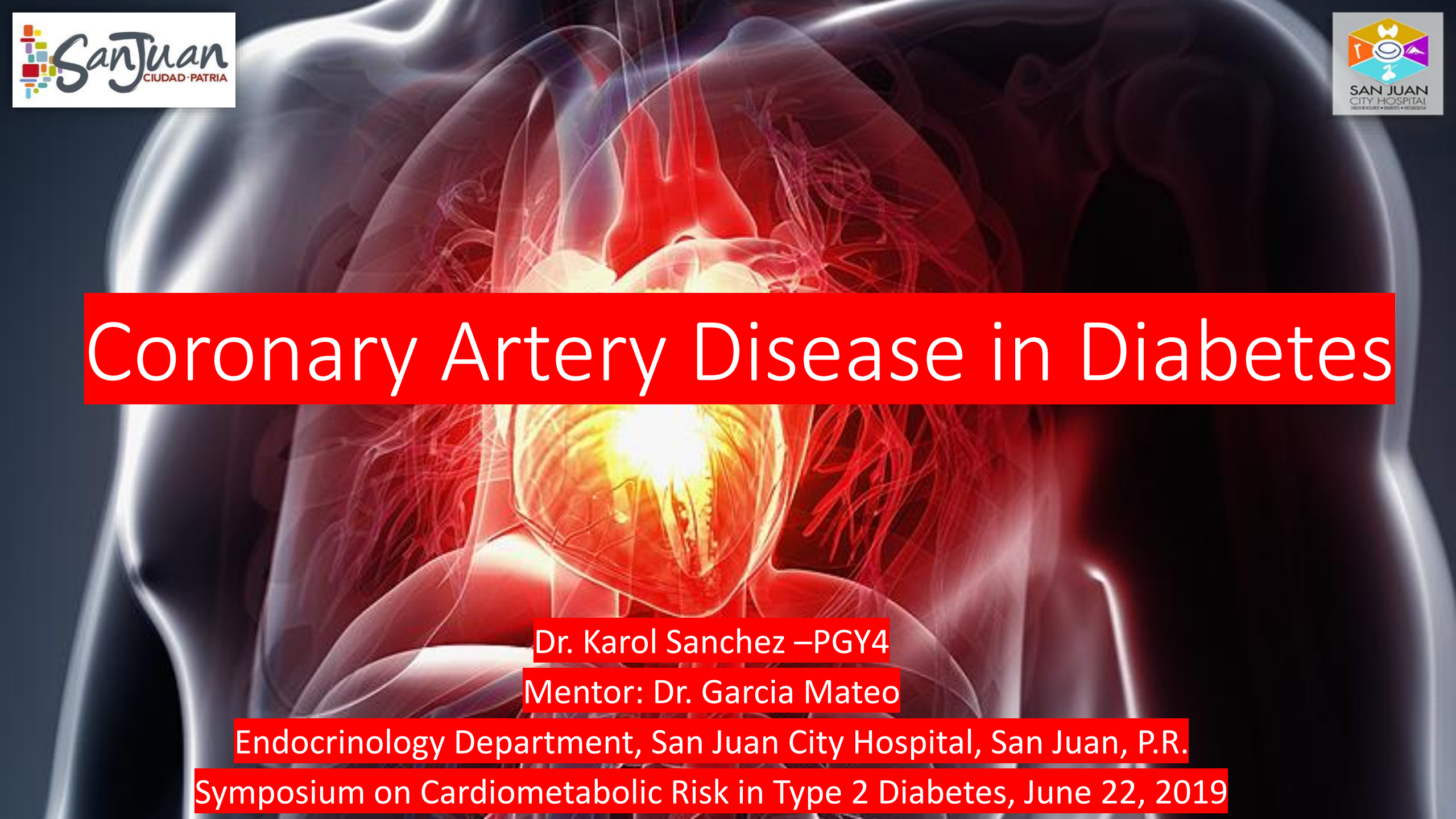


# Coronary Artery Disease in Diabetes

Dr. Karol Sanchez –PGY4

Mentor: Dr. Garcia Mateo

Endocrinology Department, San Juan City Hospital, San Juan, P.R.

Symposium on Cardiometabolic Risk in Type 2 Diabetes, June 22, 2019

# Objectives

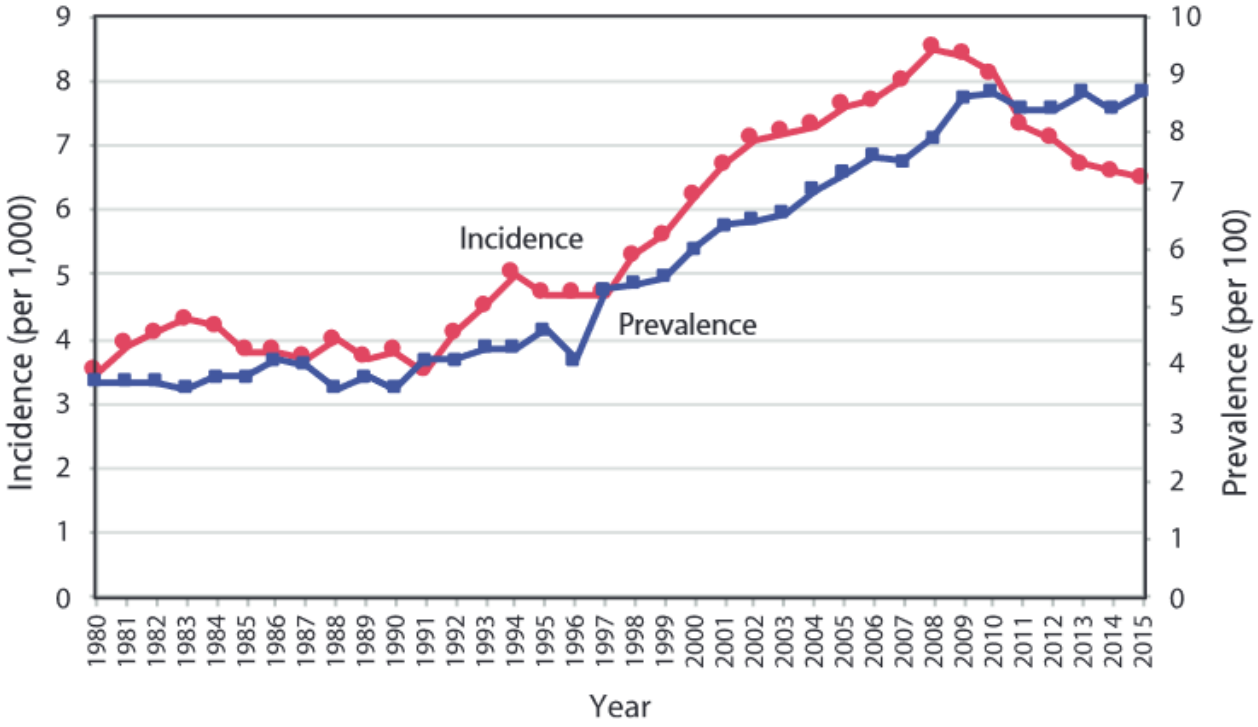
- Prevalence of CAD in patients with diabetes.
- To discuss the relationship between CAD and prediabetes.
- To discuss the prevalence of asymptomatic CAD in patients with diabetes.
- To review the mechanisms of increased CAD risk in patients with diabetes.
- To review the evidence for multifactorial risk factor reduction in the prevention of CAD

# Prevalence of Diabetes

About 30.3 million people, or 9.4% of the US population, had diabetes in 2015.

Centers for Disease Control and Prevention
National Center for Chronic Disease Prevention and Health Promotion

**Figure 1. Trends in Incidence and Prevalence of Diagnosed Diabetes Among Adults Aged 18 or Older, United States, 1980–2015**

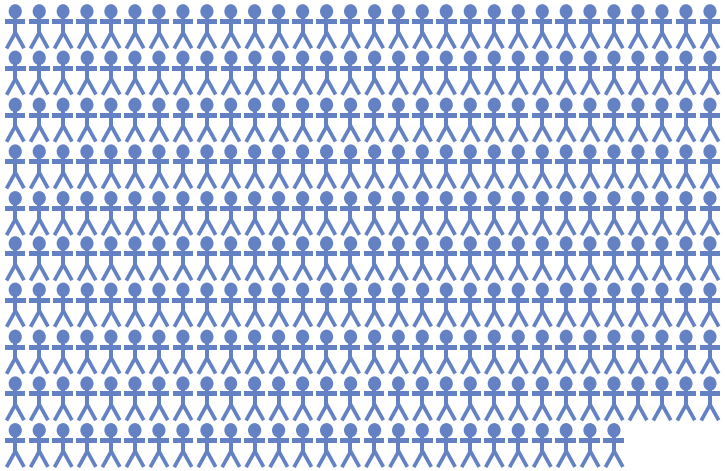



Note: Rates are age-adjusted to the 2000 US standard population.
Data sources: Centers for Disease Control and Prevention, United States Diabetes Surveillance System and National Health Interview Survey.

Centers for Disease Control and Prevention. Diabetes Report Card 2017. Atlanta, GA: Centers for Disease Control and Prevention, US Dept of Health and Human Services; 2018.

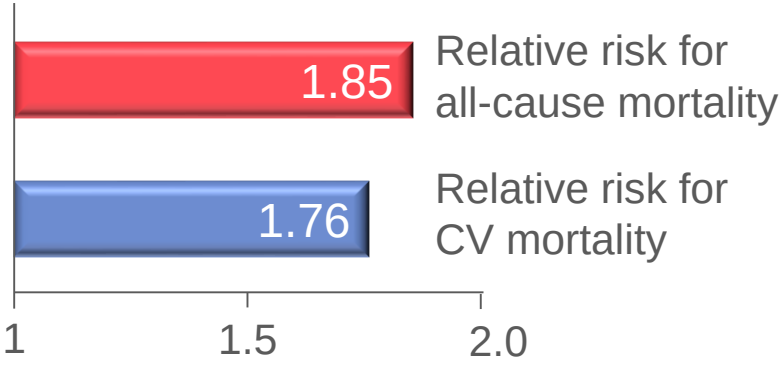
# T2D is increasingly prevalent and CVD is the leading cause of death in this population

- Globally, 387 million people are living with diabetes[1]



- Rising to 592 million by 2035[1]

- T2D approximately doubles the risk of death[2]




- Diabetes caused 4.9 million deaths in 2014[1]
- CVD is the principal cause of death in T2D[2,3]

Represents 2 million people.
Diabetes is mostly (85–95%) T2D.[1]

1. IDF Diabetes Atlas, 2014. 6th Edition. http://www.idf.org/diabetesatlas.
2. Nwaneri et al. Br J Diabetes Vasc Dis 2013;13:192–207. 3. Morrish et al. Diabetologia 2001;44(suppl 2):S14–21.

# Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007–2017

## Table 4

Summary of prevalence rates of cardiovascular comorbidities in persons with type 2 diabetes

| Sex | Cardiovascular outcome | Studies | N | Rate[a] (%) | 95% confidence interval (%) |
|---|---|---|---|---|---|
| Both | Stroke | 39 | 3,901,505 | 7.6 | 6.6–8.6 |
| | Myocardial infarction | 13 | 3,518,833 | 10.0 | 7.5–12.5 |
| | Angina pectoris | 4 | 354,743 | 14.6 | 12.0–17.3 |
| | Heart failure | 14 | 601,154 | 14.9 | 13.0–16.7 |
| | Atherosclerosis | 4 | 1153 | 29.1 | 21.7–36.4 |
| | Coronary artery disease | 42 | 3,833,200 | 21.2 | 20.3–22.2 |
| | Cardiovascular disease (any) | 53 | 4,289,140 | 32.2 | 30.0–34.4 |
| Males[b] | Stroke | 10 | 232,525 | 6.7 | 6.0–7.3 |
| | Myocardial infarction | 2 | 1170 | 11.9 | 4.3–19.5 |
| | Angina pectoris | 1 | 454 | 21.1 | 16.3–26.9 |
| | Heart failure | 4 | 73,361 | 25.3 | 11.4–39.2 |
| | Coronary artery disease | 9 | 237,367 | 18.7 | 16.5–20.8 |
| | Cardiovascular disease | 16 | 241,406 | 27.6 | 25.3–29.9 |
| Females[b] | Stroke | 10 | 202,348 | 5.9 | 5.1–6.7 |
| | Myocardial infarction | 2 | 1812 | 9.8 | 3.5–16.0 |
| | Angina pectoris | 1 | 803 | 17.4 | 15.0–20.2 |
| | Heart failure | 4 | 62,690 | 24.0 | 11.2–36.8 |
| | Coronary artery disease | 10 | 205,493 | 14.3 | 12.4–16.1 |

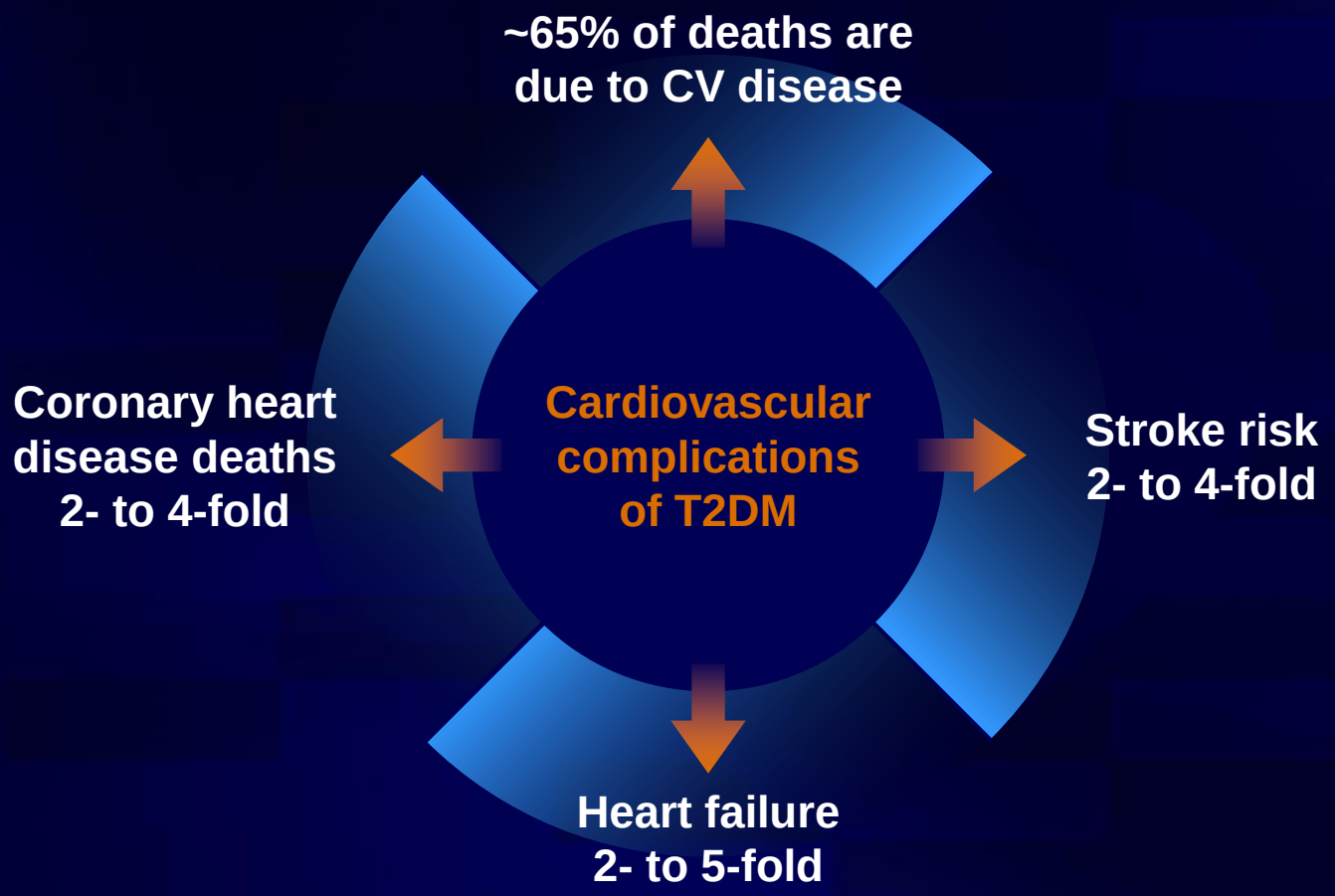
[a]Weighted by inverse variance

The International Diabetes Federation (IDF) estimates that worldwide, 415 million people have diabetes, 91% of whom have type 2 diabetes mellitus (T2DM).

People with diabetes comprise 8.8% of the world's population, and IDF predicts that the number of cases of diabetes will rise to 642 million by 2040

Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007-2017. *Cardiovasc Diabetol*. 2018;17(1):83. Published 2018 Jun 8. doi:10.1186/s12933-018-0728-6

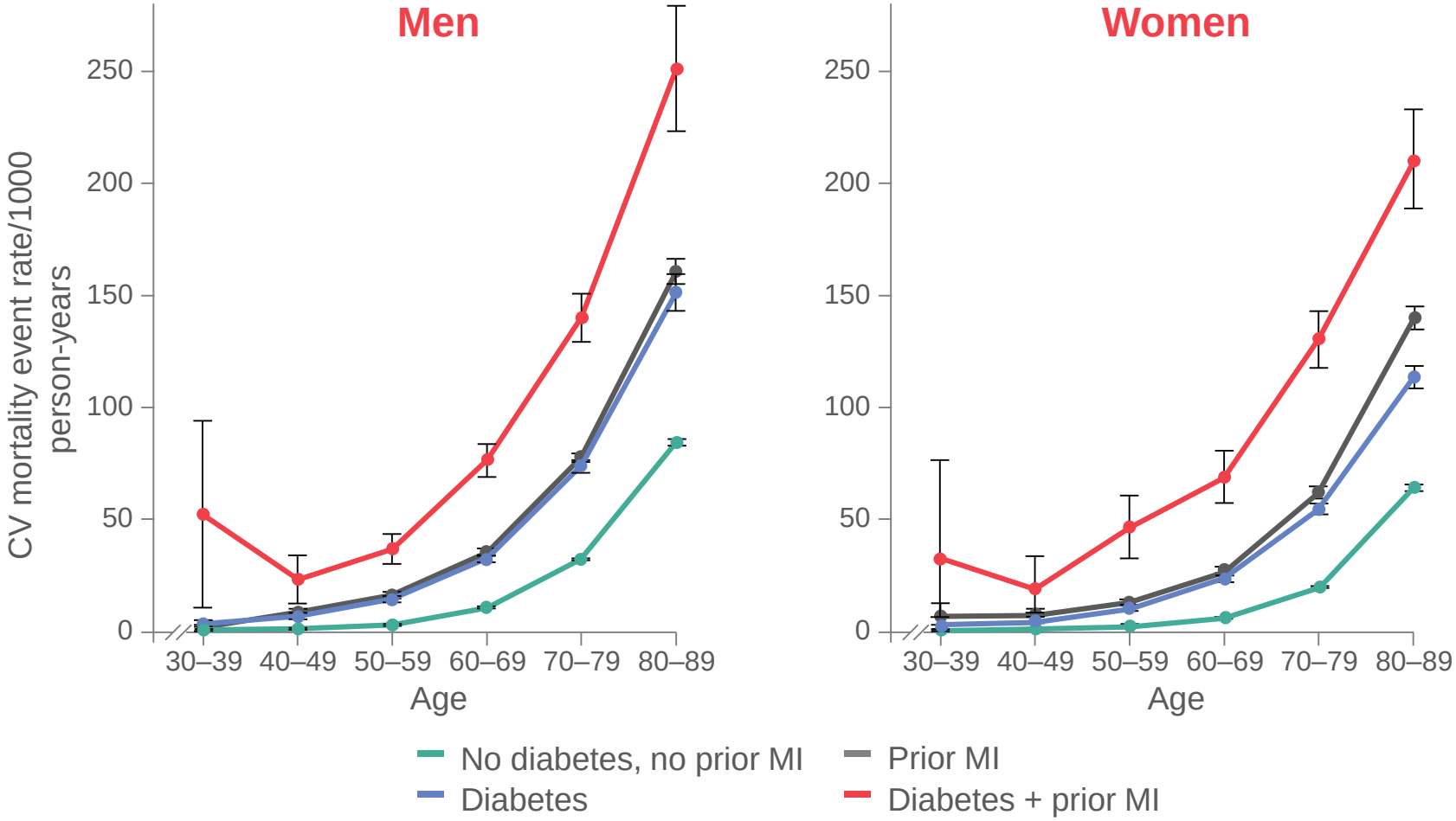
# Cardiovascular disease and diabetes




T2DM = type 2 diabetes mellitus

Bell DSH. *Diabetes Care*. 2003;26:2433-41.
Centers for Disease Control (CDC). www.cdc.gov.

# Diabetes confers significant CV risk; combination of diabetes and history of MI further increases risk




Schramm et al. Circulation 2008;117:1945–54.

# Prevalence of Asymptomatic CAD in Patients with Diabetes

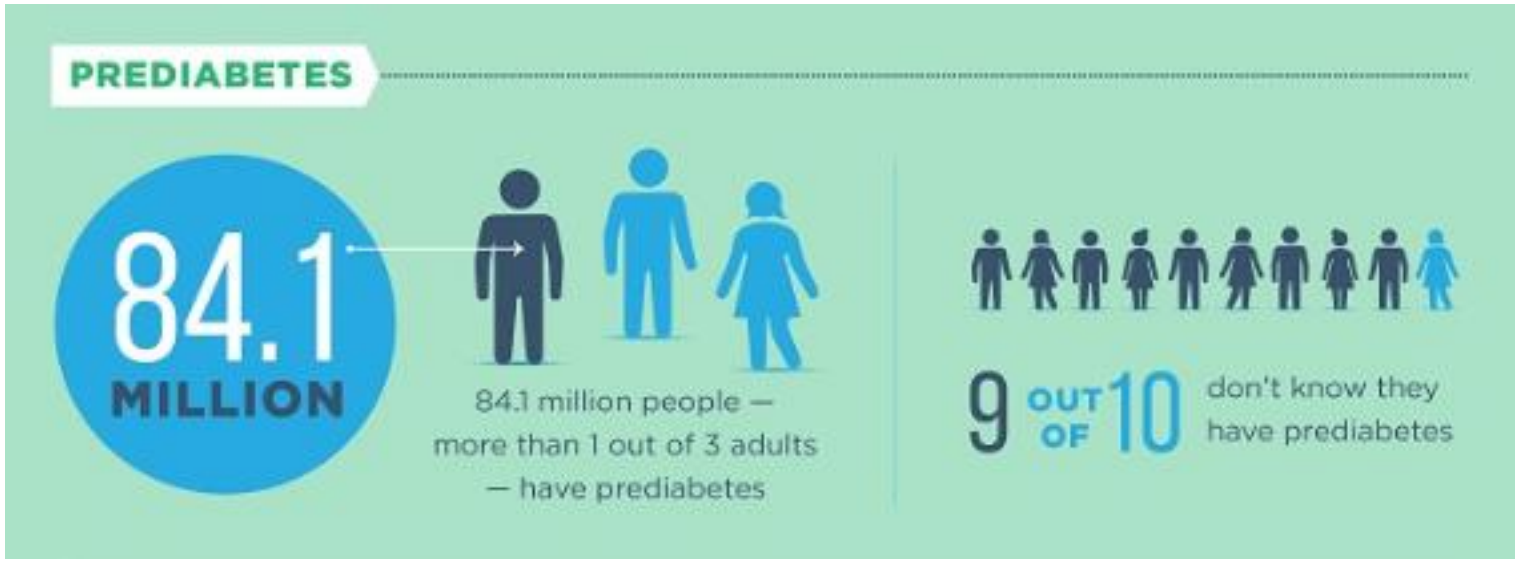
**Asymptomatic coronary artery disease and silent ischemia are frequently observed in diabetic patients.**

- **The prevalence of silent ischemia ranges from 10% to 69% in diabetic patients, compared with 5% to 35% in patients without diabetes.**
- **Almost one-third of myocardial infarctions in patients with diabetes are not associated with chest pain.**
- **The underlying mechanisms explaining the presence of silent ischemia in patients with diabetes include differences in pain threshold sensitivity and autonomic neuropathy.**
- **Symptoms of easy fatigability, atypical thoracic discomfort or exertional dyspnea can sometimes be the only factors suggesting the presence of coronary artery disease.**

Scognamiglio R, Negut C, Ramondo A, Tiengo A, Avogaro Detection of coronary artery disease in asymptomatic patients with type 2 diabetes mellitus. J Am Coll Cardiol. 2006;47(1):65. Epub 2005 Dec 9.


# Relationship between CAD and Prediabetes.

# Prediabetes Prevalence



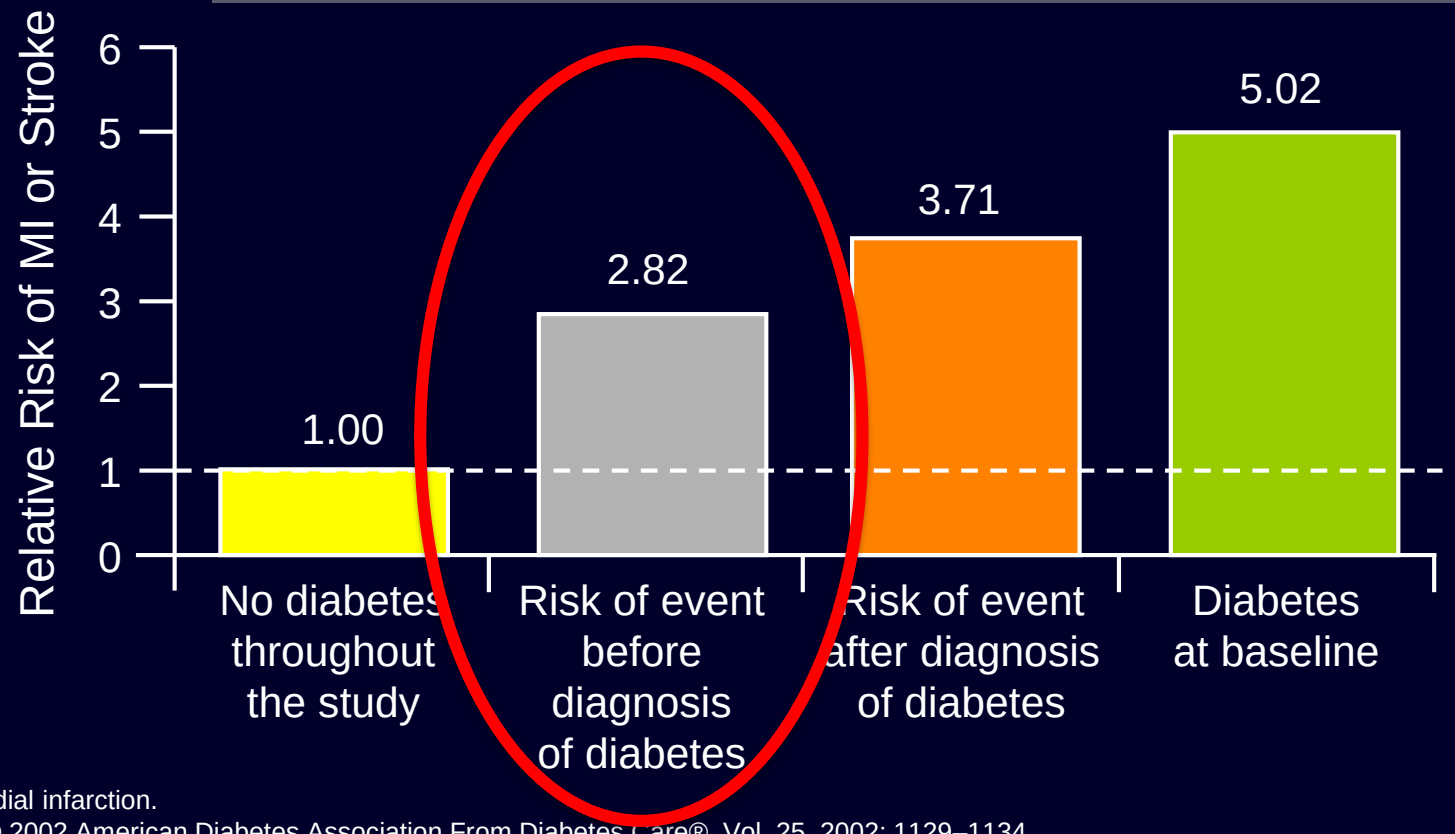

- CDC estimates that 84.1 million US adults aged 18 years or older had prediabetes in 2015.
- Prediabetes can increase a person's risk of type 2 diabetes, heart disease, and stroke.
- Although an estimated 33.9% of US adults had prediabetes in 2015, only 11.6% were aware of it.

Centers for Disease Control and Prevention. Diabetes Report Card 2017. Atlanta, GA: Centers for Disease Control and Prevention, US Dept of Health and Human Services; 2018

# Cardiovascular Risk Increases Before Increase in Glucose

Nurses' Health Study—20-year follow-up of 117,629 women:

- 1,508 had diabetes at baseline
- 5,894 developed diabetes
- 110,227 were diabetes free



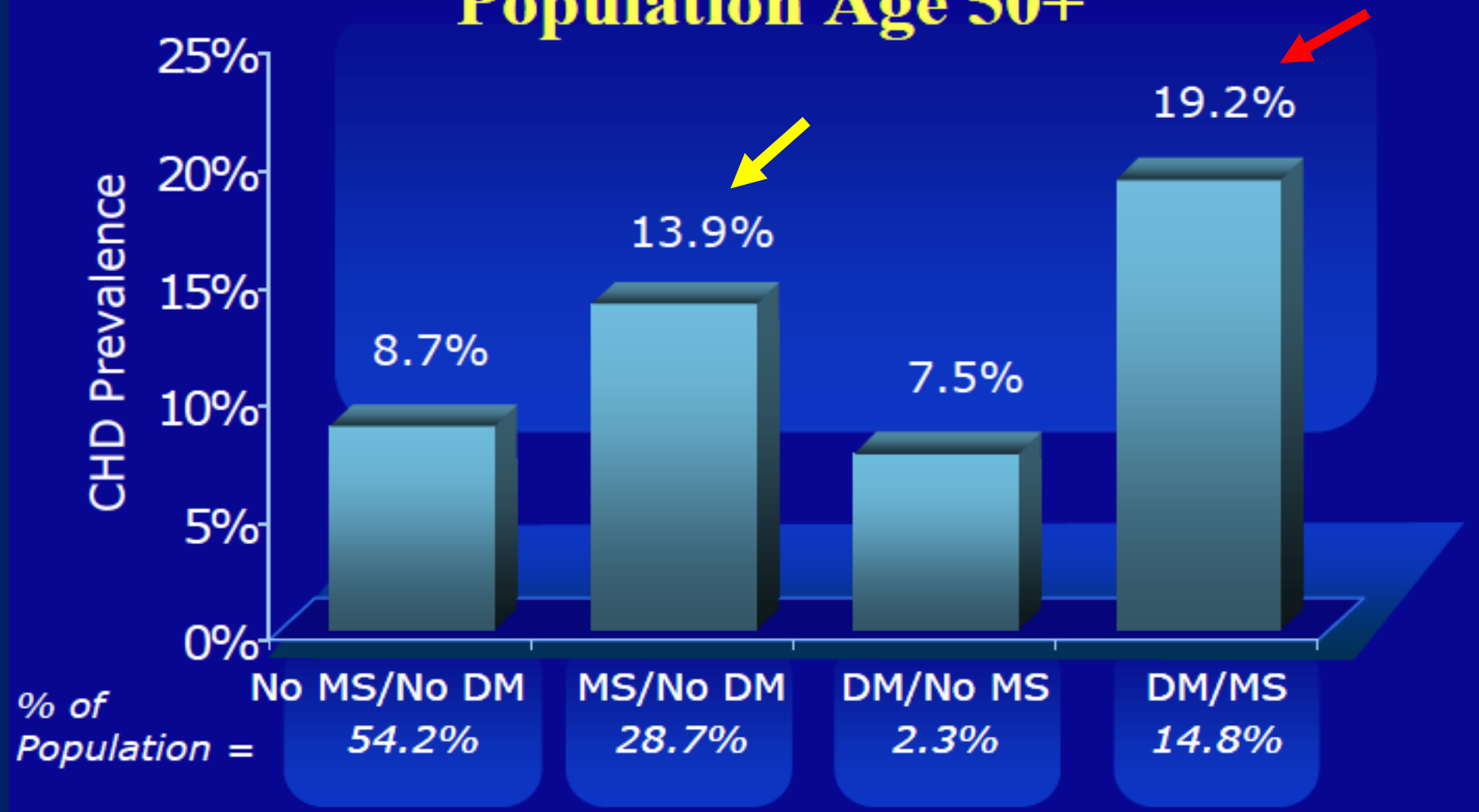

MI=myocardial infarction.

## AHA/NHLBI Statement for Clinical Diagnosis of the Metabolic Syndrome:
### 3 of 5 for diagnosis

| Risk Factor | Defining Level |
|---|---|
| **Abdominal obesity (waist circumference)** | |
| Men | >102 cm (>40 in) |
| Women | >88 cm (>35 in) |
| **Triglycerides** | ≥150 mg/dL or on drug treatment for high TG's |
| **HDL-C** | |
| Men | <40 mg/dL |
| Women | <50 mg/dL or on drug treatment for low HDL |
| **Blood pressure** | ≥130/≥85 mm Hg or on antihypertensive therapy |
| **Fasting glucose** | ≥100 mg/dL or on antidiabetes therapy |

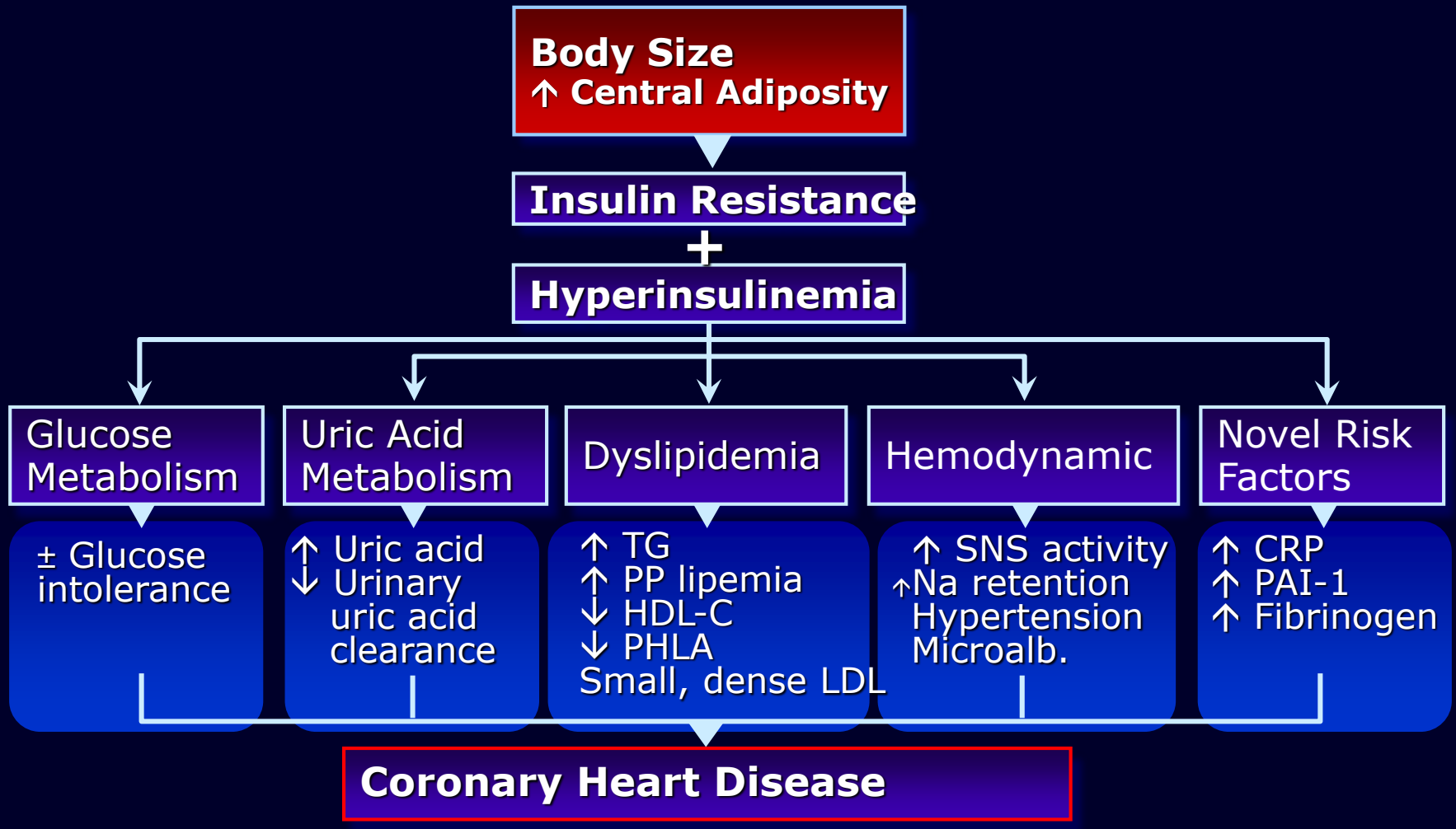
Grundy, et al. Diagnosis and Management of the Metabolic Syndrome: An AHA/NHBLI Scientific Statement. Circulation 2005;112;2735-2752.

# Prevalence of CHD by the Metabolic Syndrome and Diabetes in the NHANES Population Age 50+



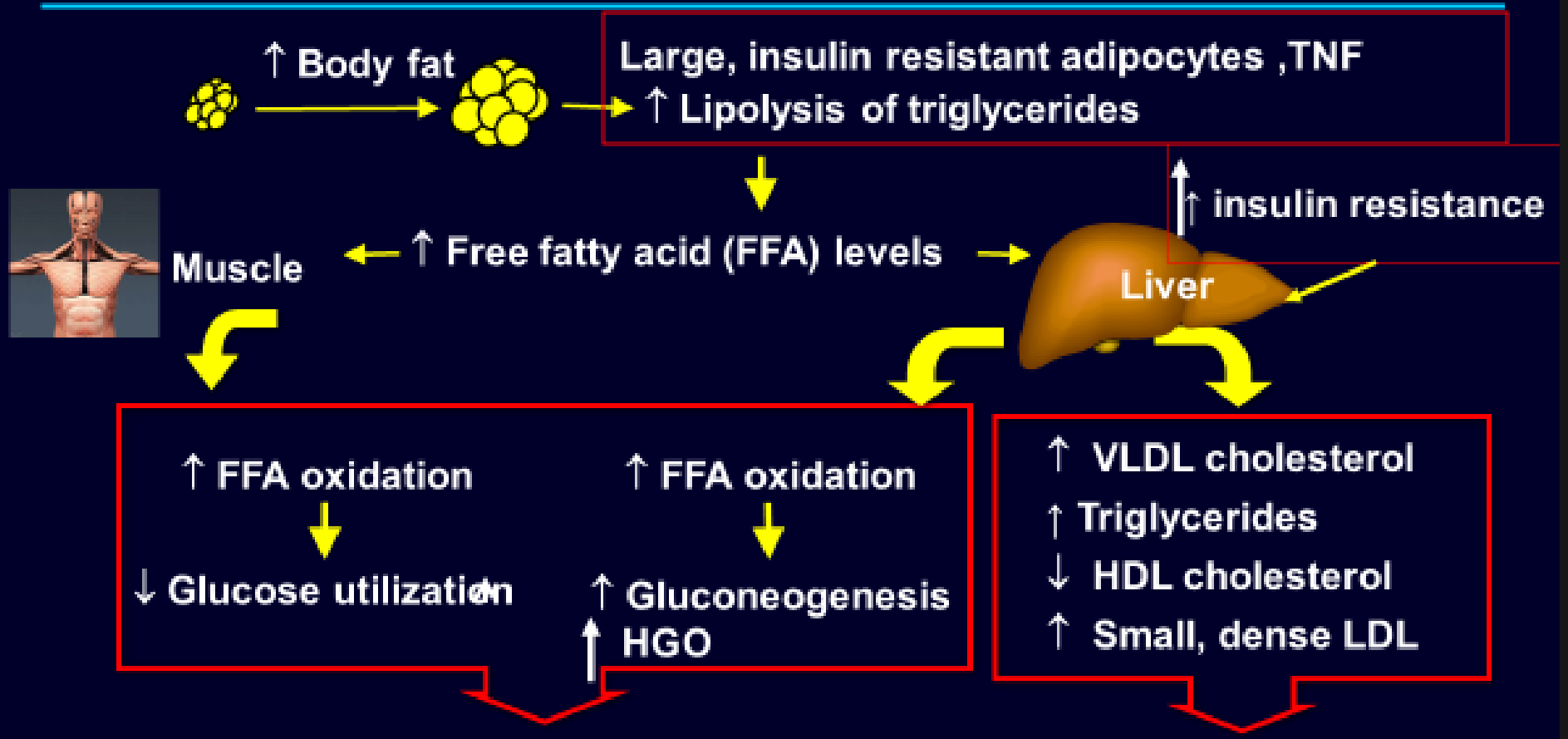

Alexander CM et al. *Diabetes* 2003;52:1210-1214.

# The Metabolic Syndrome:
## *Current Perspective*




Adapted from Reaven G. *Drugs* 1999;58(suppl):19-20 with permission from WolthersKluwer Health.

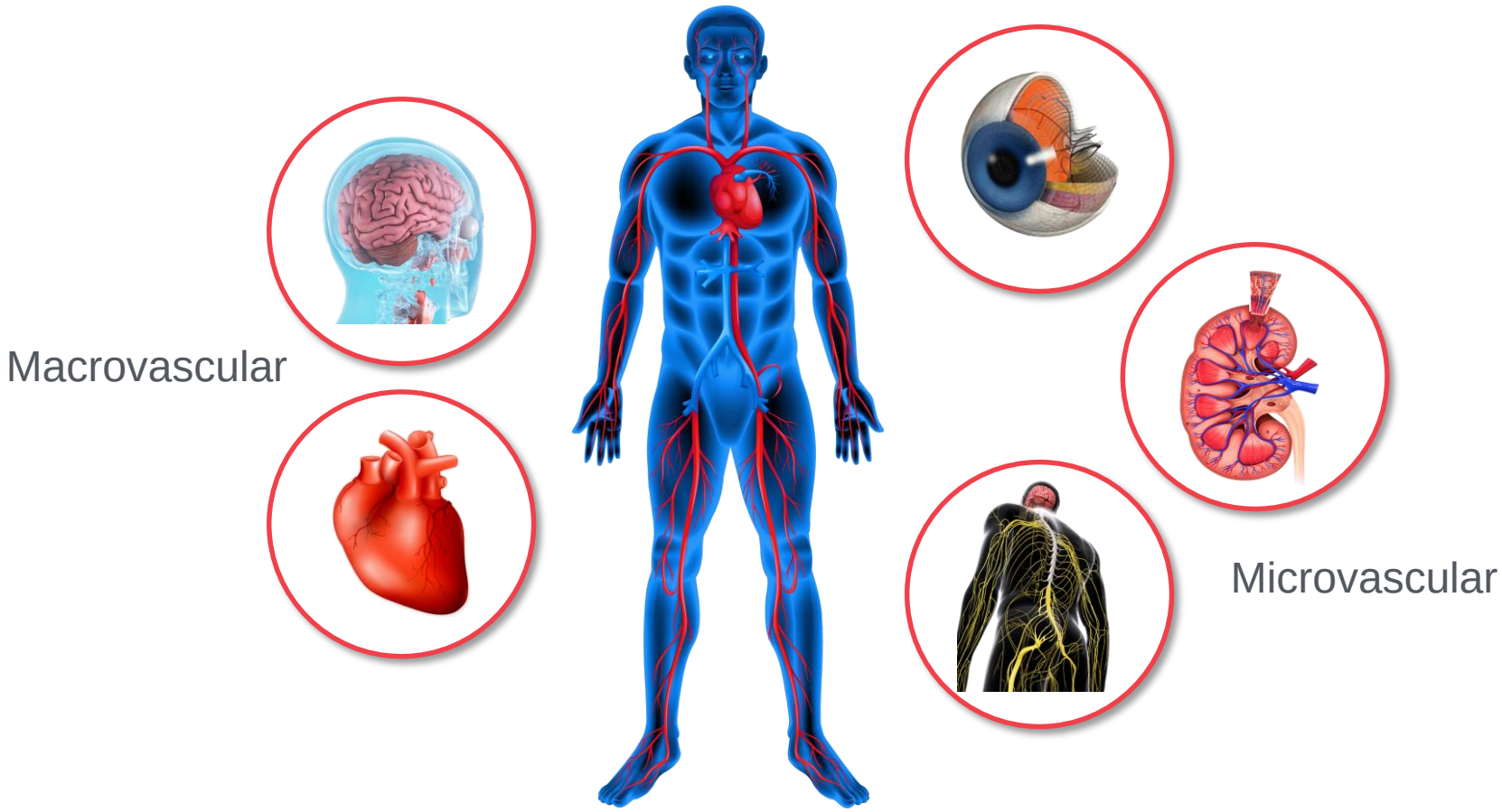
# Increased Visceral Fat Induces Increased Insulin resistance in Liver and Muscle




J Cell Physiology 2003; 194:1-12
*Obes Res.* 2002; 3: 103-112

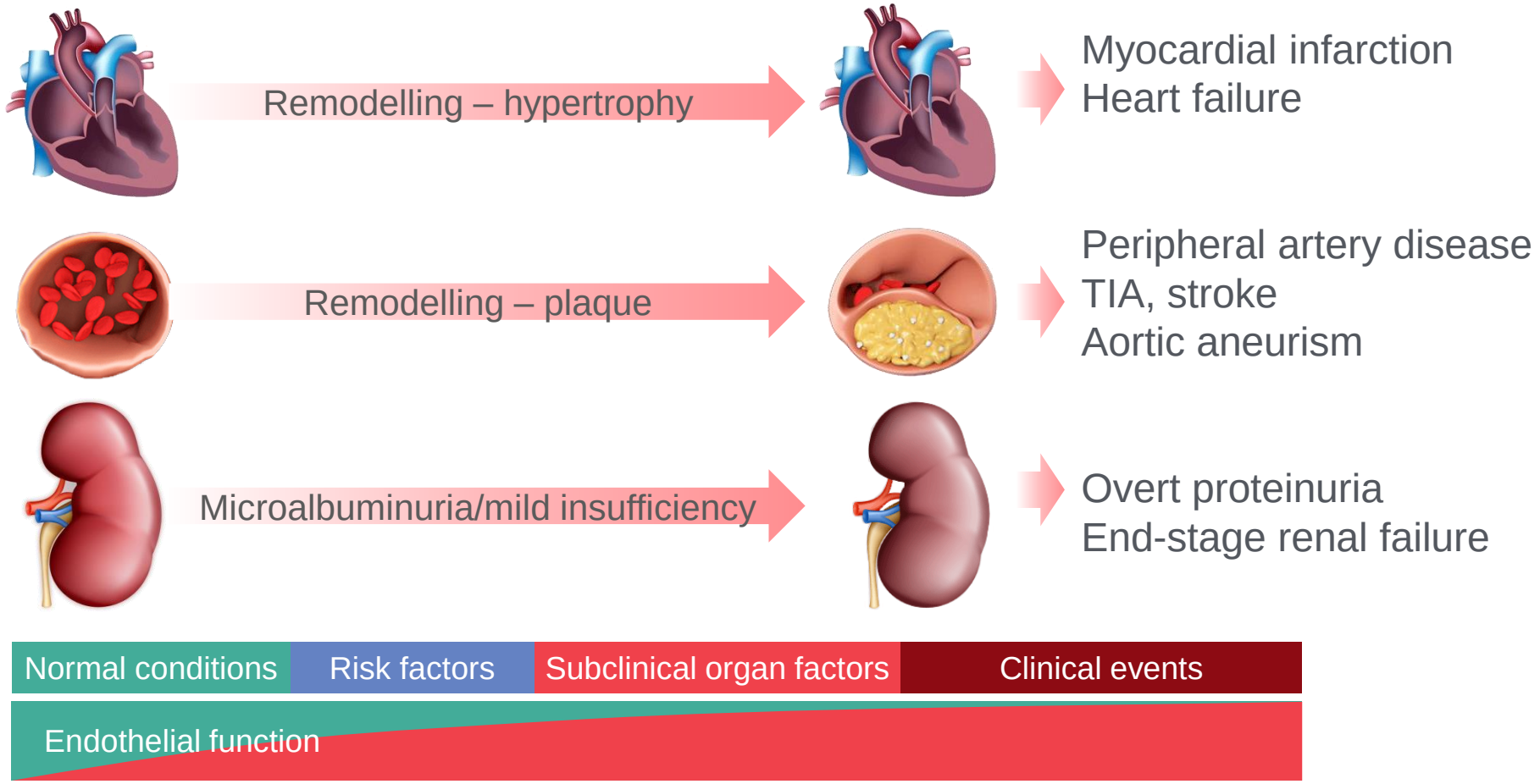
# Mechanisms of Increased CAD Risk in Patients with Diabetes.

# T2D is a major and independent risk factor for both microvascular and macrovascular complications



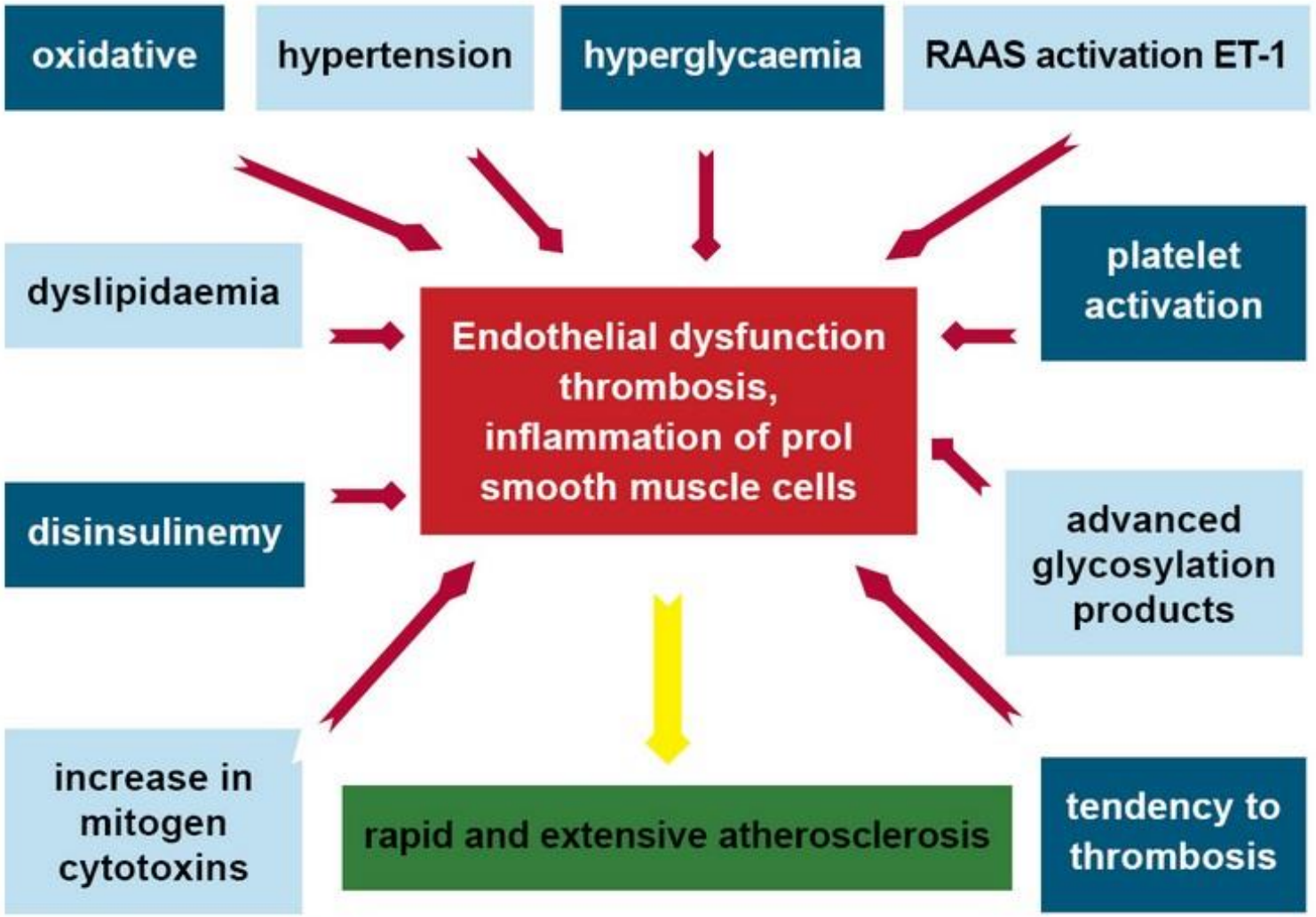

1. World Health Organization. http://www.who.int/diabetes/action_online/basics/en/index3.html

# Endothelial dysfunction is common to microvascular and macrovascular events



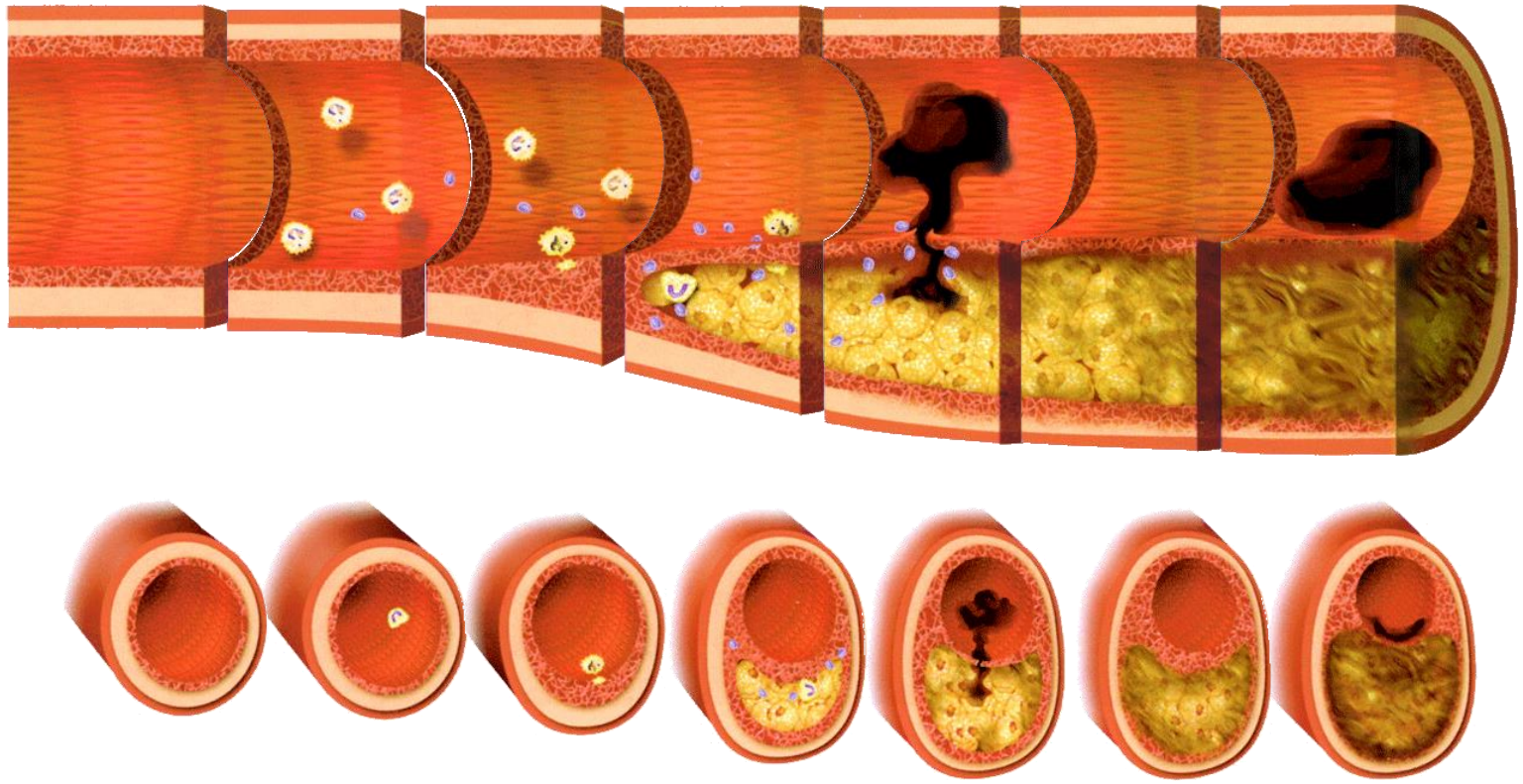

Versari et al. Diabetes Care 2009;32(suppl 2):S314-321.

*Figure 1.* ***The adverse effects of DM on cardiovascular system***




*Bartnik M,Norhammar A,Ryden L. Hyperglycemia and cardiovascular disease. J Intern Med 2007; 262: 145-56.*

# Endothelial dysfunction drives atherosclerotic progression



Atherosclerosis is accelerated in T2D by hyperglycaemia, insulin resistance, inflammation and diabetic dyslipidaemia

Figure adapted from Libby. Circulation 2001;104:365–72.
Zeadin et al. Can J Diabetes 2013;37:345e350.

# THE COMPLEX CONNECTIONS:
# Just a few of the factors that connect diabetes to heart disease

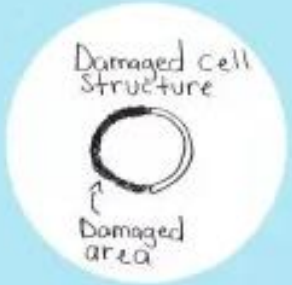
designed by: Ahmed Peterson

## DIABETES

**HIGH BLOOD SUGAR**


Increases production of free radicals

Can cause mutation which leads to ROS (reactive oxygen species) production




Damage cell structure

Can cause individual cell death

Reduces (NO) nitric oxide

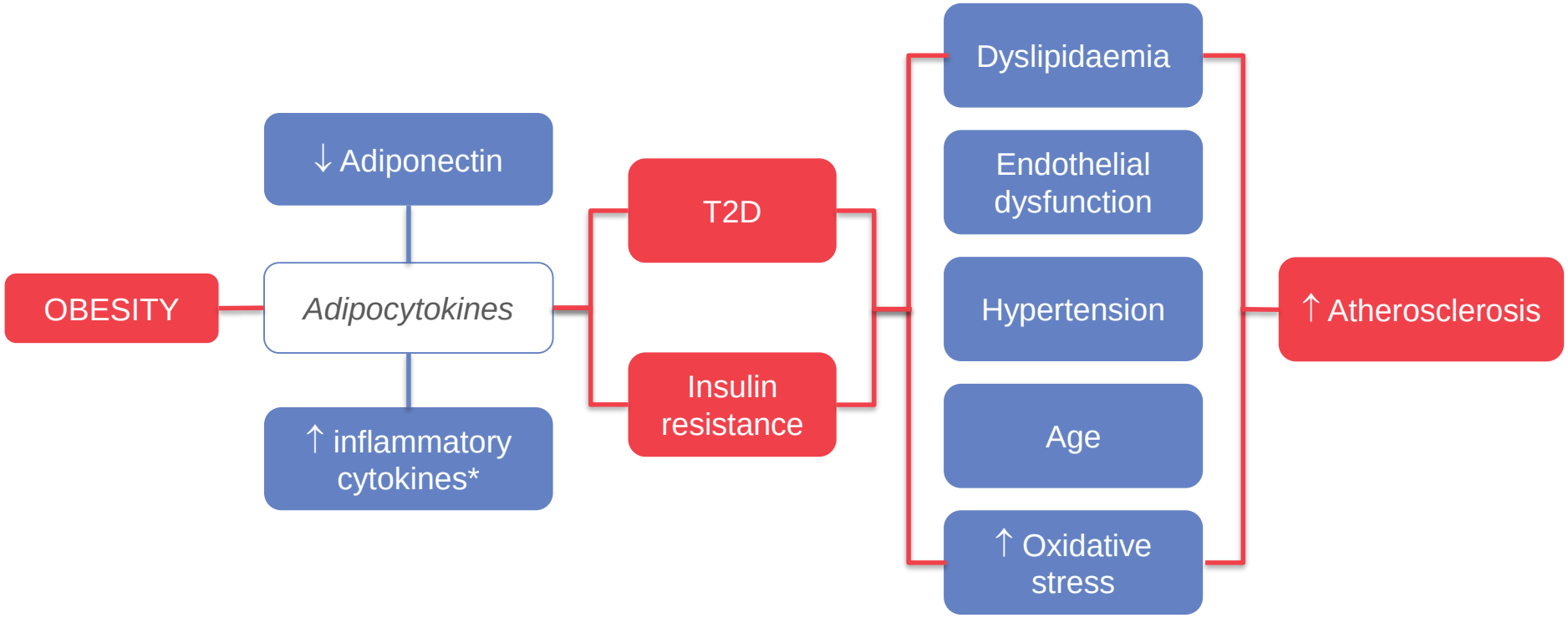

Decreased blood flow, allows fatty deposit to stick to the blood vessel wall,and the blood vessel wall becomes stiff and too thick.


**Source: CDC and American diabetes association**

## HEART DISEASE

# Visceral adiposity is related to inflammation, insulin resistance, dyslipidemia and atherosclerosis

**Interactions are complex, inter-related and not necessarily causal**




*including: TNFα, IL-6, resistin, PAI-1, angiotensinogen

Lau et al. Am J Physiol Heart Circ Physiol 2005;288:H2031–41.

# AGEs : consequences

AGEs → Crosslinking collagen → Directly ↓ function

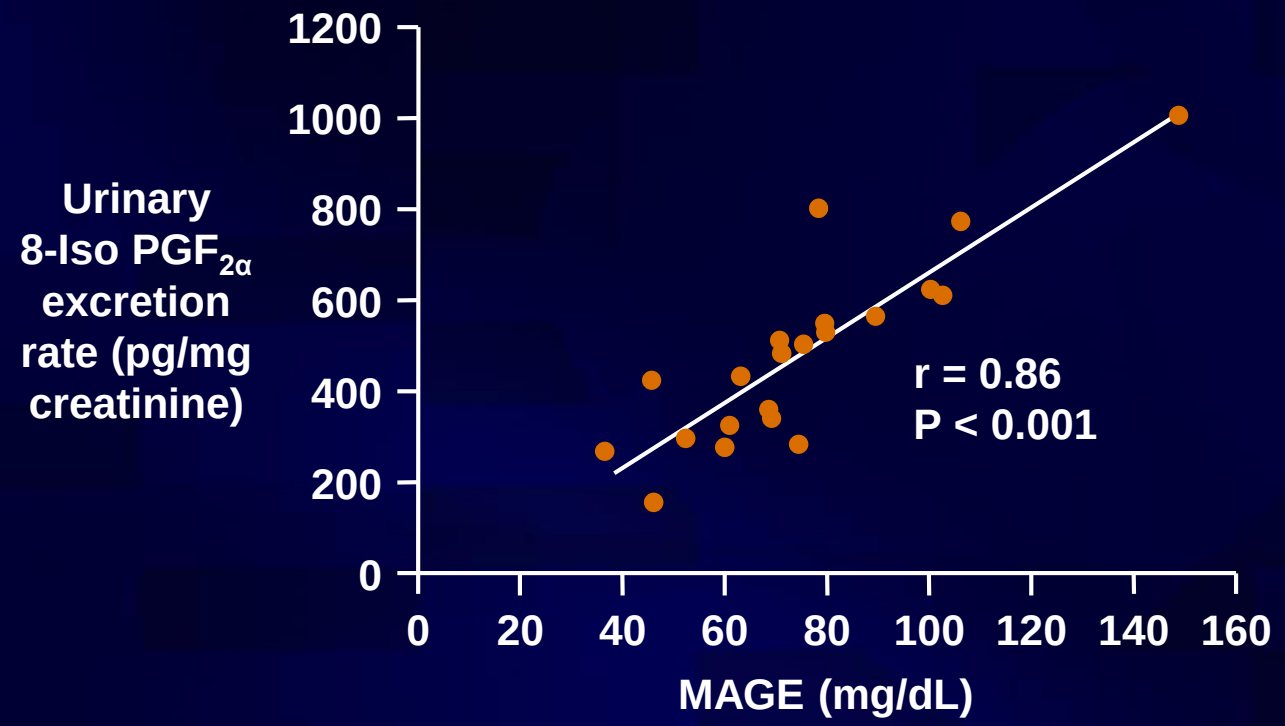
AGEs → RAGE → Inflammation
→ Oxidative stress

AGEs → Binding lipoproteins → Atherosclerosis

Lennert Van Putte[1], Sofie De Schrijver[1], Peter Moortgat[2] [1] University of Antwerp, Faculty of Medicine and Health science, Antwerp, Belgium

# Glucose fluctuations correlate with oxidative stress

**n = 21 with T2DM**

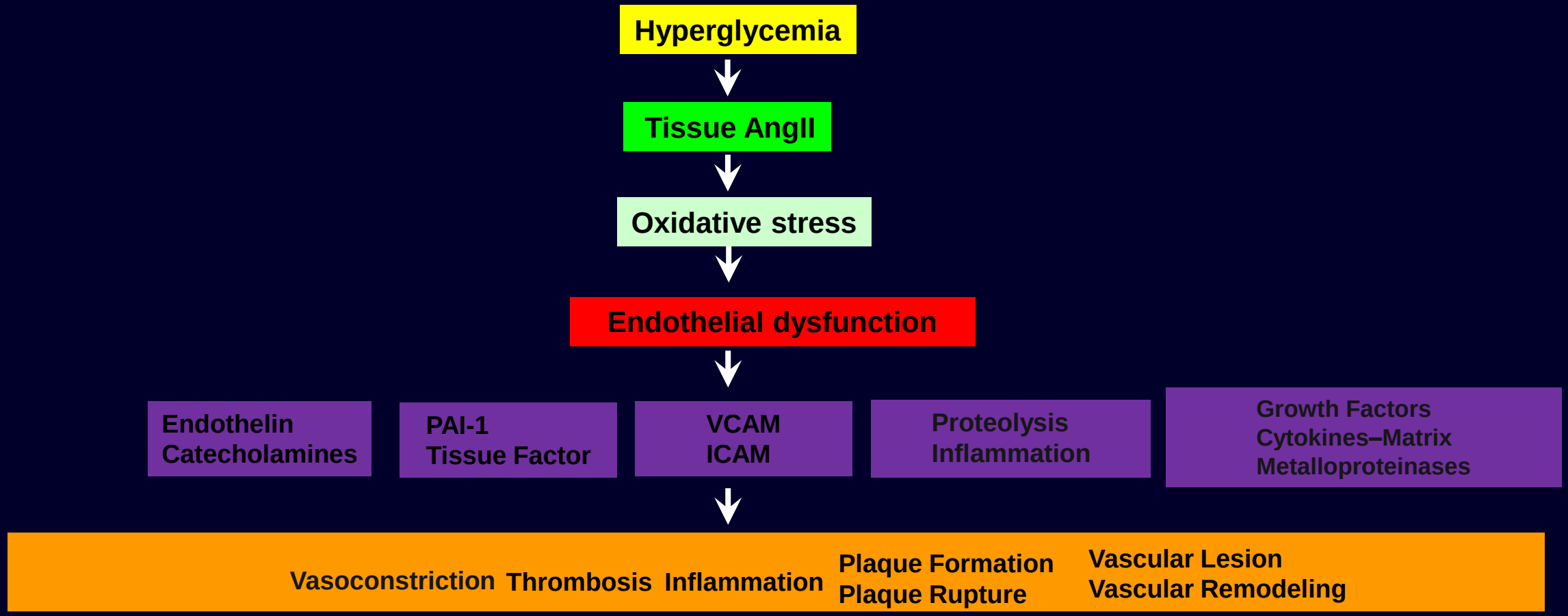



**8-iso $PGF_{2\alpha}$ formed directly from free radical-mediated arachidonic acid oxidation**

**MAGE = mean amplitude of glycemic excursions**
**PG = prostaglandin**

Monnier L et al. *JAMA*. 2006;295:1681-7.

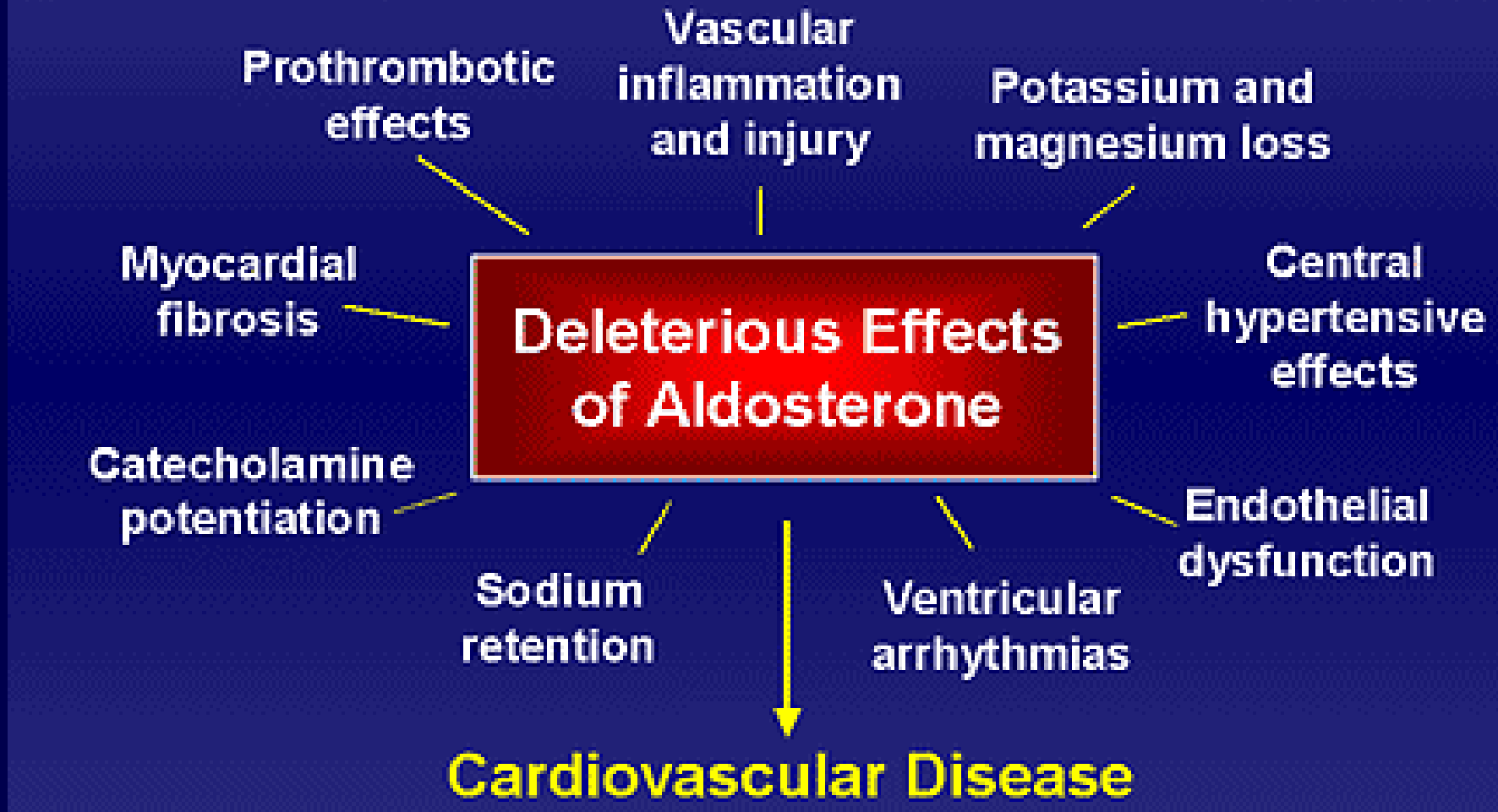
# Atherogenic Effects of AngII Are Enhanced by Hyperglycemia





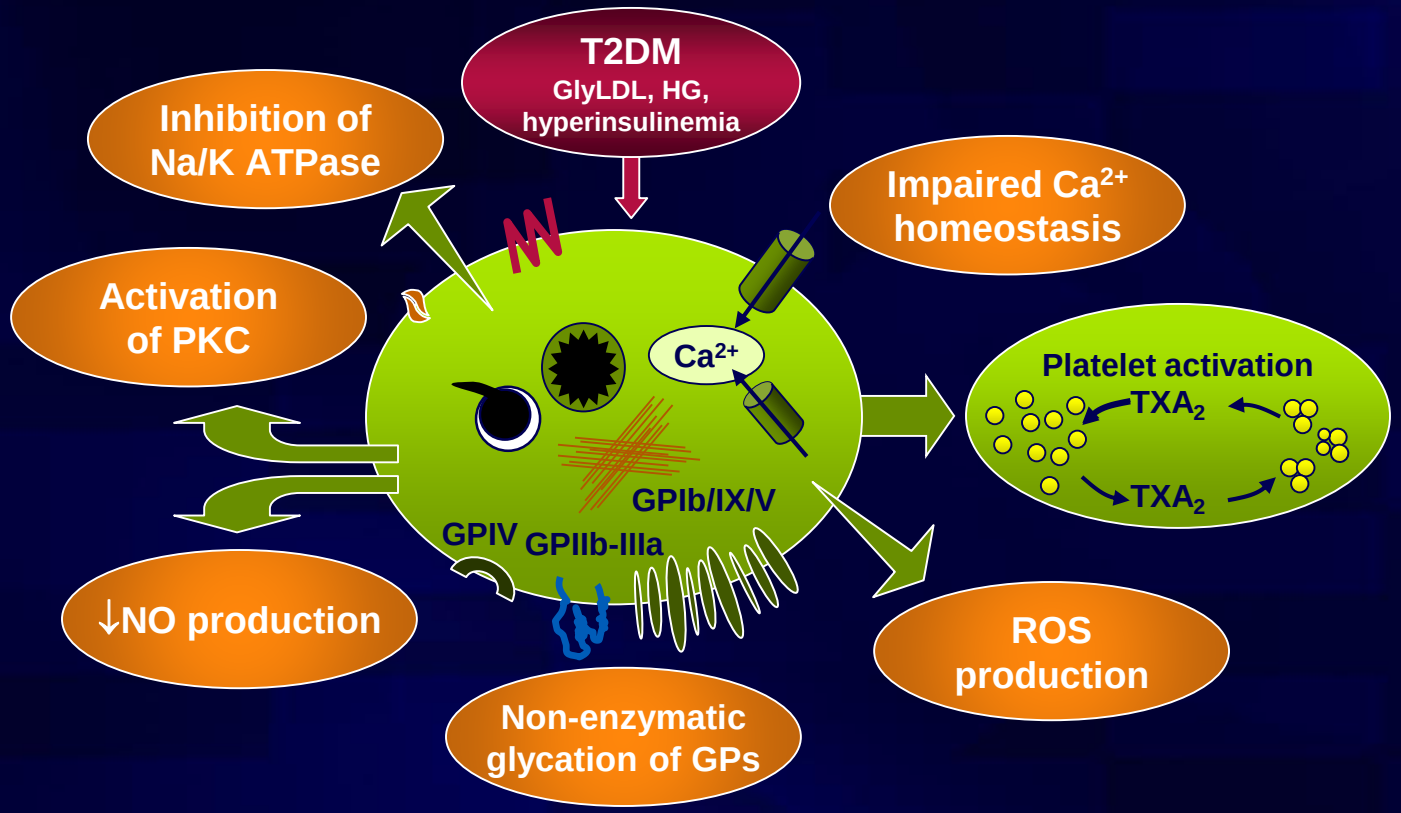

PAI = plasminogen activator inhibitor.
VCAM = vascular cell adhesion molecule.
ICAM = intercellular adhesion molecule.

# The Role of Aldosterone in Cardiovascular Disease



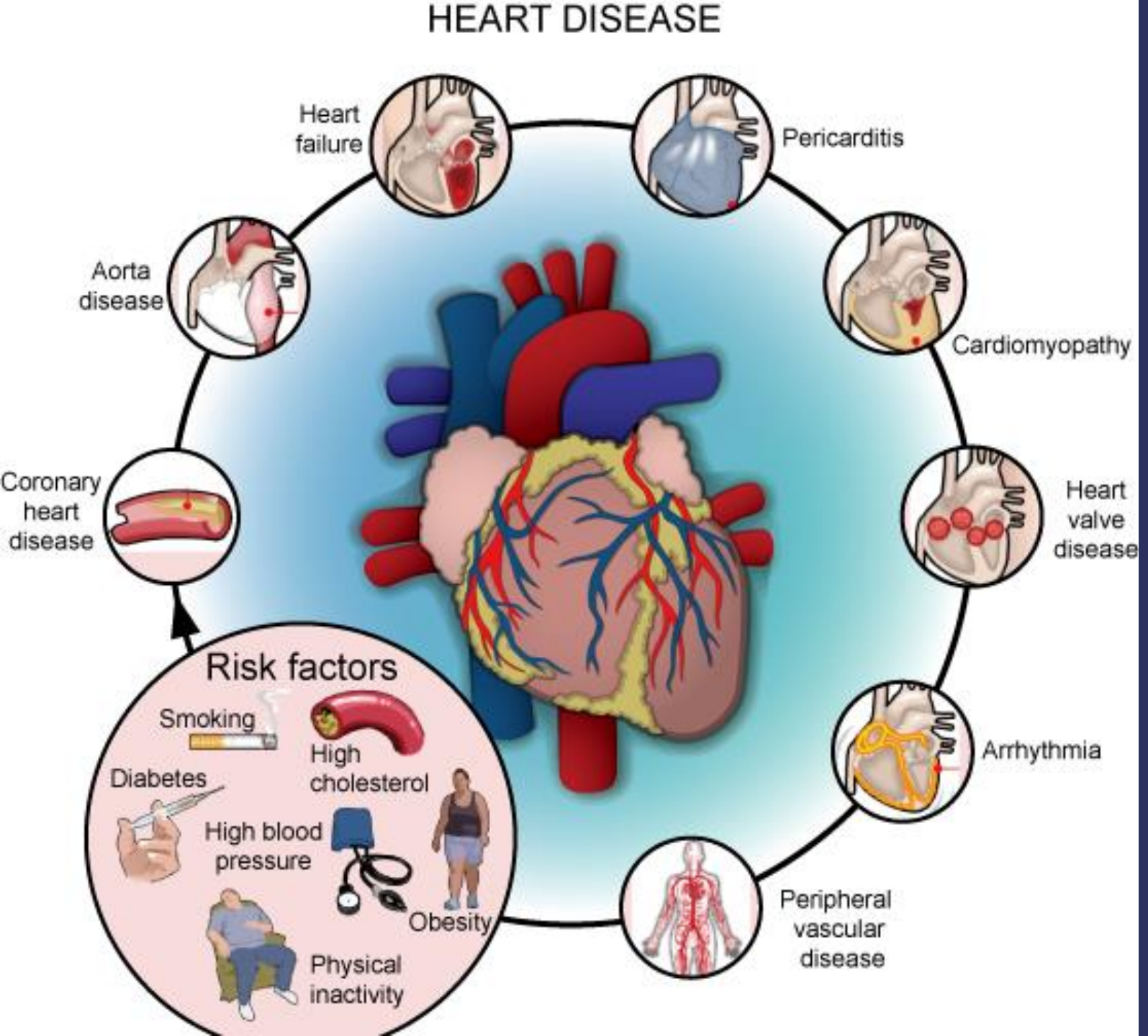

McMahon EG. *Current Opinion Pharmacol.* 2001;1:190-6.

# Impact of hyperglycemia on platelet function




PKC = protein kinase C; GlyLDL = glycated low-density lipoproteins; GP = glycoproteins; TXA = thromboxane

Ferroni P et al.
*J Thromb Haemost. 2004;2:1282-91.*




multifactorial risk factor reduction in the prevention of CAD

# Risk Factors for Macrovascular Disease

- Not modifiable
  - Genetic factors
  - Family history
- Modifiable
  - Hyperglycemia
  - Hypertension
  - **DYSLIPIDEMIA**
  - Smoking
  - Obesity
  - Physical inactivity

# Other Risk Factors for CVD in Patients With Diabetes

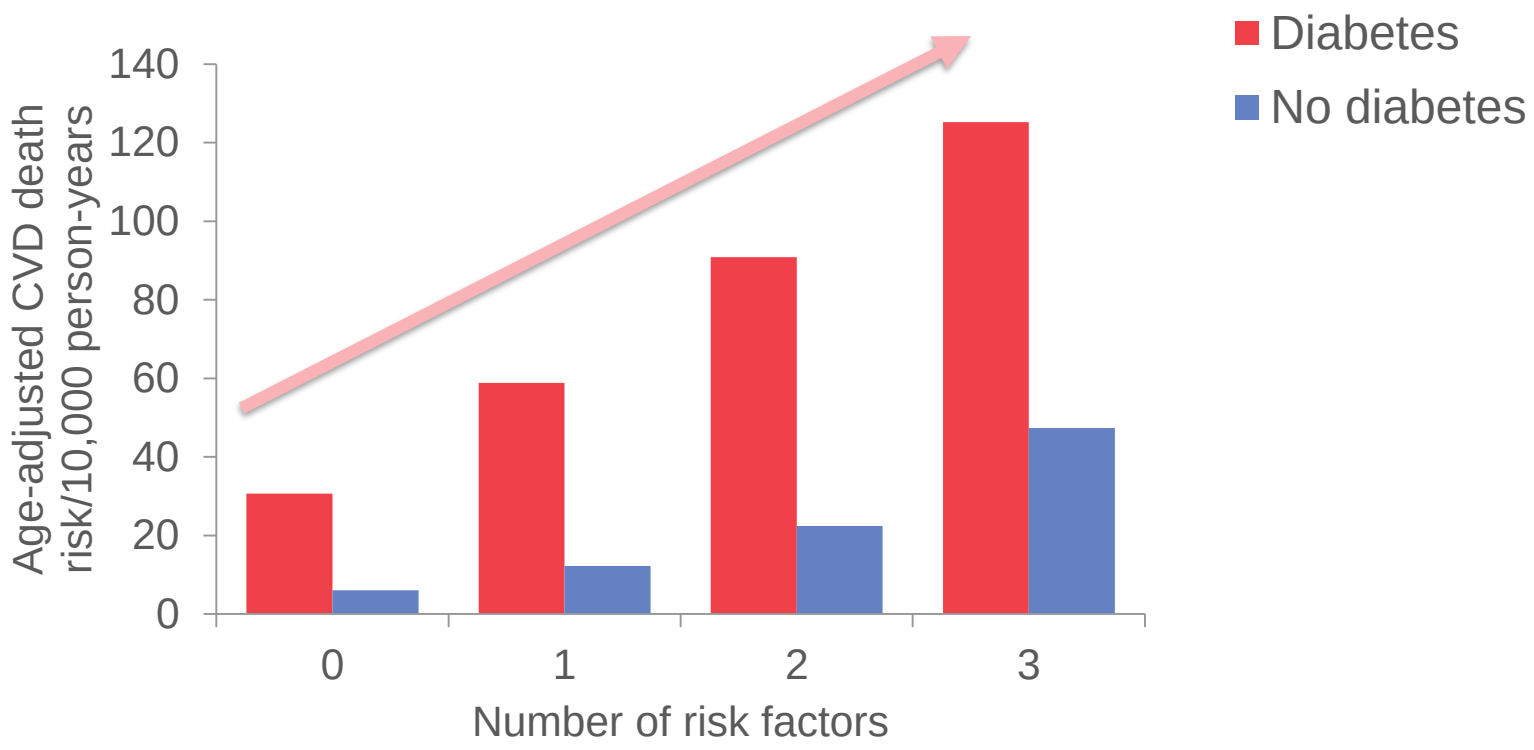
- Abnormal fibrinolysis (fibrinogen, PAI-1)
- Microalbuminuria
- Endothelial dysfunction
- Markers of inflammation (CRP, TNF-α, IL-6)
- Hyperhomocysteinemia
- Hypercoagulation

CVD=cardiovascular disease
PAI=plasminogen activator inhibitor
CRP=C-reactive protein
TNF-α=tumor necrosis factor α
IL-6=interleukin 6

Fonseca VA. *Ann Intern Med.* 2000;133:154-156

CADRE

# CV death is increased in patients with diabetes and multiple risk factors

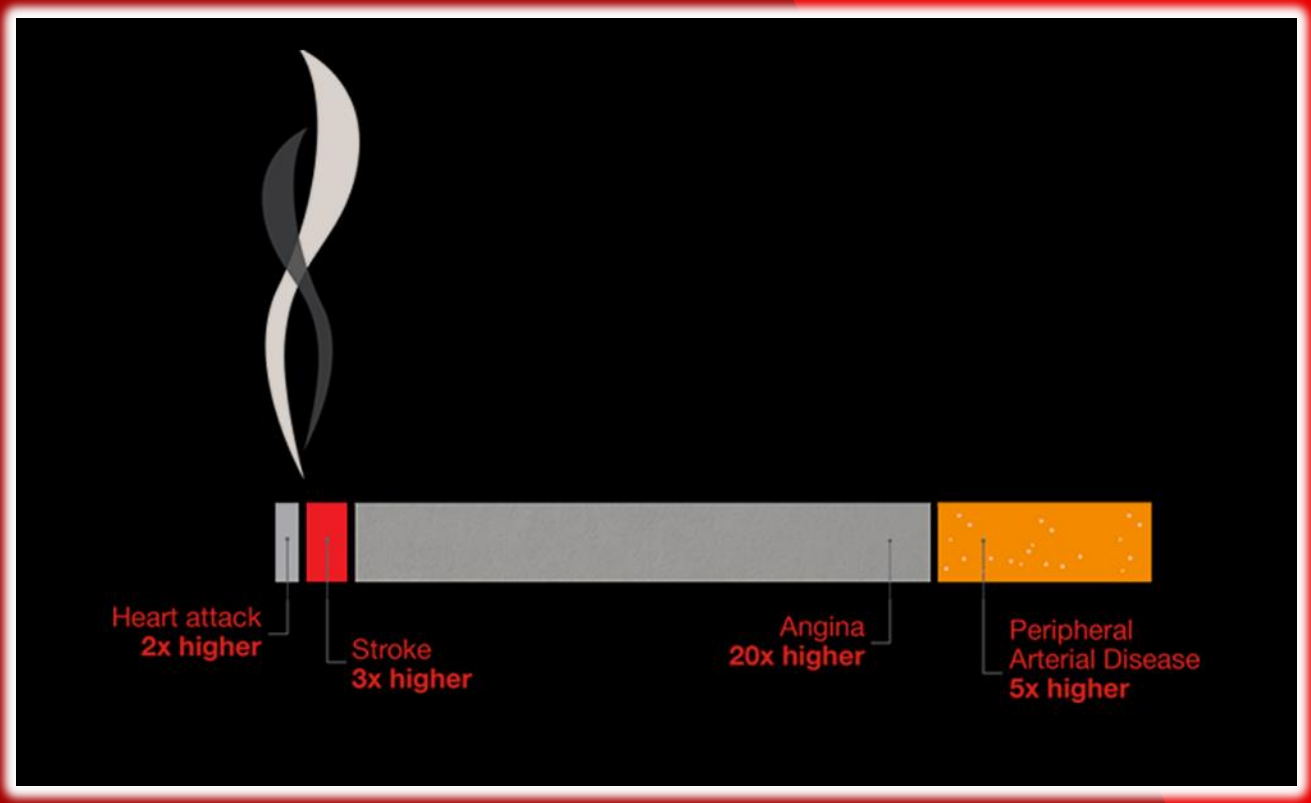



Risk factors were serum cholesterol ≥200 mg/dL, current smoker, SBP ≥120 mmHg

Stamler et al. Diabetes Care 1993;16:434.

# Smoking

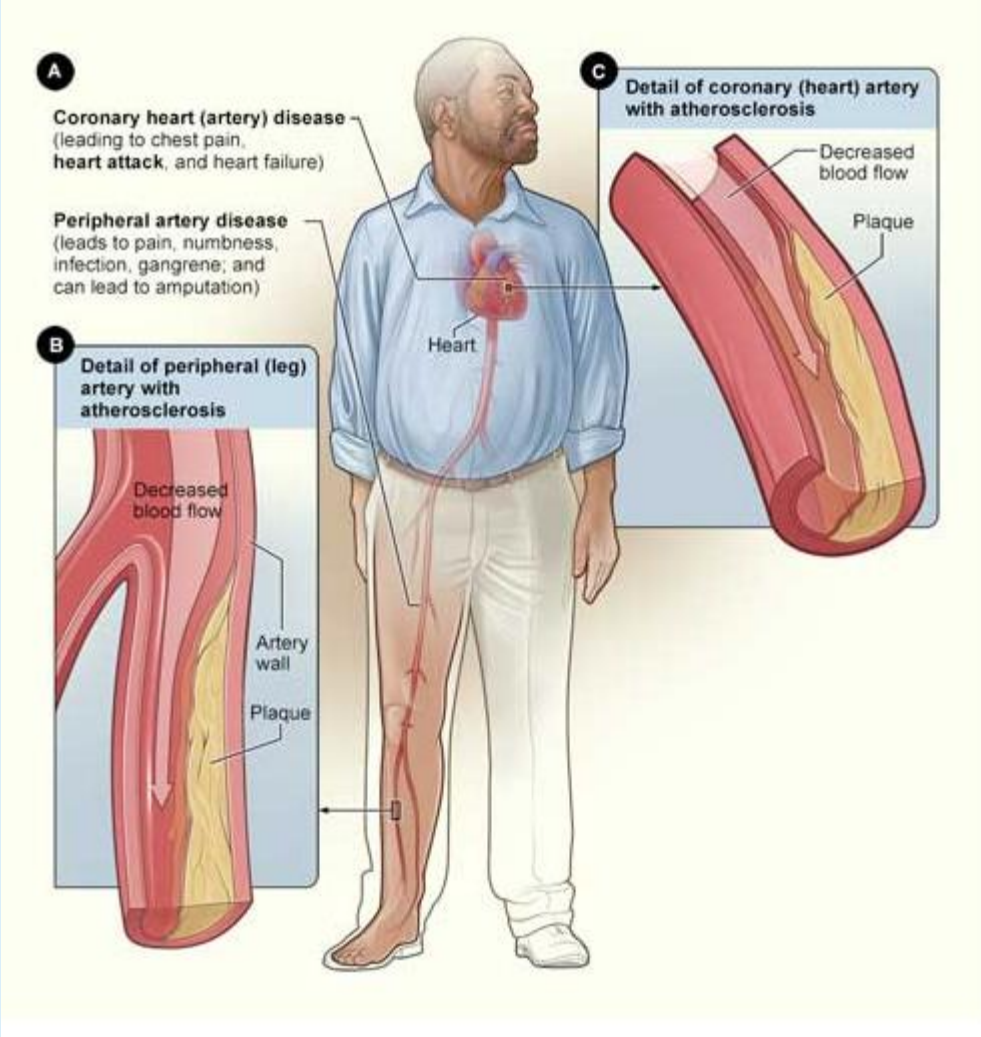
- **Increased risk for CVD**
  - active and passive smokers
  - is a major cause of cardiovascular disease (CVD)
  - causes approximately one of every four deaths from CVD
- **Three-fold increase in incidence of PAD**
  - risk tends to increase with number of cigarettes smoked (4- 5-fold in heavy smokers)
- **Affects all phases**
  - endothelial dysfunction
  - acute clinical event, thrombogenic



# Smoking

- 8% of smoke is tar
  - $10^{17}$ free radicals per gram
- 92% is gaseous
  - $10^{15}$ free radicals per puff

- Risk reduces significantly at 1-3 yrs after cessation
- **Reaches risk of  someone who never smoked at 15 yrs**




https://www.nhlbi.nih.gov/health-topics/smoking-and-your-heart

SCVEPR

# Smoking Cessation

- Strongly and repeatedly advice cessation
- All patients who smoke should receive program of physical advice, group counseling sessions, and nicotine replacement.
- **Addition of drug therapy** (bupropion, varenicline) can **increase cessation rates.**


Tonstad et al. Bupropion SR for smoking cessation in smokers with CV disease. Eur Heart J 2003; 24(10):946-55.
Jorenby et al. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. N Engl J Med 1999; 340(9):685-91.

# Unmet Clinical Need associated with Abdominal Obesity


"Persons who are naturally fat are apt to die earlier than those who are slender"
Hippocrates (460-377BC)

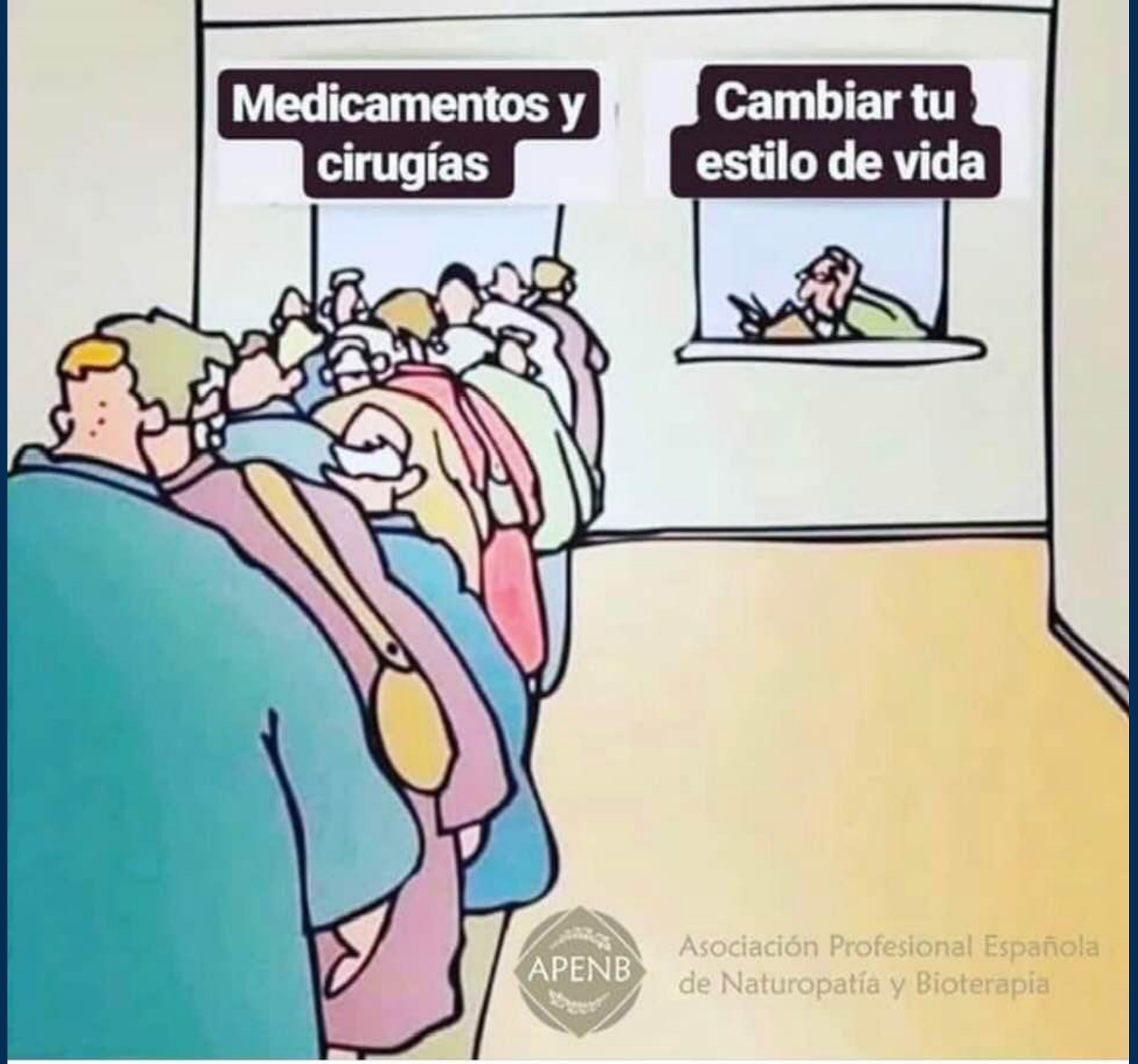
. Hypertriglyceridemia
. Low HDL-cholesterol
. Elevated apolipoprotein B
. Small, dense LDL particles
. Inflammatory profile

. Insulin resistance
. Hyperinsulinemia
. Glucose intolerance
. Impaired fibrinolysis
. Endothelial dysfunction

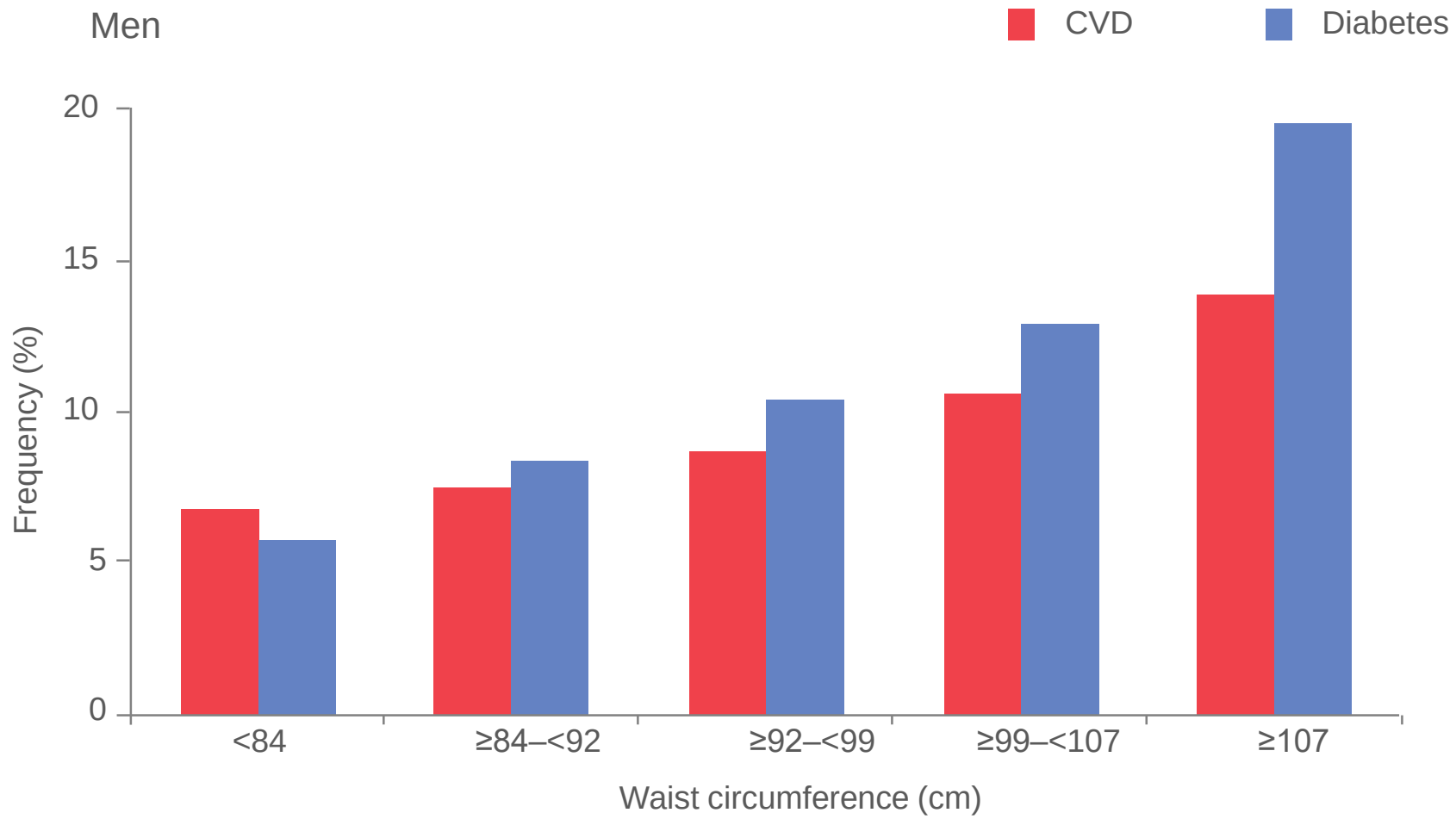
**Genetic susceptibility to DM, HBP, CAD ultimately affects the clinical features of the MS**


diet Pepsi
Diet Pepsi


The Shopping Galleries
The Offices


Medicamentos y cirugías
Cambiar tu estilo de vida
APENB
Asociación Profesional Española de Naturopatía y Bioterapia

# **Abdominal obesity** is associated with increased risk of both diabetes and CVD




Population of 168,000 primary care patients across 63 countries

Balkau et al. Circulation 2007;116:1942–51.

# Overweight/Obesity Treatment Options in T2DM

| | Body Mass Index (BMI) Category (kg/m$^2$) | | | | |
|---|---|---|---|---|---|
| **Treatment** | **25.0-26.9 (or 23.0-26.9*)** | **27.0-29.9** | **30.0-34.9 (or 27.5-32.4*)** | **35.0-39.9 (or 32.5-37.4*)** | **≥40 (or ≥37.5*)** |
| **Diet, physical activity & behavioral therapy** | ┼ | ┼ | ┼ | ┼ | ┼ |
| **Pharmacotherapy** | | ┼ | ┼ | ┼ | ┼ |
| **Metabolic surgery** | | | ┼ | ┼ | ┼ |

* Cutoff points for Asian-American individuals.

┼ Treatment may be indicated for selected, motivated patients.

Obesity Management for the Treatment of Type 2 Diabetes:
*Standards of Medical Care in Diabetes - 2018*. *Diabetes Care* 2018; 41 (Suppl. 1): S65-S72

# 3. Lifestyle Factors Affecting Cardiovascular Risk

## 3.1. Nutrition and Diet

| Recommendations for Nutrition and Diet<br>Referenced studies that support recommendations are summarized in Online Data Supplements 4 and 5. | | |
|---|---|---|
| **COR** | **LOE** | **Recommendations** |
| I | B-R | 1. A diet emphasizing intake of vegetables, fruits, legumes, nuts, whole grains, and fish is recommended to decrease ASCVD risk factors (S3.1-1–S3.1-11). |
| IIa | B-NR | 2. Replacement of saturated fat with dietary monounsaturated and polyunsaturated fats can be beneficial to reduce ASCVD risk (S3.1-12, S3.1-13). |
| IIa | B-NR | 3. A diet containing reduced amounts of cholesterol and sodium can be beneficial to decrease ASCVD risk (S3.1-9, S3.1-14–S3.1-16). |
| IIa | B-NR | 4. As a part of a healthy diet, it is reasonable to minimize the intake of processed meats, refined carbohydrates, and sweetened beverages to reduce ASCVD risk (S3.1-17–S3.1-24). |
| III: Harm | B-NR | 5. As a part of a healthy diet, the intake of *trans* fats should be avoided to reduce ASCVD risk (S3.1-12, S3.1-17, S3.1-25–S3.1-27). |

# Latin Diet Pyramid

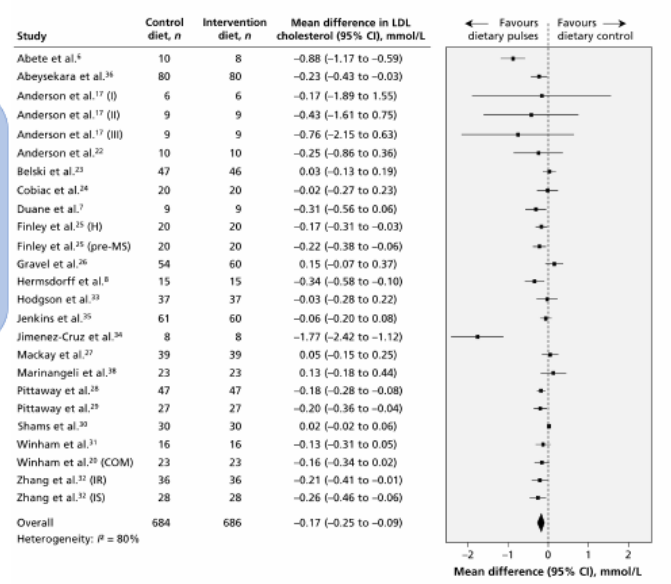
- Healthy dietary pattern in the context of foods traditional to the Latino/Hispanic culture
- Accordance
  - Traditional diet
  - Enjoy food traditional to the Latino/Hispanic culture

## *Beans (Pulses)*

Nutrients
- Fiber (8.7 g)
- Magnesium (60 mg)
- Potassium (305 mg)
- Folate (128 mg)
- Polyphenols (1780 mg)

-Average reduction in LDL cholesterol by 6.6 mg/dL

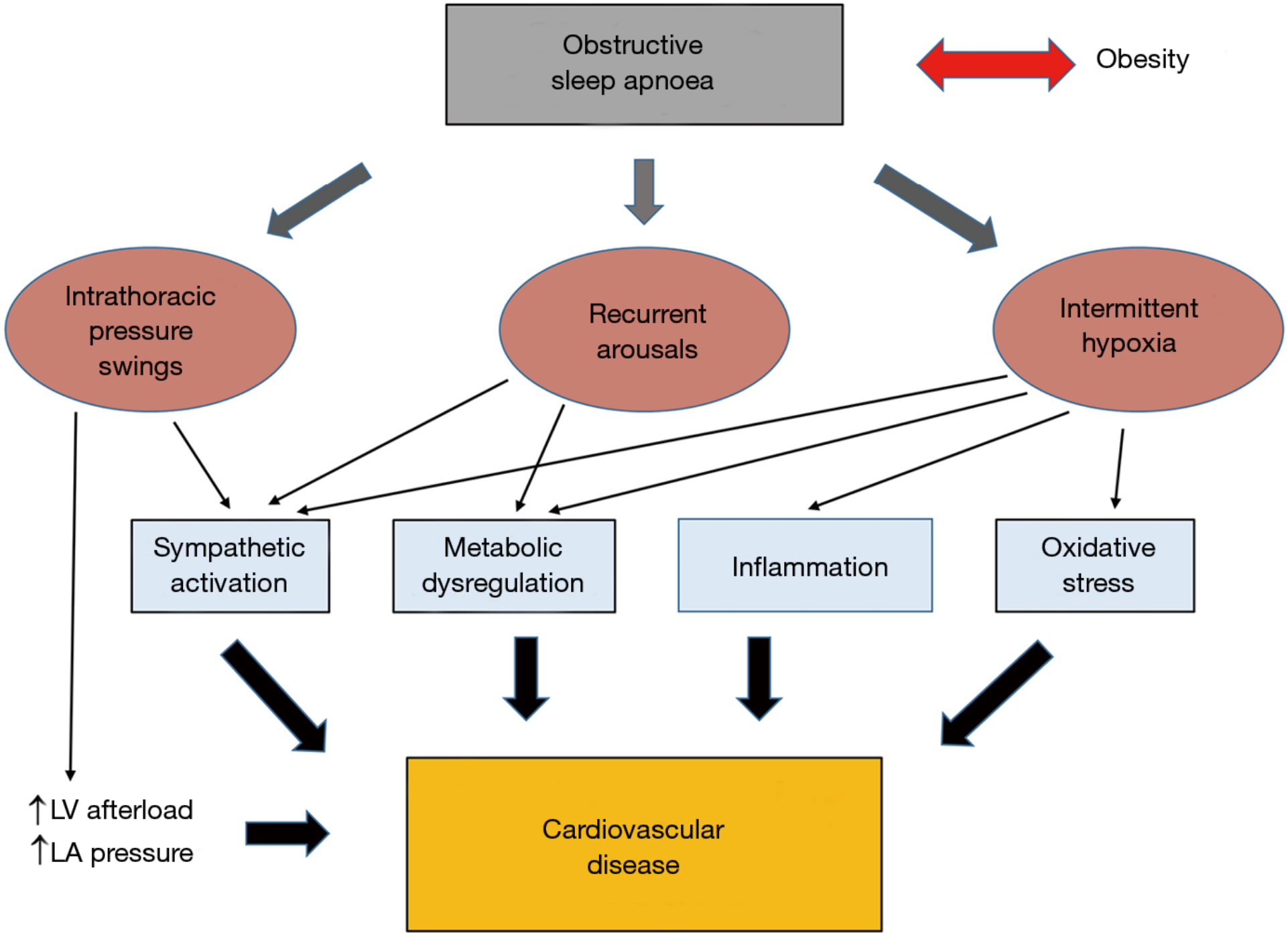
*Frijoles borrachos (pinto beans; Mexico)*
*Porotos Granados (cranberry beans; Chile)*
*Feijão em Salada (great northern beans; Brazil)*
*Frijoles negros (black beans; Cuba)*



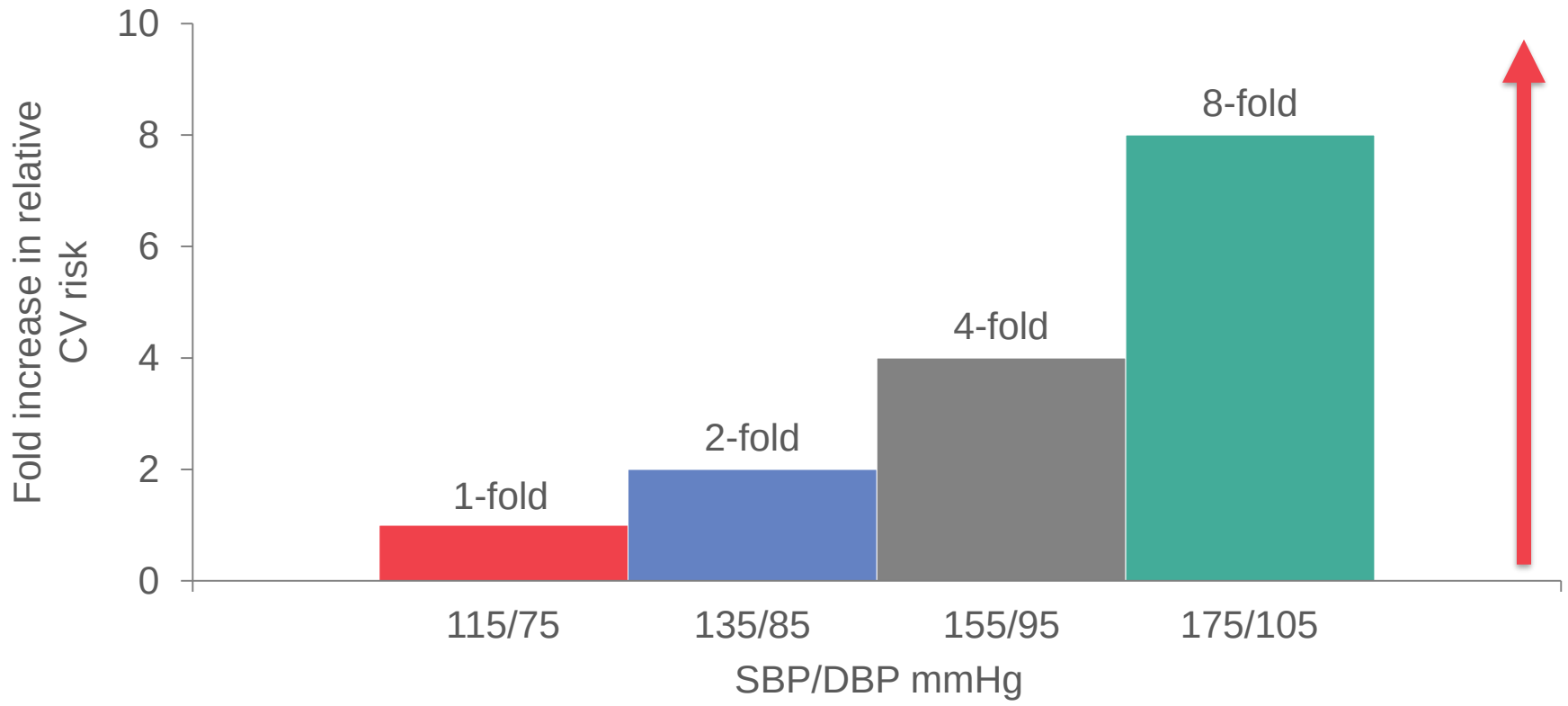
| Study | Control diet, *n* | Intervention diet, *n* | Mean difference in LDL cholesterol (95% CI), mmol/L |
|---|---|---|---|
| Abete et al.[6] | 10 | 8 | −0.88 (−1.17 to −0.59) |
| Abeysekara et al.[36] | 80 | 80 | −0.23 (−0.43 to −0.03) |
| Anderson et al.[17] (I) | 6 | 6 | −0.17 (−1.89 to 1.55) |
| Anderson et al.[17] (II) | 9 | 9 | −0.43 (−1.61 to 0.75) |
| Anderson et al.[17] (III) | 9 | 9 | −0.76 (−2.15 to 0.63) |
| Anderson et al.[22] | 10 | 10 | −0.25 (−0.86 to 0.36) |
| Belski et al.[23] | 47 | 46 | 0.03 (−0.13 to 0.19) |
| Cobiac et al.[24] | 20 | 20 | −0.02 (−0.27 to 0.23) |
| Duane et al.[7] | 9 | 9 | −0.31 (−0.56 to 0.06) |
| Finley et al.[25] (H) | 20 | 20 | −0.17 (−0.31 to −0.03) |
| Finley et al.[25] (pre-MS) | 20 | 20 | −0.22 (−0.38 to −0.06) |
| Gravel et al.[26] | 54 | 60 | 0.15 (−0.07 to 0.37) |
| Hermsdorff et al.[8] | 15 | 15 | −0.34 (−0.58 to −0.10) |
| Hodgson et al.[33] | 37 | 37 | −0.03 (−0.28 to 0.22) |
| Jenkins et al.[35] | 61 | 60 | −0.06 (−0.20 to 0.08) |
| Jimenez-Cruz et al.[34] | 8 | 8 | −1.77 (−2.42 to −1.12) |
| Mackay et al.[27] | 39 | 39 | 0.05 (−0.15 to 0.25) |
| Marinangeli et al.[38] | 23 | 23 | 0.13 (−0.18 to 0.44) |
| Pittaway et al.[28] | 47 | 47 | −0.18 (−0.28 to −0.08) |
| Pittaway et al.[29] | 27 | 27 | −0.20 (−0.36 to −0.04) |
| Shams et al.[30] | 30 | 30 | 0.02 (−0.02 to 0.06) |
| Winham et al.[31] | 16 | 16 | −0.13 (−0.31 to 0.05) |
| Winham et al.[20] (COM) | 23 | 23 | −0.16 (−0.34 to 0.02) |
| Zhang et al.[32] (IR) | 36 | 36 | −0.21 (−0.41 to −0.01) |
| Zhang et al.[32] (IS) | 28 | 28 | −0.26 (−0.46 to −0.06) |
| Overall | 684 | 686 | −0.17 (−0.25 to −0.09) |
| Heterogeneity: $I^2$ = 80% | | | |



*Ha et al. 2015;186:e252.*

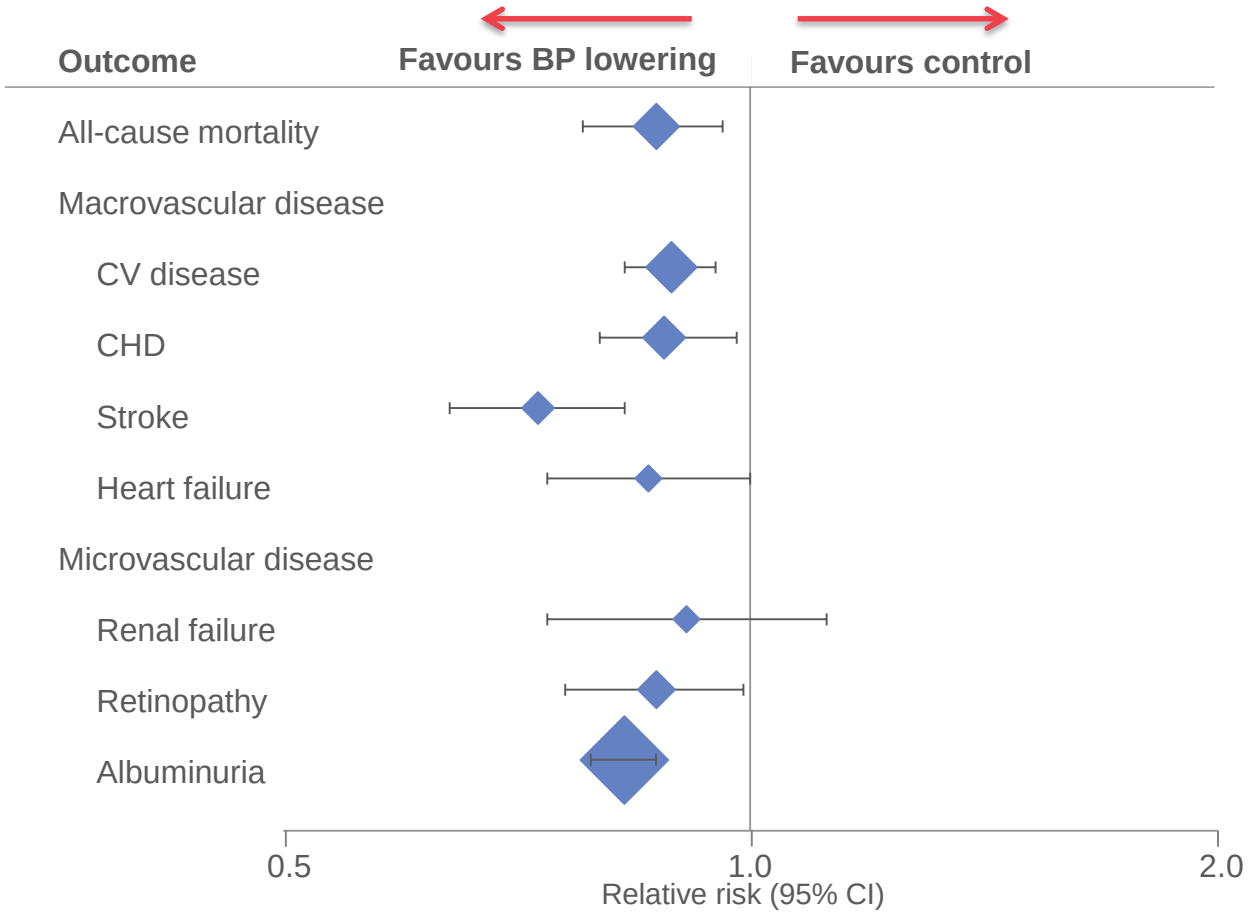

Obstructive sleep apnoea
Obesity
Intrathoracic pressure swings
Recurrent arousals
Intermittent hypoxia
Sympathetic activation
Metabolic dysregulation
Inflammation
Oxidative stress
↑LV afterload
↑LA pressure
Cardiovascular disease

# **Hypertension**: each 20/10 mmHg BP increase doubles the risk of CV mortality



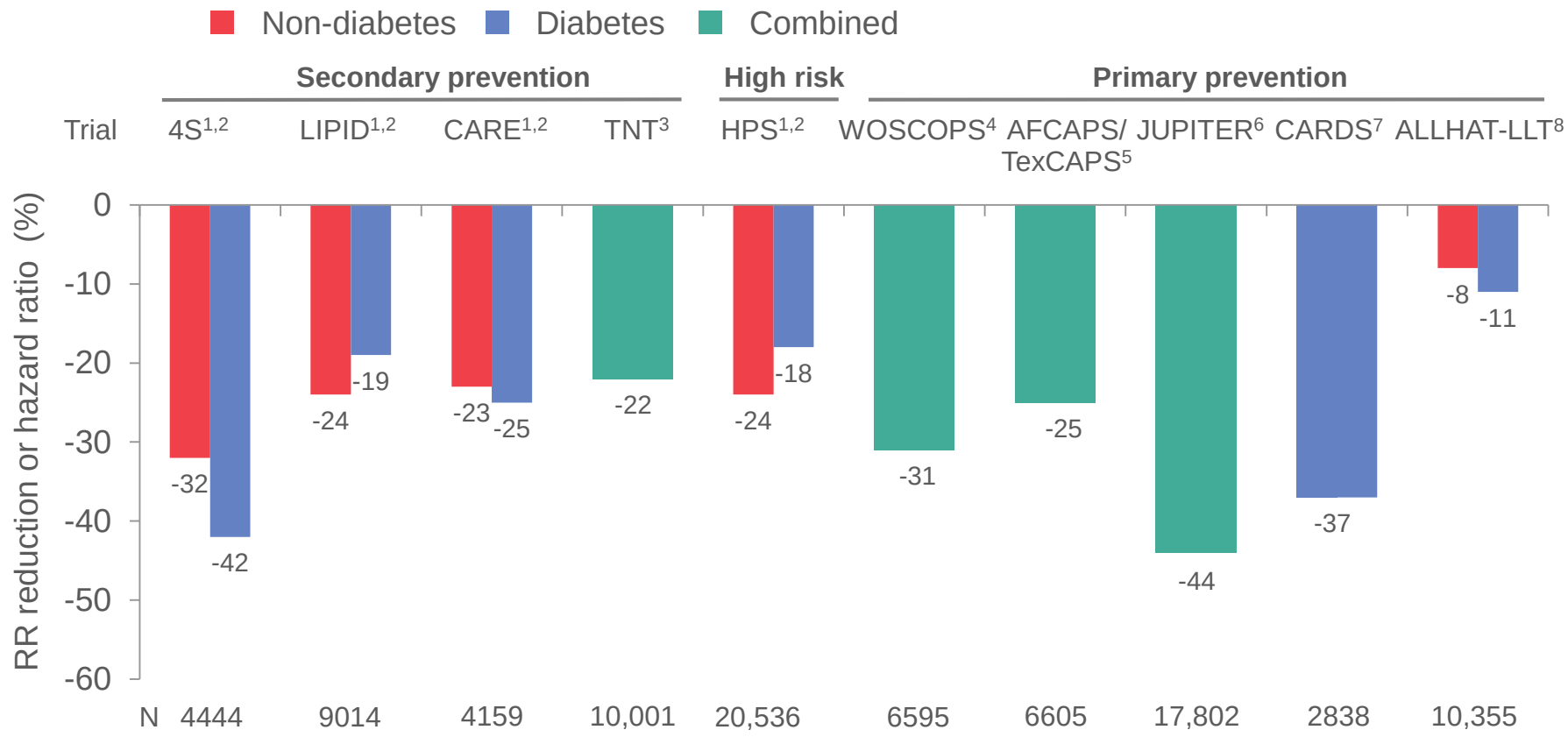

Population of 1 million adults with no previous vascular disease recorded at baseline in 61 prospective observational studies of blood pressure and mortality
Lewington et al. Lancet 2002;360:1903–13.

# 10 mmHg reduction in SBP reduces all-cause mortality, macrovascular and microvascular outcomes in T2D




Meta-analysis of 40 large scale, randomised, controlled trials of BP-lowering treatment including patients with diabetes (n=100,354 participants).
Emdin et al. JAMA 2015;313:603–15.

# Statin therapy has a pivotal role in reducing CV risk





1. Ryden et al. Eur Heart J 2007;28:88–136. 2. Libby. J Am Coll Cardiol 2005;46:1225–8. 3. LaRosa et al. N Engl J Med 2005;352:1425–35.
4. Shepherd et al. N Engl J Med 1995;333:1301–8. 5. Downs et al. JAMA 1998;279:1615–22. 6. Ridker et al. N Engl J Med 2008;359:2195.
7. Colhoun et al. Lancet 2004;364:685–96. 8. ALLHAT-LLT. JAMA 2002;288:2998–3007.

# Conclusions

IMPROVE-IT

**IMPROVE-IT: First trial demonstrating incremental clinical benefit when adding a non-statin agent (ezetimibe) to statin therapy:**

- **YES:** *Non-statin* lowering LDL-C with ezetimibe reduces cardiovascular events
- **YES:** Even Lower is Even Better (achieved mean LDL-C 53 vs. 70 mg/dL at 1 year)
- **YES:** Confirms ezetimibe safety profile

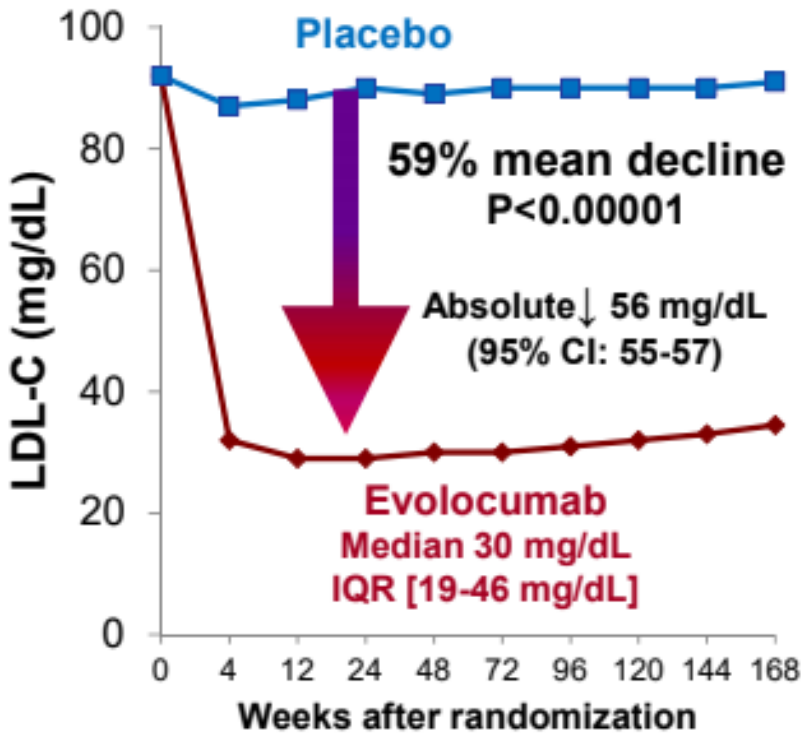
➡ **Reaffirms the LDL hypothesis, that reducing LDL-C prevents cardiovascular events**

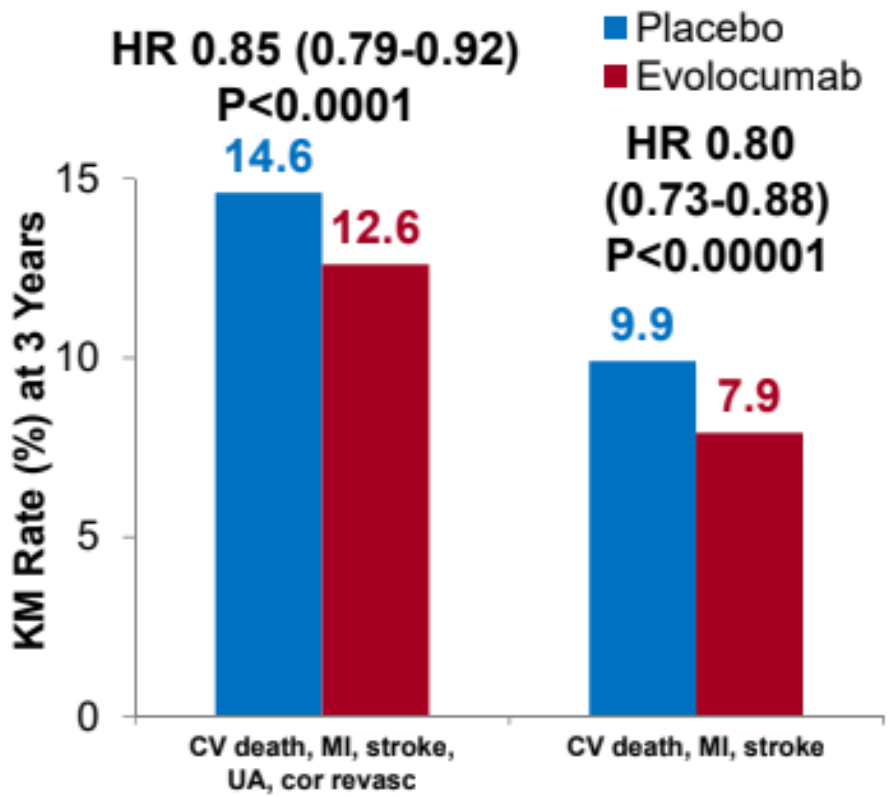
➡ **Results could be considered for future guidelines**

*Cannon CP AHJ 2008;156:826-32; Califf RM NEJM 2009;361:712-7; Blazing MA AHJ 2014;168:205-12*

# Summary of FOURIER

- ↓ LDL-C by 59% (from 92 -> 30 [19, 46] mg/dL)
- ↓ CV outcomes in patients already on statin therapy
- Evolocumab was safe and well-tolerated



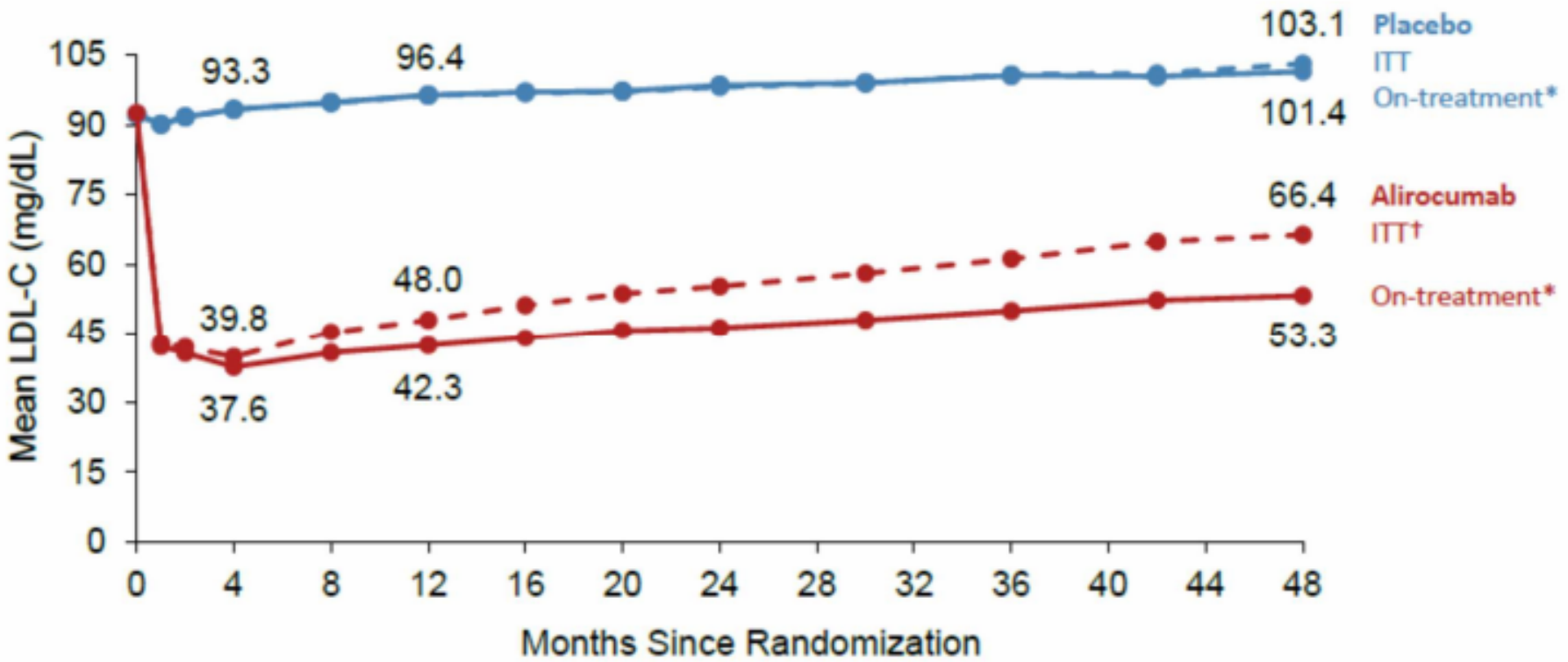






Sabatine MS et al. *New Engl J Med* 2017;376:1713-22

# ODYSSEY Outcomes Trial: LDL-C Reduction with Alirocumab in ACS

**18,924 high-risk patients with an ACS in prior 1-12 months and an LDL-C ≥70 mg/dL on high-intensity statin randomized to alirocumab or placebo for a median of 2.8 years**

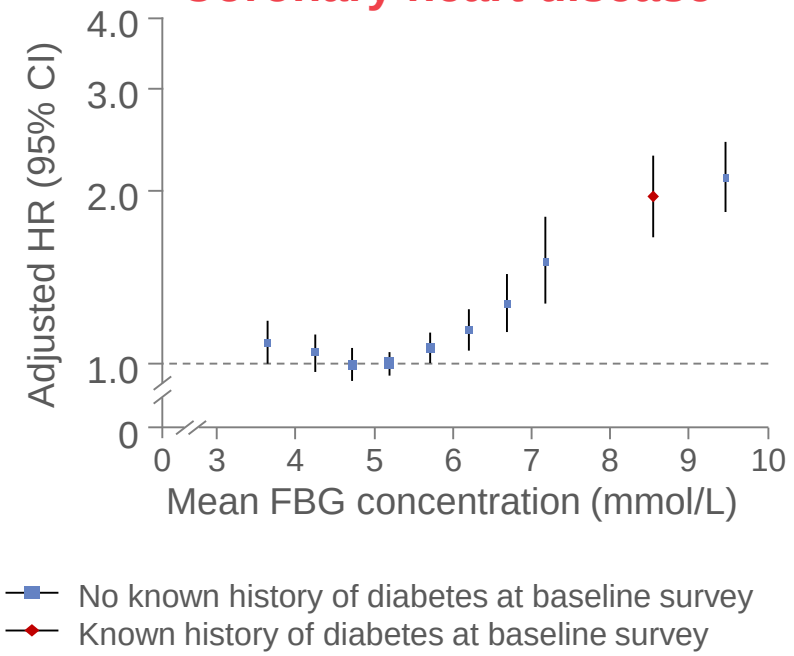



ODYSSEY OUTCOMES

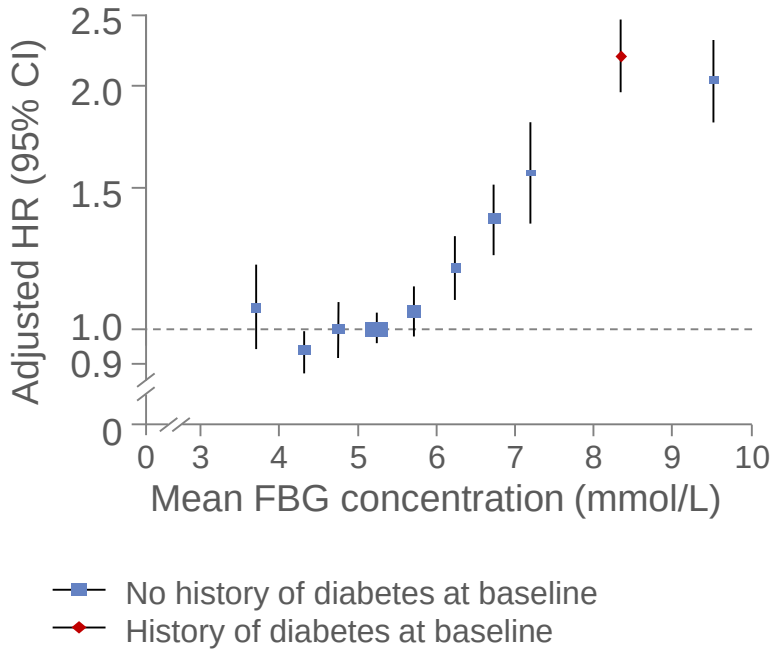
Schwartz GG, NEJM 2018;379:2097-107

# **Hyperglycemia** is an independent risk factor for adverse CV outcomes

## Coronary heart disease[1]



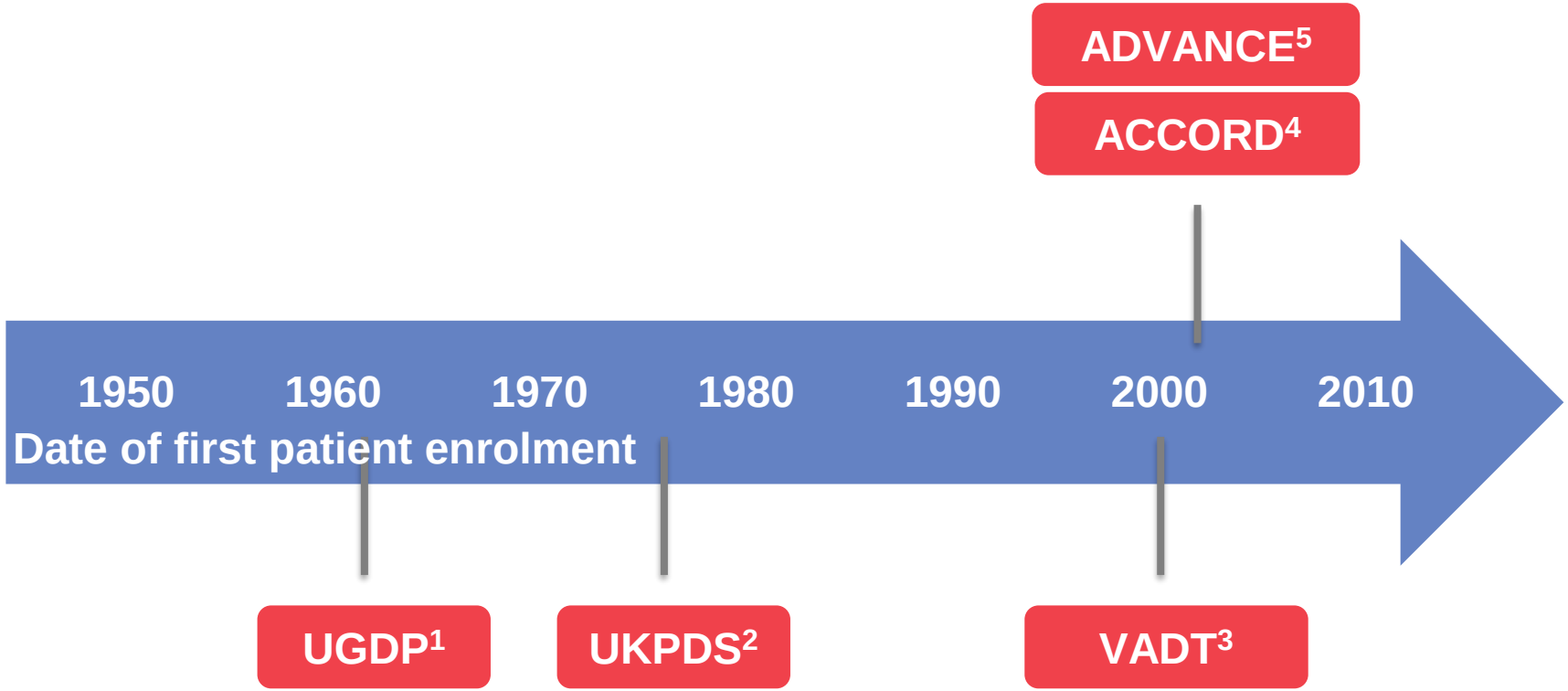

## Vascular death[2]





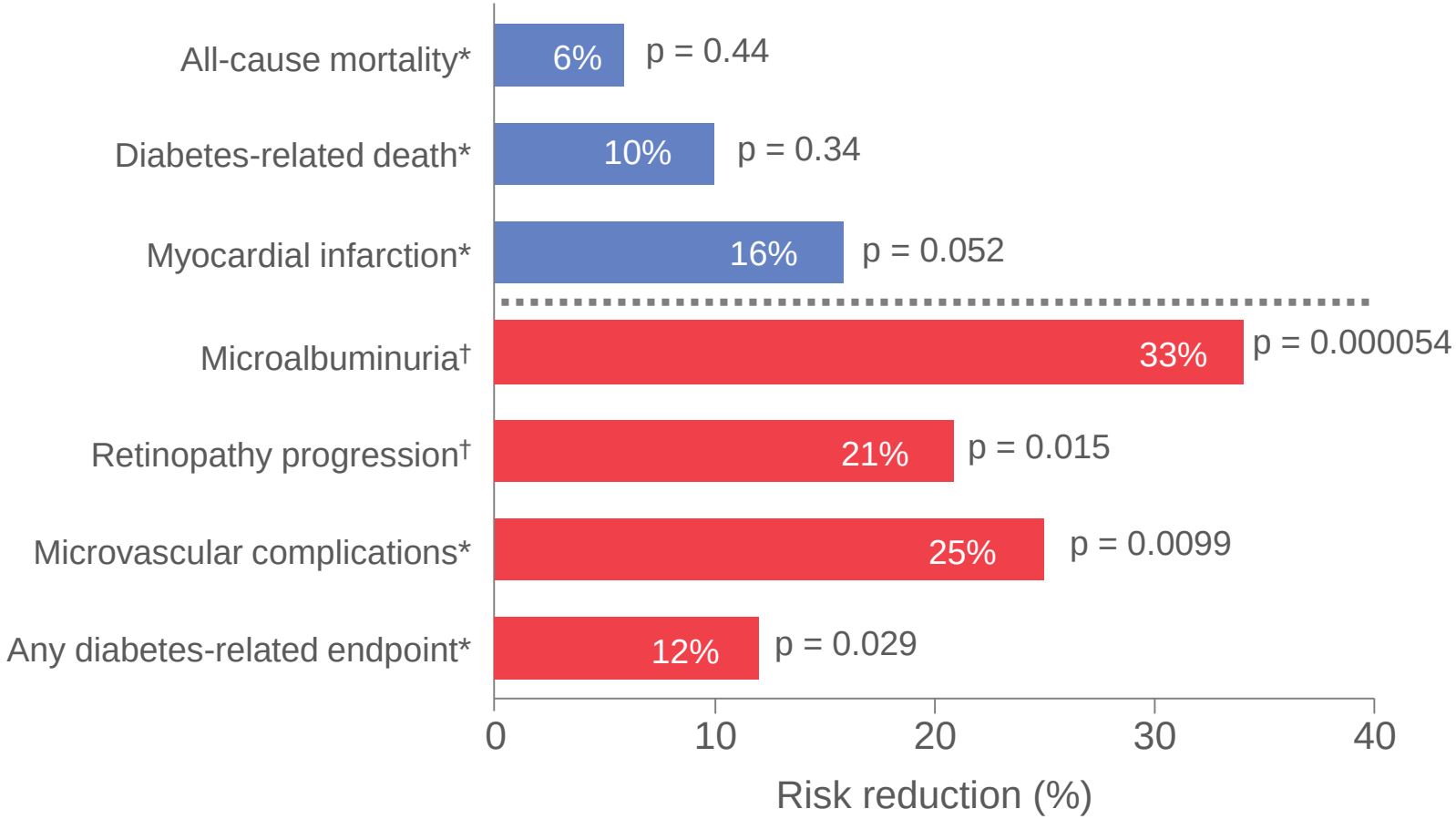
1. Sarwar et al. Lancet 2010;375:2215–22.
2. Seshasai et al. N Engl J Med 2011;364:829–41.

# Major historic T2D CV outcomes trials focused on intensive vs conventional glycemic control




1. Meinert et al. Diabetes 1970;19(suppl):789–830. 2. UKPDS 33. Lancet 1998;352:837–53.
3. Duckworth et al. N Engl J Med 2009;360:129–39. 4. Gerstein et al. N Engl J Med 2008;358:2545–59.
5. Patel et al. N Engl J Med 2008;358:2560–72.

# UKPDS: Intensive glycemic control reduced microvascular but not macrovascular outcomes

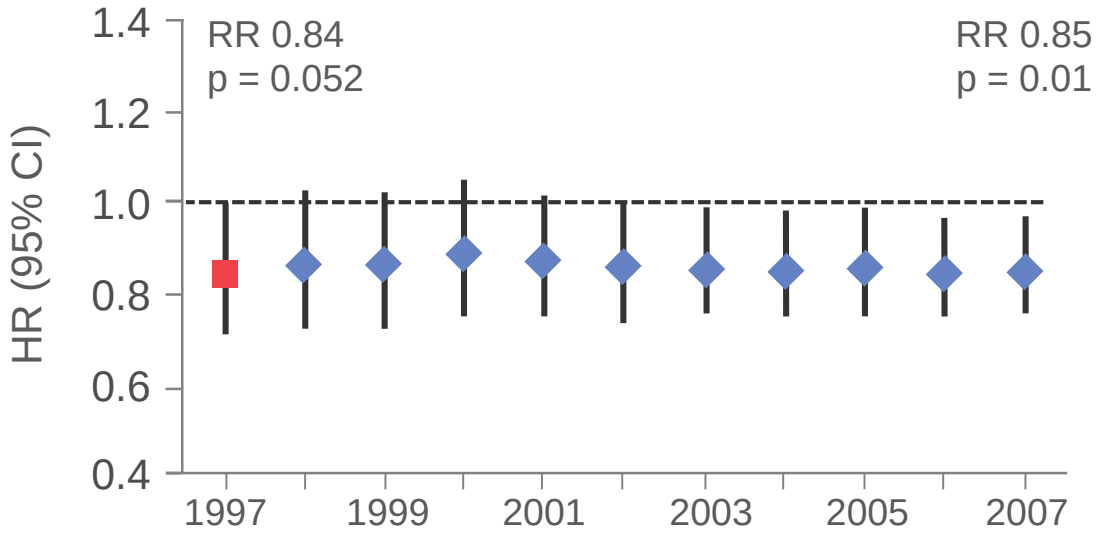



*Median follow-up, 10 years; †assessed as surrogate endpoints; follow-up, 12 years.

UKPDS 33. Lancet 1998;352:837–53.

# UKPDS: Long-term follow-up revealed significant reduction in MI associated with previous intensive glycemic control

## Fatal or non-fatal MI: Intensive treatment

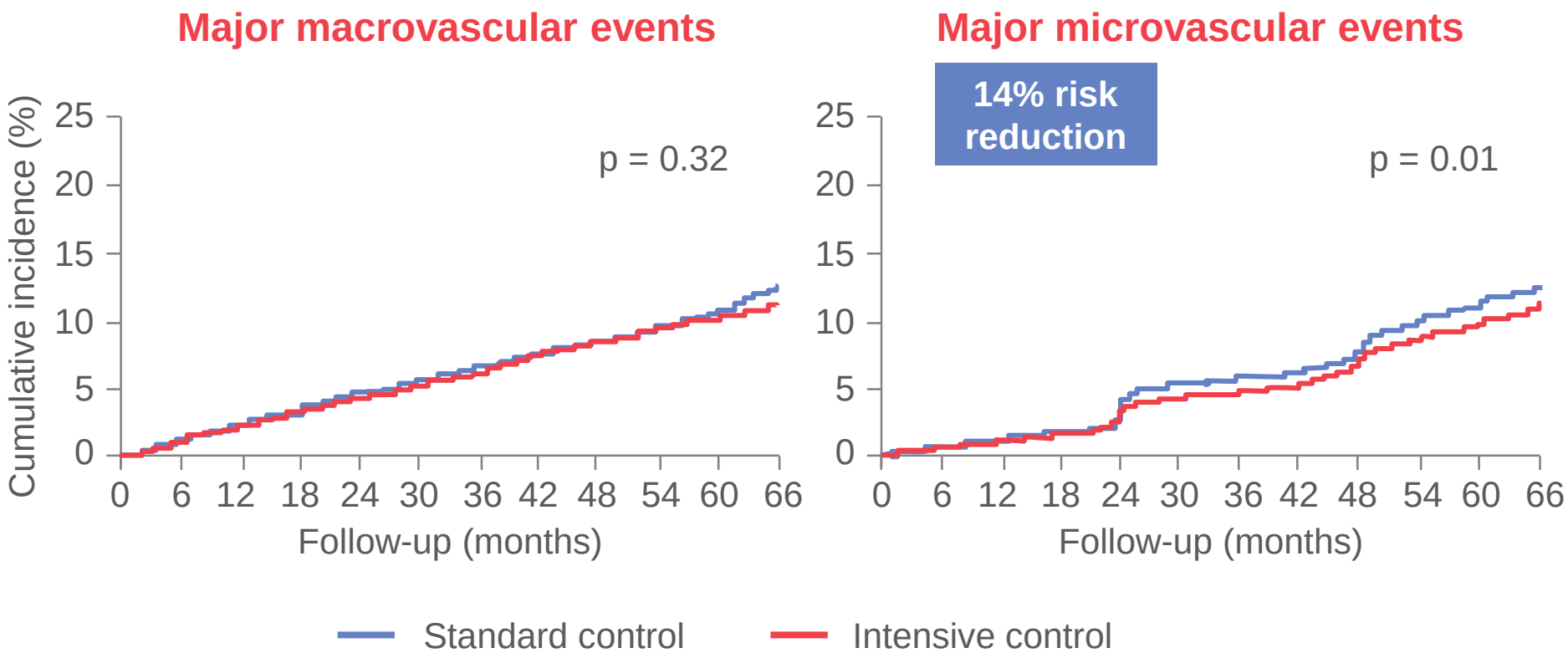



| No. of events | | | | | | |
|---|---|---|---|---|---|---|
| Conventional therapy | 186 | 212 | 239 | 271 | 296 | 319 |
| Sulphonylurea–insulin | 387 | 450 | 513 | 573 | 636 | 678 |

■ Overall values at the end of the study in 1997
◆ Annual values during the 10-year post-trial monitoring period

Holman et al. N Engl J Med 2008;359:1577–89.

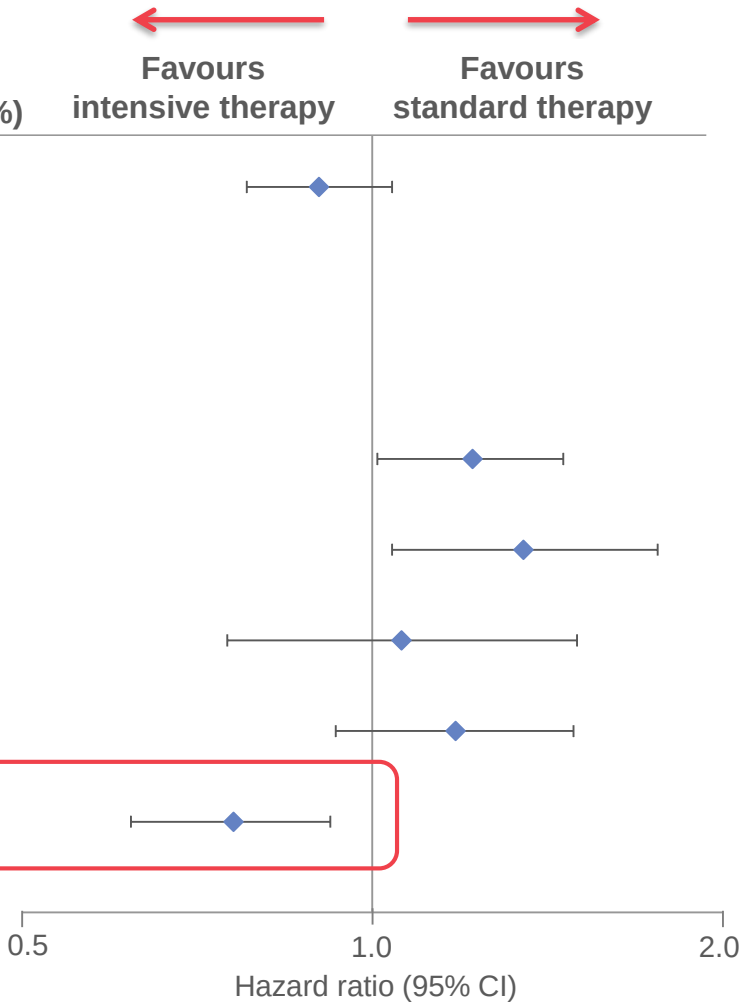
# ADVANCE: intensive glycemic control reduced microvascular but not macrovascular events




Patel et al. N Engl J Med 2008;358:2560–72.

# ACCORD: Intensive glucose-lowering arm terminated early (after 3.5 years) because of higher mortality

| Outcome | Intensive therapy (n = 5128) No. of patients (annual event rate, %) | Standard therapy (n = 5123) No. of patients (annual event rate, %) |
|---|---|---|
| Primary outcome* | 352 (2.11) | 371 (2.29) |
| Secondary outcome | | |
| Death | | |
| Any cause | 257 (1.41) | 203 (1.14) |
| CV cause | 135 (0.79) | 94 (0.56) |
| Non-fatal stroke | 67 (0.39) | 61 (0.37) |
| Fatal or non-fatal CHF | 152 (0.90) | 124 (0.75) |
| Non-fatal MI | 186 (1.11) | 235 (1.45) |

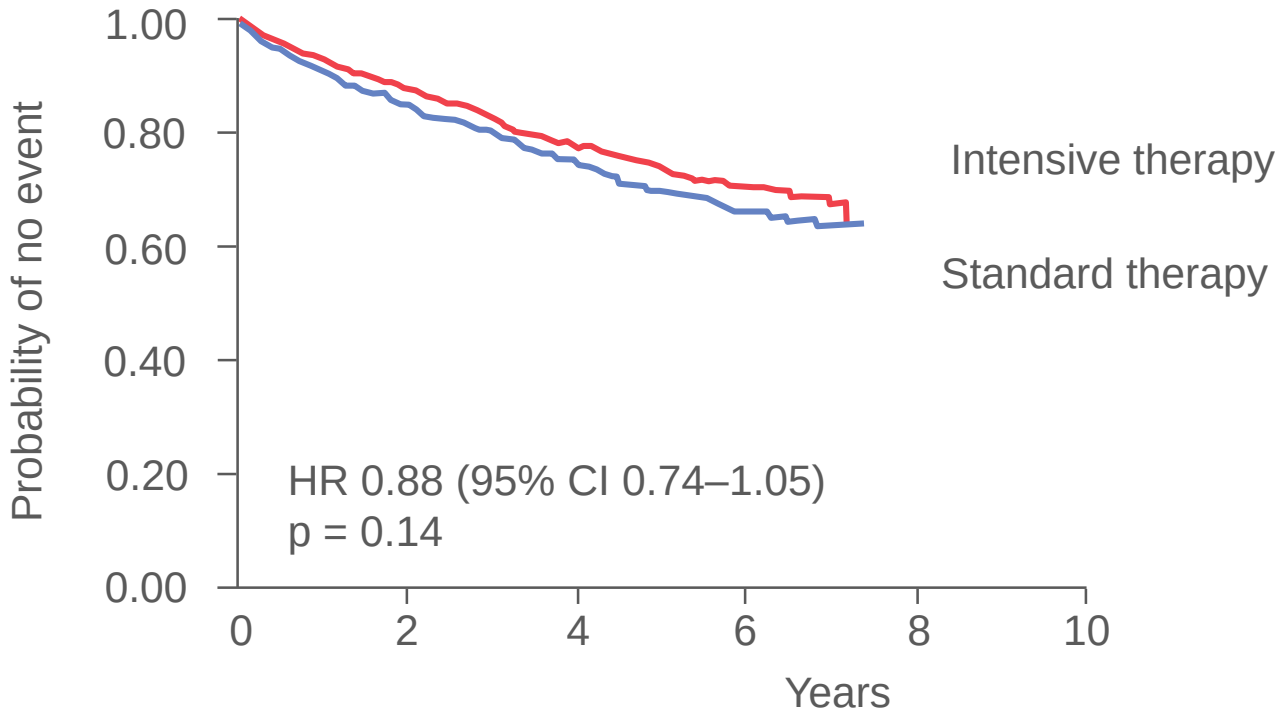



*First occurrence of non-fatal MI or non-fatal stroke or death from CV causes.

Gerstein et al. N Engl J Med 2008;358:2545–59.

# VADT: No difference in primary endpoint between intensive and standard glucose-lowering therapy after 5.6 years

**Primary outcome***

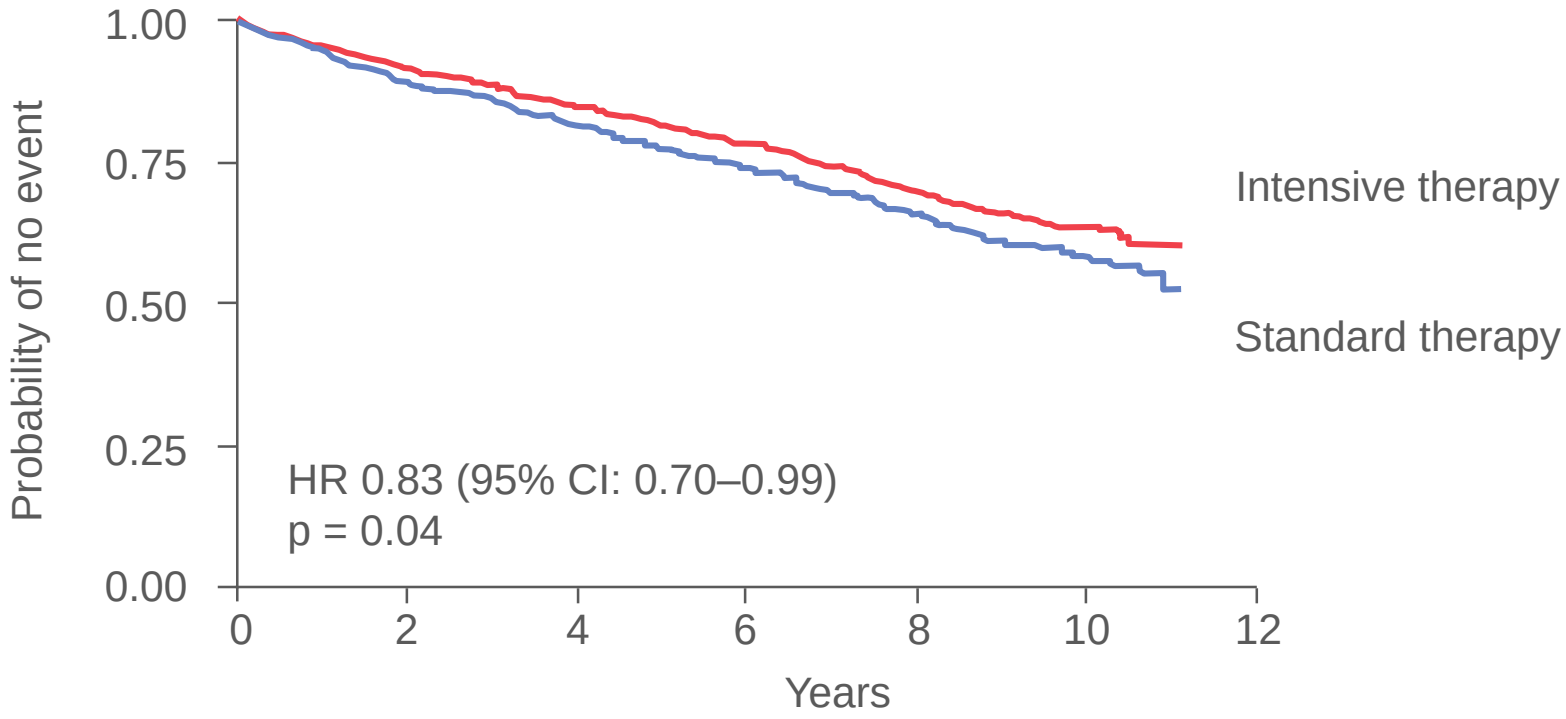



*composite of MI, stroke, CV death, CHF, surgery for vascular disease, inoperable coronary disease, and amputation for ischaemic gangrene

Duckworth et al. N Engl J Med 2009;360:129–39.

# VADT: Significant benefit of intensive vs. standard glucose-lowering therapy in primary endpoint at 10-year follow up

**Primary outcome***




*composite of heart attack, stroke, new or worsening congestive heart failure, amputation for ischemic gangrene, or death from cardiovascular causes

Hayward et al. N Engl J Med 2015;372:2197-206.

# VADT 15 year Follow up- No legacy Effect /no difference in cardiovascular events, total mortality, or quality of life in intensive group vs standard glucose-lowering therapy

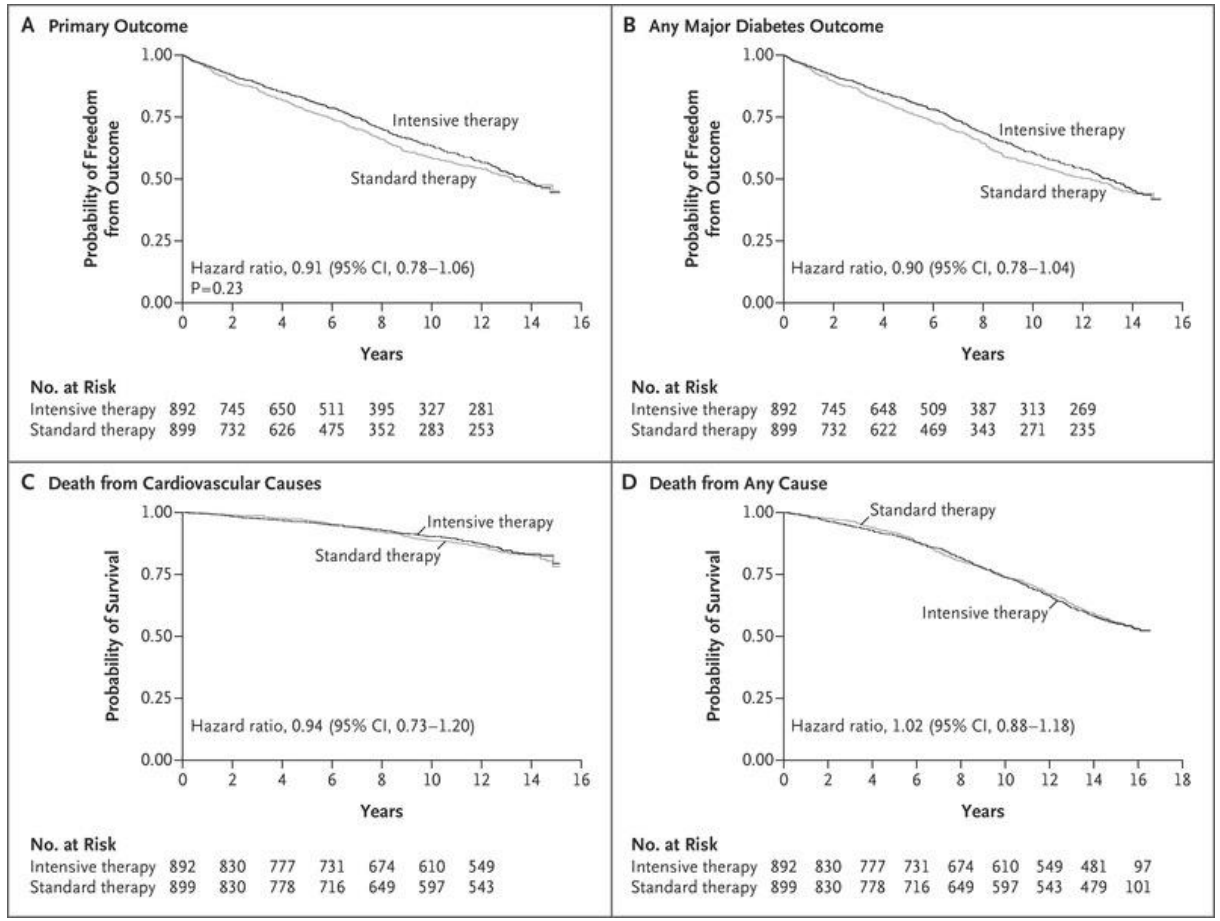



**Figure 2. Kaplan–Meier Curves for the Primary and Secondary Outcomes during the Trial and Follow-up Period.**

The primary outcome was a major cardiovascular event (a composite of myocardial infarction, stroke, new or worsening congestive heart failure, amputation for ischemic gangrene, or death from cardiovascular causes). Secondary outcomes were any major diabetes event (primary composite outcome plus nontraumatic amputation or end-stage renal disease, defined as an estimated glomerular filtration rate [GFR] of <15 during the original trial period or as an estimated GFR of <15 or dialysis or kidney transplantation during the follow-up study), death from cardiovascular causes, and death from any cause.

N Engl J Med 2019;380:2215-24.
DOI: 10.1056/NEJMoa1806802

American Heart Association.

## Glycemic Control, Preexisting Cardiovascular Disease, and Risk of Major Cardiovascular Events in Patients with Type 2 Diabetes Mellitus: Systematic Review With Meta-Analysis of Cardiovascular Outcome Trials and Intensive Glucose Control Trials

Dario Giugliano, MD; Maria Ida Maiorino, MD, PhD; Giuseppe Bellastella, MD; Paolo Chiodini, MSc; Katherine Esposito, MD, PhD

Intensive glycemic control (IGC) has an imperfect role in reducing the cardiovascular complications associated with T2DM.

IGC-was associated with a clear risk of serious hypoglycemia (HR=2.48, 95% CI 1.91-3.21).

There is some evidence favoring a delayed cardiovascular benefit of early IGC, as suggested by the 10-year follow-up of UKPDS.

On the other hand, the attainment of IGC **in long-established and poorly controlled T2DM** was associated with 22% excess cardiovascular mortality, in the intensive arm of the ACCORD trial.

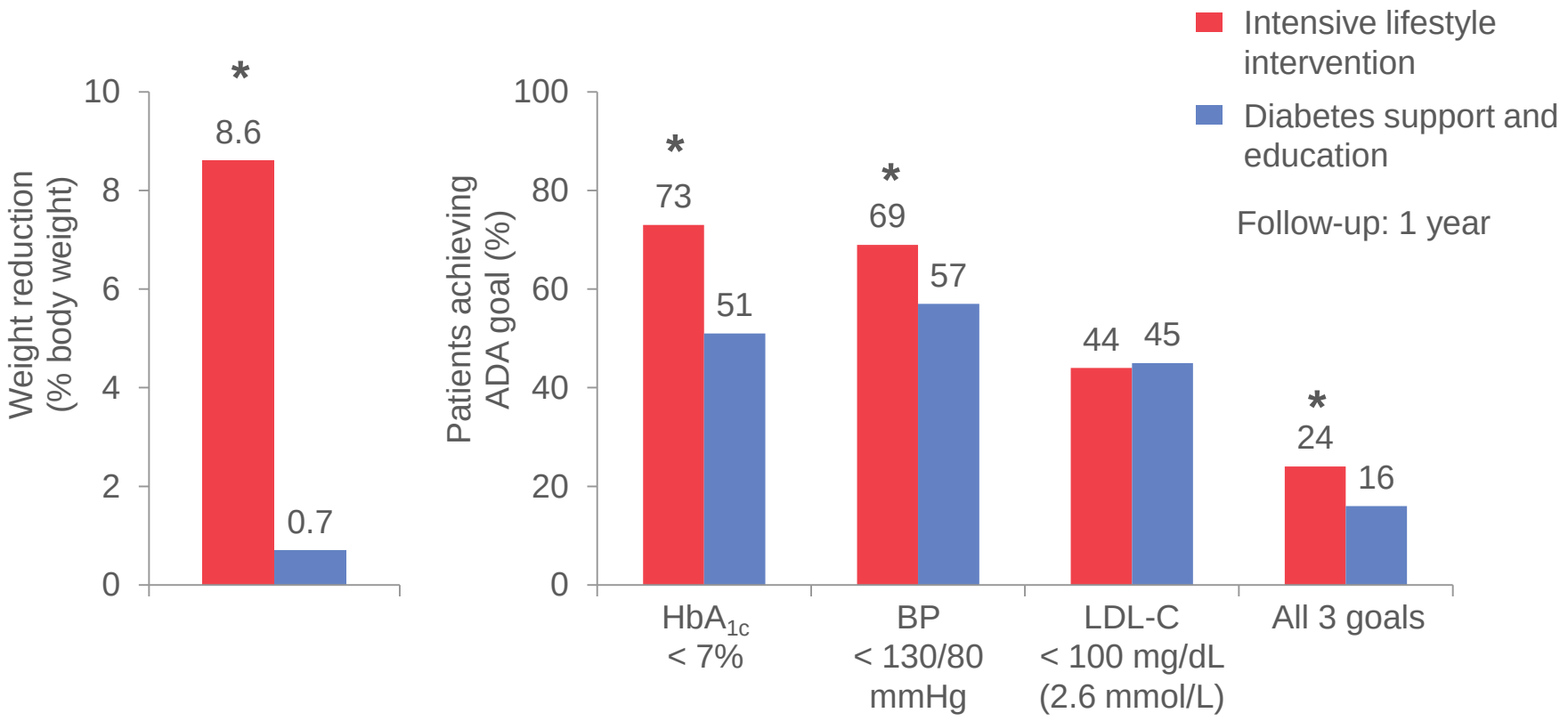
This evidence has generated the concept of "**residual vascular Risk"**

**Table 1.** IGCTs, CVOTs, and Risk of MACE in Patients With T2DM

| Trials | ΔA1C (%) | Hazard Ratio for MACE |
|---|---|---|
| IGCTs | −0.90 (−1.30 to −0.50) | 0.91 (0.84 to 0.99) |
| N=27 049 | | |
| CVOTs | −0.42 (−0.53 to −0.30) | 0.92 (0.87 to 0.96) |
| N=120 765 | | |
| CVOTs | −0.90 | 0.67 (0.49 to 0.93) |
| meta-regression | | |

CVOTs indicates cardiovascular outcome trials; ΔA1C, change in glycated hemoglobin; IGCTs, intensive glucose control trials; MACE, major cardiovascular events; T2DM, type 2 diabetes mellitus.

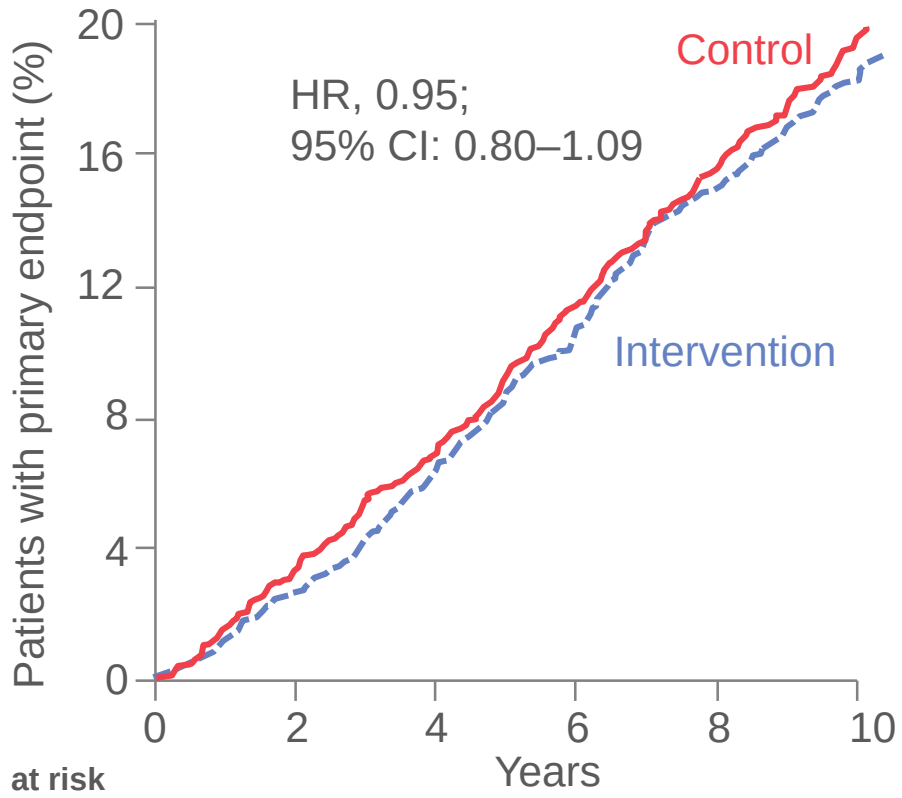
# Intensive lifestyle intervention, focused on weight loss, improved CV risk factors in T2D in the short term




*p < 0.001 vs diabetes support and education.

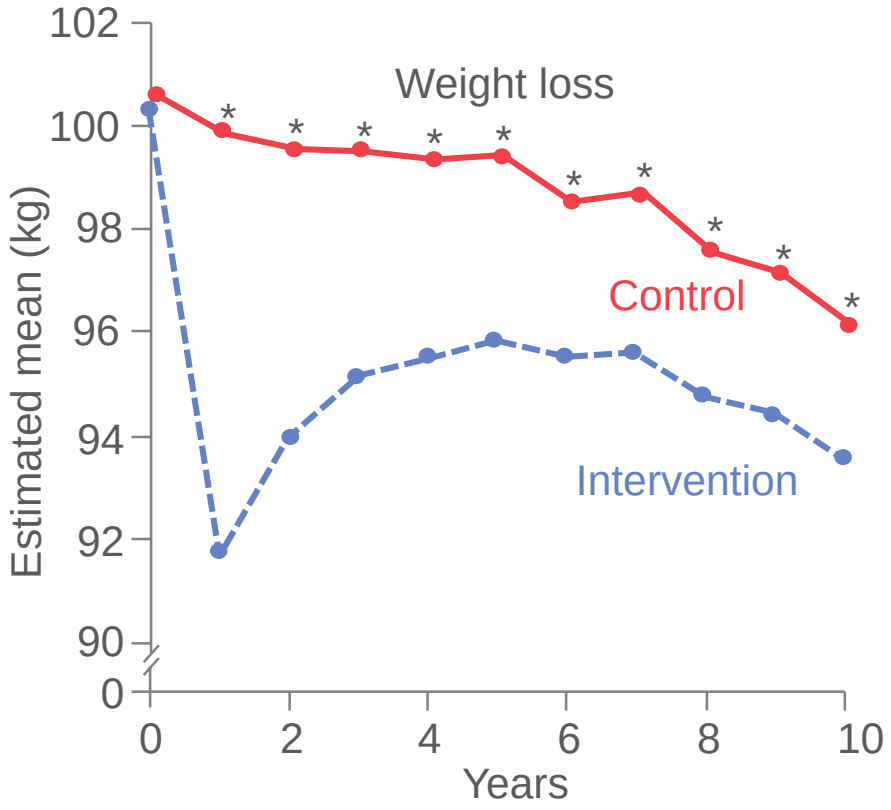
Look AHEAD Research Group. Diabetes Care 2007;30:1374–83.

# Intensive lifestyle intervention, focused on weight loss, did not improve CV risk in T2D in the long term




**No. at risk**

| | | | | | | |
|---|---|---|---|---|---|---|
| Control | 2575 | 2425 | 2296 | 2156 | 2019 | 688 |
| Intervention | 2570 | 2447 | 2326 | 2192 | 2049 | 505 |



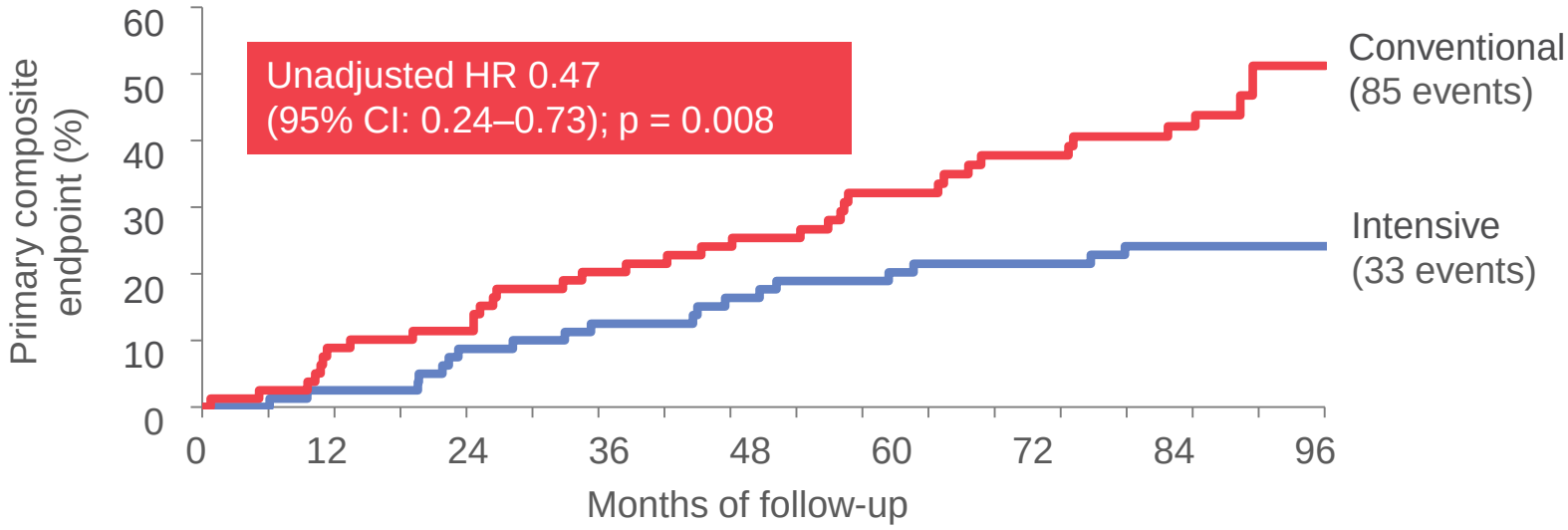

Main effect: -4 (95% CI: -5 to -3)

* $p < 0.001$

Endpoint: Composite of CV death, non-fatal MI, non-fatal stroke and hospitalisation for angina.

Look AHEAD Research Group. N Engl J Med 2013;369:145–54.

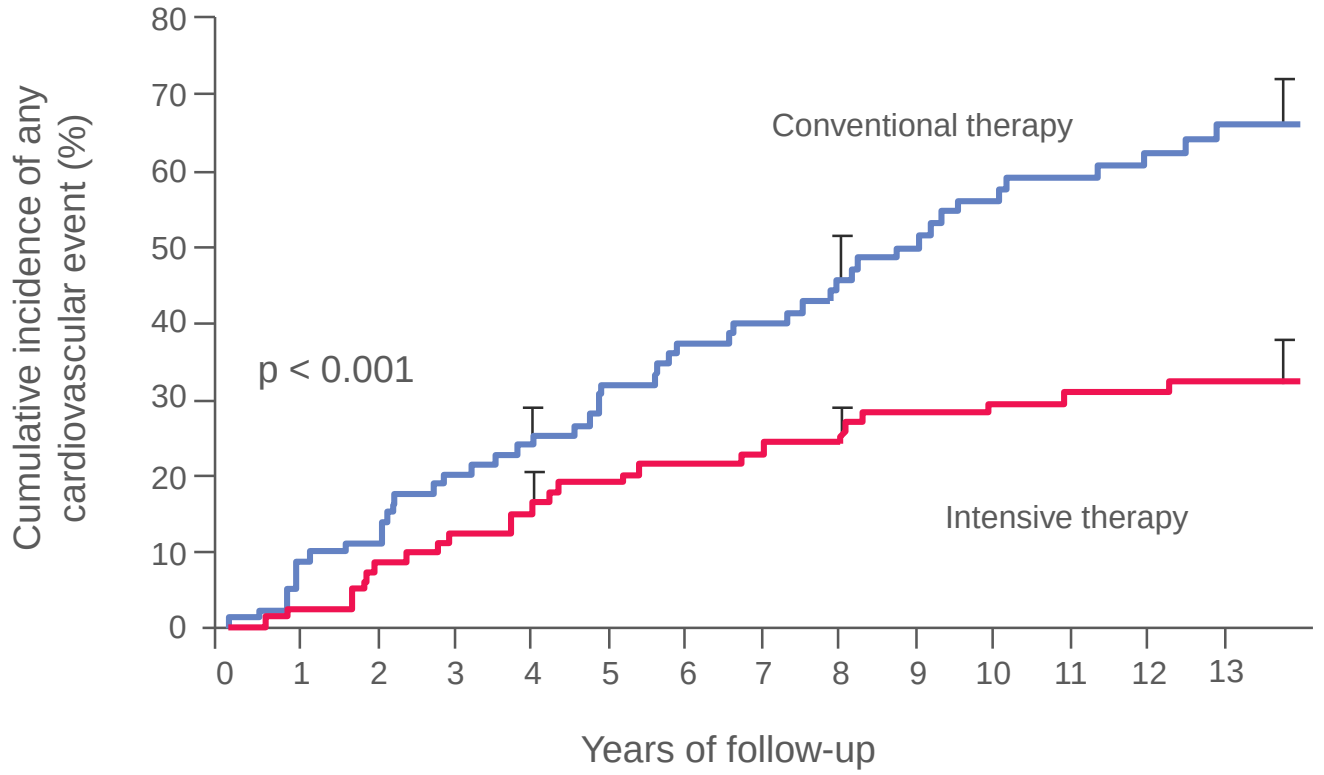
# Steno-2: Intensive multifactorial control of CV risk factors reduces CV risk in patients with T2D and microalbuminuria




Composite endpoint: CV death, non-fatal MI, non-fatal stroke revascularisation and amputation.

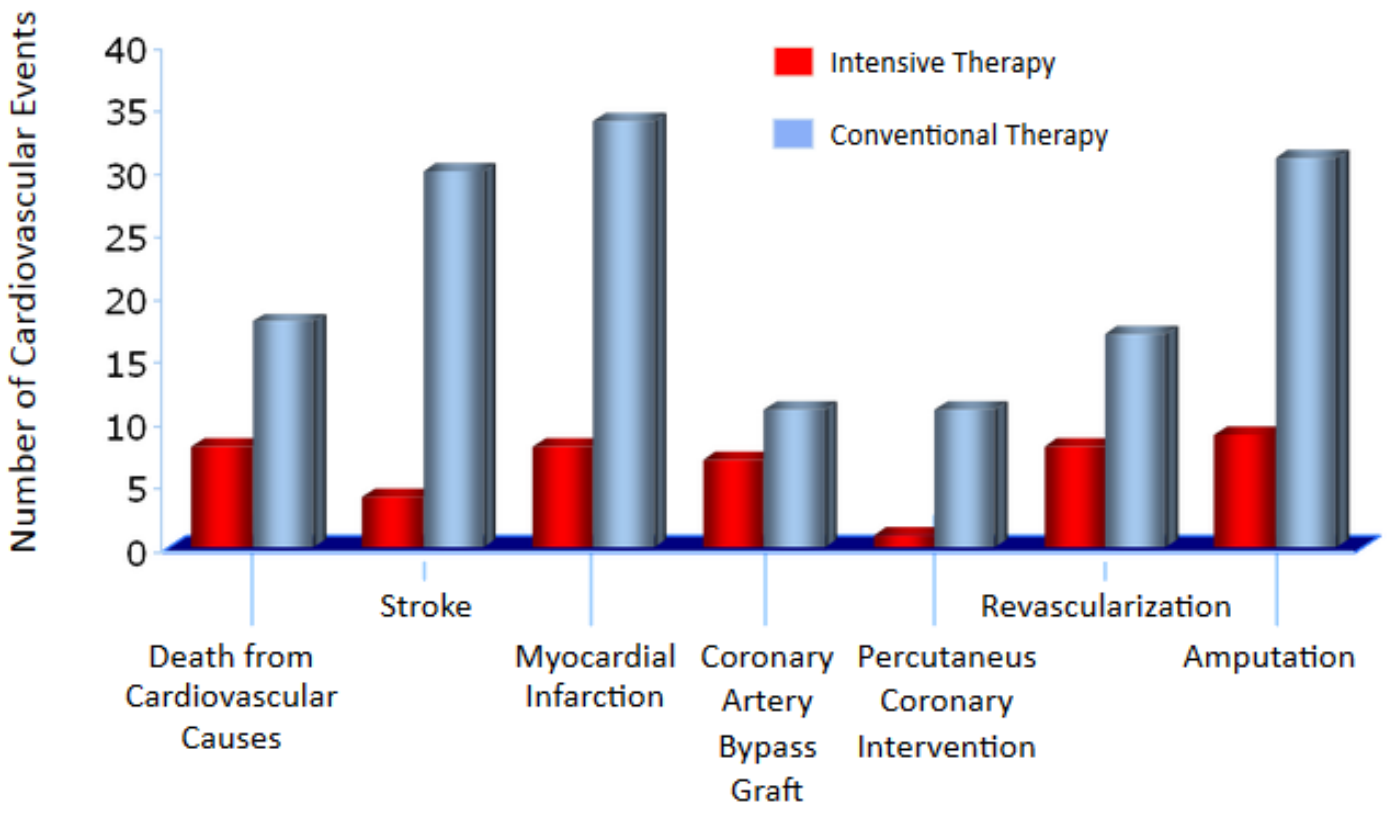
Gaede et al. N Engl J Med 2003;348:383–93.

# Steno-2: Intensive multifactorial control of CV risk factors continues to reduce CV risk over long-term follow-up




Gaede et al. N Engl J Med 2008;358:580–91.

# STENO-2: Dramatic ↓ in Cardiovascular Events




Gaede P, et al. N Engl J Med 2003;358:580–591

# A multifactorial approach is recommended for control of CV risk in patients with T2D

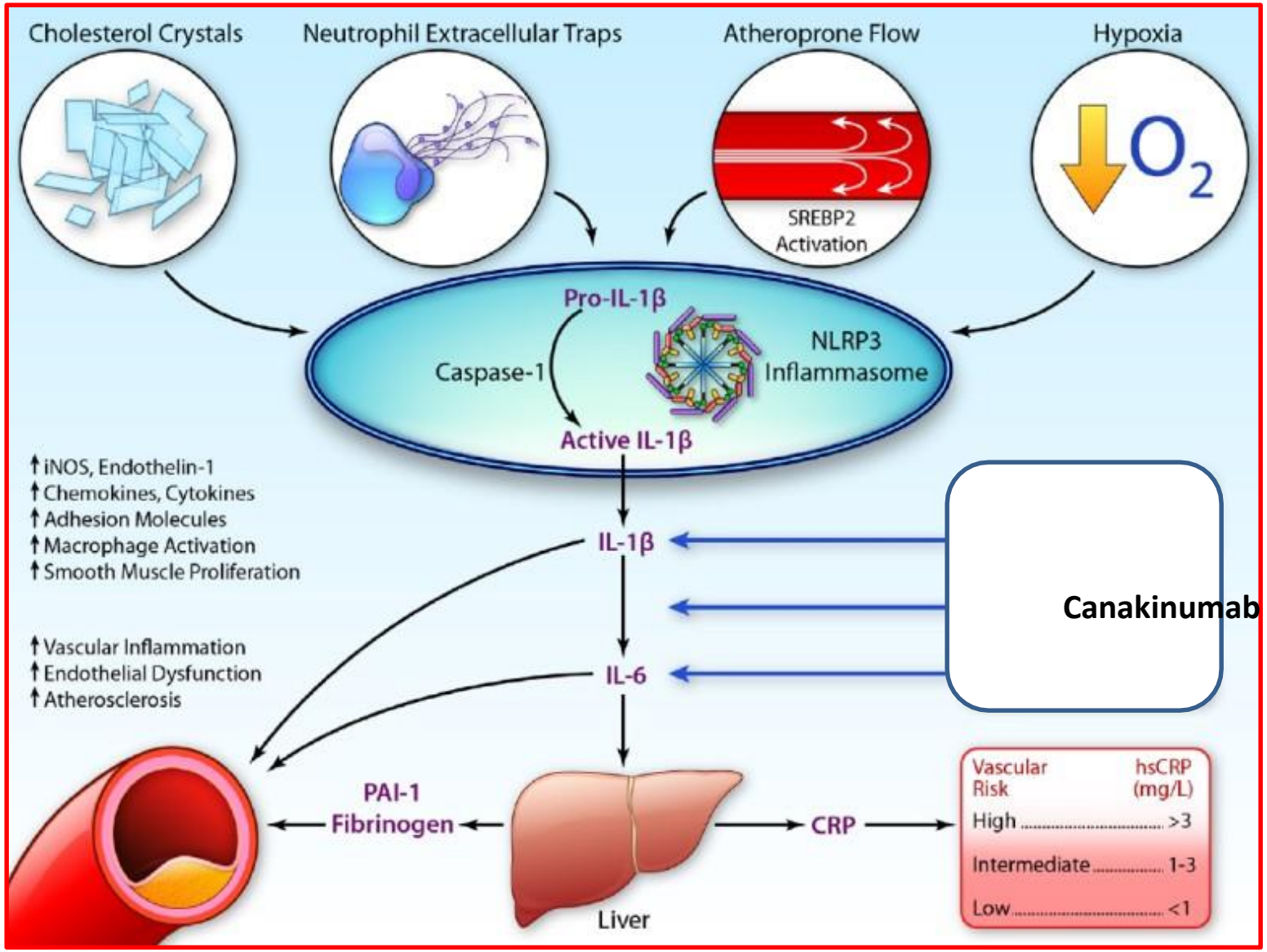
| Risk factor | Goal[1] | Recommendation[1] |
|---|---|---|
| Raised blood pressure | < 140/90 mmHg* | ACE inhibitor or ARB |
| Abnormal blood lipids | LDL cholesterol < 100 mg/dL (< 2.6 mmol/L) | Lifestyle modification and statin therapy |
| Tobacco use | Smoking cessation | Counselling and pharmacological therapy |
| Hyperglycaemia | $HbA_{1c}$ < 7%† (< 53 mmol/mol) | Lifestyle modification and then metformin as initial monotherapy |
| Raised CV risk: 10-year risk > 10% | Antiplatelet use | ASA (75–162 mg/day)‡ |

- American[1] and European[2] recommendations on CV risk factor management are similar

*Lower targets (e.g., <130/80 mmHg) may be appropriate for certain individuals, such as younger patients, if they can be achieved without undue treatment burden. †More or less stringent goals may be appropriate for individuals. ‡Not recommended for those at low CV risk.

1. American Diabetes Association. Diabetes Care 2015;38(suppl. 1):S1–S94. 2. Rydén et al. Eur Heart J 2013;34:3035–87.

# From CRP to IL-6 to IL-1: Moving Upstream to Identify Novel Targets for Atheroprotection

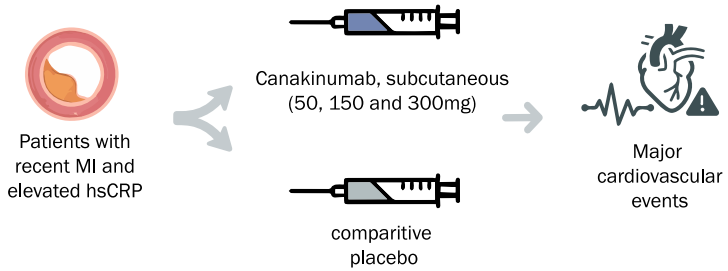



Ridker PM. Circ Res 2016;118:145-156.

# CANTOS: Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease

Randomized, double-blind, placebo-controlled, event-driven phase 3 trial

Objective: To assess if canakinumab (Ab against interleukin-1β) reduce the recurrence CV events in patients with a history of MI and hs-CRP ≥ 2mg/L.




**10,061** patients (age ≥ 18) with history of MI in prior 30 days and hsCRP of ≥2 mg/L. > (results only for 150 mg)


**Primary Outcome**

3.86 — Myocardial infarction, stroke, or CV death (per 100 person-yr) — 4.5

HR 0.85; 95% CI 0.74–0.98; P=0.02

**Secondary Outcome**

4.29 — MI, stroke, hospitalization for UA that led to unplanned revascularization, or CV death — 5.13

HR 0.83; 95% CI 0.73–0.95; P=0.005

4.77 — MI, stroke, or death from any cause — 5.56

HR 0.85; 95% CI 0.75–0.96; P=0.01

Antiinflammatory therapy targeting the interleukin-1β innate immunity pathway with canakinumab at a dose of 150 mg every 3 months led to a significantly lower rate of recurrent cardiovascular events than placebo.

Ridker PM, et al. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. *NEJM 2017. 377(12):1119-1131.*

Visualmed

## ACZ885 (canakinumab) reduces the risk of MACE by 15% in overall studied population

**150mg canakinumab**
administered as a
*quarterly injection*


15% Reduction in risk of MACE incl. positive trend in CV death

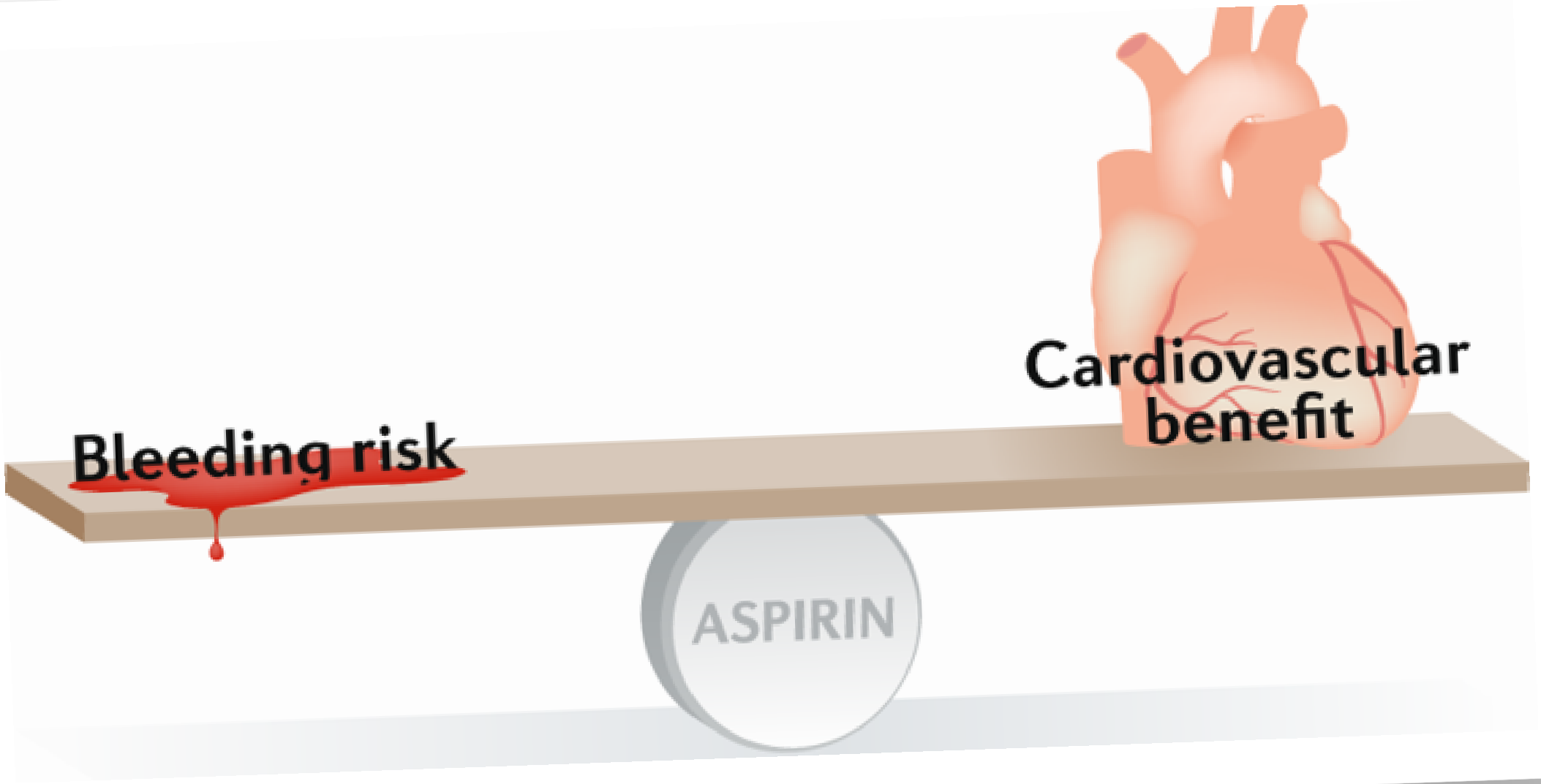
24% Reduction in risk of MI

36% Reduction in urgent revascularization procedures

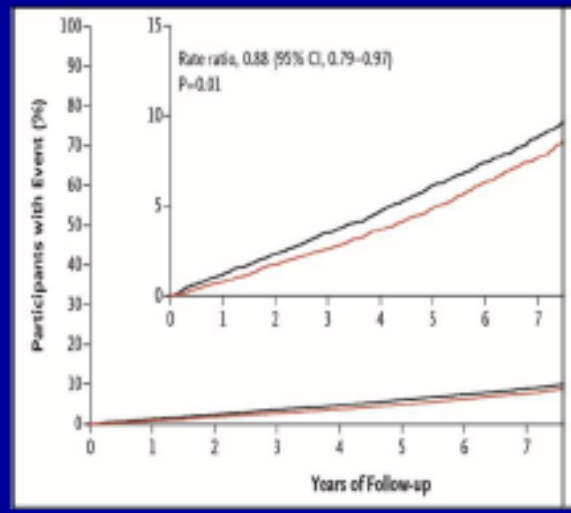
Ridker et al. NEJM 2017; DOI: 10.1056/NEJMoa1707914 MACE: CANTOS primary endpoint a composite of MI, Stroke and CV death MI: Myocardial infarction, component of primary endpoint
Urgent revascularization procedures is a component of a statistically significant key secondary endpoint

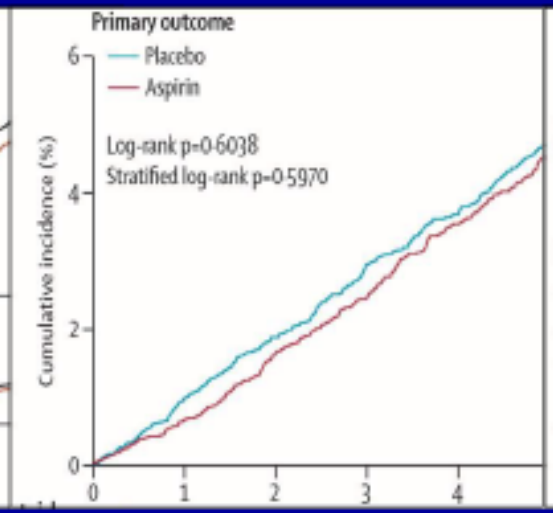
Market Realist

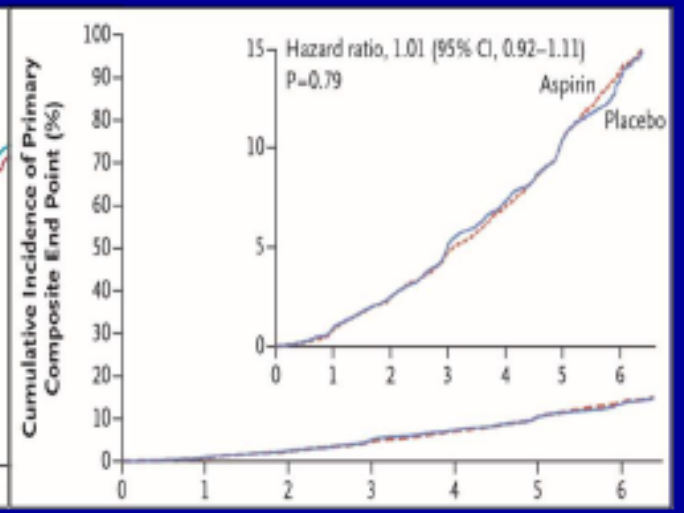
Source: Novartis Investor Presentation


Bleeding risk
Cardiovascular benefit
ASPIRIN

# New Trials: Aspirin for Primary Prevention




| ASCEND | ARRIVE | ASPREE, 2018 |
|---|---|---|
| 15,480 with diabetes and no evident CVD. | 12,546 with Moderate CVD risk w/o DM or high risk of GI bleeding | 19,114 adults > 70 yr with no cardiovascular disease. |
| 100 mg of aspirin vs. placebo | 100 mg aspirin vs. placebo | 100 mg aspirin vs. placebo |
| Reduction in vascular events was counterbalanced by bleeding | No difference in a composite of CV death, MI, UA, CVA, or TIA. With increased risk of bleeding | Aspirin did not prolong disability free survival but increased major hemorrhage |

N Engl J Med. 2018;379:1529-39

Lancet. 2018;392:1036-46

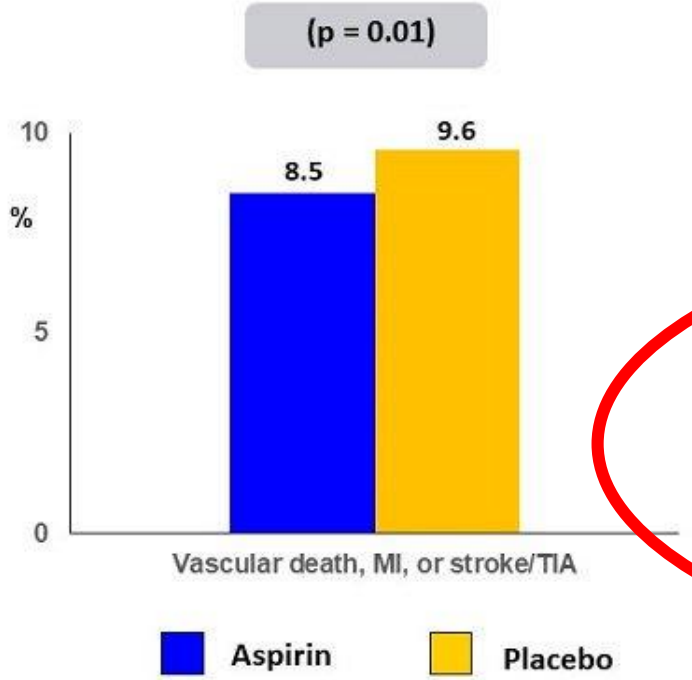
N Engl J Med 2018; 379:1509-1518

Slide Courtesy: Dr. Abdulhamied Al Faddagh

# ASCEND Aspirin

#ESCCongress

**Trial design:** Patients with diabetes and no known CVD were randomized to aspirin 100 mg daily (n = 7,740) vs. placebo (n = 7,740).




**RESULTS**

- Major adverse cardiovascular events (vascular death, MI, or stroke/TIA): 8.5% of the aspirin group vs. 9.6% of the placebo group (p = 0.01)
- Major bleeding (intracranial hemorrhage, GI hemorrhage, or sight-threatening eye bleeding): 4.1% of the aspirin group vs. 3.2% of the placebo group (p = 0.003)

**CONCLUSIONS**

- Among diabetic patients with no known CVD, aspirin was associated with a 12% relative reduction in major adverse cardiovascular events compared with placebo
- Aspirin was associated with a 29% relative increase in major bleeding events compared with placebo

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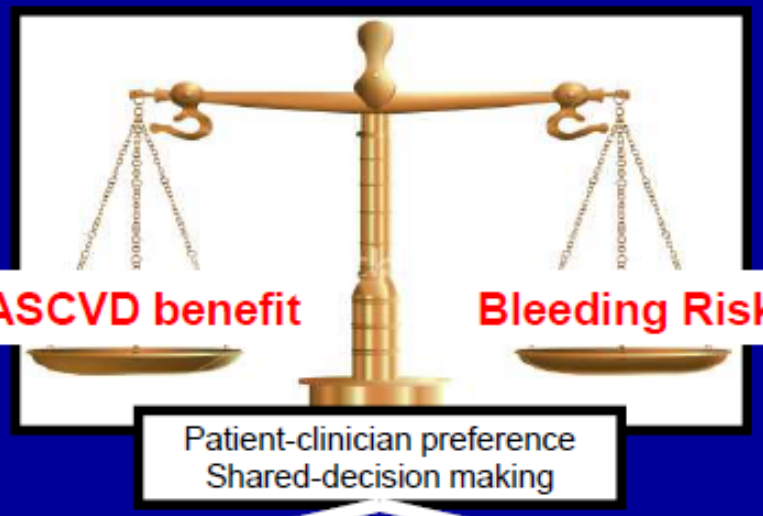
ASCEND Study Collaborative Group. N Engl J Med 2018;Aug 26.[Epub]

# Prescribing based on totality of evidence

Elevated PCE
+ CAC
+ risk enhancing factors
Inability to achieve lipid or BP targets




Previous GIB or PUD
Bleeding from other sites
Age >70 years
Thrombocytopenia
Coagulopathy
CKD
Use of NSAIDs, steroids,
DOAC, and warfarin

Low dose ASA
(Class IIb)

Avoid ASA (Class III)
Focus on other risk factors

Slide Courtesy: Dr. Abdulhamied Al Faddagh

# 2019 ACC/AHA Guidelines

| Recommendations for Aspirin Use<br>Referenced studies that support recommendations are summarized in Online Data Supplements 17 and 18. | | |
|---|---|---|
| **COR** | **LOE** | **Recommendations** |
| IIb | A | 1. Low-dose aspirin (75-100 mg orally daily) might be considered for the primary prevention of ASCVD among select adults 40 to 70 years of age who are at higher ASCVD risk but not at increased bleeding risk (S4.6-1–S4.6-8). |
| III: Harm | C-LD | 3. Low-dose aspirin (75-100 mg orally daily) should not be administered for the primary prevention of ASCVD among adults of any age who are at increased risk of bleeding (S4.6-10). |

*J Am Coll Cardiol*. 2019 Mar 17; *Circulation*. 2019 Mar 17

# Summary

- T2D is a major independent risk factor for CVD[1]
- Endothelial dysfunction and progression of atherosclerosis is accelerated in patients with T2D[2,3]
- Patients with T2D are at significantly increased CV risk[4]
- Additional risk factors associated with T2D[4-9]
  - Hypertension, dyslipidaemia, visceral adiposity, hyperglycaemia and renal dysfunction are all associated with further increasing CV risk

1. World Health Organization. http://www.who.int/diabetes/action_online/basics/en/index3.html. 2. Libby P. Circulation. 2001;104:365-372. 3. Zeadin, et al. Can J Diabetes. 2013;37:345e350. 4. Sarwar et al. Lancet. 2010;375(9733):2215–2222. 5. Seshasai et al. N Engl J Med. 2011;364:829–841. 6. Lewington S, et al. Lancet. 2002;360:1903–1913. 7. Grundy et al. Arteriosclerosis, Thrombosis, and Vascular Biology. 2004;24:e149-e161. 8. Taylor AJ. European Heart Journal. Supplement 2006;8:F74–80. 9. Balkau B, et al. Circulation. 2007;116:1942–1951.


Thanks for your Attention!

# References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