβητής αρτηριακής επασβέστωσης

Υπεργλυκαιμία → η τροποποιημένη ρύθμιση της οστεοπρωτεγερίνης και της οστεοκαλσίνης → μπορεί να προάγει την αρτηριακή επασβέστωση σε ασθενείς με ΣΔ.



Cecilia C. Low Wang. Circulation. Clinical Update: Cardiovascular Disease in Diabetes Mellitus, Volume: 133, Issue: 24, Pages: 2459-502.

Macrovascular Complications Affect Multiple Organs and Can Occur Early in the T2D Disease Course

Coronary Artery Disease[a]	Heart Failure[b]	Peripheral Arterial Disease[c]	Stroke[d]
▪ **More than 25%** of asymptomatic patients with T2D have findings for coronary alterations when screened	▪ **2- to 4-fold higher rate of hospitalization** from heart failure in patients with T2D versus those without	▪ **2- to 4-fold increase** risk of developing PAD for patients with T2D	▪ **2-fold increased risk** of stroke within 5 years of diagnosis of T2D compared with the general population

OR, odds ratio; PAD, peripheral arterial disease.

a. Tavares CAF, et al. Endocrinol Metab. 2016;60:143-151; b. Diabetes Canada Clinical Practice Guidelines Expert Committee. Can J Diabetes. 2018;42:S196-S200; c. Thiruvoipati T, et al. World J Diabetes. 2015;6:961-969; d. Jeerakathil T, et al. Stroke. 2007;38:1739-1743.

Management of Diabetes and Its Complications

Recommended targets in adults with diabetes

HbA_{1c}

< 7.0% (<53 mmol/mol)

Physical activity

≥ 150 minutes per week†

(Diet and exercise for weight management)

Blood pressure

< 130/80 mmHg

(ACE-I and ARB))

LDL-C

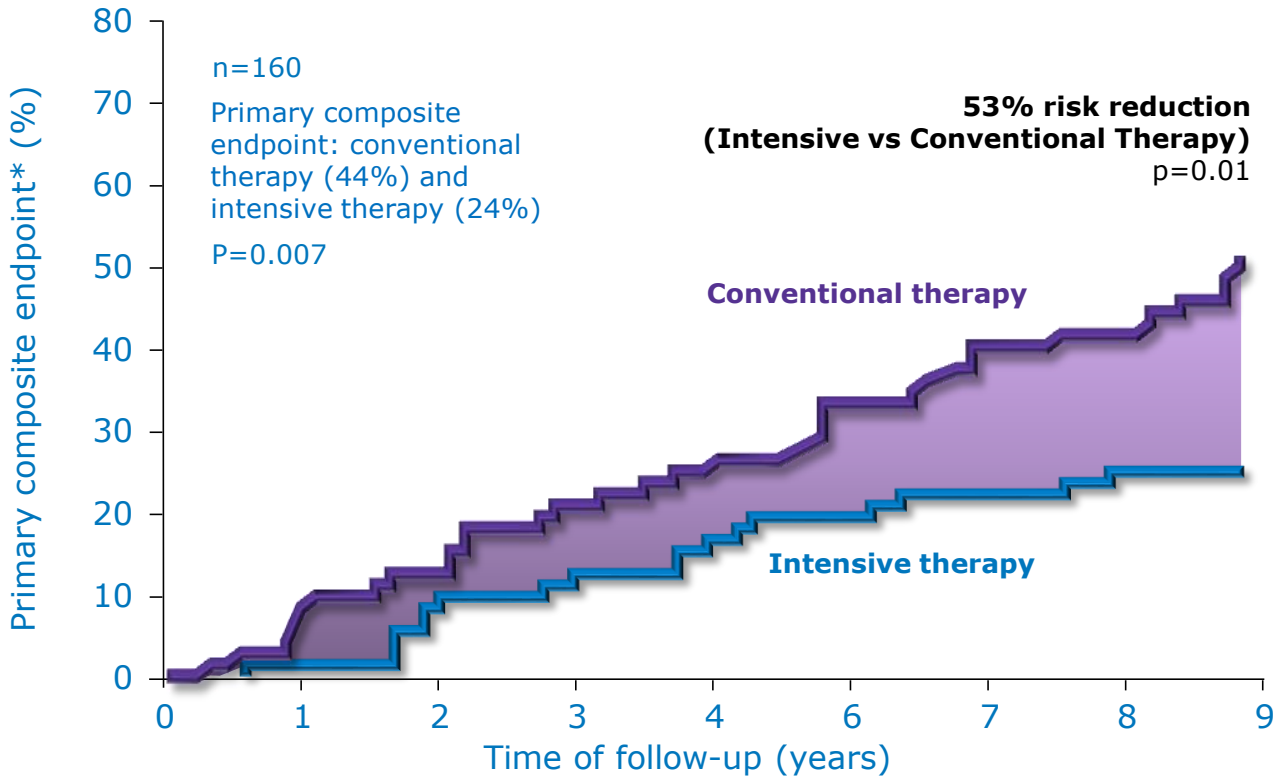
(Statins intensified with ezetimibe)

- < 100mg/dL: (2.6mmol/L) at moderate CV risk
- < 70mg/dL: (1.8mmol/L) at high CV risk
- < 55mg/dL: (1.4mmol/L) at very high CV risk

A multifactorial approach can improve management of type 2 diabetes and its complications

Only primary prevention strategies; platelet inhibition is recommended as secondary prevention (in patients with T2D at high/very high CV risk, it may be considered in primary prevention in the absence of clear contraindications). †Physical activity of moderate to vigorous intensity.
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; HbA1c, glycated hemoglobin; LDL-C, low-density lipoprotein cholesterol.
Cosentino F, et al. Eur Heart J. 2020;41:255-323.

STENO-2: Η πολυπαραγοντική αντιμετώπιση μειώνει τα καρδιαγγειακά συμβάματα



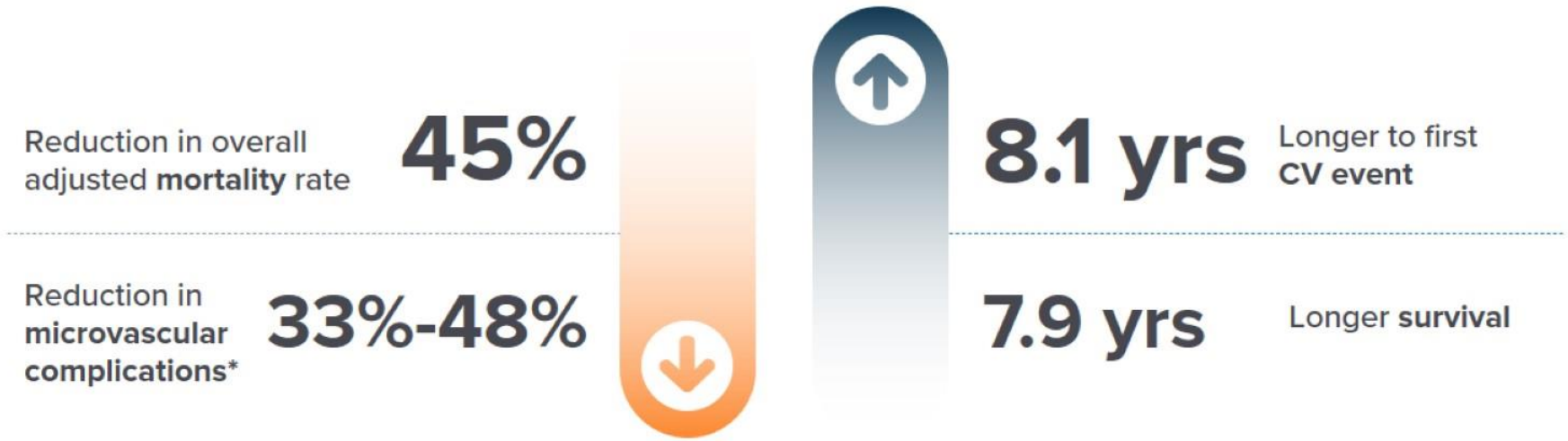
- In addition to ~50% relative risk reduction in the primary composite endpoint, a sustained benefit on CV events was also observed in the intensive management group over an additional 5.5 years[2]

*Death from CV causes, non-fatal MI, CABG, PCI, non-fatal stroke, amputation, or surgery for peripheral atherosclerotic artery disease

1. Gaede P, et al. N Engl J Med. 2003;348:383-93. 2. Gaede P, et al. N Engl J Med. 2008;358(6):580-91.

Benefits of Multifactorial Intensive Therapy Over Conventional Therapy
Steno-2 Trial

After 21 y of follow-up (mean, 7.8 years of treatment):



*Except for peripheral neuropathy, which increased by 12%.

Gæde P, et al. Diabetologia. 2016;59:2298-2307.

Importance of Glycemic Control

Intensive glycemic control reduces the risk of some diabetes-related complications

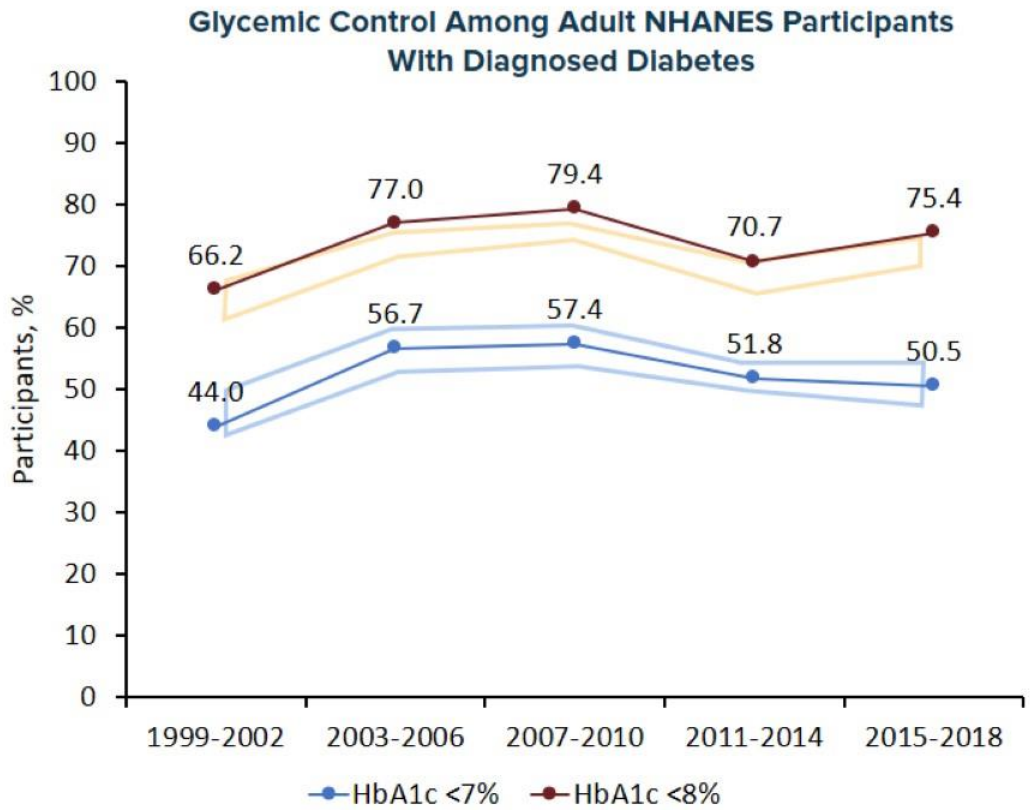
	Microvascular Complications	CV Complications	CV Mortality
UKPDS 33[a,b]	↓	↓	↓*
ACCORD[c,d]	NR	↔	↑
ADVANCE[e,f]	↔†	↔	↔
VADT[g,h]	NR	↓	↔

↓ Reduction in risk ↔ No difference in risk ↑ Increase in risk

*Diabetes-related mortality. †Reduction in the incidence of nephropathy, no significant effect on retinopathy.
CV, cardiovascular; NR, not reported.

a. UKPDS Group. Lancet. 1998;352:837-853; b. Holman RR, et al. N Engl J Med. 2008;359:1577-1589; c. Action to Control Cardiovascular Risk in Diabetes Study Group; Gerstein HC, et al. N Engl J Med. 2008;358:2545-2559; d. ACCORD Study Group. Diabetes Care. 2016;39:701-708; e. ADVANCE Collaborative Group; Patel A, et al. N Engl J Med. 2008;358:2560-2572; f. Zoungas S, et al. N Engl J Med. 2014;371:1392-1406; g. Duckworth W, et al. N Engl J Med. 2009;360:129-139; h. Hayward RA, et al. N Engl J Med. 2015;372:2197-2206.

Glycemic Control Among Patients With T2D

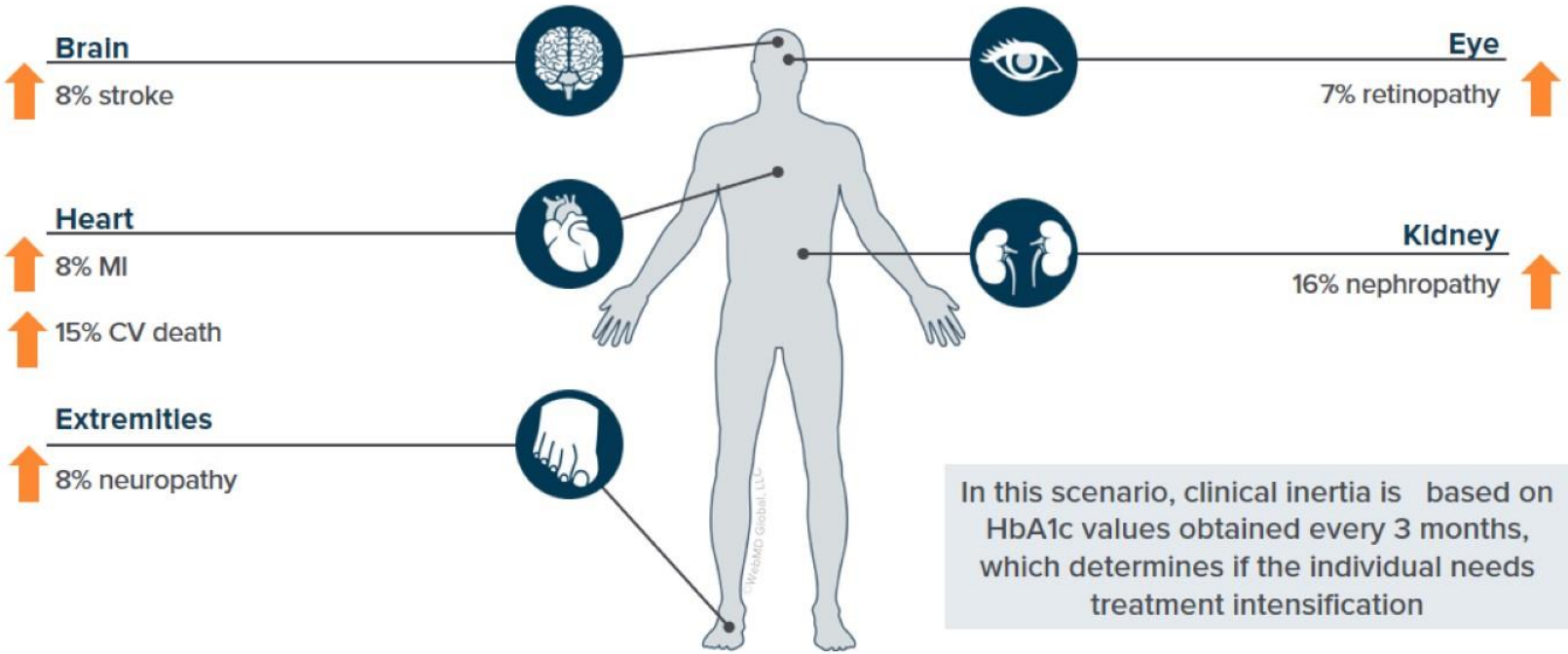


NHANES, National Health and Nutrition Examination Survey.
Fang M, et al. New Engl J Med. 2021;384:2219-2128.

Clinical Inertia Is Associated With Significant Increased Risk

Clinical inertia: failure to set appropriate targets and escalate treatment to achieve goals[a]

A 1-y clinical inertia scenario is associated with a significant increase in risk for the following comorbidities:[b]



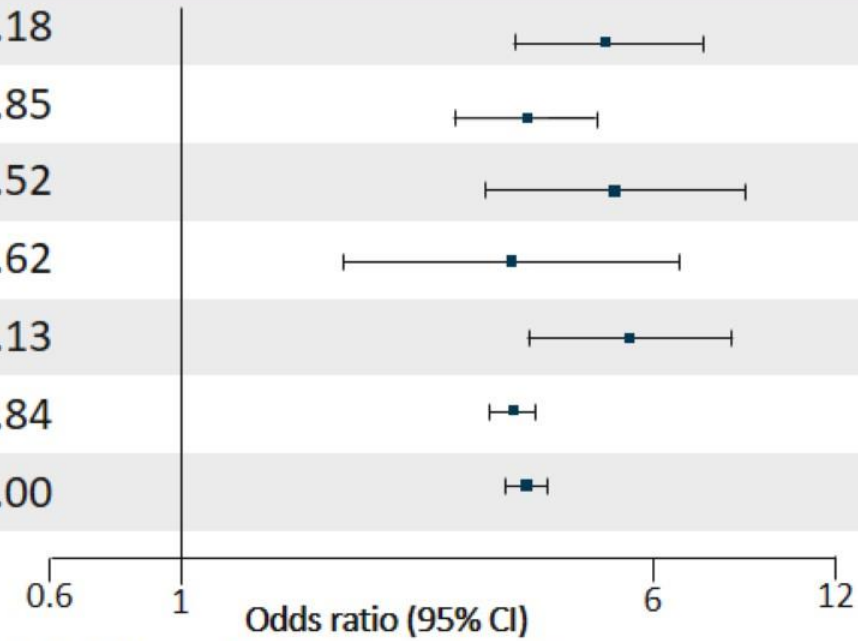
In this scenario, clinical inertia is based on HbA1c values obtained every 3 months, which determines if the individual needs treatment intensification

a. Strain WD, et al. Diabetes Ther. 20145:347-54. b. Correa MF, et al. J Gen Intern Med. 2019;34:372-378.

Consequences of Delaying Intensification of Therapy in T2DM

Failure to achieve glycemic target at 3 months is associated with increased risk of not achieving it at 24 months[a]

Country	OR	95% CI
France	5.04	3.53-7.18
Germany	3.71	2.84-4.85
Italy	5.22	3.19-9.52
Spain	3.50	1.85-6.62
UK	5.51	3.73-8.13
USA	3.51	3.21-3.84
Overall	3.70	3.41-4.00



Mauricio D, et al. *Diabetes Obes Metab*. 2017;19:1155-1164 Copyright © 2017, John Wiley and Sons

A range of complications can arise from failure to achieve early glycemic control, eg increased risk for CVD[b]

a. Mauricio D, et al. *Diabetes Obes Metab*. 2017;19:1155-1164; b. Khunti K, et al. *Prim Care Diabetes*. 2017;11:3-12.

Consequences of Therapeutic Inertia in Diabetes

Therapeutic inertia is an important contributor to excess CV events in patients with T2D

- **Increased macrovascular complications, including MI, HF, stroke, and CV events**
- **Increased microvascular complications, including retinopathy, neuropathy, nephropathy**
- **Poor management of diabetes, including increased healthcare system and public health costs**
- **Higher HbA1c levels, leading to reduced likelihood of achieving target levels**
- **Increased mortality**
- **Reduced quality of life**

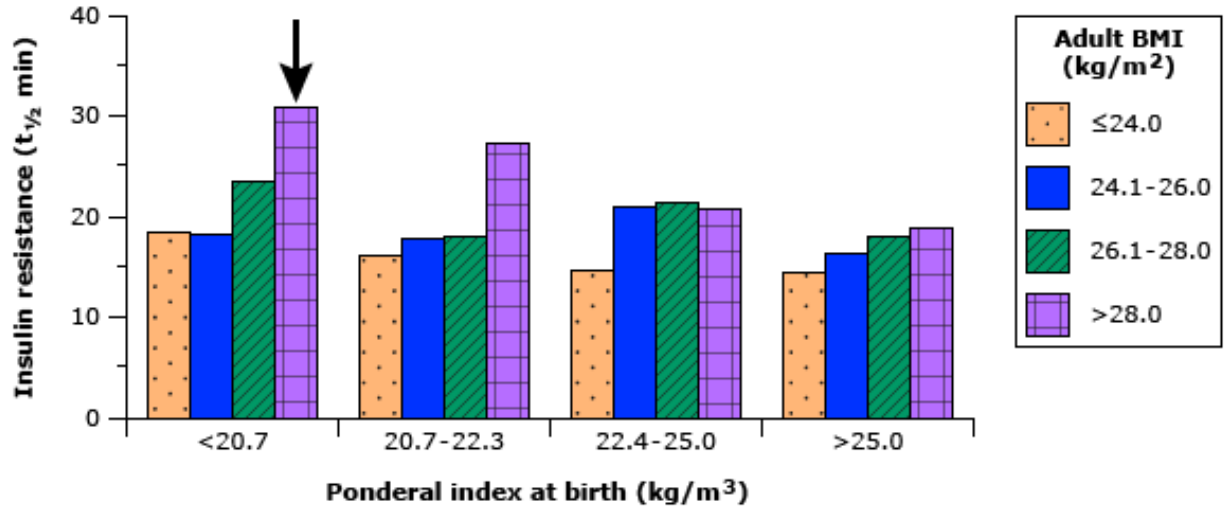
HF, heart failure; MI, myocardial infarction.

a. Khunti S, et al. Ther Adv Endocrinol Metab. 2019;10.1177/2042018819844694; b. Safford MM, et al. J Gen Intern Med. 2007;22:1648-1655.

Diabetes + Obesity = Diabesity

Διαβήτης + Παχυσαρκία = Επιδημία της δεκαετίας του 1990

Birth weight and insulin resistance

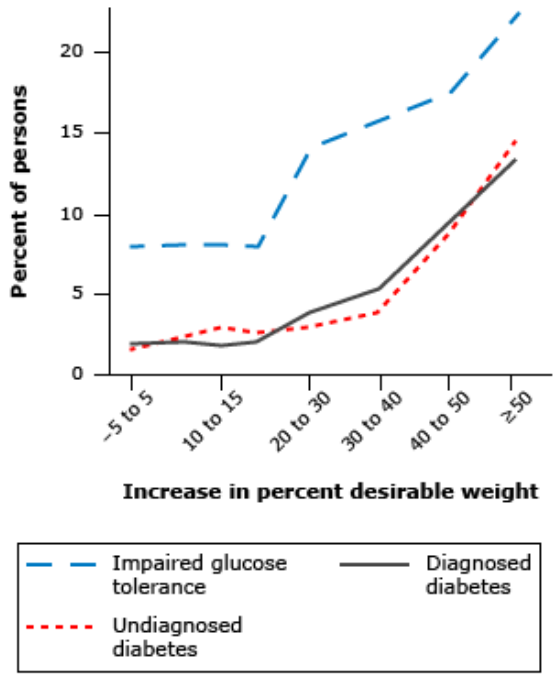


Contrasting relationship between ponderal index at birth (kg/m^3) and BMI (kg/m^2) in adulthood on mean insulin resistance. Insulin resistance varies directly with adult BMI and inversely with ponderal index at birth. Thus, the degree of insulin resistance is greatest with lower ponderal index at birth and higher BMI in adulthood (arrow). Insulin resistance is measured as the half-life ($t_{½}$) of the fall in blood glucose during an intravenous insulin tolerance test.

BMI: body mass index.

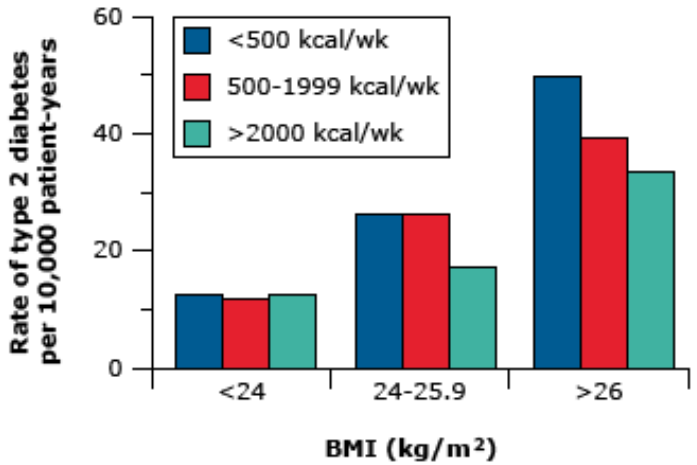
Data from: Phillips DI, Barker DJ, Hales CN, et al. Thinness at birth and insulin resistance in adult life. Diabetologia 1994; 37:150.

Increasing body weight increases risk of diabetes



Rates of impaired glucose tolerance and diagnosed and undiagnosed type 2 diabetes in the United States adult population according to increase in percent desirable weight from age 25 years to age at maximum adult weight (approximately 50 years).

Importance of body weight and exercise on development of type 2 diabetes



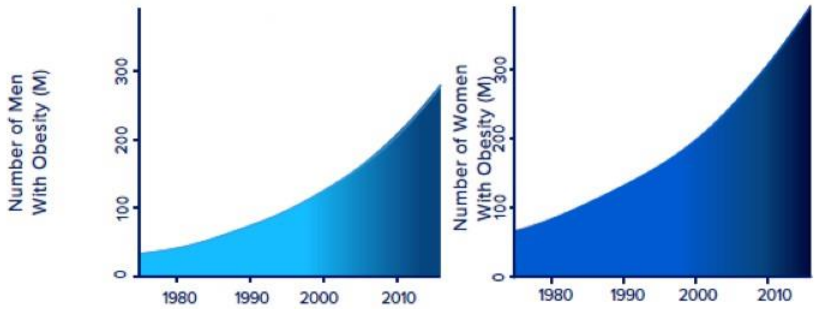
Adjusted incidence of type 2 diabetes mellitus in 5990 males in relation to BMI (in kg/m^2) and the level of physical activity (in kcal/week). The risk of type 2 diabetes was directly related to BMI, while regular exercise was protective except for in males with a BMI below 24 kg/m^2.

BMI: body mass index.

Data from: Helmrich SP, Ragland DR, Leung RW, Paffenbarger RS Jr. Physical activity and reduced occurrence of non-insulin-dependent diabetes mellitus. N Engl J Med 1991; 325:147.

Obesity Is a Serious Chronic Disease

Global Prevalence of Obesity[a]



Obesity Rates Are Increasing Globally

- **764 M adults live with obesity (WHO 2022 data)**
- **39% to 49% of world's population are overweight/ or have obesity (2.8-3.5 B people)**
- **Socioeconomic factors contribute to obesity, which drives health inequalities**

Life Expectancy Decreases as BMI Increases

Normal BMI	BMI 35 to 40 kg/m²	BMI 40 to 50 kg/m²
80%	60%	50%

Chance of reaching age 70 y

BMI, body mass index; WHO, World Health Organization. a. Adapted from NCD-RisC. Lancet 2017:390(suppl);2627-2642; b. WHO. Accessed August 11th, 2022. https://apps.who.int/gho/data/node.main.A896?lang=en and https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight ; c. WHO, Obesity & Overweight; Prospective Studies Collaboration. Lancet 2009;373:1083-1096.

Obesity Is Associated With Multiple Complications

- Depression
- Anxiety
- Asthma
- NAFLD
- Gallstones
- Chronic Back Pain
- Infertility
- Incontinence
- Knee Osteoarthritis
- Cancers

Physical Functioning

- CKD
- CVDs
  - Stroke
  - Dyslipidaemia
  - Hypertension
  - Coronary artery disease
  - Pulmonary embolism
  - HFpEF
- T2D
  Prediabetes
- Sleep Apnea
- Thrombosis
- Gout

CKD, chronic kidney disease; CVD, cardiovascular disease.HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reserved ejection fraction; NAFLD, non-alcoholic fatty liver disease. T2D, type 2 diabetes.

Sharma AM. Obes Rev. 2010;11:808-809; Guh DP, et al. BMC Public Health. 2009;9:88; Luppino FS, et al. Arch Gen Psychiatry. 2010;67:220-229; Simon et al. Arch Gen Psychiatry. 2006;63:824-830; Church TS, et al. Gastroenterology. 2006;130:2023-2030; Li C, et al. Prev Med. 2010;51:18-23; Hosler AS. Prev Chronic Dis. 2009;6:A48.

Obesity Is Associated With Multiple Complications

- Depression, Anxiety
- Asthma
- NAFLD
- Gallstones
- Chronic Back Pain
- Subfertility, hypogonadism (male)
- PCOS, pregnancy complications
- Incontinence
- Knee Osteoarthritis

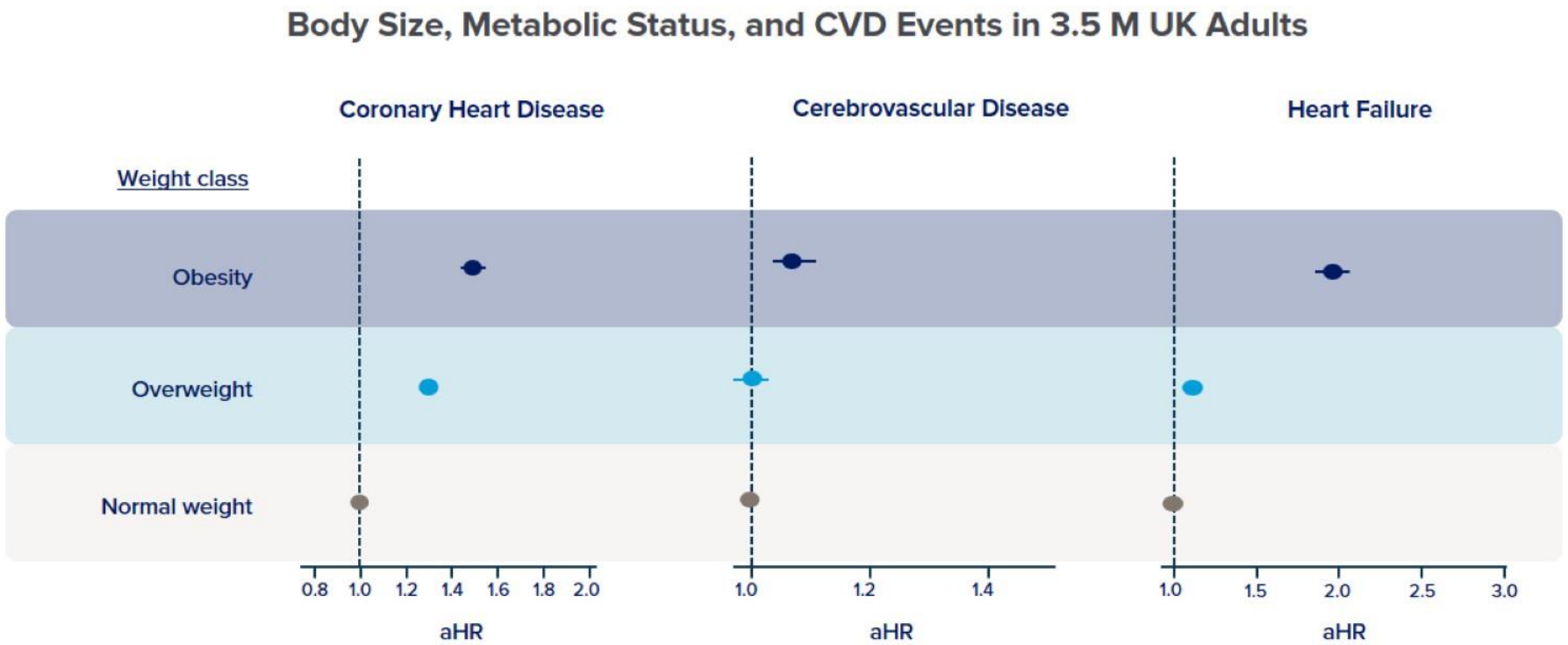
- CKD
- CVDs
  - Stroke
  - Dyslipidaemia
  - Hypertension
  - Coronary artery disease
  - Pulmonary embolism
  - HFpEF
- T2D
  Prediabetes
- Sleep Apnea
- Thrombosis

Increased BMI led to 4 M deaths in 2015, with > 2/3 from CVD

CKD, chronic kidney disease; CVD, cardiovascular disease.HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reserved ejection fraction; NAFLD, non-alcoholic fatty liver disease. T2D, type 2 diabetes.

Sharma AM. Obes Rev. 2010;11:808-809; Guh DP, et al. BMC Public Health. 2009;9:88; Luppino FS, et al. Arch Gen Psychiatry. 2010;67:220-229; Simon et al. Arch Gen Psychiatry. 2006;63:824-830; Church TS, et al. Gastroenterology. 2006;130:2023-2030; Li C, et al. Prev Med. 2010;51:18-23; Hosler AS. Prev Chronic Dis. 2009;6:A48.

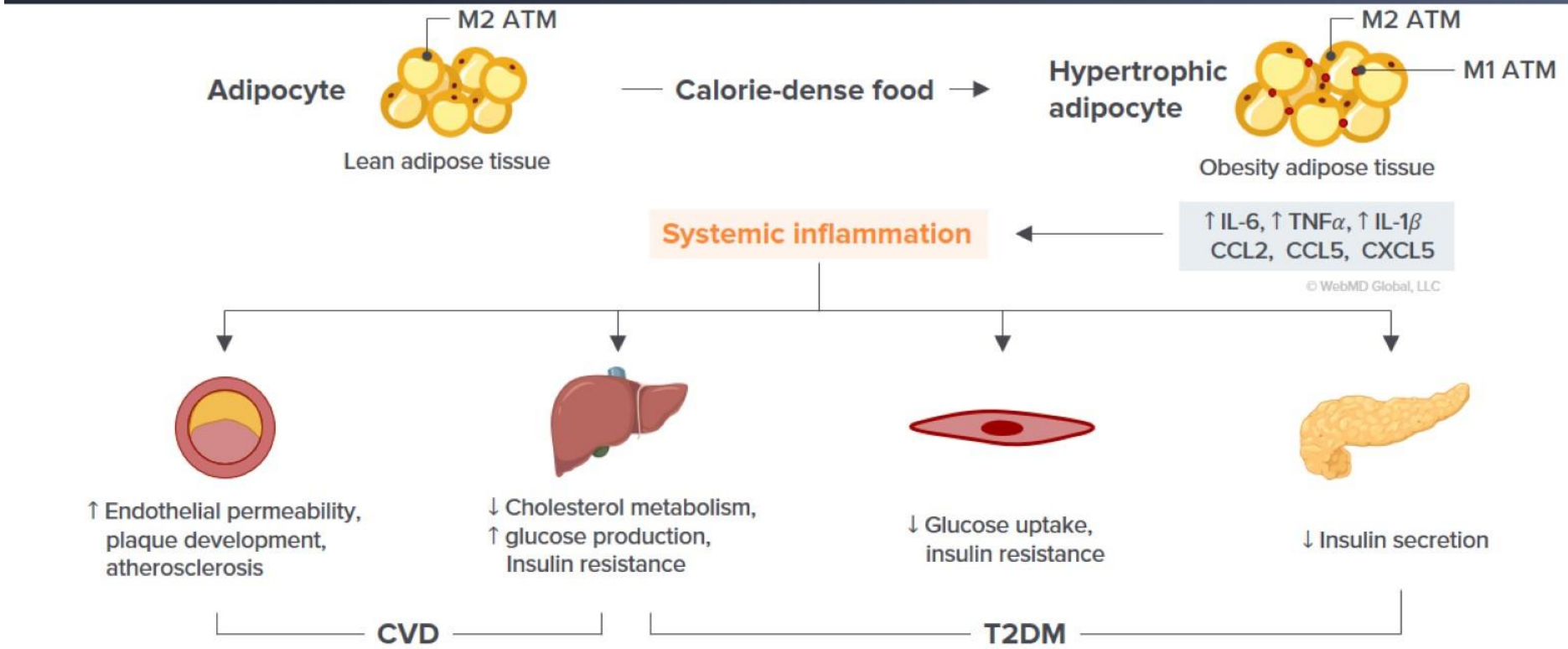
Overweight and Obesity Increase the Risk for CVD, Even in the Absence of Metabolic Abnormalities



aHR, adjusted HR.

Caleyachetty R, et al. J Am Coll Cardiol. 2017;70:1429-1437.

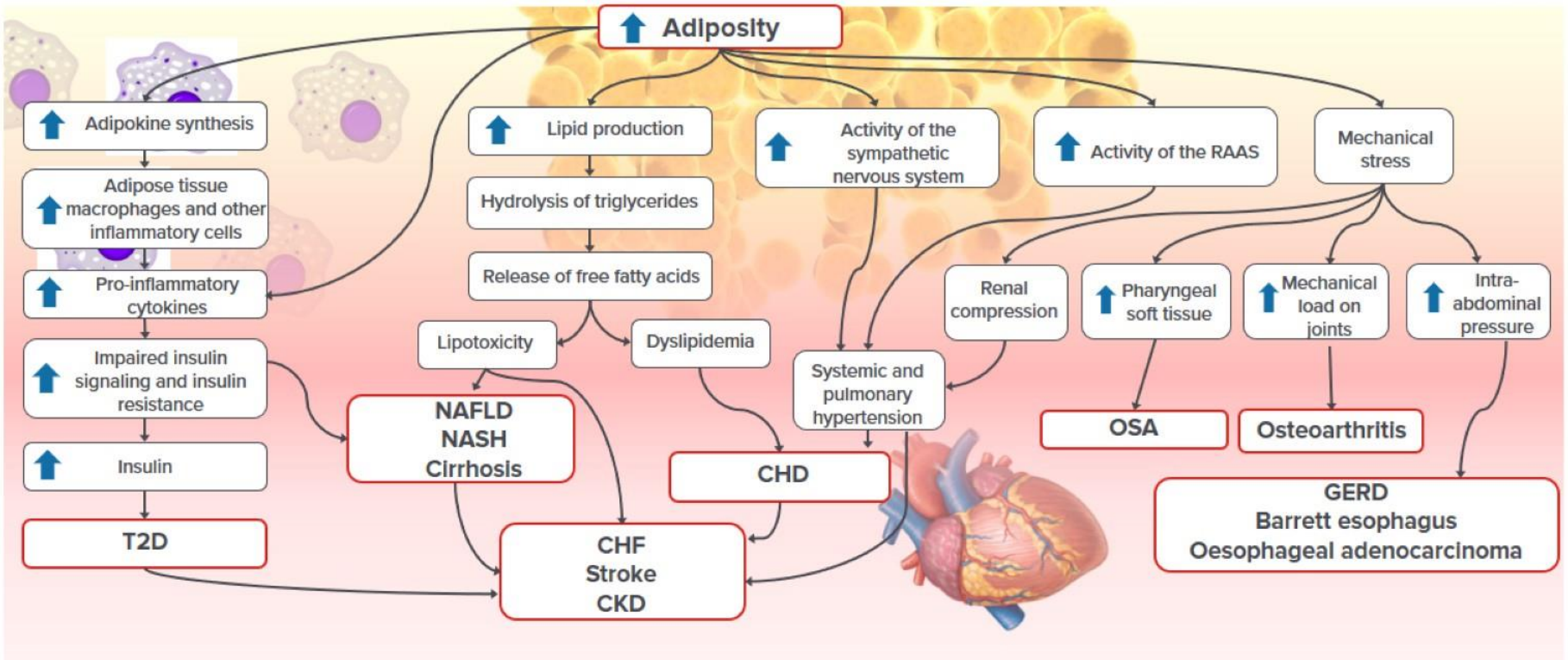
Consequences of Inflammation in Obesity
Adipose Tissue



CCL, chemokine (C-C motif) ligand; CXCL, chemokine (C-X-C motif) ligand; IL, interleukin; TNF, tumour necrosis factor; M1 ATM, classically activated adipose tissue macrophages; M2 ATM, alternatively activated adipose tissue macrophages.

Yao L, et al. J Immunol Res. 2014;2014:181450.

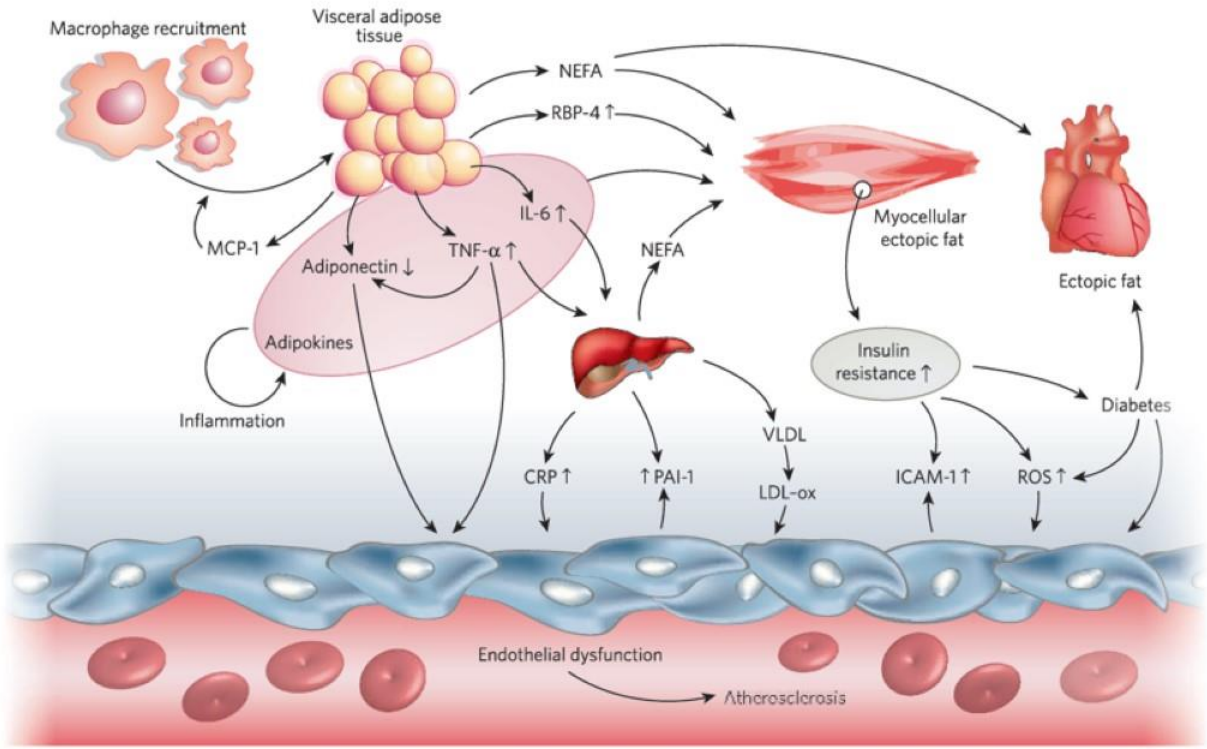
Excess Adiposity Leads to Major Risk Factors and Common Chronic Diseases



CHD, coronary heart disease; CHF, coronary heart failure; GERD, gastro-esophageal reflux disease; NASH, non-alcoholic steatohepatitis; OSA, obstructive sleep apnea; RAAS, renin-angiotensin-aldosterone system.

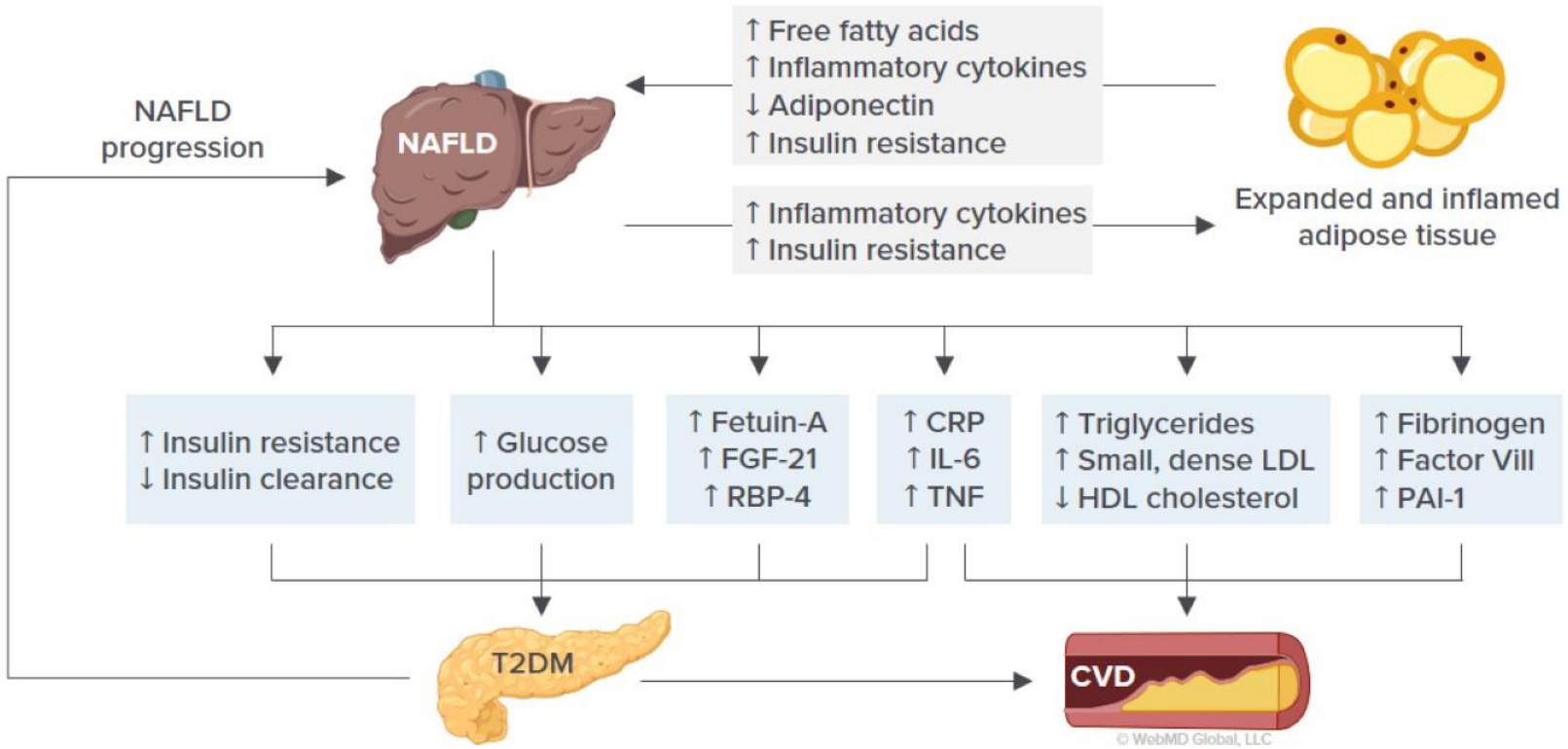
Heymsfield SB, et al. N Engl J Med. 2017;376:254-266.

A Link Among Obesity, Inflammation, and CVD
Role of Ectopic Fat



CRP, C-reactive protein; ICAM, intercellular adhesion molecule 1; LDL-ox, oxidised low-density lipoprotein; MCP-1, monocyte chemoattractant protein 1; NEFA, non-esterified fatty acids; PAI, plasminogen activator inhibitor; RBP, retinol binding protein; ROS, reactive oxygen species; VLDL, very low-density lipoprotein.
Van Gaal LF, et al. Nature. 2006;444:875-880.

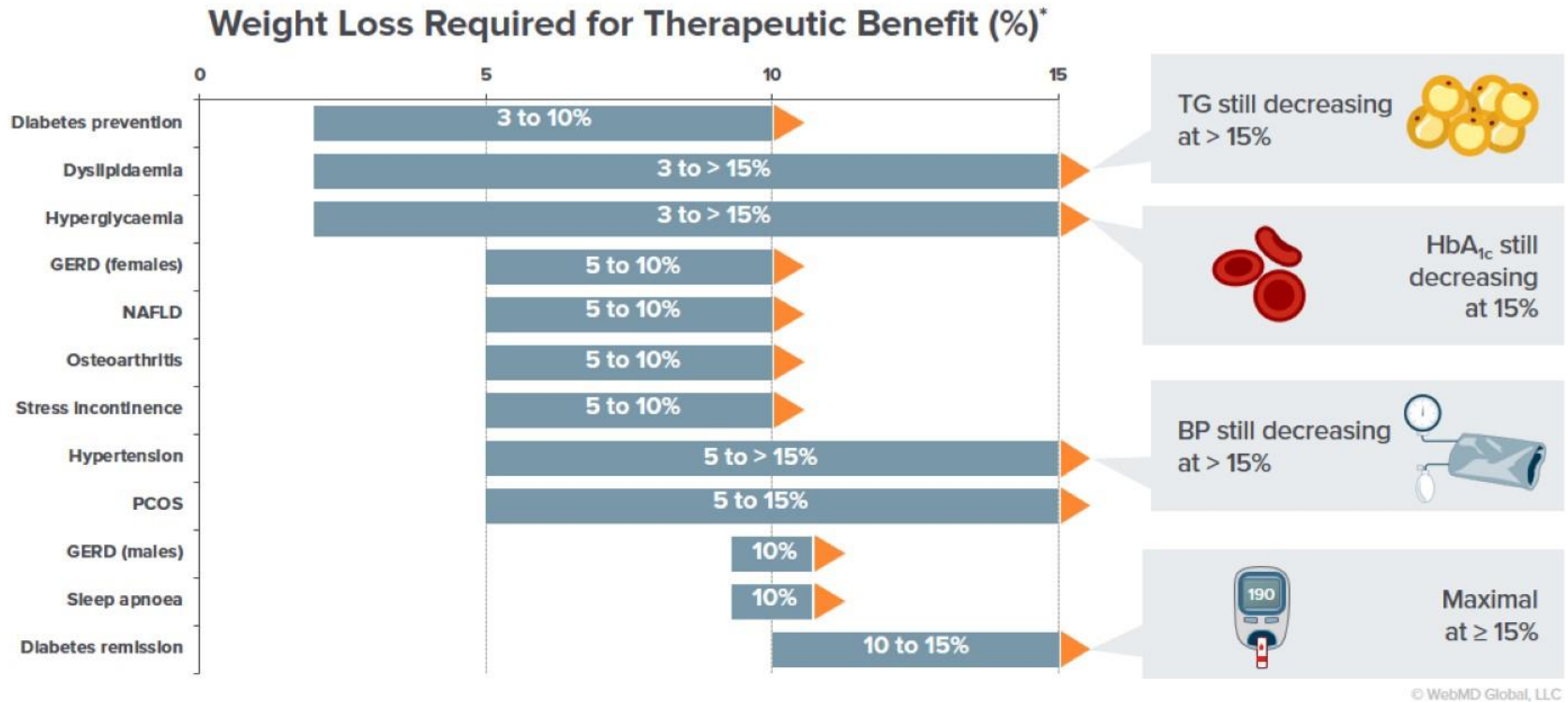
From NAFLD or NASH to Diabetes and CVD



FGF, fibroblast growth factor; RBP, retinol-binding protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; T2DM, type 2 diabetes mellitus.

Anstee QM, et al. Nat Rev Gastroenterol Hepatol. 2013;10:330-344.

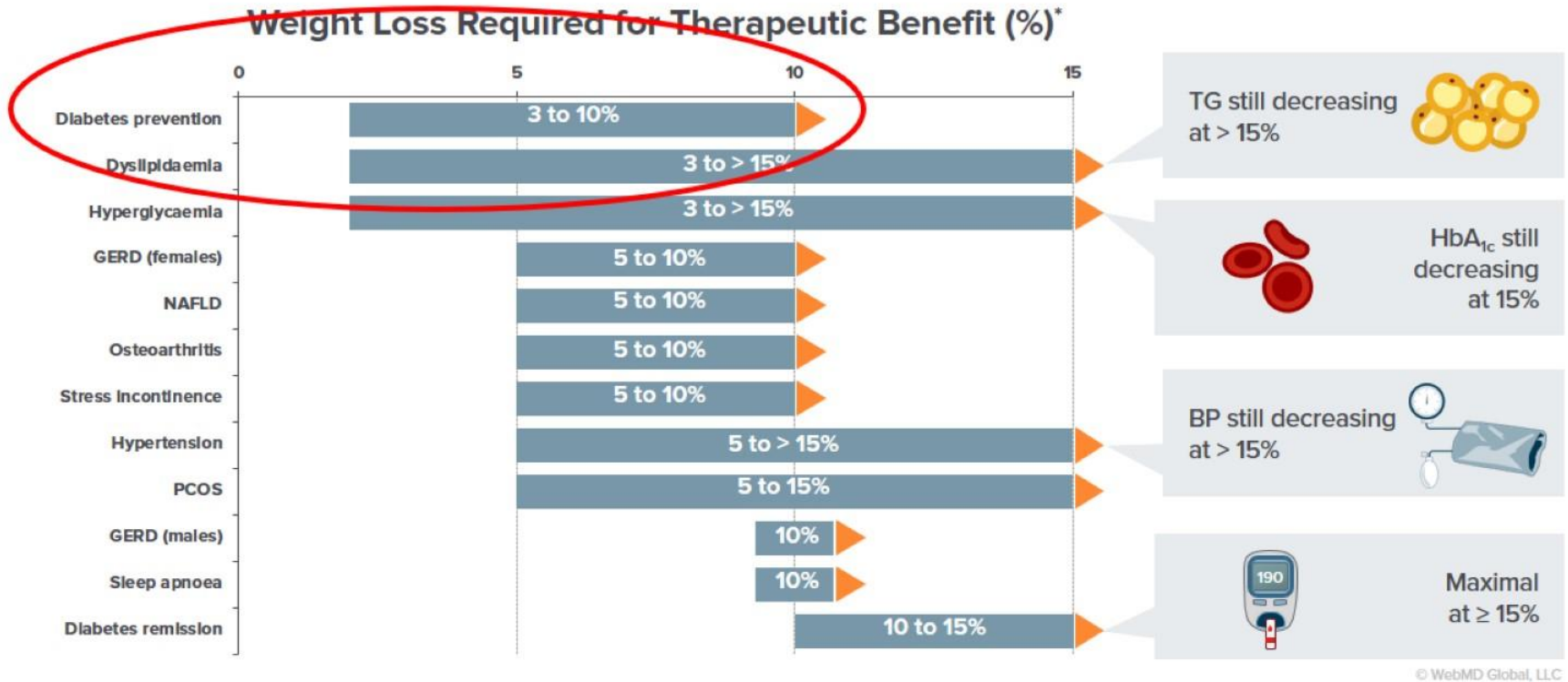
How Much Weight Loss Is Needed to Improve Obesity-Related Complications?



HbA1c, glycated hemoglobin; PCOS, polycystic ovary syndrome; TG, triglyceride.
*Figure displays weight loss ranges examined in the studies (impact of > 10% weight on NAFLD, and sleep apnea symptoms were not reported).

Garvey WT, et al. Endocr Pract. 2016;22(Suppl 3):S1-S203; Cefalu WT, et al. Diabetes Care. 2015;38:1567-1582; Lean ME, et al. Lancet. 2018;391:541-551; Hannah WN Jr, et al. Clin Liver Dis. 2016;20:339-350.

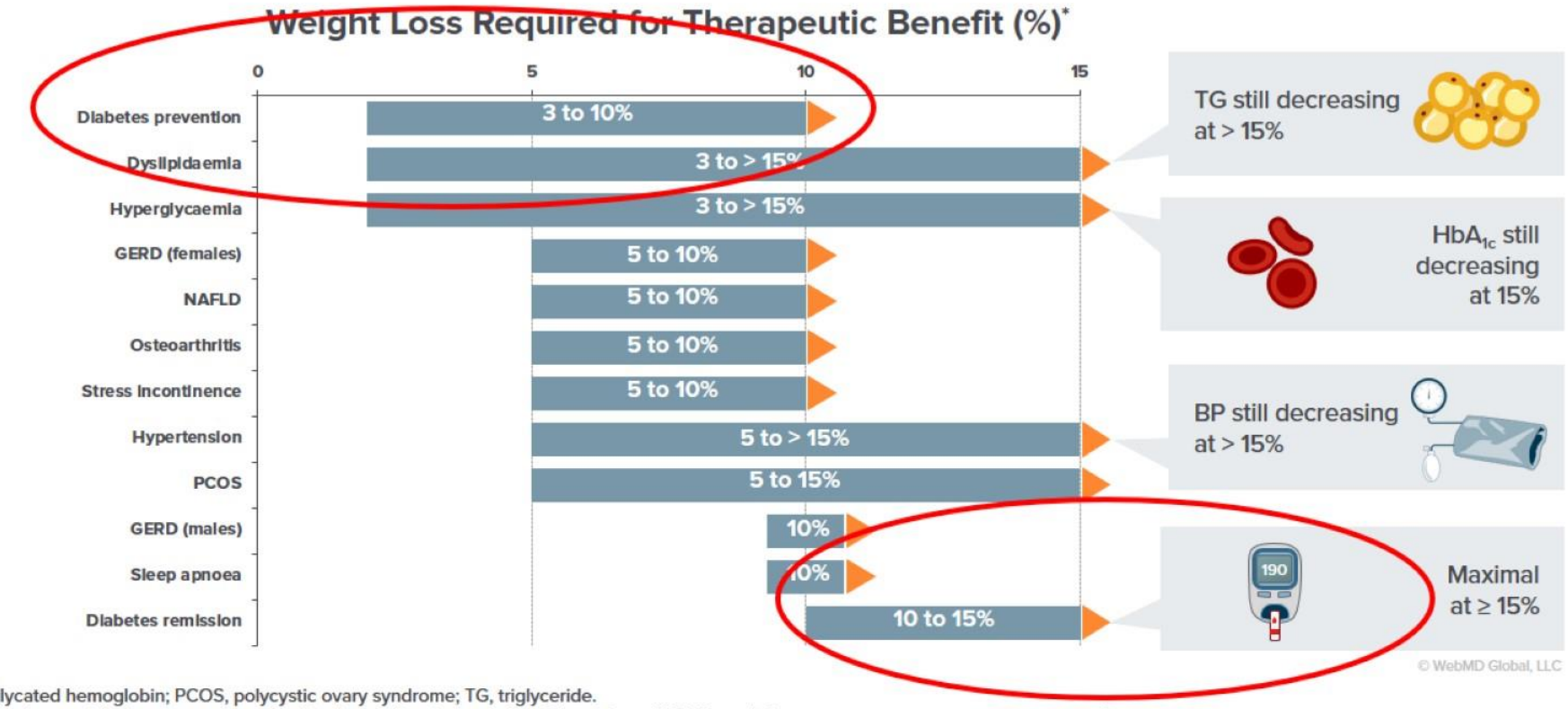
How Much Weight Loss Is Needed to Improve Obesity-Related Complications?



HbA1c, glycated hemoglobin; PCOS, polycystic ovary syndrome; TG, triglyceride.
*Figure displays weight loss ranges examined in the studies (impact of > 10% weight on NAFLD, and sleep apnea symptoms were not reported).

Garvey WT, et al. Endocr Pract. 2016;22(Suppl 3):S1-S203; Cefalu WT, et al. Diabetes Care. 2015;38:1567-1582; Lean ME, et al. Lancet. 2018;391:541-551; Hannah WN Jr, et al. Clin Liver Dis. 2016;20:339-350.

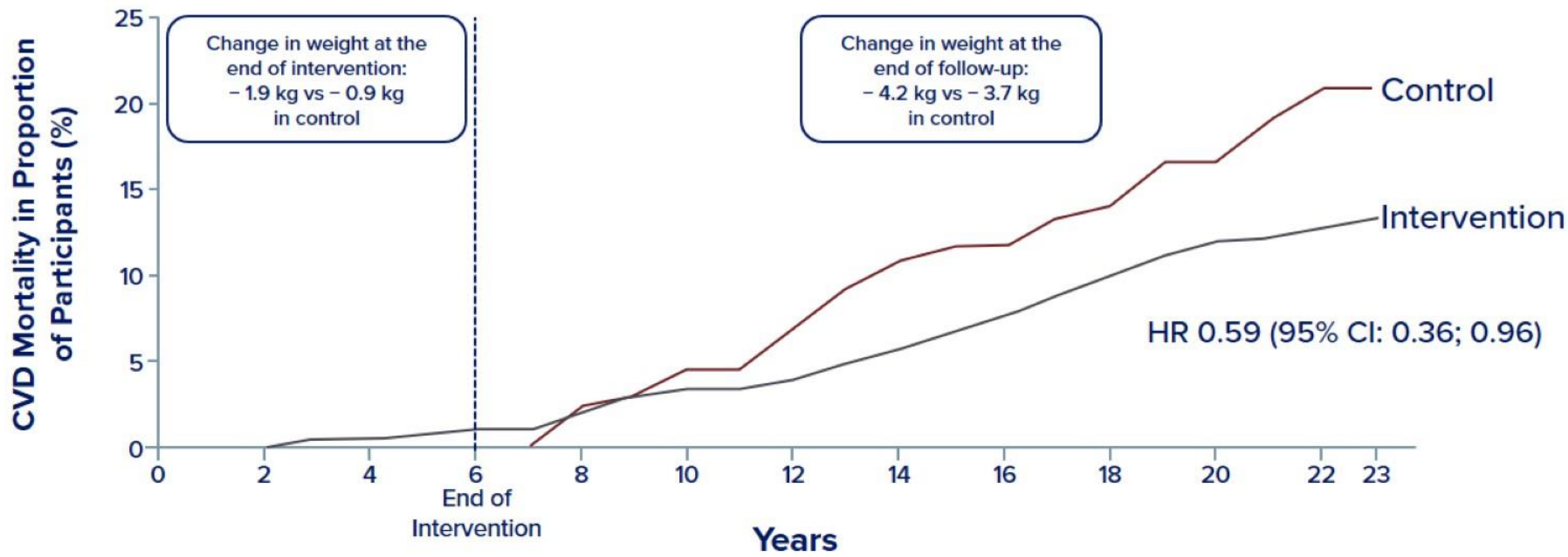
How Much Weight Loss Is Needed to Improve Obesity-Related Complications?



HbA1c, glycated hemoglobin; PCOS, polycystic ovary syndrome; TG, triglyceride.
*Figure displays weight loss ranges examined in the studies (impact of > 10% weight on NAFLD, and sleep apnea symptoms were not reported).

Garvey WT, et al. Endocr Pract. 2016;22(Suppl 3):S1-S203; Cefalu WT, et al. Diabetes Care. 2015;38:1567-1582; Lean ME, et al. Lancet. 2018;391:541-551; Hannah WN Jr, et al. Clin Liver Dis. 2016;20:339-350.

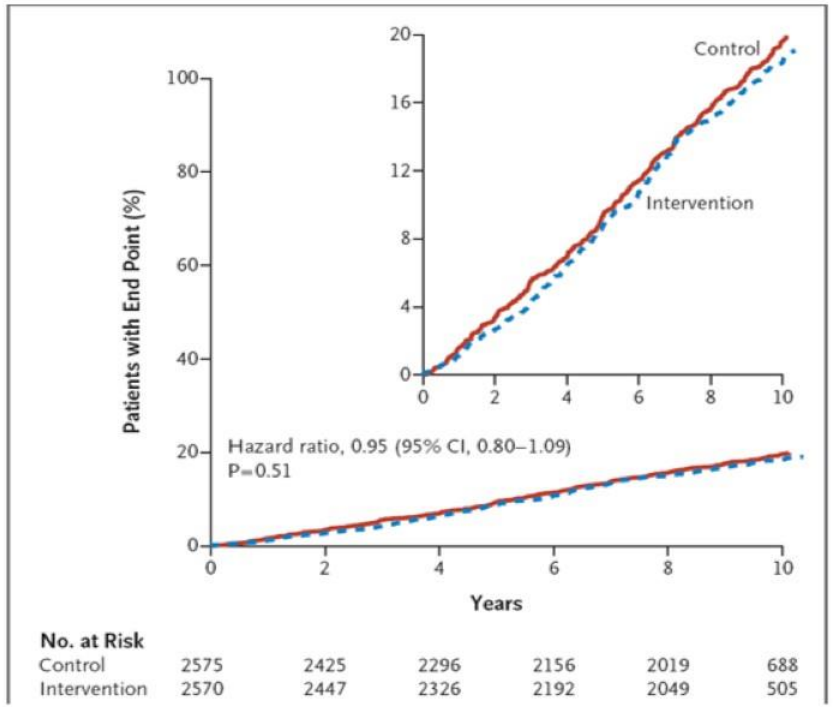
Weight Loss Effect on CV Mortality



DPS, Diabetes Prevention Study; IGT, impaired glucose tolerance.
Image courtesy Luc Van Gaal, MD, PhD.
Li G, et al. Lancet Diabetes Endocrinol. 2014;2:474-480; Li G, et al. Lancet. 2008;371:1783-1789.

Look AHEAD
No CV Benefit Unless…

Cumulative Effect on the Primary Composite Endpoint in the Look AHEAD Trial



Look AHEAD Research Group, et al. N Engl J Med. 2013;369:145-154.

Look AHEAD: Association Between Magnitude of Weight Loss and Incidence of CVD in Patients With T2D

	Intensive lifestyle intervention weight-change categories (percentage weight loss in first year)							Intensive lifestyle intervention fitness-change categories (change in metabolic equivalents in first year)						
	Overall control group (reference)	Gain or stable (<2% loss)	Small loss (≥2–<5%)	Medium loss (≥5–<10%)	Large loss (≥10%)	Hazard ratio per SD weight change	p value	Overall control group (reference)	Loss or stable (<0·5 loss)	Small gain (≥0·5–<1·0)	Medium gain (≥1·0–<2·0)	Large gain (≥2·0)	Hazard ratio per SD fitness change	p value
Primary outcome														
Events per person-years	351/20 891	58/3087	69/3766	114/6446	120/8266	..	..	303/19 025	148/8025	53/3081	64/4743	59/4190	..	..
Crude rate per 100 person-years	1·68	1·88	1·83	1·77	1·45	..	..	1·59	1·84	1·72	1·35	1·41	..	..
Unadjusted hazard ratio (95% CI)	1·00	1·14 (0·86–1·51)	1·09 (0·85–1·42)	1·06 (0·86–1·31)	0·84 (0·68–1·04)	0·88 (0·79–0·98)	0·02	1·00	1·18 (0·97–1·43)	1·06 (0·79–1·42)	0·84 (0·64–1·10)	0·87 (0·66–1·15)	0·90 (0·80–1·01)	0·08
Adjusted hazard ratio*(95% CI)	1·00	1·29 (0·96–1·72)	1·04 (0·80–1·36)	1·15 (0·92–1·43)	0·80 (0·65–0·99), p=0·039†	0·85 (0·76–0·95)	0·006	1·00	1·19 (0·97–1·46)	1·06 (0·78–1·43)	0·85 (0·64–1·13)	0·90 (0·68–1·21)	0·91 (0·80–1·03)	0·15
Secondary outcome														
Events per person-years	503/20 436	82/3009	108/3643	151/6335	173/8136	..	..	433/18 657	211/7844	78/3041	92/4663	86/4111	..	..
Crude rate per 100 person-years	2·46	2·72	2·96	2·38	2·13	..	..	2·32	2·69	2·57	1·97	2·09	..	..
Unadjusted hazard ratio (95% CI)	1·00	1·14 (0·90–1·44)	1·22 (0·99–1·50)	0·97 (0·81–1·17)	0·85 (0·72–1·02)	0·86 (0·78–0·94)	0·0007	1·00	1·18, (1·00–1·39), p=0·048†	1·09 (0·86–1·39)	0·85 (0·68–1·06)	0·90 (0·71–1·13)	0·91 (0·83–1·01)	0·07
Adjusted hazard ratio* (95% CI)	1·00	1·28 (1·01–1·64), p=0·045†	1·19 (0·96–1·47)	1·02 (0·84–1·23)	0·79 (0·66–0·95), p=0·011†	0·82 (0·74–0·90)	<0·0001	1·00	1·17 (0·99–1·39)	1·08 (0·84–1·38)	0·83 (0·66–1·05)	0·93 (0·73–1·18)	0·92 (0·83–1·02)	0·12

Data are for primary and secondary outcomes associated with percentage weight loss and fitness changes over the first year. *Adjusted for sex, age, baseline weight (from weight-change models), baseline fitness (from fitness-change models), history of cardiovascular disease, insulin use, diabetes duration, smoking status, LDL cholesterol, systolic blood pressure, and diastolic blood pressure. † p value refers to pairwise comparison with overall control group.

Look AHEAD Research Group, et al. Lancet Diabetes Endocrinol. 2016;4:913-921.

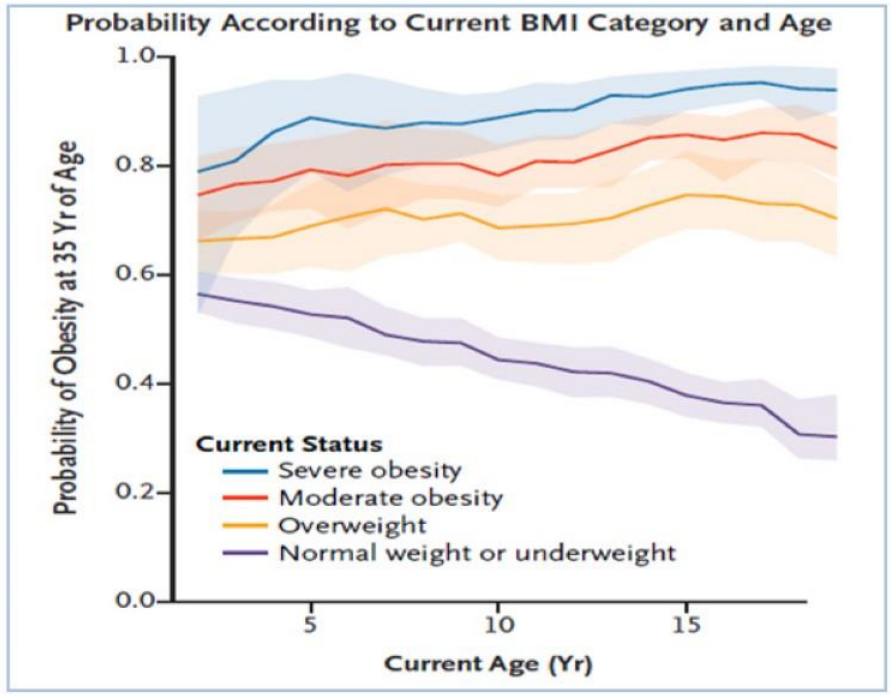
Look AHEAD: Association Between Magnitude of Weight Loss and Incidence of CVD in Patients With T2D

	Intensive lifestyle intervention weight-change categories (percentage weight loss in first year)							Intensive lifestyle intervention fitness-change categories (change in metabolic equivalents in first year)						
	Overall control group (reference)	Gain or stable (<2% loss)	Small loss (≥2–<5%)	Medium loss (≥5–<10%)	Large loss (≥10%)	Hazard ratio per SD weight change	p value	Overall control group (reference)	Loss or stable (<0·5 loss)	Small gain (≥0·5–<1·0)	Medium gain (≥1·0–<2·0)	Large gain (≥2·0)	Hazard ratio per SD fitness change	p value
Primary outcome														
Events per person-years	351/20 891	58/3087	69/3769	114/6446	120/8266	..	..	303/19 025	148/8025	53/3081	64/4743	59/4190	..	..
Crude rate per 100 person-years	1·68	1·88	1·83	1·77	1·45	..	..	1·59	1·84	1·72	1·35	1·41	..	..
Unadjusted hazard ratio (95% CI)	1·00	1·14 (0·86–1·51)	1·09 (0·85–1·42)	1·06 (0·86–1·31)	0·84 (0·68–1·04)	0·88 (0·79–0·98)	0·02	1·00	1·18 (0·97–1·43)	1·06 (0·79–1·42)	0·84 (0·64–1·10)	0·87 (0·66–1·15)	0·90 (0·80–1·01)	0·08
Adjusted hazard ratio*(95% CI)	1·00	1·29 (0·96–1·72)	1·04 (0·80–1·36)	1·15 (0·92–1·43)	0·80 (0·65–0·99), p=0·039†	0·85 (0·76–0·95)	0·006	1·00	1·19 (0·97–1·46)	1·06 (0·78–1·43)	0·85 (0·64–1·13)	0·90 (0·68–1·21)	0·91 (0·80–1·03)	0·15
Secondary outcome														
Events per person-years	503/20 436	82/3009	108/3643	151/6335	173/8136	..	..	433/18 657	211/7844	78/3041	92/4663	86/4111	..	..
Crude rate per 100 person-years	2·46	2·72	2·96	2·38	2·13	..	..	2·32	2·69	2·57	1·97	2·09	..	..
Unadjusted hazard ratio (95% CI)	1·00	1·14 (0·90–1·44)	1·22 (0·99–1·50)	0·97 (0·81–1·17)	0·85 (0·72–1·02)	0·86 (0·78–0·94)	0·0007	1·00	1·18, (1·00–1·39), p=0·048†	1·09 (0·86–1·39)	0·85 (0·68–1·06)	0·90 (0·71–1·13)	0·91 (0·83–1·01)	0·07
Adjusted hazard ratio* (95% CI)	1·00	1·28 (1·01–1·64), p=0·045†	1·19 (0·96–1·47)	1·02 (0·84–1·23)	0·79 (0·66–0·95), p=0·011†	0·82 (0·74–0·90)	<0·0001	1·00	1·17 (0·99–1·39)	1·08 (0·84–1·38)	0·83 (0·66–1·05)	0·93 (0·73–1·18)	0·92 (0·83–1·02)	0·12

Weight loss beyond 10% may be associated with CV benefit

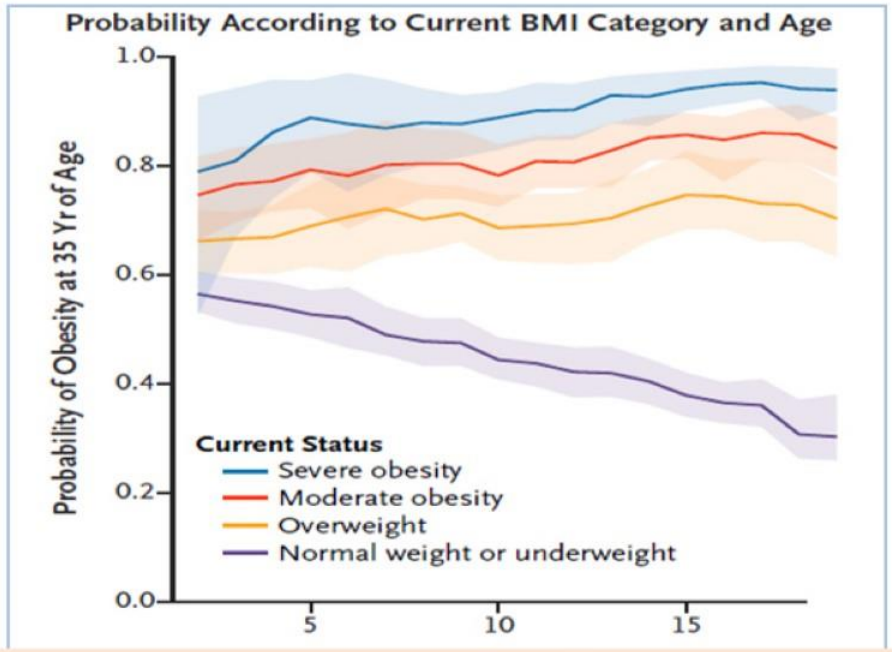
Look AHEAD Research Group, et al. Lancet Diabetes Endocrinol. 2016;4:913-921.

Obesity at Age 2 Predicts Status at Age 35



Ward ZJ, et al. N Engl J Med 2017;377:2145-2153.

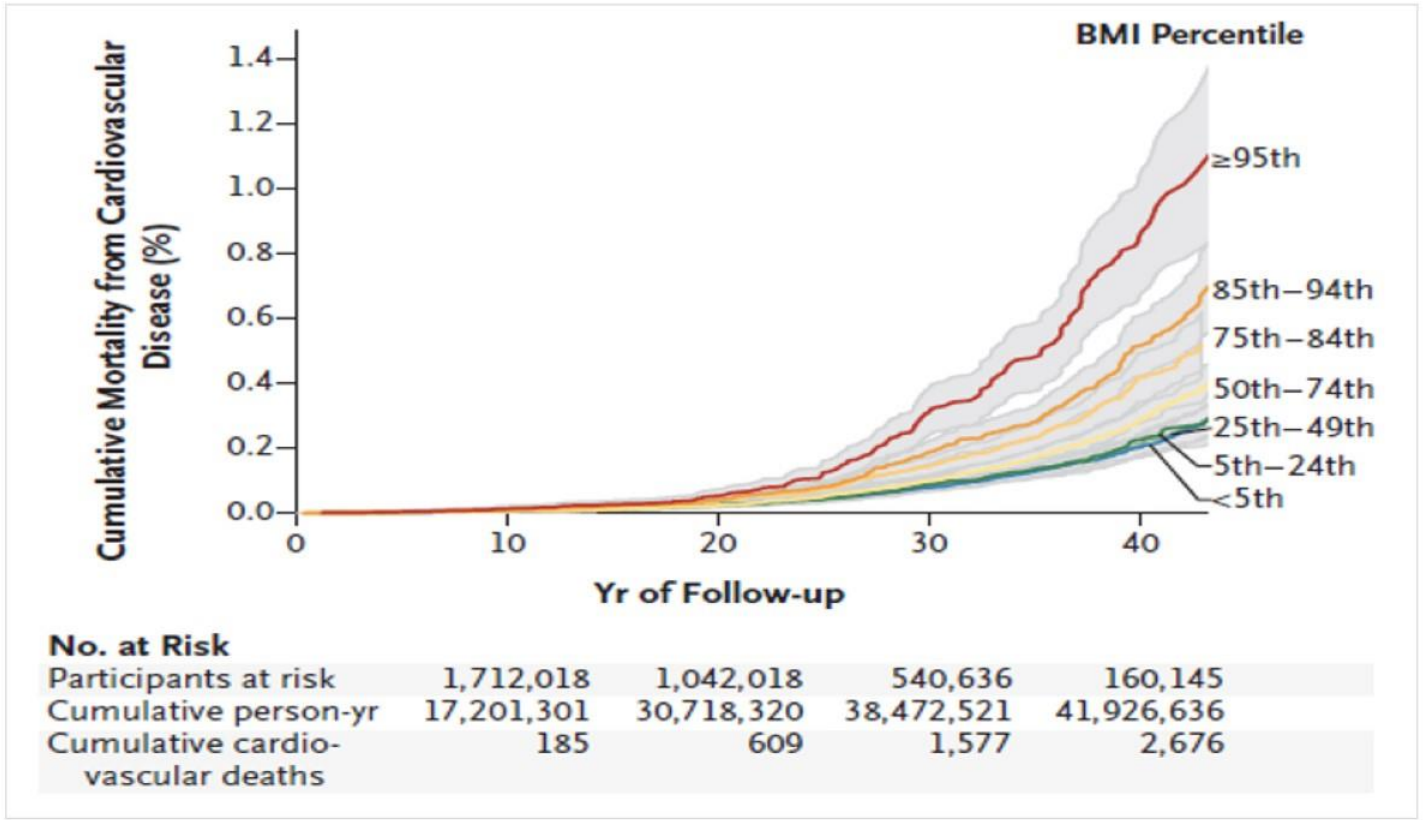
Obesity at Age 2 Predicts Status at Age 35



57% of today's children will experience obesity at age 35 y (WHO projection)

Ward ZJ, et al, N Engl J Med. 2017;377:2145-2153.

BMI During Adolescence and Outcome

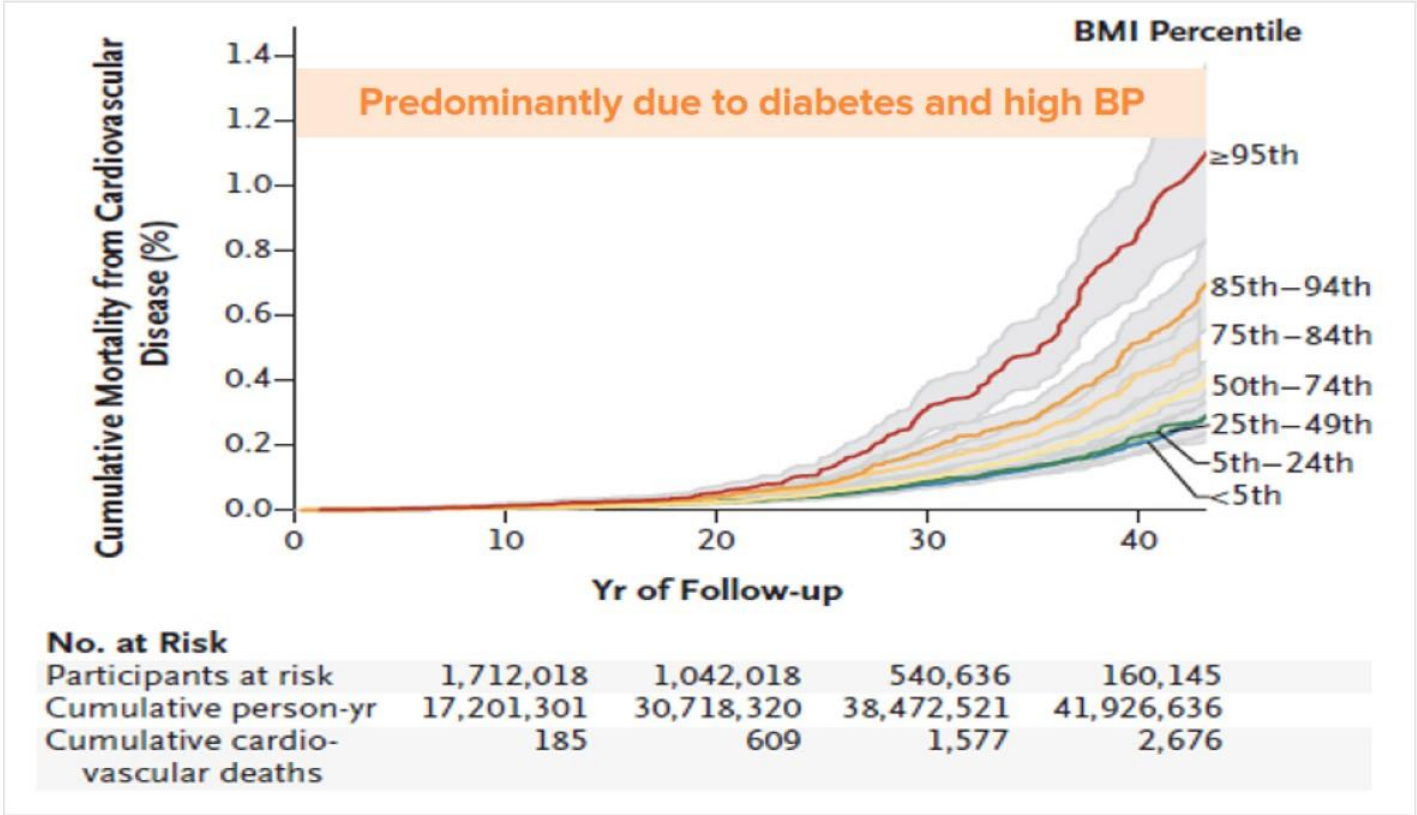


No. at Risk

Participants at risk	1,712,018	1,042,018	540,636	160,145
Cumulative person-yr	17,201,301	30,718,320	38,472,521	41,926,636
Cumulative cardio-vascular deaths	185	609	1,577	2,676

Twig G, et al. N Engl J Med. 2016;374:2430-2440.

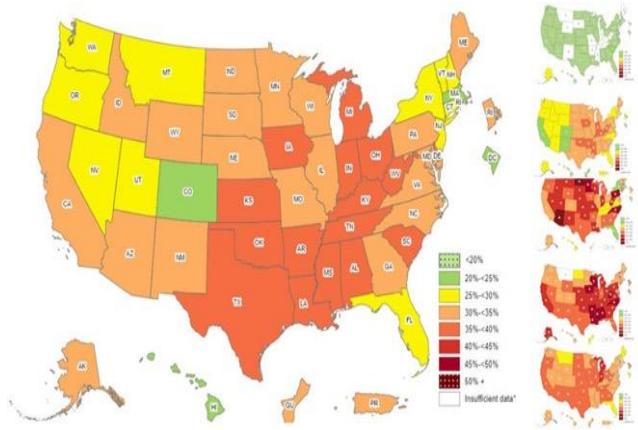
BMI During Adolescence and Outcome



No. at Risk

Participants at risk	1,712,018	1,042,018	540,636	160,145
Cumulative person-yr	17,201,301	30,718,320	38,472,521	41,926,636
Cumulative cardio-vascular deaths	185	609	1,577	2,676

Twig G, et al. N Engl J Med. 2016;374:2430-2440.



The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

Projected U.S. State-Level Prevalence of Adult Obesity and Severe Obesity

Zachary J. Ward, M.P.H., Sara N. Bleich, Ph.D., Angie L. Cradock, Sc.D., Jessica L. Barrett, M.P.H., Catherine M. Giles, M.P.H., Chasmine Flax, M.P.H., Michael W. Long, Sc.D., and Steven L. Gortmaker, Ph.D.

One Billion People Globally Estimated to be Living with Obesity by 2030

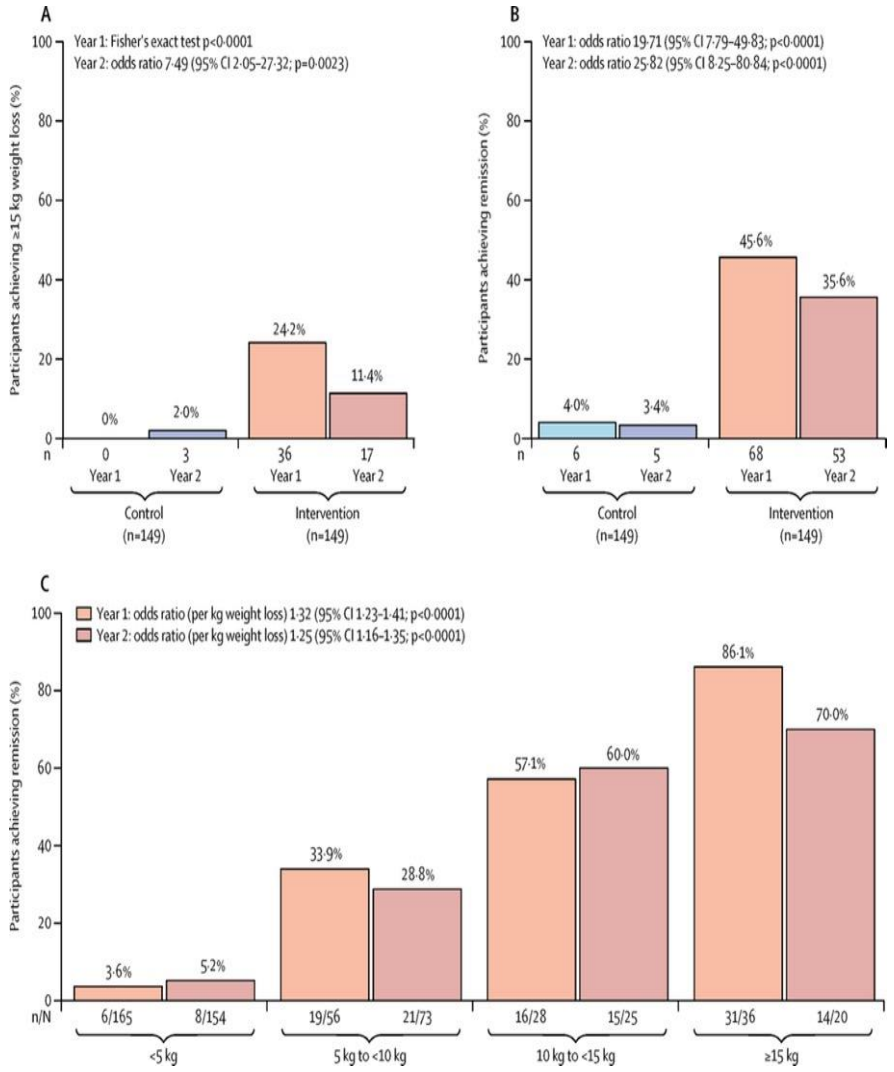
Call for Global Action Plan on Obesity at World Health Assembly in May 2022

- The World Obesity Atlas 2022, published by the World Obesity Federation, predicts that one billion people globally, including 1 in 5 women and 1 in 7 men, will be living with obesity by 2030.
- The findings highlight that countries will not only miss the 2025 WHO target to halt the rise in obesity at 2010 levels, but that the number of people with obesity is on course to double across the globe.
- The greatest number of people living with obesity are in low- and middle-income countries (LMICs), with numbers more than doubling across all LMICs, and tripling in low income countries, compared to 2010.

By 2030 **~50% obesity** **~25% morbid obesity**

Ward ZJ *et al*; *NEJM* 2019; 381: 2440-2450
https://www.worldobesity.org/resources/resource-library/world-obesity-atla
https://www.cdc.gov/obesity/data/prevalence-maps.html, Accessed 04 June, 2022

Intensive Structured Weight Management: the DiRect RCT



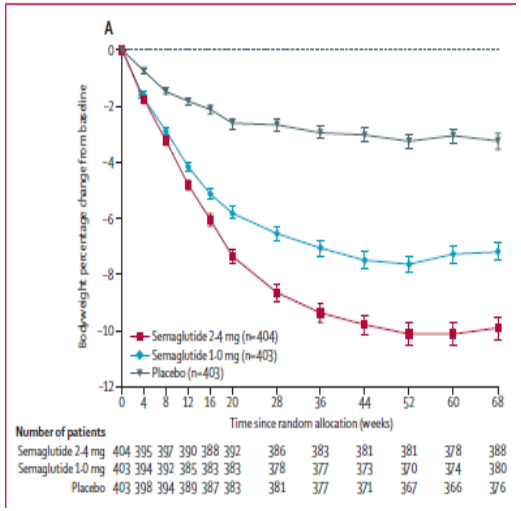
- 10 kg at 2 year follow-up = 64% diabetes remission

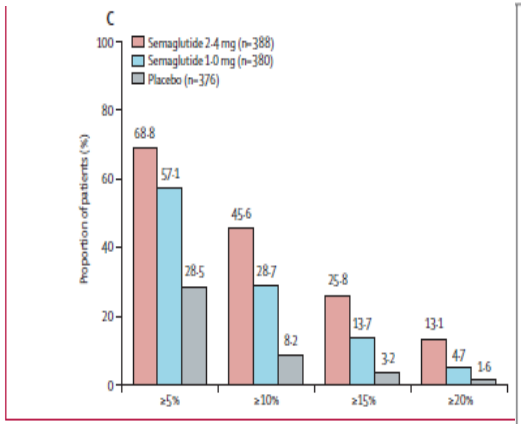
Lean et al. *The Lancet Diabetes & Endocrinology* 2019;7:344-355.

Weight Management in Type 2 Diabetes

Semaglutide 2·4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial

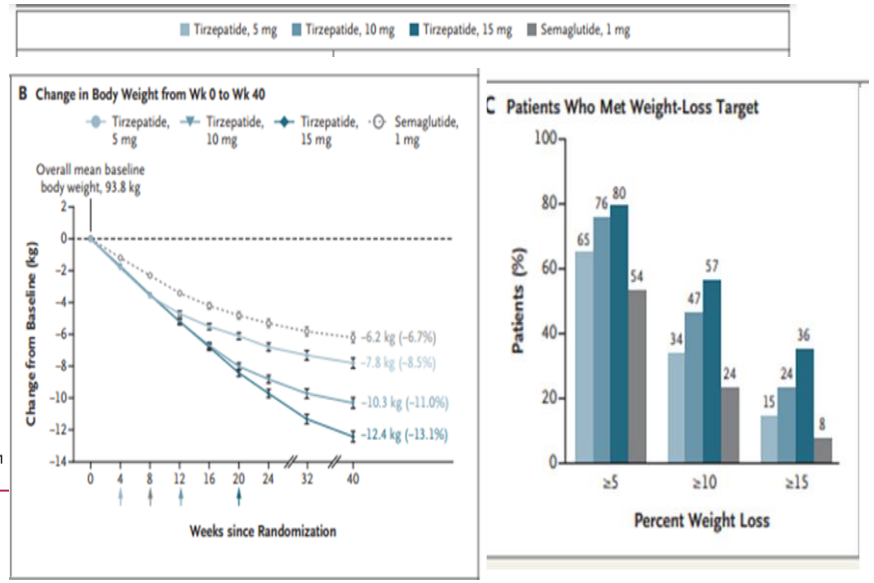
*Melanie Davies, Louise Færch, Ole K Jeppesen, Arash Pakseresht, Sue D Pedersen, Leigh Perreault, Julio Rosenstock, Ichiro Shimomura, Adie Viljoen, Thomas A Wadden, Ildiko Lingvay, for the STEP 2 Study Group**





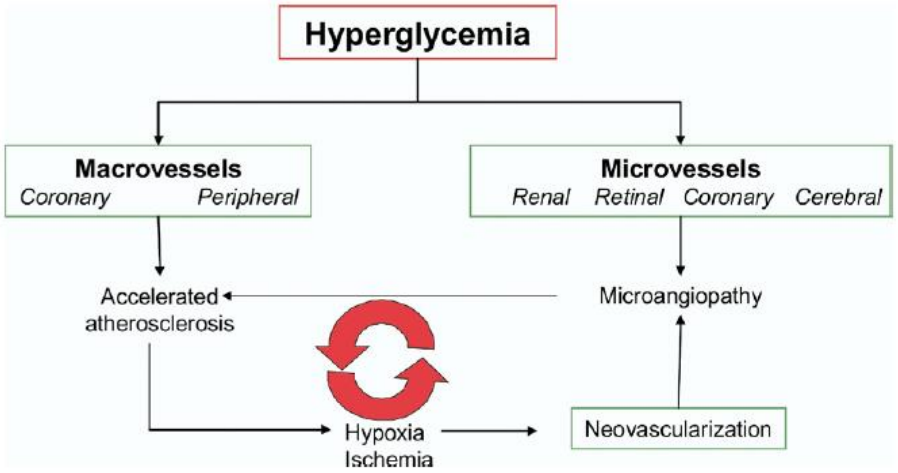
Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes

Juan P. Frías, M.D., Melanie J. Davies, M.D., Julio Rosenstock, M.D., Federico C. Pérez Manghi, M.D., Laura Fernández Landó, M.D., Brandon K. Bergman, Pharm.D., Bing Liu, Ph.D., Xuewei Cui, Ph.D., and Katelyn Brown, Pharm.D., for the SURPASS-2 Investigators*



Davies M *et al; Lancet* 2021; 397: 971-84
Frías JP *et al. N Engl J Med* 2021;385:503-515

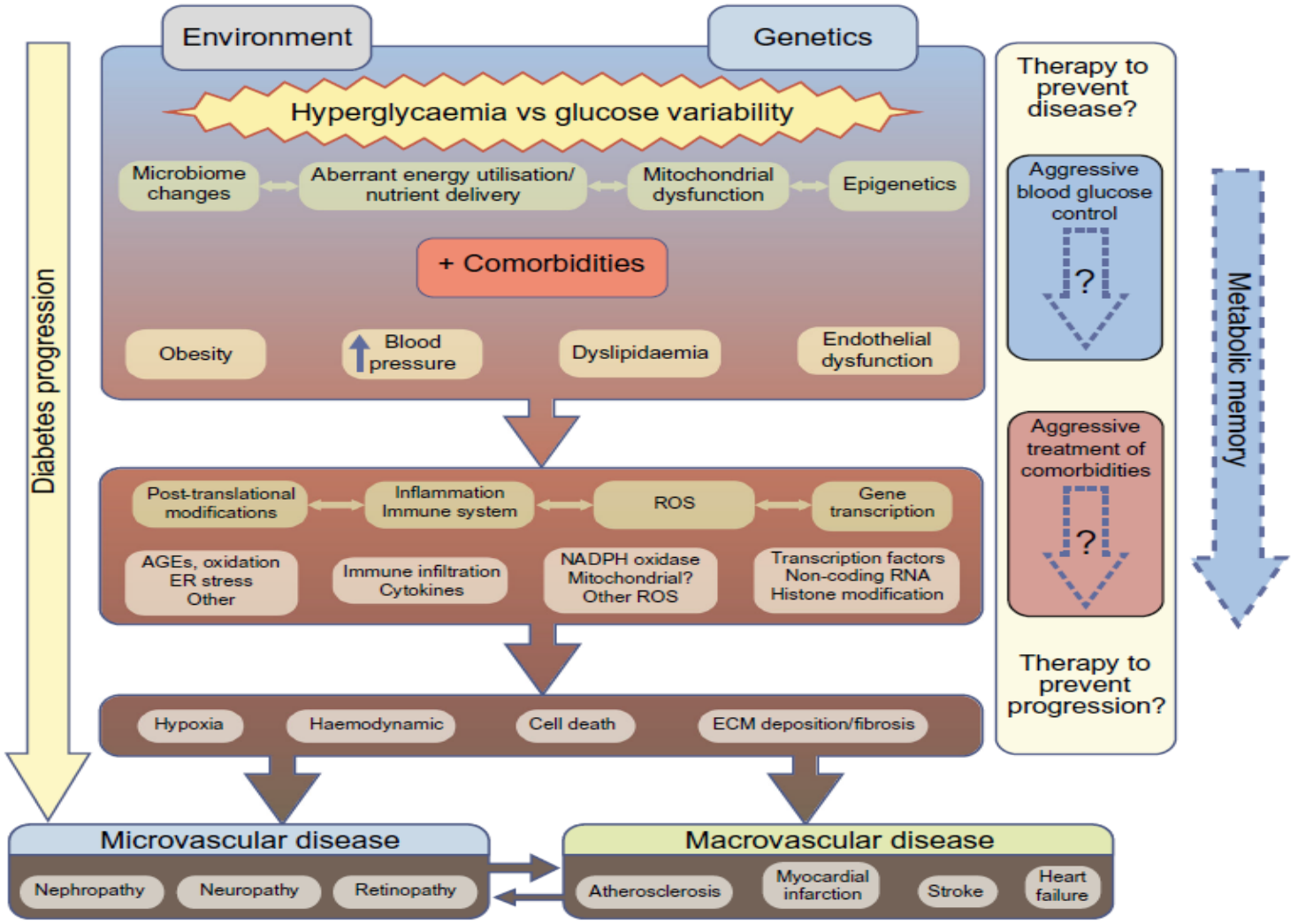
Διασύνδεση μικρο και μακροαγγειακών επιπλοκών σε επιταχυνόμενη αθηροσκλήρωση



J Am Coll Cardiol 2009;53:S35–42

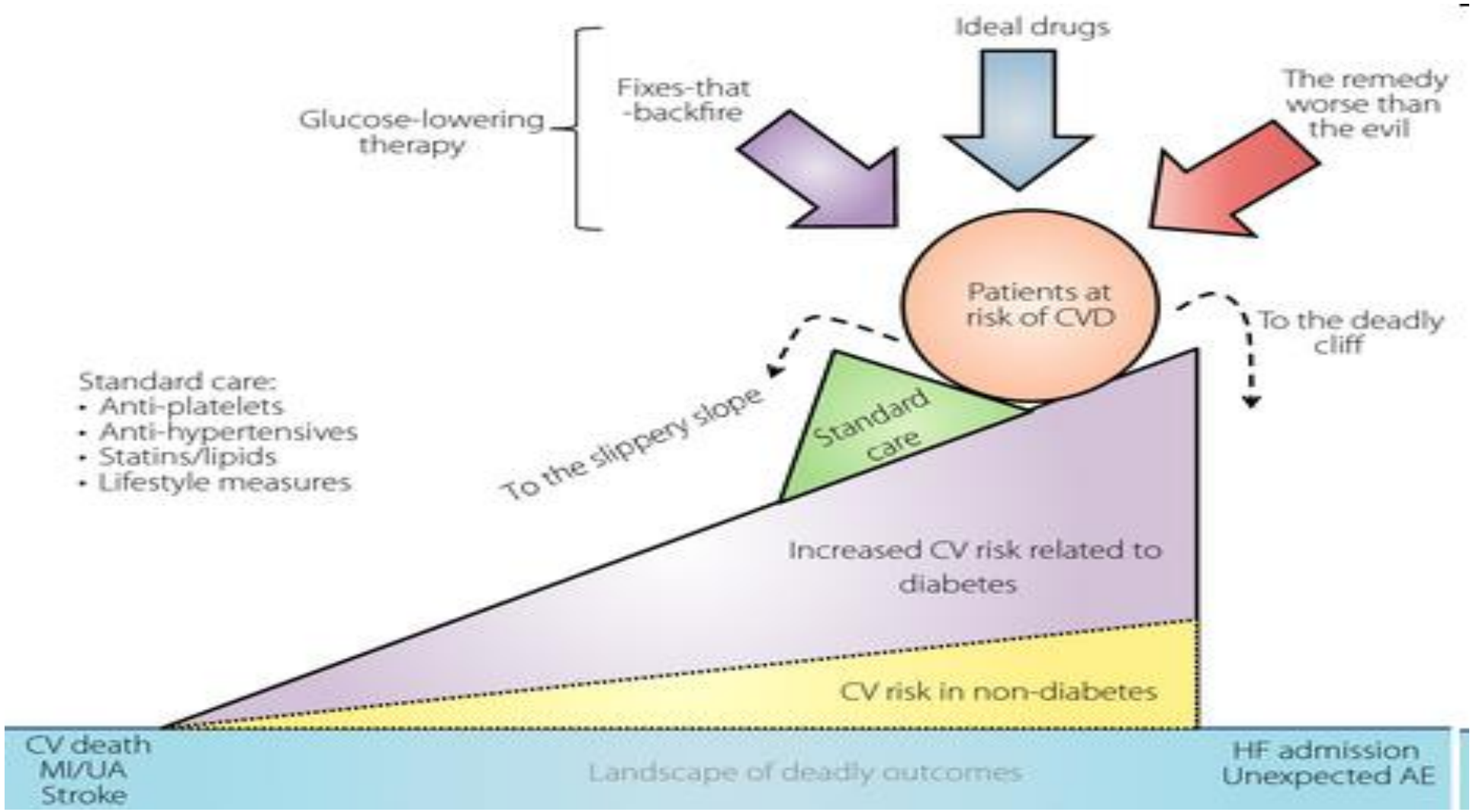
In T2DM, angiogenesis is increased and associated with plaque rupture .
Neovasculature microangiopathy may accelerate diabetic atherosclerosis
The initial angiogenic response in the adventitial vasa vasorum appears stimulated by hypoxia and ischemia, perhaps through **increased hypoxia-induced factor-1 and VEGF action**
VEGF also increases vascular permeability to macromolecules,monocyte chemotaxis, and tissue factor production,
possible contributors to microvascular complications
.

Η διαδρομή ως στις διαβητικές επιπλοκές



Diabetologia
DOI 10.1007/s00125-017-4360-x

The good, the bad, or the ugly?



Journal of Diabetes Investigation 2015; 6: 597-599