



## Update Management of CVD in DM



KO KO

DEPARTMENT OF DIABETES AND ENDOCRINOLOGY

UM2

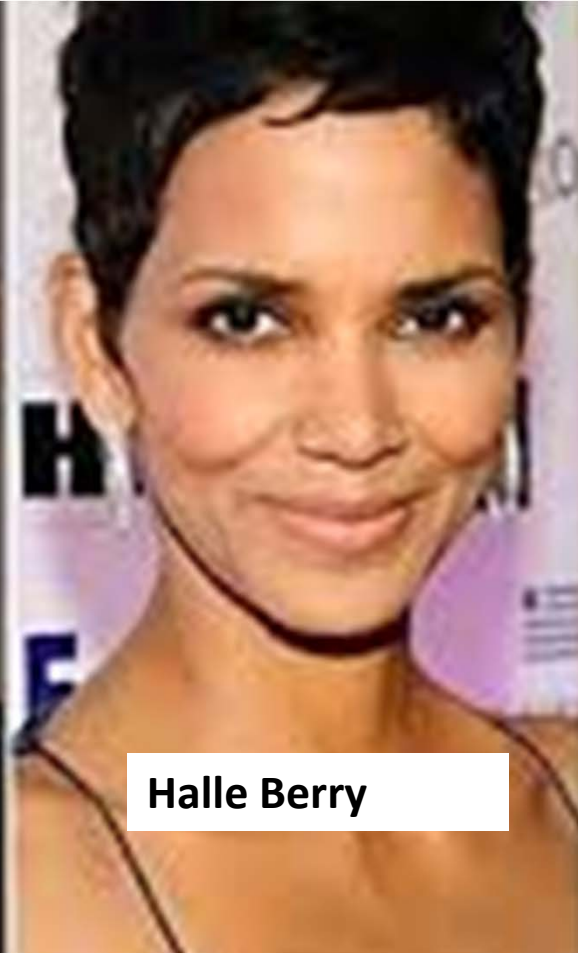
EDUCATIONAL GRANT BY ZIFAM

MMA 2018( 21.1.18)

# Celebrities with DM



**Tom Hanks**



**Halle Berry**



**Celebrity chef Paula Deen**

# DIABETES AND HEART DISEASE



## Diabetes & Heart Disease By The #s

U.S. DIABETES PATIENTS HAVE:



**2-3x**

increased risk for  
heart disease



**TYPE 2**

diabetes often goes  
undiagnosed for  
many years



**280,000**

heart attacks  
annually



**INCREASED**

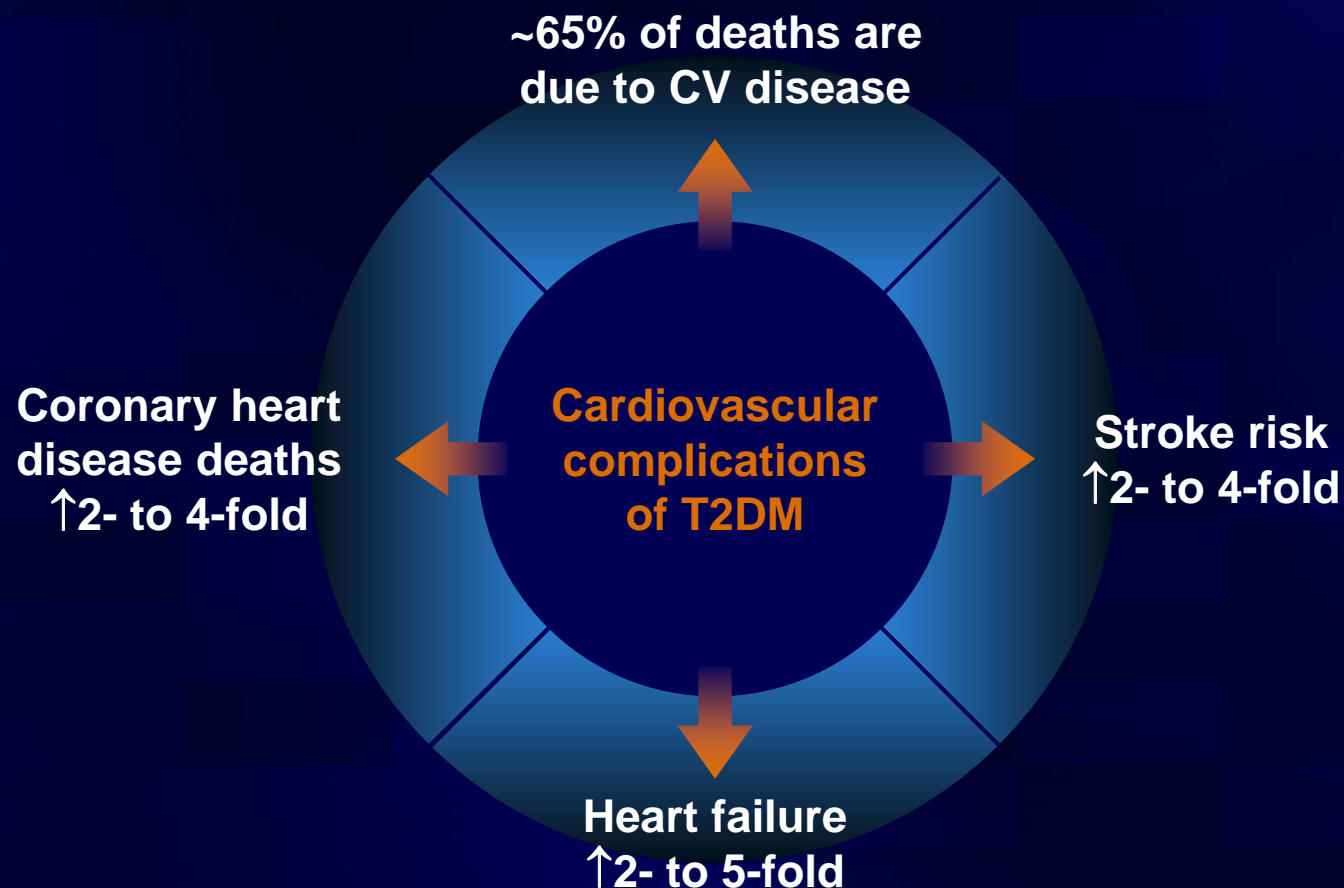
risk for microvascular  
and macrovascular  
complications



**60%**

chance of dying from  
heart disease

# 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](http://www.cdc.gov).



# Type 2 diabetes: a vascular problem

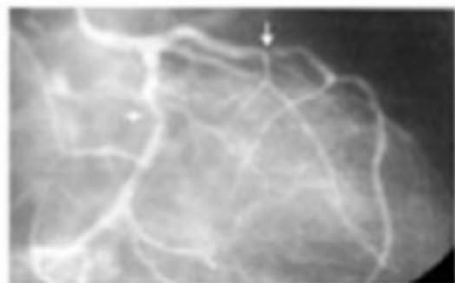
- Life expectancy is reduced by 10 years
- 75% of patients with type 2 diabetes die of CVD
- 75% of hospital admissions are for CVD
- Diabetic: Non diabetic

Acute MI 3:1, Non-fatal CHD 5:1,

CVA 4:1

## CHD

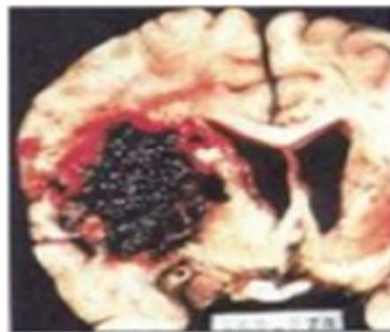
ANGIOGRAM OF PARTIALLY BLOCKED CORONARY ARTERIES  
(Source: Elżbieta Karłowicz, Katowice, Poland)



## PVD



## Stroke



## Cardiovascular Reduction

- GLP1
- SGLT2 inhibitor

## Cardiovascular safe

Metformin

DPP4 inhibitors

Pioglitazone

# Cardiac friendly DM drugs

- GLP1 or DPP4 inhibitors

+

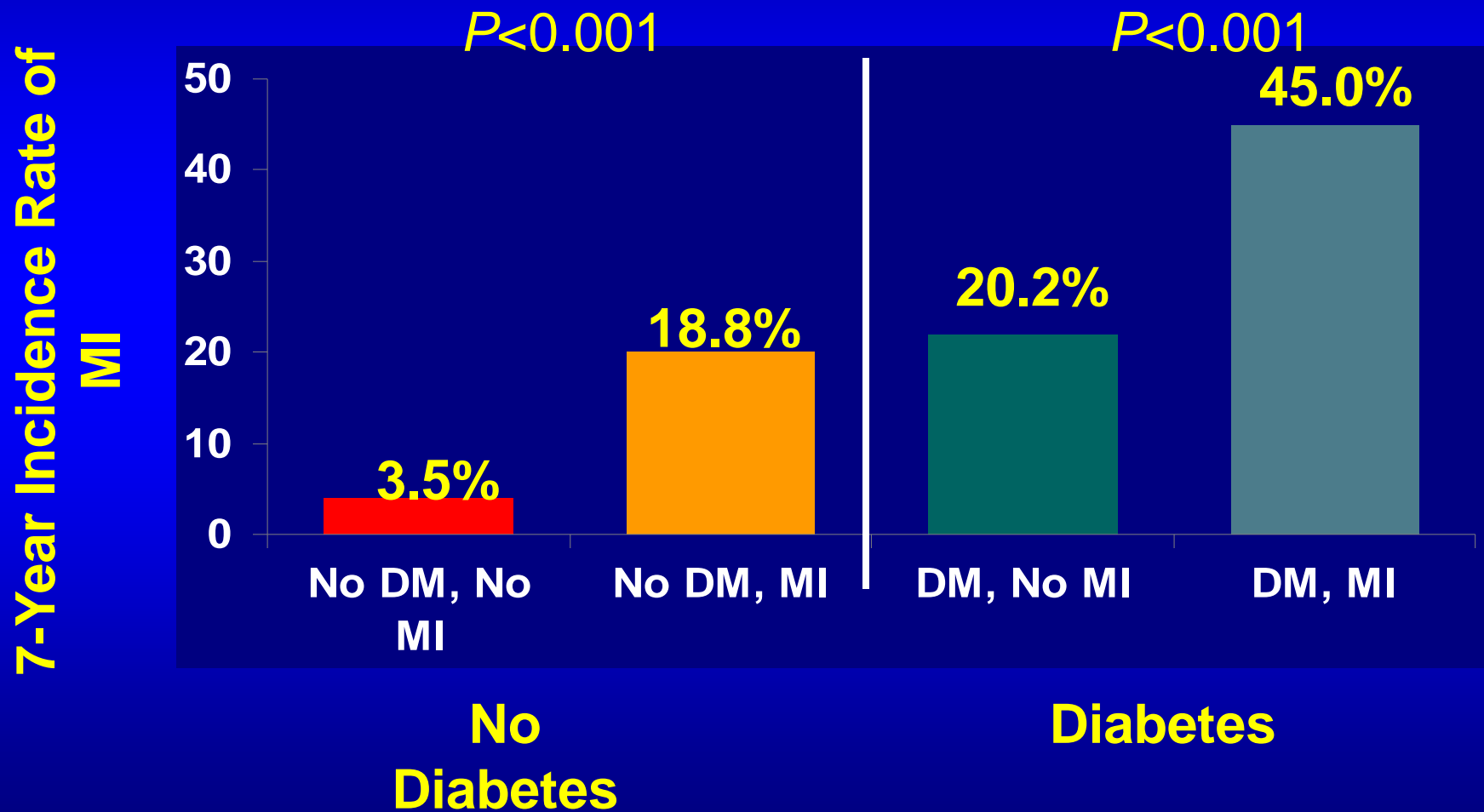
- SGLT 2 Inhibitors

+

- Metformin

# Type 2 Diabetes and CHD

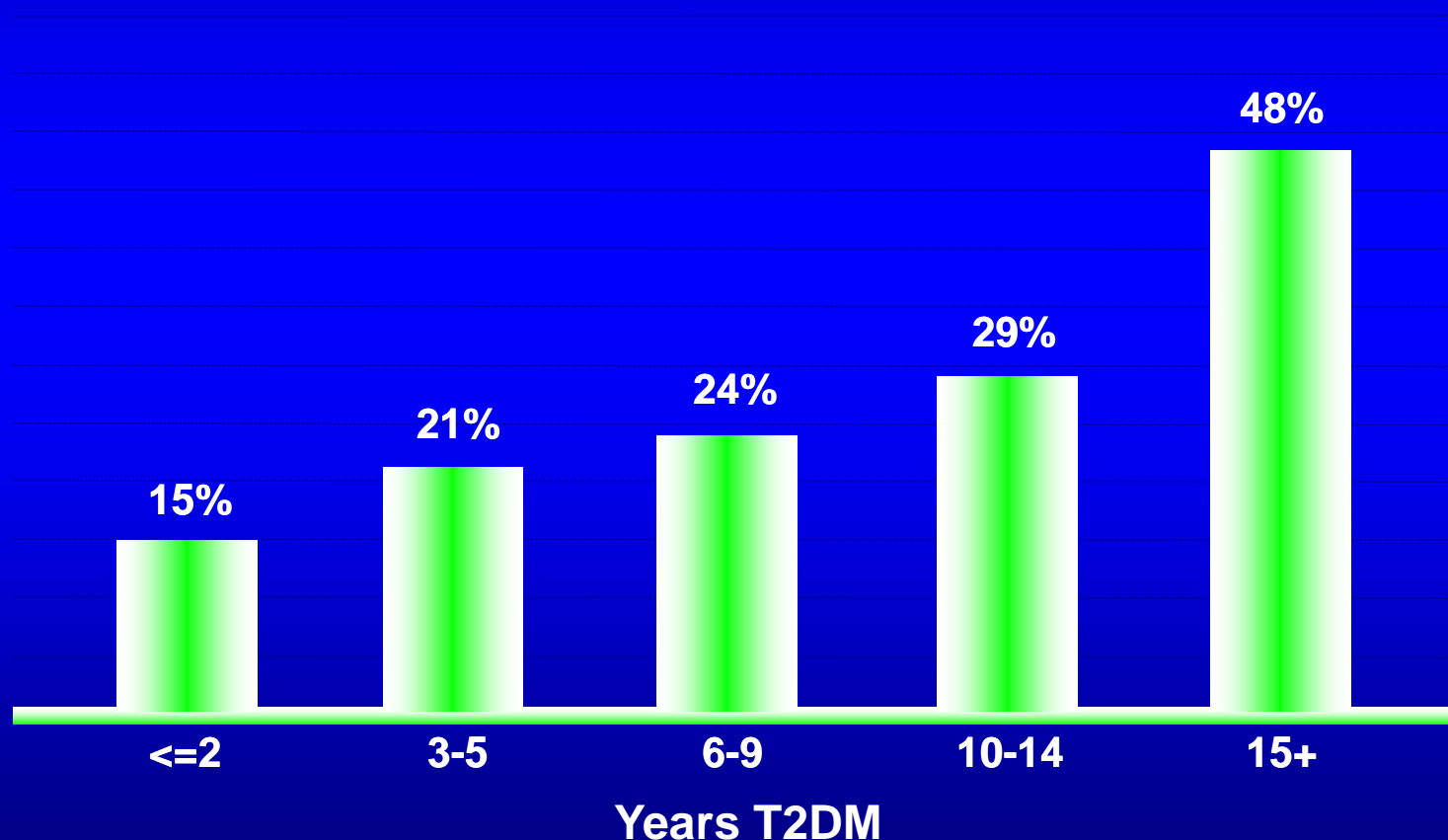
## 7-Year Incidence of Fatal/Nonfatal MI (East West Study)



CHD=coronary heart disease; MI=myocardial infarction; DM=diabetes mellitus



# Proportion of patients with cardiovascular disease increases with duration of type 2 diabetes





**2014 STEP SURVEY**



**26.4% of adults have high blood pressure  
10.5% have Diabetes  
36.7% have raised cholesterol**

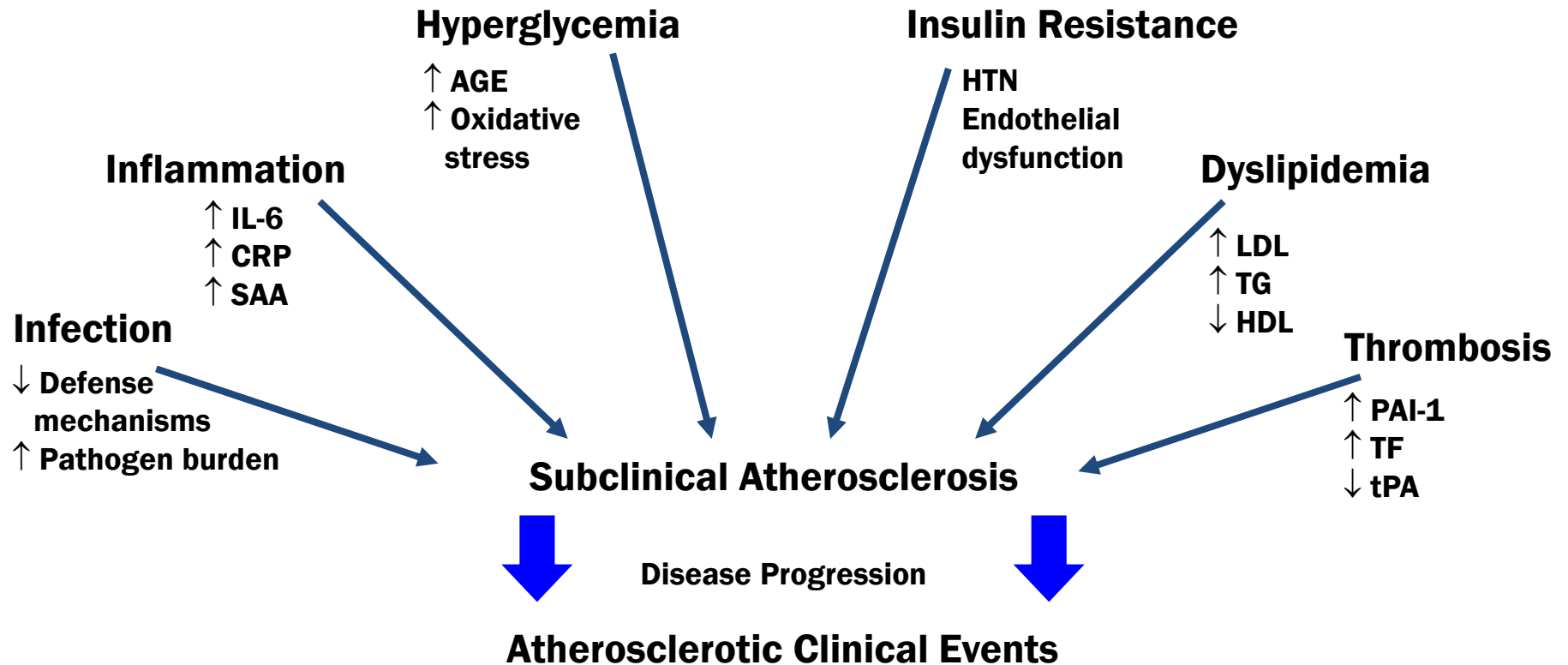


## How is CAD Different in Diabetes ?

- > CAD extent
  - Multi-vessel disease
  - Distal disease – more difficult to revascularize
- Silent ischemia/MI
- Younger
- Women
- Worse outcomes despite revascularization
  - Increased re-stenosis after PCI even with stents
  - ACB: worse periop & long-term outcomes

# Mechanisms by which Diabetes Mellitus Leads to Coronary Heart Disease

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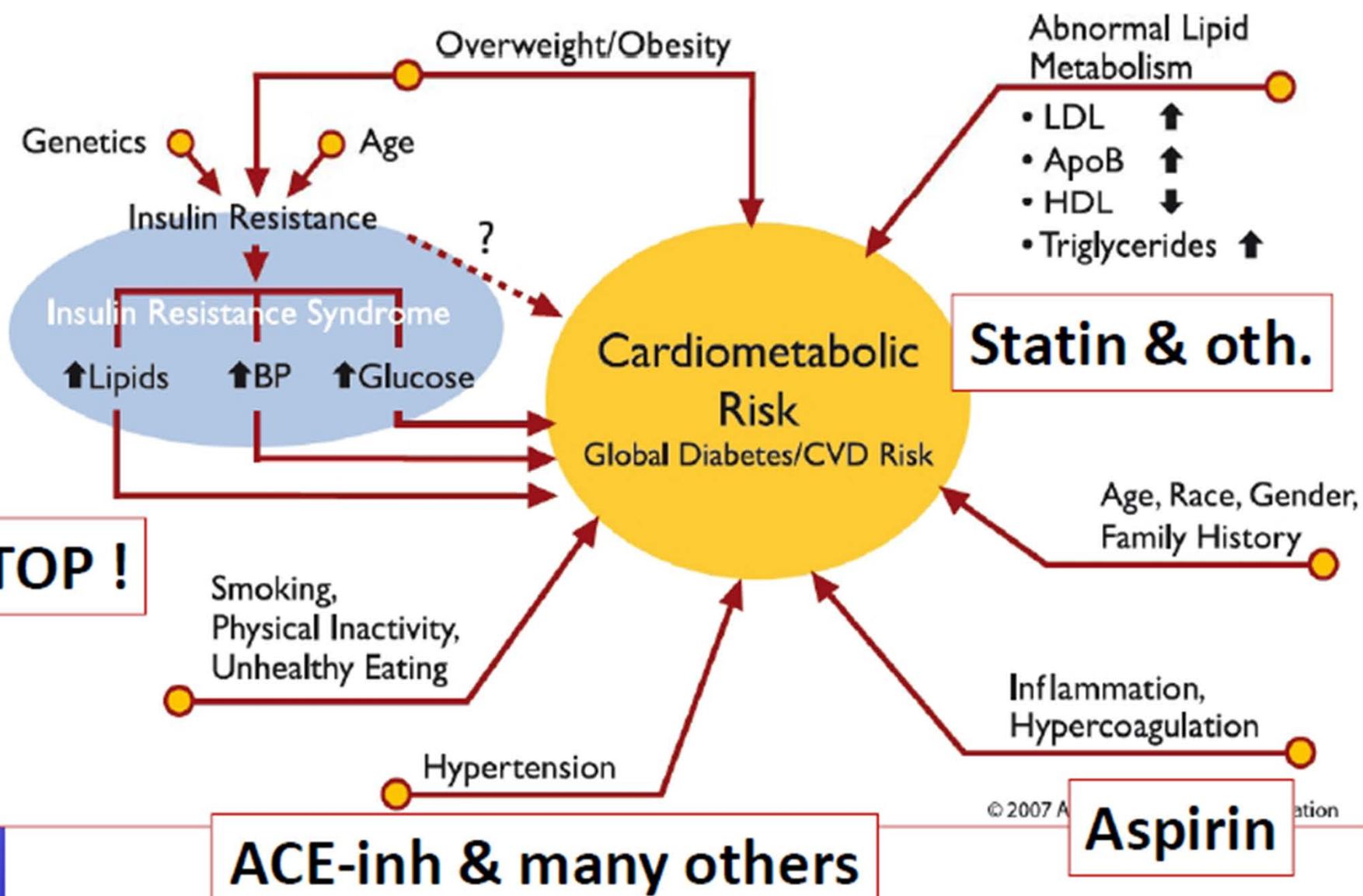
AGE=Advanced glycation end products, CRP=C-reactive protein, CHD=Coronary heart disease HDL=High-density lipoprotein, HTN=Hypertension, IL-6=Interleukin-6, LDL=Low-density lipoprotein, PAI-1=Plasminogen activator inhibitor-1, SAA=Serum amyloid A protein, TF=Tissue factor, TG=Triglycerides, tPA=Tissue plasminogen activator

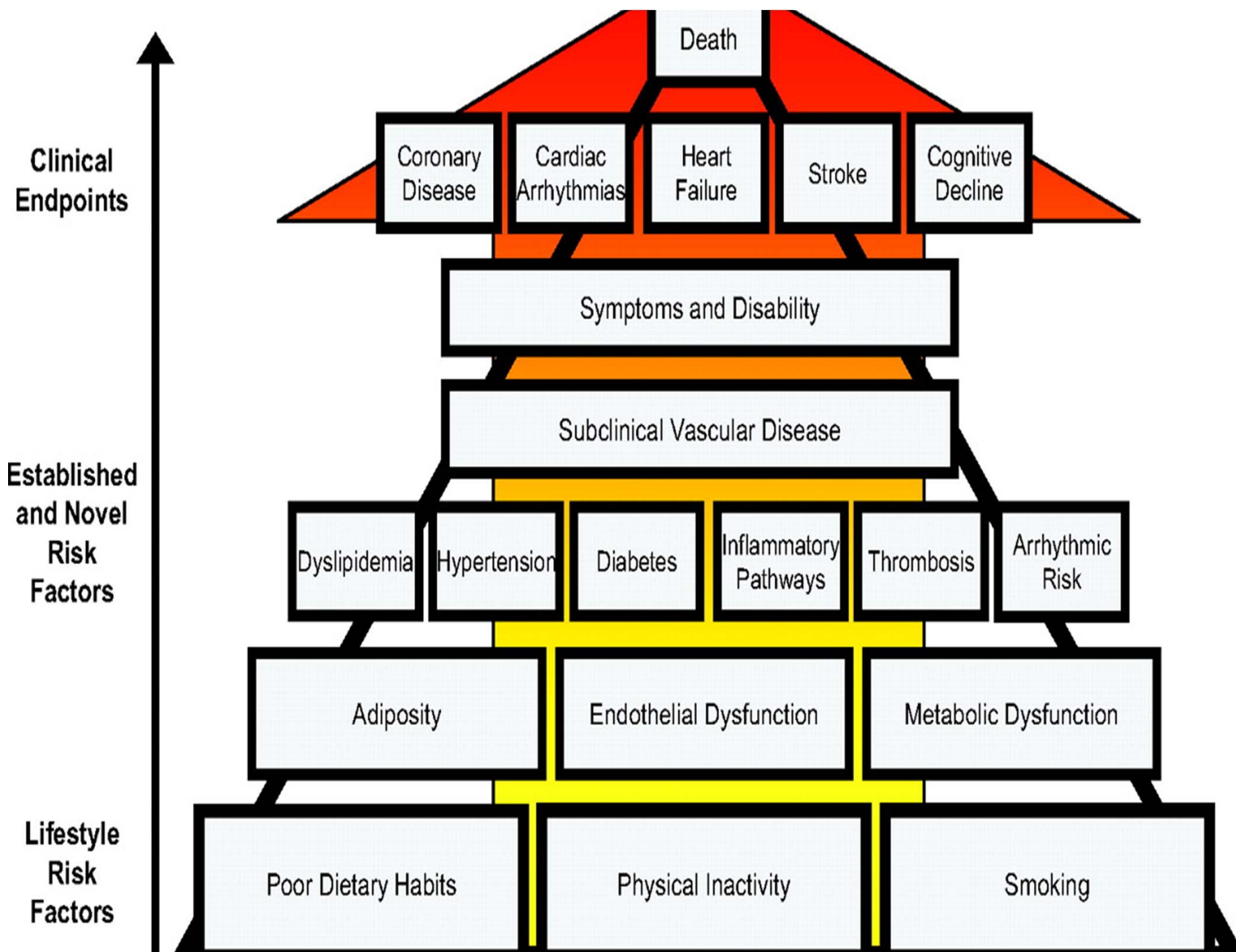
Source: Biondi-Zoccai GGL et al. JACC 2003;41:1071-1077





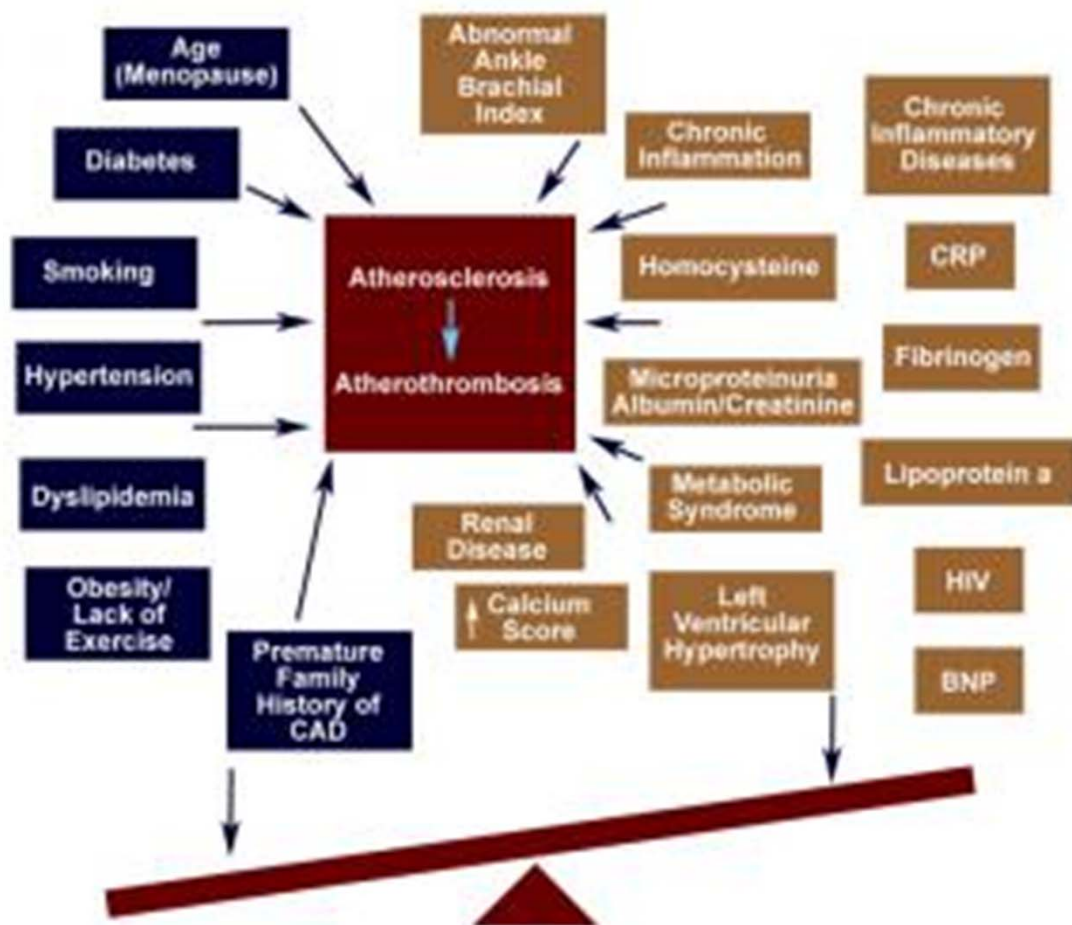
## Type 2 diabetes: a complicated way to get cardiovascular disease and die young





# Traditional Risk Factors

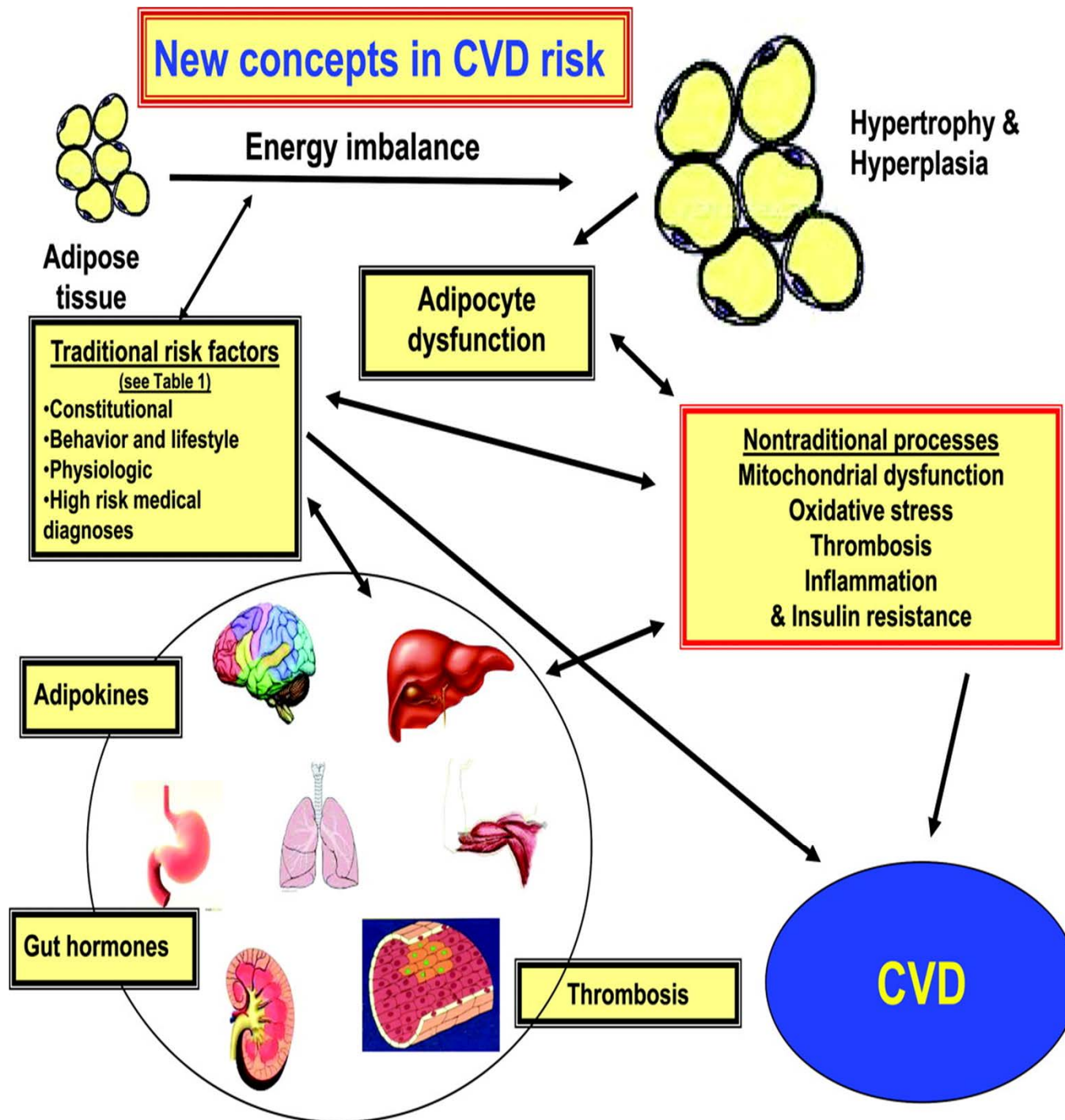
# Non-Traditional Risk Factors



## Major Risk Factors for Coronary Artery Disease

- Age (men  $\geq 45$  years; women  $\geq 55$  years)
- Family history of premature coronary artery disease (CAD in male first-degree relative  $< 65$  years)
- Hypertension (BP  $> 140/90$  mmHg or on antihypertensive medications)
- Cigarette Smoking
- Diabetes
- Hypercholesterolemia
- Low HDL cholesterol ( $< 40$  mg/dl)
- Hypertriglyceridemia ( $> 200$  mg/dl)
- Obesity







# Coronary Events and Asymptomatic Patients

- Symptoms are important predictor of outcomes
  - Among 5,558 who were administered the Seattle Angina Questionnaire, increasing frequency of symptoms and physical limitation were strongly associated with one year mortality.<sup>1</sup>
- Asymptomatic status provides limited reassurance
  - Over ½ of patients presenting with sudden cardiac death are previously asymptomatic.<sup>2</sup>
  - Among patients presenting with first acute MI, only ½ have had preceding angina.<sup>3</sup>
  - Silent MI may represent up to 1/3 of MI with increasing prevalence over age 60 and with CAD risk factors.<sup>4</sup>

1. Spertus JA, Jones P, McDonell M, Fan V, Fihn SD. Health Status Predicts Long-Term Outcome in Outpatients With Coronary Disease. *Circulation*. 2002;106:43-49.

2. Lerner DJ, Kannel WB. Patterns of Coronary Heart Disease Morbidity and Mortality in the Sexes: a 26-year Follow-Up of the Framingham Population. 1986;111:383-390.

3. Pierard LA, Dubois C, Smeets JP, Boland J, Carlier J, Kulbertus HE. Prognostic Significance of Angina Pectoris Before First Acute Myocardial Infarction. *Am J Cardiol*. 1988;61:984-987.

4. Sigurdsson E, Thorgeirsson G, Sigvaldason H, Sigfusson N. Unrecognized Myocardial Infarction: Epidemiology, Clinical Characteristics, and the Prognostic Role of Angina Pectoris: The Reykjavik Study. *Ann Intern Med*. 1995;122:96-102.

# CARDIOVASCULAR DISEASE (CVD) IN INDIVIDUALS WITH DIABETES

- Diabetes reflected by the four-fold greater incidence of CAD.
- Early detection of CAD in patients with diabetes may be of paramount importance and could improve outcome.
- However, a complicating issue is the silent progression of CAD in patients with diabetes. The disease is frequently already in an advanced state when it becomes clinically manifest.
- In addition, recent studies have indicated that conventional coronary risk factors are of limited value for detection of CAD in asymptomatic type 2 diabetes patients.
- These observations have raised the question of whether or not asymptomatic patients with diabetes should be screened for CAD.

## RECOMMENDATIONS: CORONARY HEART DISEASE SCREENING

### According to ADA (American Diabetes Association)

...

- Screening for CAD is reviewed in a recently updated consensus statement
- However, recent studies concluded that using this approach fails to identify which patients with type 2 diabetes will have silent ischemia on screening tests
- **Recommendations:**
  - **In asymptomatic patients, routine screening for CAD is not recommended**, as it does not improve outcomes as long as CVD risk factors are treated (A)

# **Screening for Coronary Disease in Diabetes: When and How** **(Ali and Maron, Clinical Diabetes 2006)**

**“ Screening patients according to traditional risk factors and current guidelines alone will frequently fail to identify CHD, thus losing the opportunity for early diagnosis and intensified management”**

**“A more aggressive approach to identifying asymptomatic coronary disease should therefore be considered in this (diabetic) patient population”**



# Evolution of CVD Screening Guidelines in DM

- **ACCF/AHA 2010 Guideline:** CAC Scoring for CV risk assessment in asymptomatic adults aged 40 and over with diabetes (Class IIa-B)
- **ACCF/AHA 2010 Guideline:** Stress MPI may be considered for advanced CV risk assessment in asymptomatic adults with diabetes or when previous risk assessment testing suggests a high risk of CHD, such as a CAC score of 400 or greater (Class IIb – Level of Evidence C)

# Do screening tests detect patients at higher risk of MI or sudden cardiac death?

Yes. Despite the absence of symptoms, a positive screening test for ischemia in our patient would indicate a higher risk for subsequent cardiac death or MI.



# CONTEXT, EVIDENCE, & GUIDELINES

March 17, 2015

## CLINICAL GUIDELINE



## Cardiac Screening With Electrocardiography, Stress Echocardiography, or Myocardial Perfusion Imaging: Advice for High-Value Care From the American College of Physicians

Roger Chou, MD, for the High Value Care Task Force of the American College of Physicians\*

**Background:** Cardiac screening in adults with resting or stress electrocardiography, stress echocardiography, or myocardial perfusion imaging can reveal findings associated with increased risk for coronary heart disease events, but inappropriate cardiac testing of low-risk adults has been identified as an important area of overuse by several professional societies.

**Methods:** Narrative review based on published systematic reviews; guidelines; and articles on the yield, benefits, and harms of cardiac screening in low-risk adults.

**Results:** Cardiac screening has not been shown to improve patient outcomes. It is also associated with potential harms due to false-positive results because they can lead to subsequent, potentially unnecessary tests and procedures. Cardiac screening is likely to be particularly inefficient in adults at low risk for coronary

heart disease given the low prevalence and predictive values of testing in this population and the low likelihood that positive findings will affect treatment decisions. In this patient population, clinicians should focus on strategies for mitigating cardiovascular risk by treating modifiable risk factors (such as smoking, diabetes, hypertension, hyperlipidemia, and overweight) and encouraging healthy levels of exercise.

**High-Value Care Advice:** Clinicians should not screen for cardiac disease in asymptomatic, low-risk adults with resting or stress electrocardiography, stress echocardiography, or stress myocardial perfusion imaging.

*Ann Intern Med.* 2015;162:438-447. doi:10.7326/M14-1225 [www.annals.org](http://www.annals.org)  
For author affiliation, see end of text.

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**Annals of Internal Medicine**



Beth Israel Deaconess  
Medical Center

# American College of Cardiology

## 2010

- Exercise echocardiography and exercise MPI **not indicated** in asymptomatic low and intermediate risk adults (Class III)
- **Consider** exercise ECG for intermediate risk asymptomatic patient including those planning to begin a vigorous exercise program (Class IIb)
  - Exercise time, ST segment changes, chronotropic response, and heart rate recovery each predict CHD events
- **Consider** exercise MPI in asymptomatic adults with diabetes, strong family history, or high coronary calcium score (Class IIb)

\*Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, et al. 2010  
ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults: a  
Report of the American College of Cardiology Foundation/American Heart Association  
Task Force on Practice Guidelines. J Am Coll Cardiol. 2010;56:e50-103.

# Risk Calculators and Asymptomatic Patients

## *Identifying patients for additional screening*

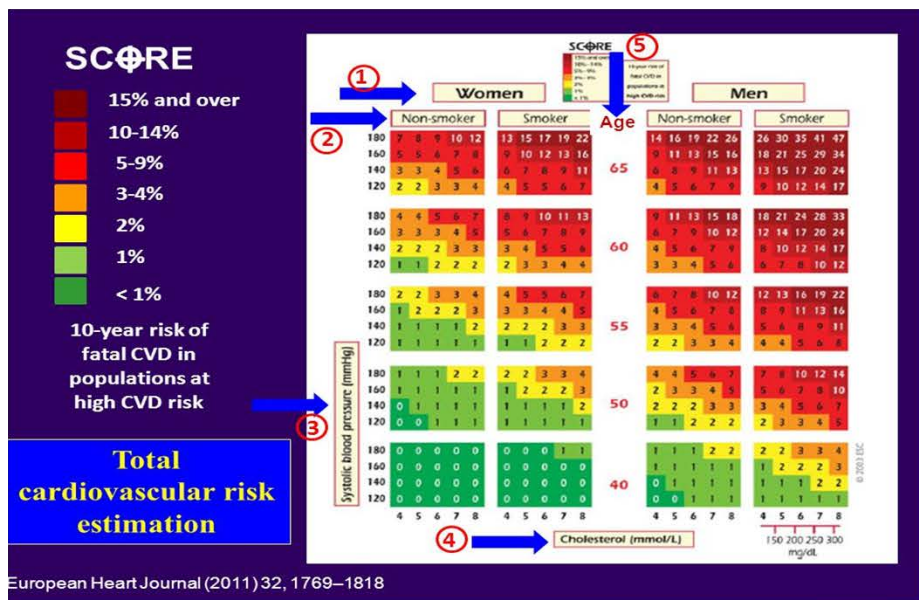
### Asymptomatic Population aged 40-79 (NHANES Overall)

| Category     | 10-year risk | Proportion of Population |       | Appropriate Use Criteria for ETT |
|--------------|--------------|--------------------------|-------|----------------------------------|
|              |              | Men                      | Women |                                  |
| Low          | <10%         | 65.8%                    | 82.5% | Rarely Appropriate               |
| Intermediate | 10-20%       | 20.9%                    | 10.0% | May Be Appropriate               |
| High         | >20%         | 13.3%                    | 7.5%  | Appropriate*                     |

\* May be appropriate for ETT with imaging

- Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, et al. 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: a Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129:S49-73.
- Wolk MJ, Bailey SR, Doherty JU, Douglas PS, Hendel RC, Kramer CM, et al. ACCF/AHA/ASE/ASNC/HFSA/HRS/SCAI/SCCT/SCMR/STS 2013 Multimodality Appropriate Use Criteria for the Detection and Risk Assessment of Stable Ischemic Heart Disease: a Report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2014;63:380-406.





**Global Cardiovascular Risk Score**

Last Updated/Reviewed 09/19/2013

Enter each of the five parameters below and click "Calculate."  
You may click "Import" to pull the values in from the physical exam.

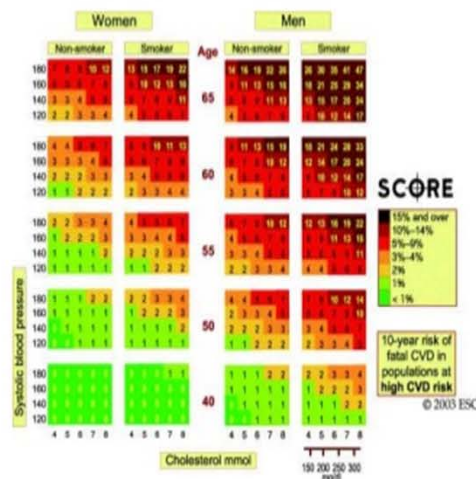
Cholesterol 212.0  
HDL 36.0  
HgbA1c Import >> 8.1  
Systolic BP 144  
Packs Per Day 0

Calculate >> 8.4 points

## Framingham Risk Calculator

- Age
- Gender
- Smoker
- Total cholesterol
- HDL-C
- Systolic BP
- HTN Rx

Calculates 10-year risk for CHD death or nonfatal MI

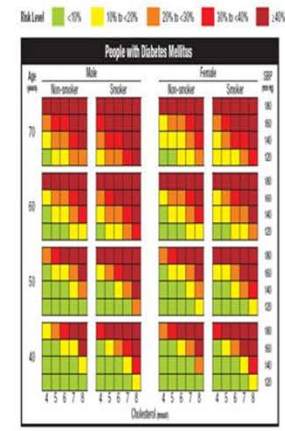


High risk: > 20%  
Intermediate risk: 10-20%  
Low risk: < 10%

## WHO/ISH risk prediction chart

- Enables integrated risk assessment and risk prediction for management of CVD
- Uses easily measurable indicators of risk to quantify the 10-year cardiovascular risk. These include gender, systolic blood pressure, smoking status, type 2 diabetes mellitus and total serum cholesterol.
- Selects those who would benefit most from treatment, and guide the intensity and nature of drug treatment.

Figure 4. WHO/ISH risk prediction chart for use in settings where blood cholesterol can be measured. 10-year risk of a total or non-fatal cardiovascular event by gender, age, systolic blood pressure, total blood cholesterol, smoking status and presence or absence of diabetes mellitus.



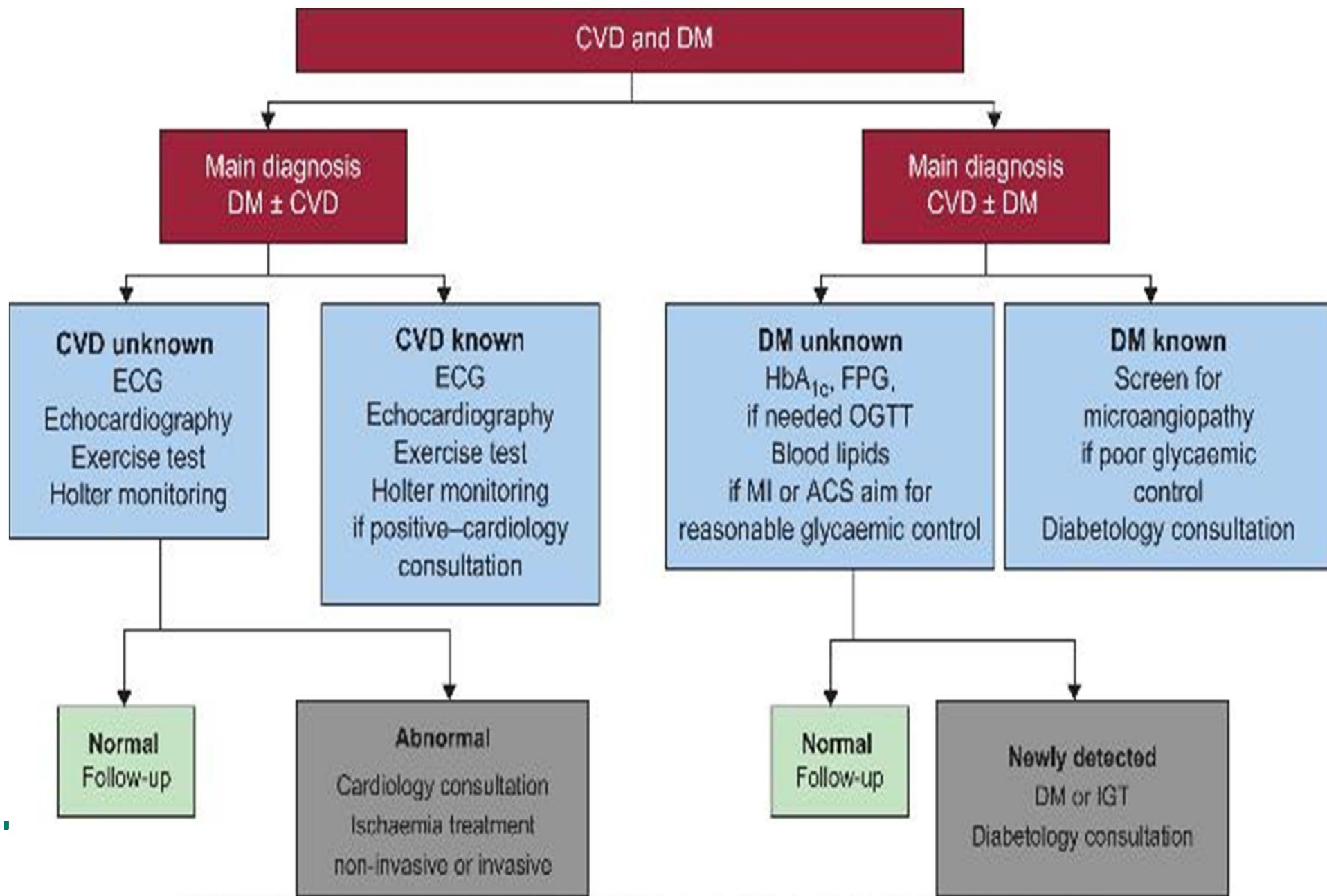


# Risk Calculators and Asymptomatic Patients

## *Assessing Individual Risk*

- Assessing sub-clinical coronary artery disease
  - Silent ischemia: Important but less frequent in low and intermediate risk patients
  - Vulnerable plaque (most <50% stenosis) and subsequent acute coronary syndrome as initial manifestation of disease
- ACC/AHA guideline advises consideration of newer markers (hsCRP, Coronary CT Calcium score [CCS], ABI). (Class IIb)
- CCS as a surrogate of plaque burden is a strong prognostic indicator and adds individual risk stratification.

\*Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, et al. 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: a Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129:S49-73.



## FUNCTIONAL INDIRECT TESTS THAT DETECT MYOCARDIAL ISCHEMIA

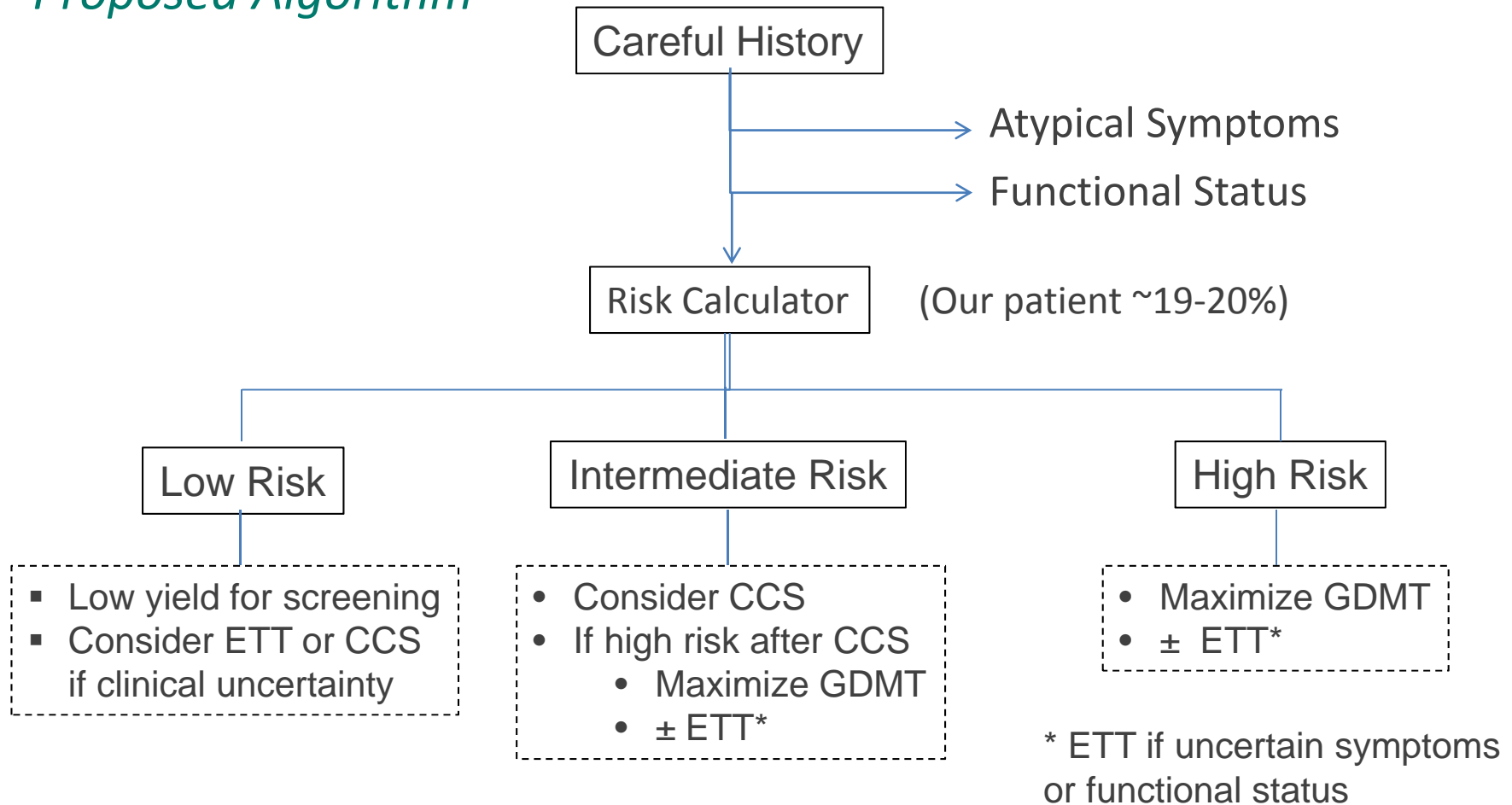
- Resting ECG
- Exercise ECG(sensitivity and specificity of 68% and 77% )
- Myocardial perfusion imaging (SPECT – single photon emission computed tomography) sensitivity (80-90%) and
- specificity (75-90%) main advantage is its high negative predictive value (95%).
- Stress echocardiography (dobutamine,adenosine) 81% and 85%

### **Imaging methods most commonly used to define the anatomic extent of atherosclerotic disease**

- Echo-Doppler ultrasound of the carotid (carotid Intimal Thickness)
- Calcium score (CS)
- Multislice computed tomography (MSCT) When compared to invasive angiography, MSTC with 64 rows of detectors, demonstrated high sensitivity (between 83% to 99%), specificity (93% to 98%) and negative predictive value (99%)
-

# Screening for CAD in Asymptomatic Patients

## *Proposed Algorithm*



# The 1st SHAPE Guideline

Toward the National Screening for Heart Attack Prevention and Education (SHAPE) Program

Apparently Healthy Population Men >45 yr, Women >55 yr\*

Step 1

Very Low Risk†

Ext

Ext

All >75 yr receive unconditional treatment‡

**Atherosclerosis Test**

• CACS  
or  
• CIMT & Carotid Plaque§

Step 2

**Negative Test**

- CACS = 0
- CIMT <50th percentile

No Risk Factors†

Risk Factors

**Positive Test**

- CACS ≥1
- CIMT ≥50th percentile or Carotid Plaque

• CACS <100 & <75th percentile  
• CIMT <1 mm & <75th percentile & No Carotid Plaque

• CACS 100 – 399 or >75th percentile  
• CIMT ≥1 mm or >75th percentile or <50% Stenotic Plaque

• CACS ≥400 or >90th percentile or CACS ≥400 or >50% Stenotic Plaque†

Step 3

**Lower Risk**

**Moderate Risk**

**Moderately High Risk**

ABI <0.9  
CRP >4 mg/L  
Optional

**High Risk**

**Very High Risk**

LDL Target

<160 mg/dL

<130 mg/dL

<130 mg/dL

<100 mg/dL Optional

<100 mg/dL

<70 mg/dL Optional

<70 mg/dL

Retest Interval

5–10 years

5–10 years

Individualized

Individualized

Individualized

Follow Existing Guidelines

Angiography

Myocardial Ischemia Test

Yes

No



**Asymptomatic Persons with DM Over Age 40**

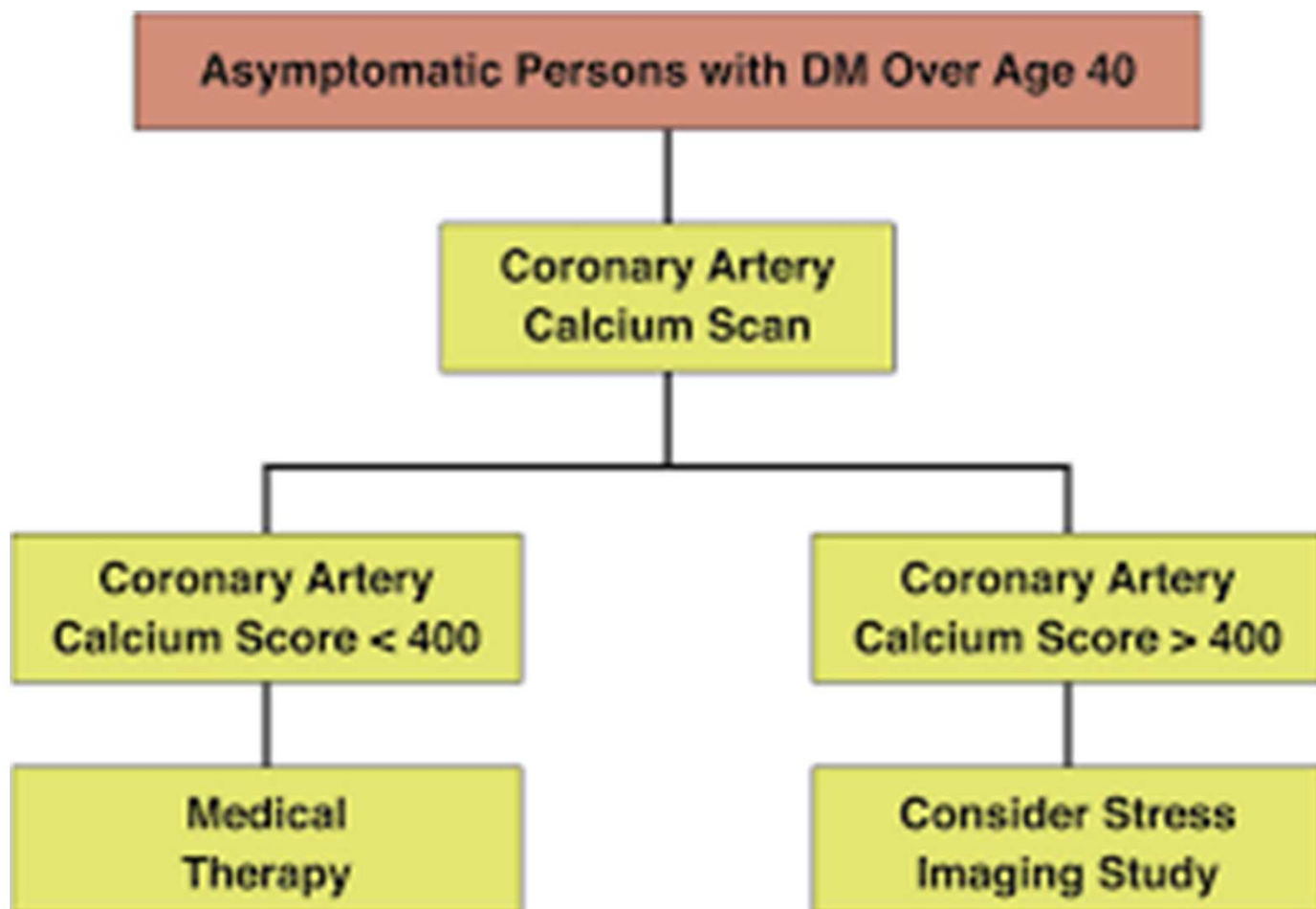
**Coronary Artery  
Calcium Scan**

**Coronary Artery  
Calcium Score < 400**

**Medical  
Therapy**

**Coronary Artery  
Calcium Score > 400**

**Consider Stress  
Imaging Study**



# ADA 2007 Consensus Statement (Bax et al. Diab Care 2007)

**“If coronary calcium testing is performed, it appears reasonable to proceed with further testing in diabetic patients with calcium scores  $>400$ .....using single photon emission tomography to assess myocardial perfusion or stress echocardiography to assess ischemic wall motion abnormalities”**

**Table 1.** Summary of the characteristics of the most important methods for diagnosing CAD in DM 2 patients

| Diagnostic method               | Technique   | Contrast | Cost | Sens. | Spec. | Complications                                  | Advantages                                | Disadvantages  |
|---------------------------------|-------------|----------|------|-------|-------|--|---|--|
| Conventional angiography        | Invasive    | Yes      | High | High  | High  | AMI, arrhythmias, bleeding, infections, stroke | Gold standard                             | Invasive   |
| Ergometric test                 | Noninvasive | No       | Low  | Low   | Low   | Rare: arrhythmias, AMI                         | Low cost                                  | Inconclusive results                                 |
| Myocardial scintigraphy         | Noninvasive | Yes      | High | High  | High  | Rare   | Physical stress or pharmacological        | Functional test < sens   specif MSTC                 |
| Stress echocardiography         | Noninvasive | No       | Low  | High  | High  | Rare: arrhythmias                              | Low cost                                  | Difficulties: obese achieve submax HR                |
| Carotid Doppler ultrasonography | Noninvasive | No       | Low  | Low   | Low   | No   | Low cost fast                             | Indirect method No standard                          |
| Calcium Score                   | Noninvasive | Yes      | High | Low   | Low   | Rare   | Noninvasive                               | Indirect method does not show percentage obstruction |
| Intravascular ultrasound (IVUS) | Invasive    | No       | High | High  | High  | AMI, arrhythmias, bleeding, infections, stroke | Gold standard characterize plates         | Invasive   |
| Angiotomography coronary (MSTC) | Noninvasive | Yes      | High | High  | High  | nephrotoxicity                                 | Sens/Specif slightly lower of angiography | Not applicable in obesity and arrhythmias; cost      |

Do medical therapies or percutaneous coronary interventions improve outcomes in asymptomatic patients who “screen positive” for coronary artery disease?

Yes. Anti-ischemia therapies reduce risk for death or MI in patients with stable ischemic heart disease, including those with silent ischemia.



## How to prevent CVD in DM

**THERAPEUTIC LIFESTYLE**

**GOOD GLYCEMIC CONTROL**

**TREATMENT OF HYPERTENSION**

**REDUCTIONS OF LIPIDS**

**SMOKING CESSATION**

**OBESITY REDUCTION**

**ASPIRIN**

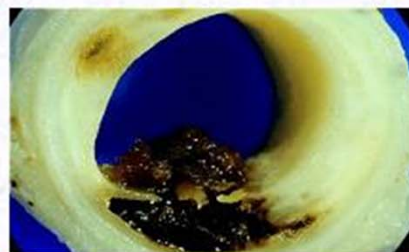


# Principles for multifactorial management of people with diabetes

## Life style modification

**Glycaemic control**

**Antiplatelet therapy**



**Blood pressure control**

**Lipid control**

# Treating the ABCs Reduces Diabetic Complications

| Strategy                      | Complication                       | Reduction of Complication |
|-------------------------------|------------------------------------|---------------------------|
| <b>Blood glucose control</b>  | Heart attack                       | ↓ <b>37%</b> <sup>1</sup> |
|                               | Cardiovascular disease             | ↓ <b>51%</b> <sup>2</sup> |
| <b>Blood pressure control</b> | Heart failure                      | ↓ <b>56%</b> <sup>3</sup> |
|                               | Stroke                             | ↓ <b>44%</b> <sup>3</sup> |
|                               | Diabetes-related deaths            | ↓ <b>32%</b> <sup>3</sup> |
| <b>Lipid control</b>          | Coronary heart disease mortality   | ↓ <b>35%</b> <sup>4</sup> |
|                               | Major coronary heart disease event | ↓ <b>55%</b> <sup>5</sup> |
|                               | Any atherosclerotic event          | ↓ <b>37%</b> <sup>5</sup> |
|                               | Cerebrovascular disease event      | ↓ <b>53%</b> <sup>4</sup> |

<sup>1</sup> UKPDS Study Group (UKPDS 33). *Lancet*. 1998;352:837-853.

<sup>2</sup> Hansson L, et al. *Lancet*. 1998;351:1755-1762.

<sup>3</sup> UKPDS Study Group (UKPDS 38). *BMJ*. 1998;317:703-713.

<sup>4</sup> Grover SA, et al. *Circulation*. 2000;102:722-727.

<sup>5</sup> Pyörälä K, et al. *Diabetes Care*. 1997;20:614-620.

# Major new key messages

- **Blood pressure:**

- Lifestyle measures needed for hypertensive patients,
- All major antihypertensives equal for clinical use,
- Target blood pressure <140/90 mmHg,
- Threshold values for ambulatory and home measurement.

- **Diabetes mellitus:**

- Target HbA<sub>1c</sub> for CVD prevention: <7.0% (<53 mmol/mol),
- Target blood pressure <140/80 mmHg.

- **Blood lipids:**

- Target LDL-cholesterol:
  - <1.8 mmol/L for very high risk patients,
  - <2.5 mmol/L for high risk patients,
  - <3.0 mmol/L for all others.



# Steno-2: Goals of intensive pharmacologic strategy

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| Therapy         | Goal  |
|-----------------|---|
| ACE inhibitors  | All patients (ARBs, if contraindicated)                                     |
| Aspirin         | All patients (150 mg/d)   |
| BP control      | 130/80 mm Hg  |
| Glucose control | A1C <6.5%   |
| Lipid control   | Total-C <175 mg/dL (<4.53 mmol/L)<br>Triglycerides <150 mg/dL (<1.7 mmol/L) |

# Aggressive medical therapy in diabetes-ADD

**SGLT-2 Inh.**  
**Bromocriptine QR**  
Pioglitazone  
Incretins,  
Metformin  
Ranolazine

Hyperglycemia/  
Insulin resistance

ACE inhibitors  
ARBs  
 $\beta$ -blockers  
CCBs  
Diuretics

Hypertension

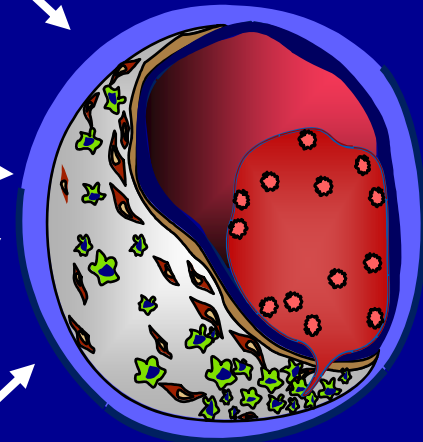
Statins  
Fibric acid derivatives  
Colsevalam  
PCSK-9 Inh

Dyslipidemia

ASA  
Clopidogrel  
Ticlopidine

Platelet activation  
and aggregation

Atherosclerosis,  
CV Outcomes,  
CV Risk Factors,  
Mortality



Adapted from Beckman JA et al. *JAMA*. 2002;287:2570-81.

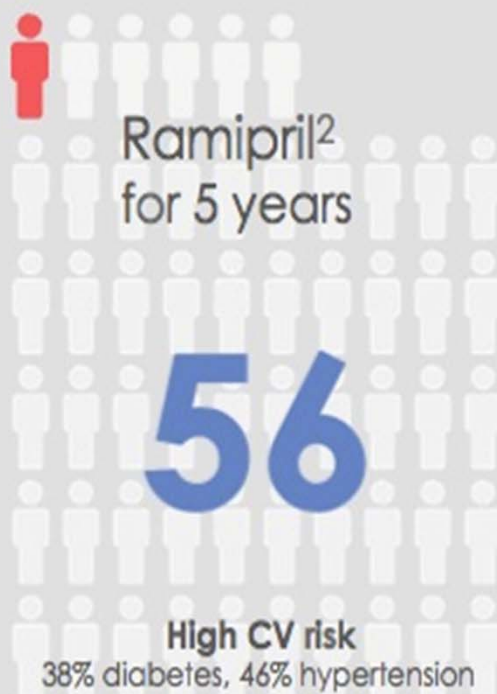


## Number needed to treat (NNT) to prevent one death across landmark trials in patients with high CV risk

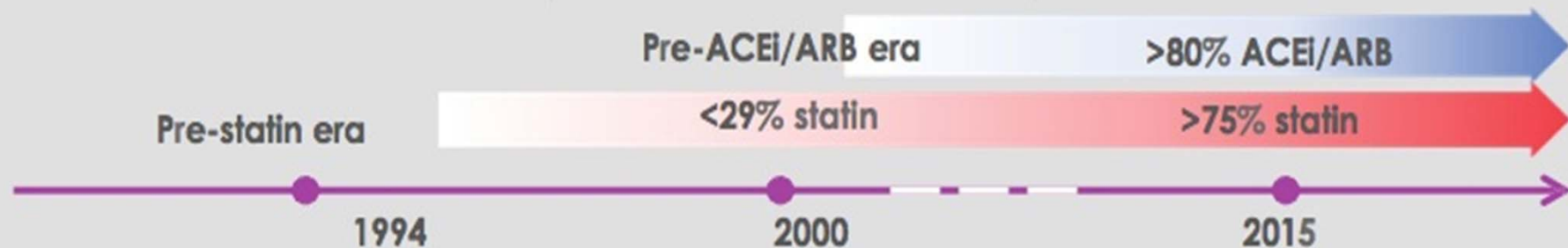
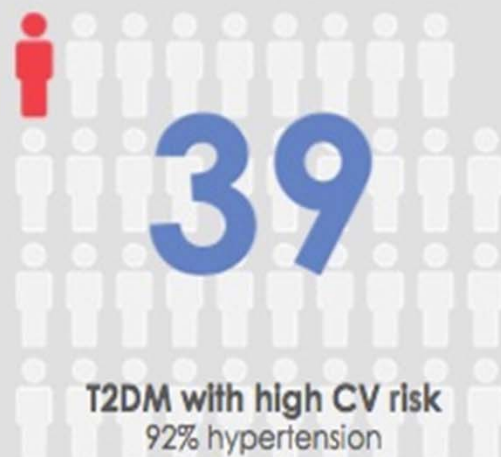
Simvastatin<sup>1</sup>  
for 5.4 years



Ramipril<sup>2</sup>  
for 5 years



Empagliflozin  
for 3 years



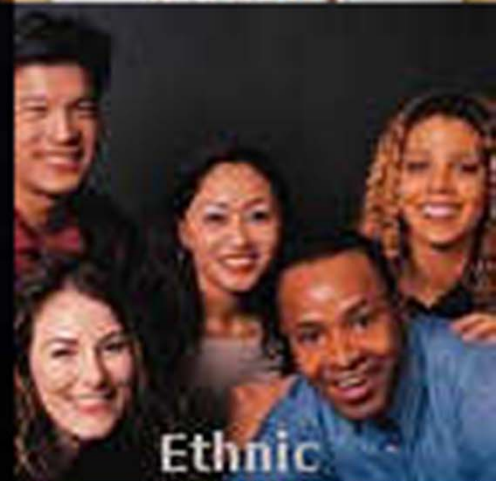
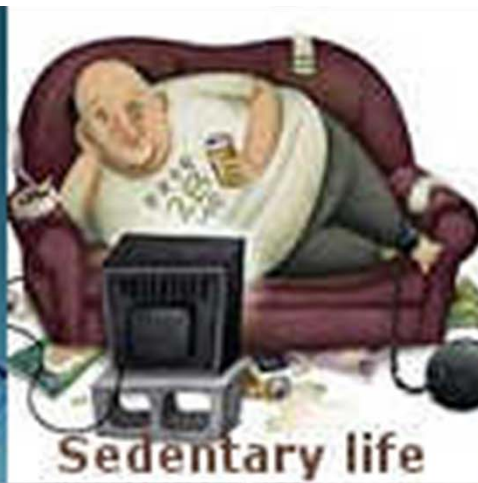
1.4S Investigator. Lancet 1994; 344: 1383-89, <http://www.trialresultscenter.org/study2590-4S.htm>

2.HOPE Investigator N Engl J Med 2000;342:145-53, <http://www.trialresultscenter.org/study2606-HOPE.htm>

# Benefit of Interventions Over 5 Years

- Lowering systolic BP 4 mm Hg:
  - -12.5 cardiovascular events/200 patients
- Lowering LDL cholesterol 1 mmol/L
  - -8.2 cardiovascular events/200 patients
- Lowering HbA1c 0.9%
  - -2.9 cardiovascular events/200 patients





# General ( life style modification)

- Stop smoking
- Exercise regularly
- Low salt diet
- Fat free food
- Control body weight
- Avoid alcohol
- Reduce stress
- Early detection and treatment of risk factors





# Elvis Presley

**Age:** Died at 42 (1935-1977) **DIABETES**



Photo: via Tumblr

Reportedly, Elvis Presley was shocked by his Type II diabetes diagnosis. Presley did not change his lifestyle after the diagnosis and many people believe that it contributed to his early death.

# Larry King (CNN)

Larry King stopped smoking, changed his diet, and adopted a healthier lifestyle after his Type II diabetes diagnosis.

**Age:** 83

**Birthplace:** New York City,  
New York, United States of  
America

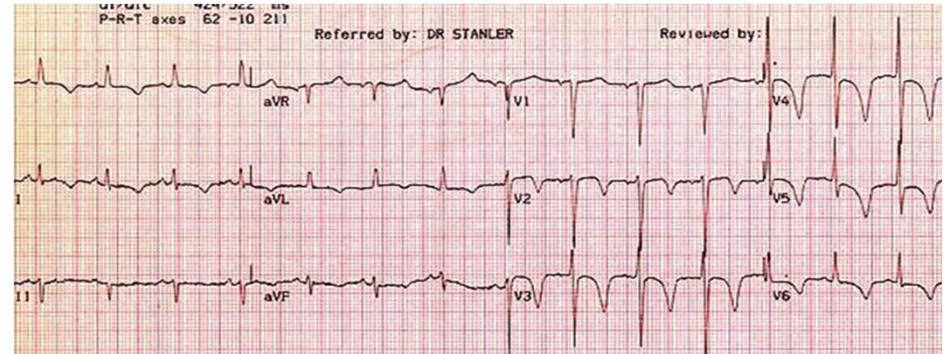
**Profession:** Talk show  
host, Journalist, Radio  
personality, Actor, Voice  
acting, + more



# DM,H/T,IHD

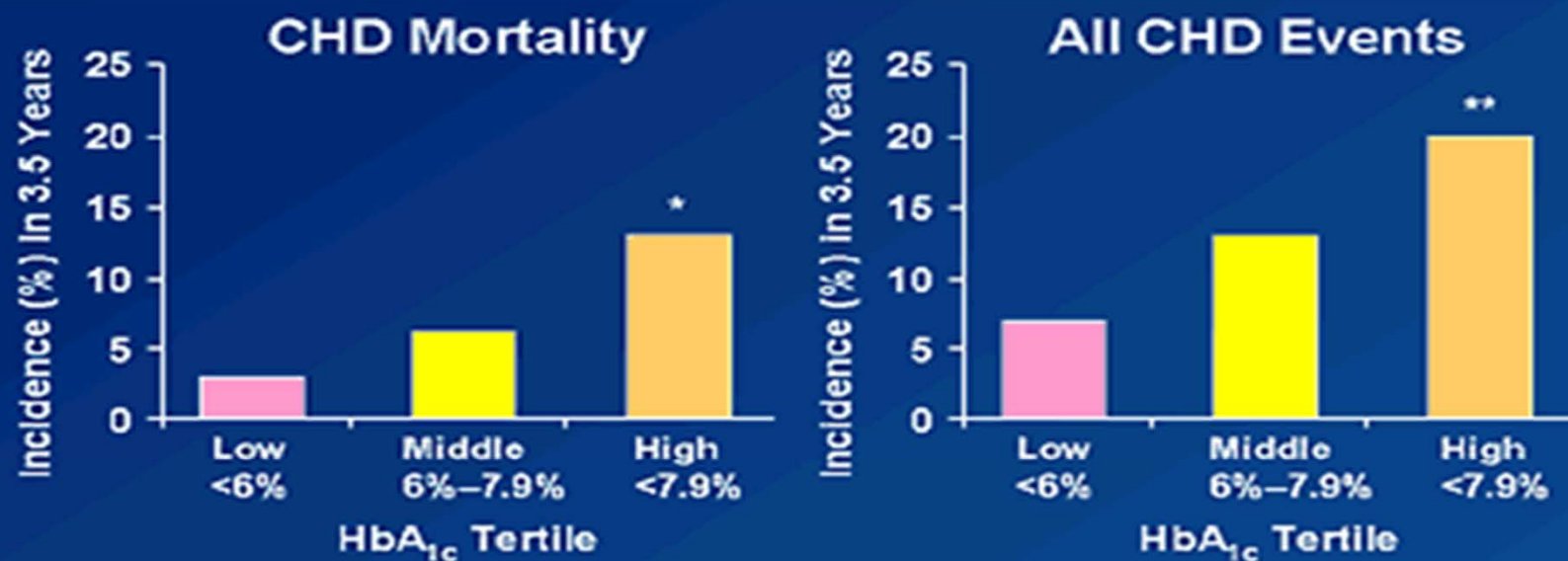
45 male ,160/100,FBS 200,HbA1c 9%

- Aspilet 1 od
- Clopidogrel 75 mg od
- Metoprolol XL 50 mg morning
- Perindopril 5 mg at night
- Rosuvastatin 20 mg HS
- If there is chest pain,monotrate 25 mg od
- S/L nitrate prn
- Trimetazidine,Ivabradine,Nicorandil
- Metformin 500 mg BD
- Sitagliptin 100 mg od



# Glycemic control and CVD

## Coronary Heart Disease Incidence by HbA<sub>1c</sub> Levels in Type 2 Diabetes



\* $P < 0.01$  vs lowest tertile; \*\* $P < 0.05$  vs lowest tertile.

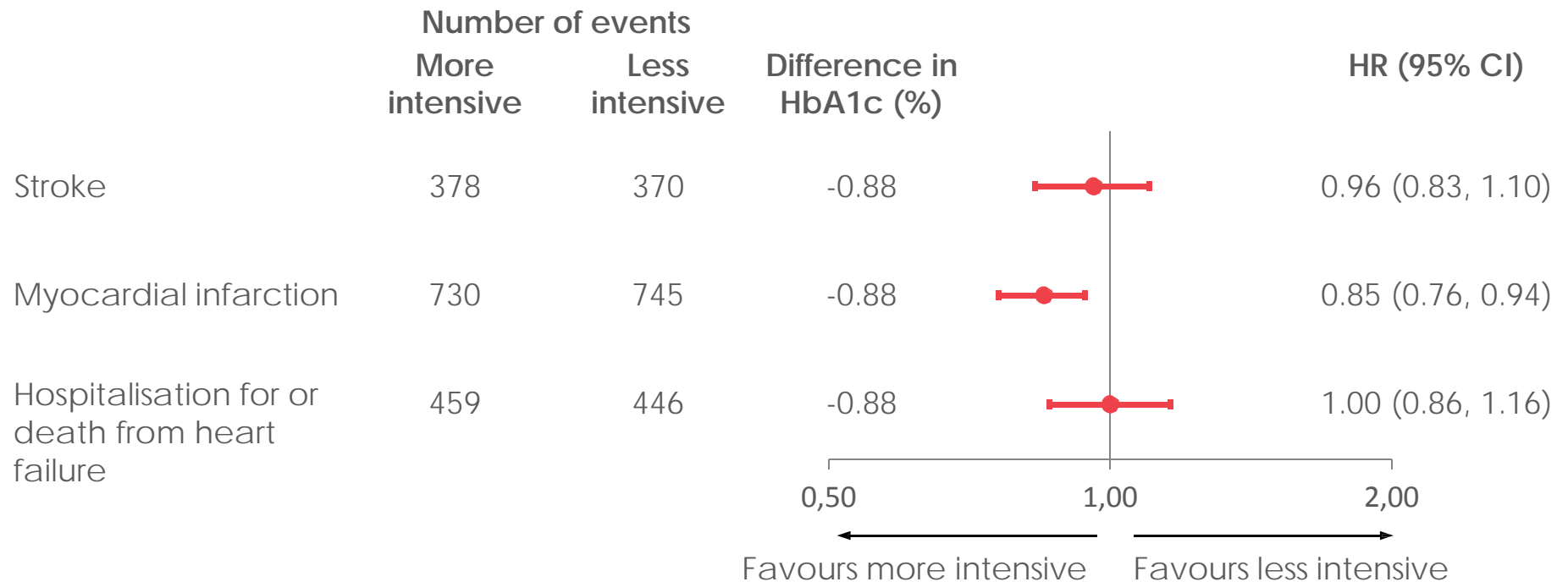
N = 1298 men and women.

Patients 65–75 years old with or without type 2 diabetes at baseline.

Kuusisto J, et al. *Diabetes*. 1994;43:660–667.



# Meta-analysis of intensive glucose control in T2DM: major CV events including heart failure



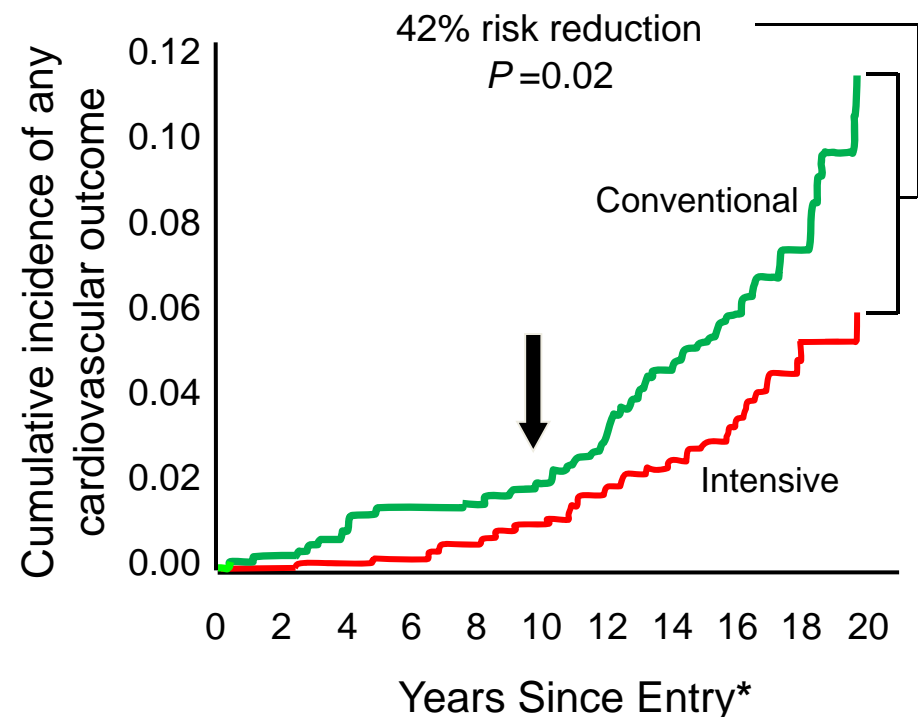
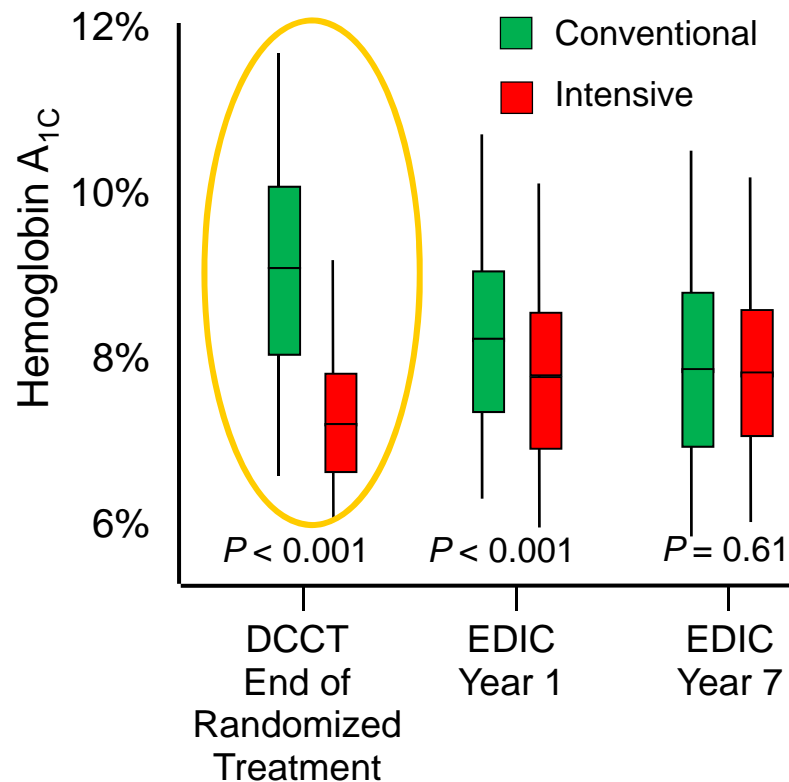
- Meta-analysis of 27,049 participants and 2370 major vascular events from:
  - ADVANCE
  - UKPDS
  - ACCORD
  - VADT

HR, hazard ratio; CV, cardiovascular  
Turnbull FM et al. Diabetologia 2009;52:2288–2298



# Diabetes Mellitus (Type I): Effect of Intensive Glycemic Control

Diabetes Control and Complications Trial (DCCT) and Epidemiology of Diabetes Interventions and Complications (EDIC)



Intensive glycemic control in DM reduces long-term CV risk

Sources:  
DCCT/EDIC Research Group. *JAMA* 2002;287:2563-2569  
DCCT/EDIC Research Group. *NEJM* 2005;353:2643-2653

# Glycemic Legacy?

THE NEW ENGLAND JOURNAL of MEDICINE

## ORIGINAL ARTICLE

### 10-Year Follow-up of Intensive Glucose Control in Type 2 Diabetes

Rury R. Holman, F.R.C.P., Sanjoy K. Paul, Ph.D., M. Angelyn Bethel, M.D.,  
David R. Matthews, F.R.C.P., and H. Andrew W. Neil, F.R.C.P.

#### CONCLUSIONS


Despite an early loss of glycemic differences, a continued reduction in microvascular risk and emergent risk reductions for myocardial infarction and death from any cause were observed during 10 years of post-trial follow-up. A continued benefit after metformin therapy was evident among overweight patients. (UKPDS 80; Current Controlled Trials number, ISRCTN75451837.)

N Engl J Med 2008;359:1577-89.

# A1C and CVD Outcomes

- DCCT: Trend toward lower risk of CVD events with intensive control (T1D)
- EDIC: 57% reduction in risk of nonfatal MI, stroke, or CVD death (T1D)
- UKPDS: nonsignificant reduction in CVD events (T2D).
- ACCORD, ADVANCE, VADT suggested no significant reduction in CVD outcomes with intensive glycemic control. (T2D)

# Early vs late glycaemic intervention: UKPDS enrolled newly diagnosed patients

|  | UKPDS <sup>1</sup><br>(n=3867) | ADVANCE <sup>2</sup><br>(n=11,140) | ACCORD <sup>3</sup><br>(n=10,251) | VADT <sup>4</sup><br>(n=1791) |
|--|--------------------------------|------------------------------------|-----------------------------------|-------------------------------|
|  |                                |                                    |                                   |                               |
| Duration of diabetes (years)   | 0*                             | 8                                  | 10                                | 11.5                          |
| Mean baseline HbA <sub>1c</sub> (%)  | 7.1                            | 7.5                                | 8.3                               | 9.4                           |
| Mean baseline FPG (mmol/L)   | 8.0                            | 8.5                                | 9.7                               | 11.4                          |
| Mean age (years)   | 53                             | 66                                 | 62                                | 60                            |

\*Newly diagnosed patients  
FPG: fasting plasma glucose

<sup>1</sup>UKPDS Group. *Lancet* 1998;352:837–853. <sup>2</sup>ADVANCE Collaborative Group. *N Engl J Med* 2008;358:2560–2572. <sup>3</sup>ACCORD Study Group. *N Engl J Med* 2008;358:2545–2559. <sup>4</sup>Meyers C, et al. *Am J Cardiol* 2006;98:63–65.

# Blood Pressure Control in Diabetes

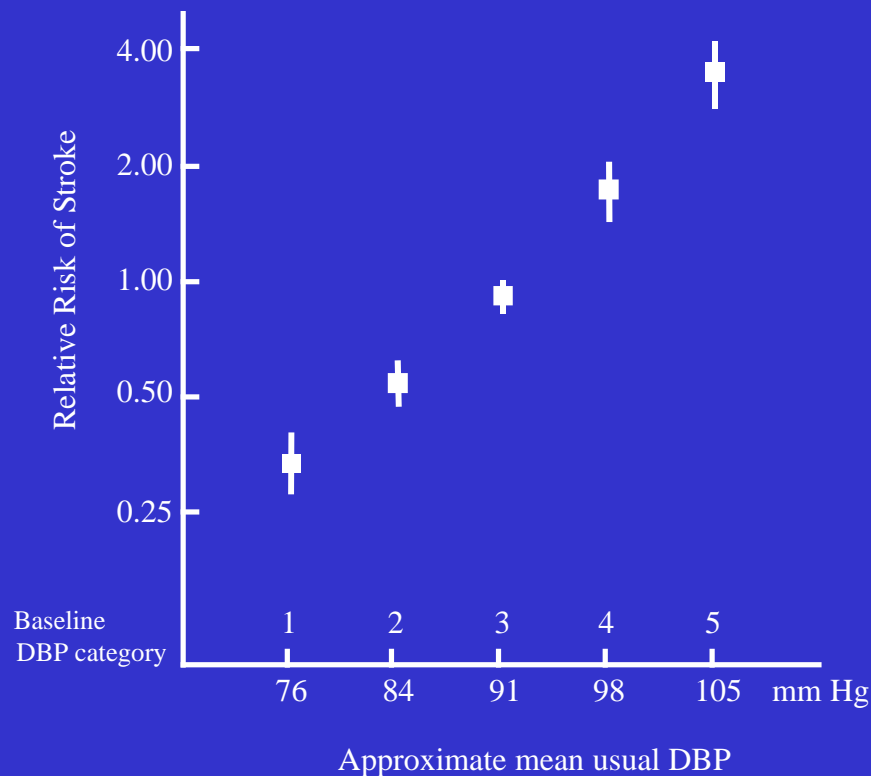




# Relative Risk of Stroke and of CHD Increases with Increasing DBP

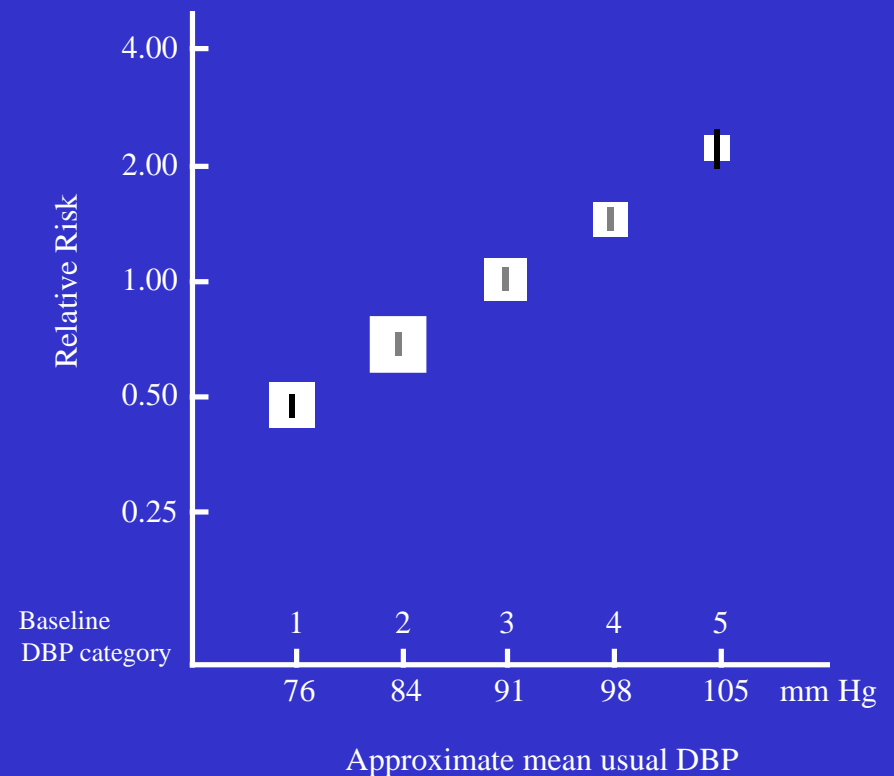
## Stroke and usual DBP

(in 5 categories defined by baseline DBP)  
7 prospective observational studies: 843 events



## Coronary Heart Disease and usual DBP

(in 5 categories defined by baseline DBP)  
9 prospective observational studies: 4856 events



# Hypertension in individuals with diabetes

- Volume expansion
- Increased salt sensitivity
- Isolated systolic hypertension
- Masked hypertension
- Nocturnal dipping of BP and pulse
- Orthostatic hypotension
- Albuminuria
- Frequent presence of other risk factors
- Association of several drugs often required to obtain adequate control



## Q7. How should hypertension be managed?

# Blood Pressure Treatment

- Employ therapeutic lifestyle modification
  - DASH or other low-salt diet
  - Physical activity
- Select antihypertensive medications based on BP-lowering effects and ability to slow progression of nephropathy and retinopathy
  - ACE inhibitors
  - or
  - ARBs
- Add additional agents when needed to achieve blood pressure targets
  - Calcium channel antagonists
  - Diuretics
  - Combined  $\alpha/\beta$ -adrenergic blockers
  - $\beta$ -adrenergic blockers
  - Do not combine ACE inhibitors with ARBs

ACE = angiotensin converting enzyme; ARB = angiotensin II receptor blocker; BP = blood pressure; DASH = Dietary Approaches to Stop Hypertension.

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## Recommendations: Hypertension/ Blood Pressure Control (2)

### Systolic Targets:

- People with diabetes and hypertension should be treated to a systolic blood pressure goal of <140 mmHg. **A**
- Lower systolic targets, such as <130 mmHg, may be appropriate for certain individuals at high risk of CVD, if they can be achieved without undue treatment burden. **C**

## Recommendations: Hypertension/ Blood Pressure Control (3)

### Diastolic Targets:

- Patients with diabetes should be treated to a diastolic blood pressure <90 mmHg. **A**
- Lower diastolic targets, such as <80 mmHg, may be appropriate for certain individuals at high risk for CVD if they can be achieved without undue treatment burden. **C**



## Recommendations: Hypertension/ Blood Pressure Treatment (3)

- Treatment for hypertension should include **A**
  - ACE inhibitor
  - Angiotensin II receptor blocker (ARB)
  - Thiazide-like diuretic
  - Dihydropyridine calcium channel blockers
- Multiple drug therapy (two or more agents at maximal doses) generally required to achieve BP targets.

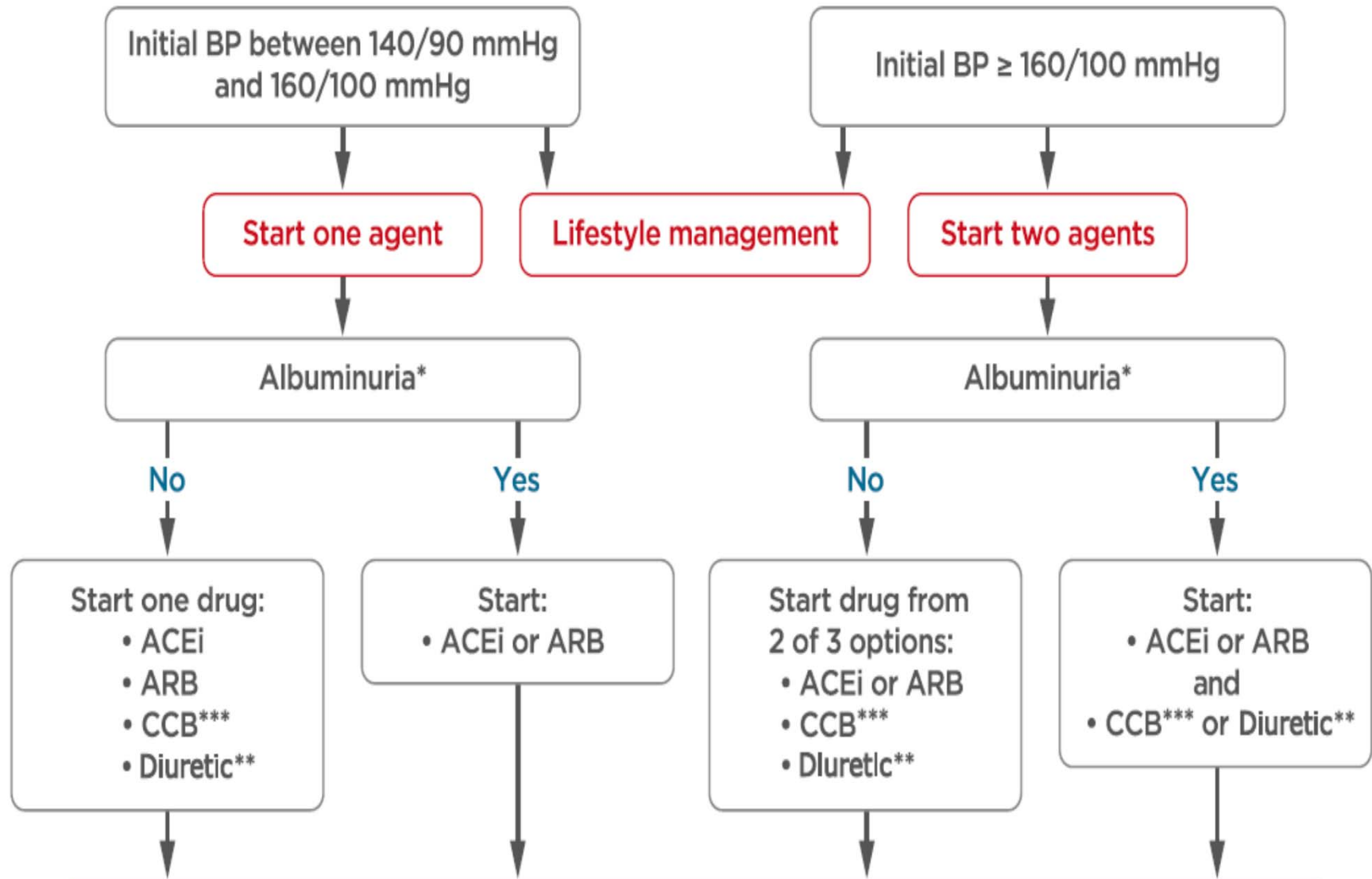
## Recommendations: Hypertension/ Blood Pressure Treatment (4)

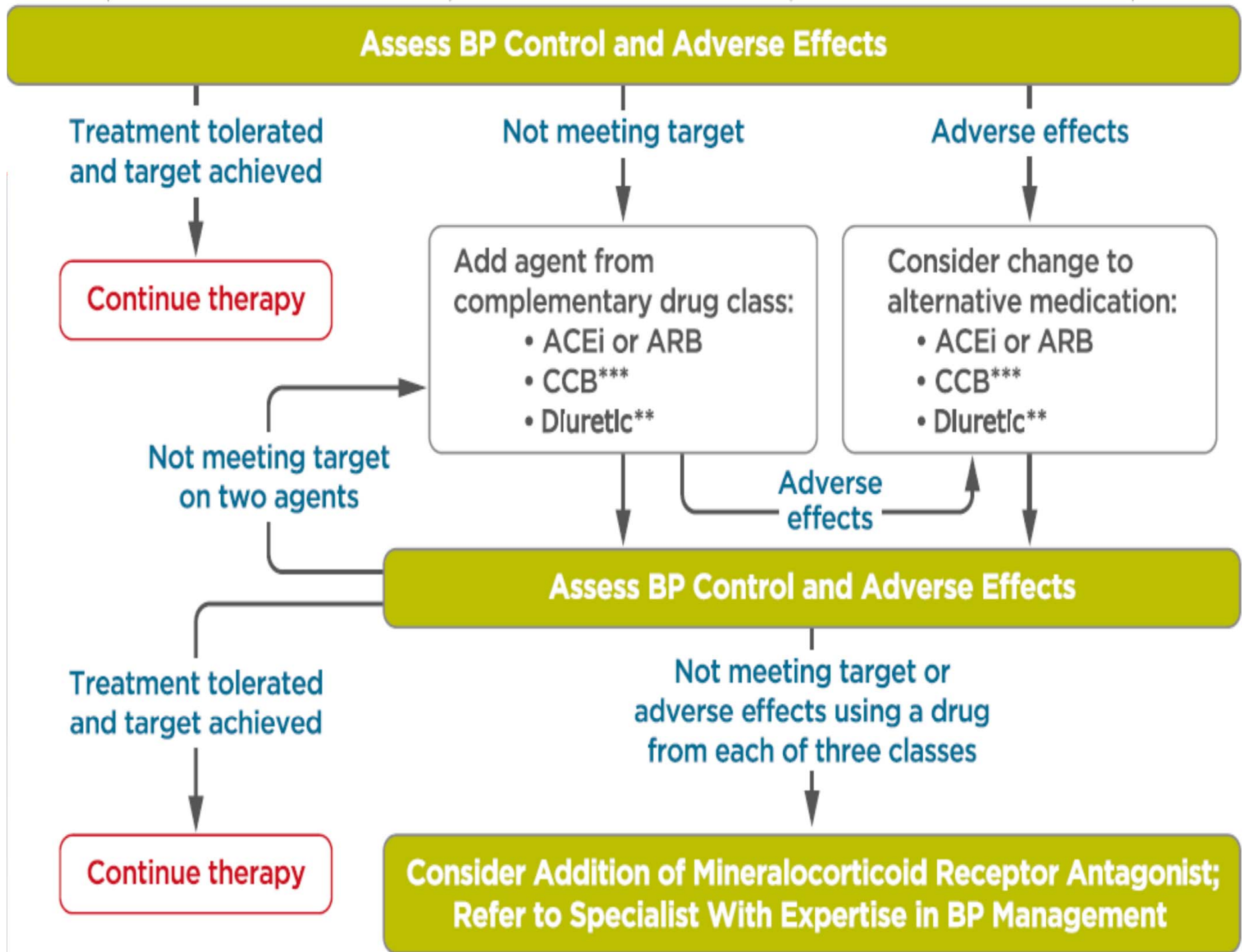
- An ACE inhibitor or angiotensin receptor blocker, at the maximum tolerated dose indicated for blood pressure treatment, is the recommended first-line treatment for hypertension in patients with diabetes and urinary albumin-to-creatinine ratio  $\geq 300$  mg/g creatinine (A) or 30–299 mg/g creatinine (B). If one class is not tolerated, the other should be substituted. B

## Recommendations: Hypertension/ Blood Pressure Treatment (5)

- If using ACE inhibitors, ARBs, or diuretics, monitor serum creatinine / eGFR & potassium levels. **B**

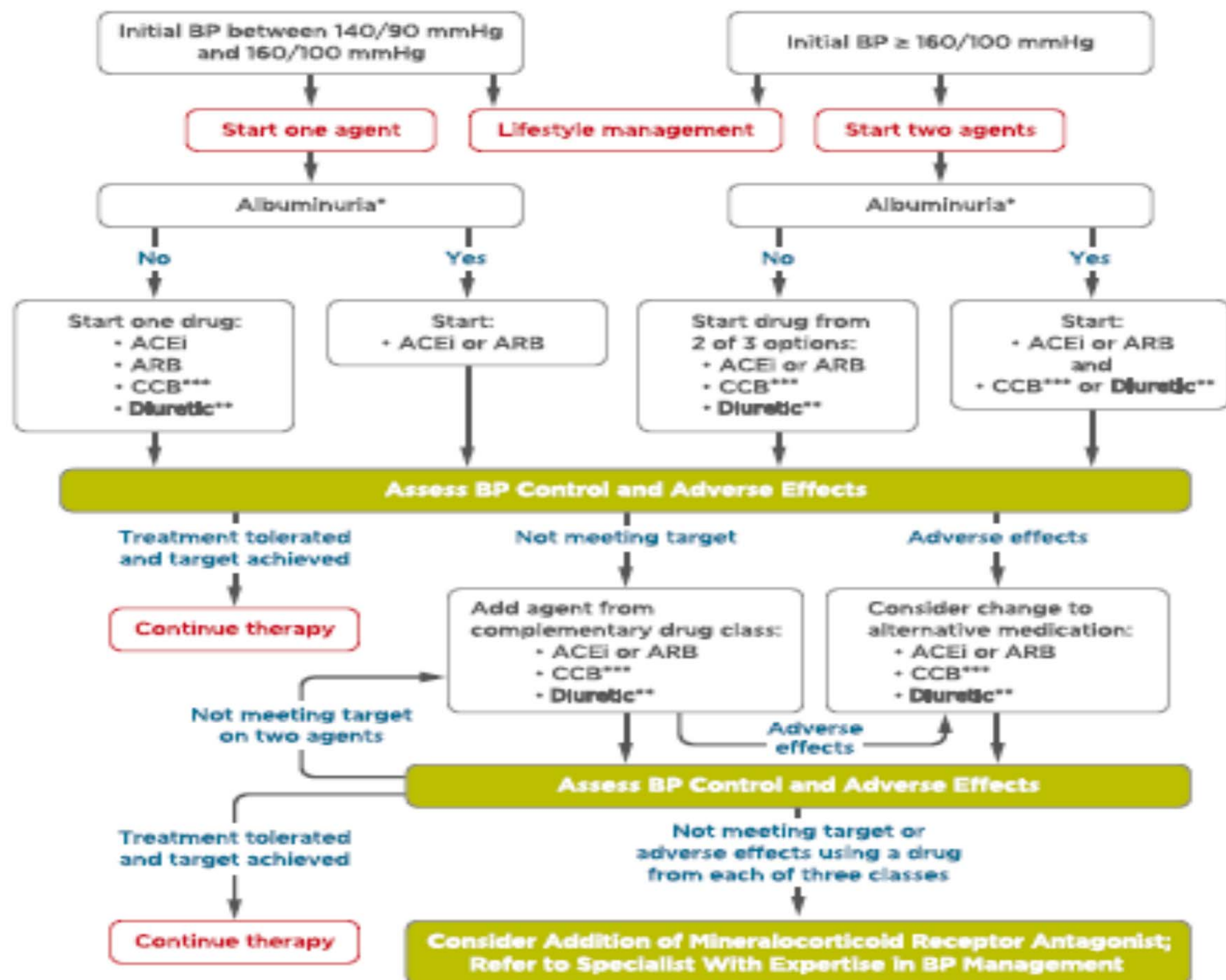
## Recommendations for the Treatment of Confirmed Hypertension in People With Diabetes





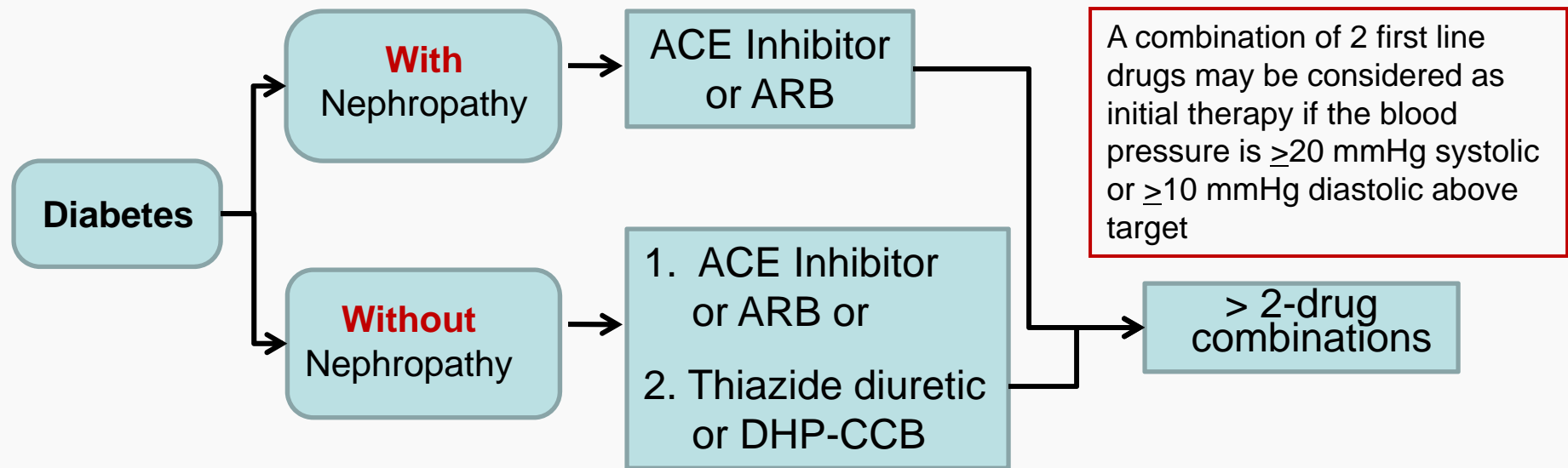


## Recommendations for the Treatment of Confirmed Hypertension in People With Diabetes



# Pharmacotherapy for Hypertension in Patients with Diabetes – Summary

Threshold equal or over 130/80 mmHg and Target below 130/80 mmHg



Monitor serum potassium and creatinine carefully in patients with CKD prescribed an ACEI or ARB

Combinations of an ACEI with an ARB are specifically not recommended in the absence of proteinuria

**More than 3 drugs may be needed to reach target values for diabetic patients**

If Creatinine over 150  $\mu\text{mol/L}$  or creatinine clearance below 30 ml/min ( 0.5 ml/sec), a loop diuretic should be substituted for a thiazide diuretic if control of volume is desired

**Table 2** Summary conclusions

| When?                         | Which one to give?  |  | Which one to avoid?                   |
|-------------------------------|---|--|---------------------------------------|
| Clinical condition of concern | First ARBs of choice  | ARBs with potentially beneficial effects                     | ARBs with potentially negative effect |
| Cardiovascular prevention     | Telmisartan [10–12]   | Losartan [13]  |                                       |
| Heart failure                 | Valsartan [14]<br>Candesartan [15, 16]<br>Losartan [17–19]          |  |                                       |
| Myocardial infarction         | Valsartan [20, 21]  | Telmisartan [10, 22]   |                                       |
| Stroke                        | Losartan [23]   | Telmisartan [24, 25]<br>Candesartan [27]<br>Eprosartan [28]  |                                       |
| Atrial fibrillation           | Telmisartan [34–36]   | Losartan [29, 33]<br>Candesartan [30]<br>Valsartan [31, 32]  |                                       |
| Diabetes mellitus             | Telmisartan [47, 50, 54, 55]<br>Valsartan [47, 53, 55]              | Losartan [47, 53]<br>Irbesartan [47]<br>Candesartan [47, 53] | Olmesartan [47]                       |
| Diabetic nephropathy          | Losartan [60]<br>Irbesartan [61, 62]                                | Telmisartan [63]<br>Valsartan [64–66]<br>Candesartan [67]    | Olmesartan [68–70]                    |
| Metabolic syndrome            | Telmisartan [72, 75, 77–79]   | Valsartan [81, 82]   |                                       |
| Hyperuricemia                 | Losartan [89–91]  | Irbesartan [93]  | Candesartan [89–91]                   |
| Erectile dysfunction          | Valsartan [101–104]<br>Losartan [105, 106]<br>Irbesartan [106, 108] |  |                                       |
| Cognitive decline             |   | Candesartan [116]<br>Irbesartan [116]                        |                                       |

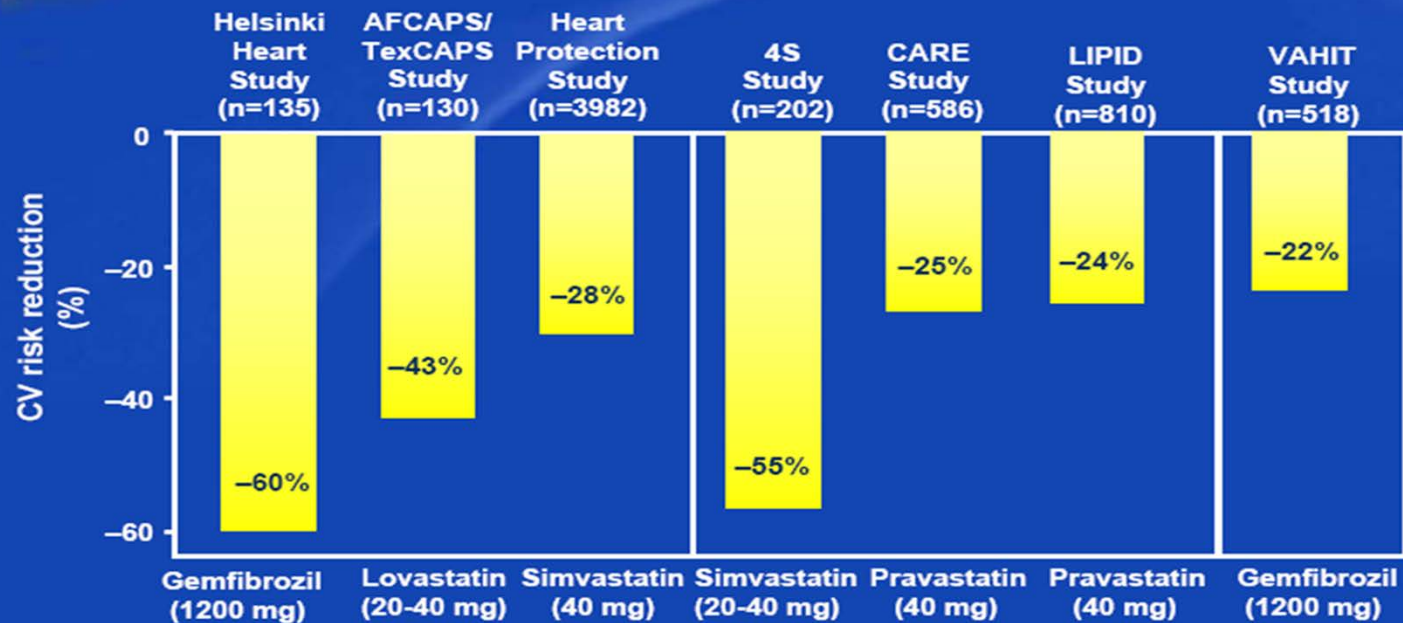
# Managing Cholesterol



## Lipid treatment in diabetes and CV risk reduction

### Primary prevention

### Secondary prevention





## Q12. How is CVD managed in patients with diabetes?

### Statin Use

- Majority of patients with T2D have a high cardiovascular risk
- People with T1D are at elevated cardiovascular risk
- LDL-C target: <70 mg/dL—for the majority of patients with diabetes who are determined to have a high risk
- Use a statin regardless of LDL-C level in patients with diabetes who meet the following criteria:
  - >40 years of age
  - ≥1 major ASCVD risk factor
    - Hypertension
    - Family history of CVD
    - Low HDL-C
    - Smoking

ASCVD = atherosclerotic cardiovascular disease; CVD = cardiovascular disease; HDL-C = high density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

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# Recommendations for Statin Treatment in People with Diabetes

| Age         | Risk Factors   | Statin Intensity*    |
|-------------|--|----------------------|
| <40 years   | None   | None                 |
|             | ASCVD risk factor(s)   | Moderate or high     |
|             | ASCVD  | High                 |
| 40–75 years | None   | Moderate             |
|             | ASCVD risk factors   | High                 |
|             | ACS & LDL $\geq 50$ or in patients with history of ASCVD who can't tolerate high dose statin | Moderate + ezetimibe |
| >75 years   | None   | Moderate             |
|             | ASCVD risk factors   | Moderate or high     |
|             | ASCVD  | High                 |
|             | ACS & LDL $\geq 50$ or in patients with history of ASCVD who can't tolerate high dose statin | Moderate + ezetimibe |

American Diabetes Association Standards of Medical Care in Diabetes.

Cardiovascular disease and risk management. Diabetes Care 2017; 40 (Suppl. 1): S75-S87

# High- and Moderate-Intensity Statin Therapy\*

## High-Intensity Statin Therapy

Lowers LDL by  $\geq 50\%$

Atorvastatin 40-80 mg

Rosuvastatin 20-40 mg

## Moderate-Intensity Statin Therapy

Lowers LDL by 30 -  $< 50\%$

Atorvastatin 10-20 mg

Rosuvastatin 5-10 mg

Simvastatin 20-40 mg

Pravastatin 40-80 mg

Lovastatin 40 mg

Fluvastatin XL 80 mg

Pitavastatin 2-4 mg

\* Once-daily dosing. XL, extended release

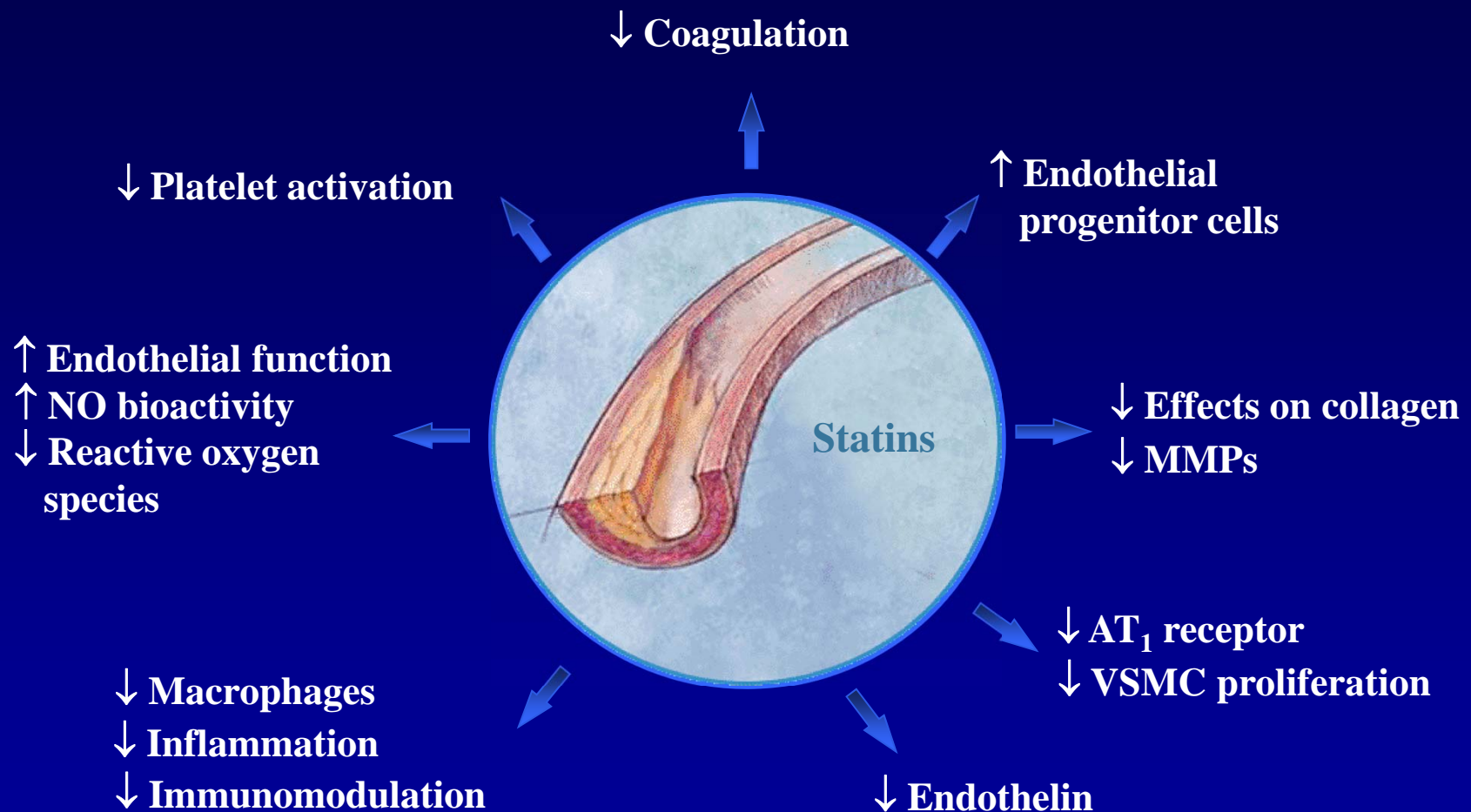
# Recommendations: Lipid Management (5)

- Combination therapy (statin/fibrate) doesn't improve ASCVD outcomes and is generally not recommended **A**. Consider therapy with statin and fenofibrate for men with *both* trigs  $\geq 204$  mg/dL (2.3 mmol/L) and HDL  $\leq 34$  mg/dL (0.9 mmol/L). **B**
- Combination therapy (statin/niacin) hasn't demonstrated additional CV benefit over statins alone, may raise risk of stroke & is not generally recommended. **A**
- Statin therapy is contraindicated in pregnancy. **B**

# Anti HT Drugs and Lipids

| Anti hypertensive agents | On Lipids |
|--------------------------|-----------|
| ACEi and ARBS            | ↓ ↓       |
| CCBs                     | ↔         |
| Diuretics                | ↑         |
| β Blockers               | ↑ ↑       |
| α Blockers               | ↑         |

# Pleiotropic effects of statins

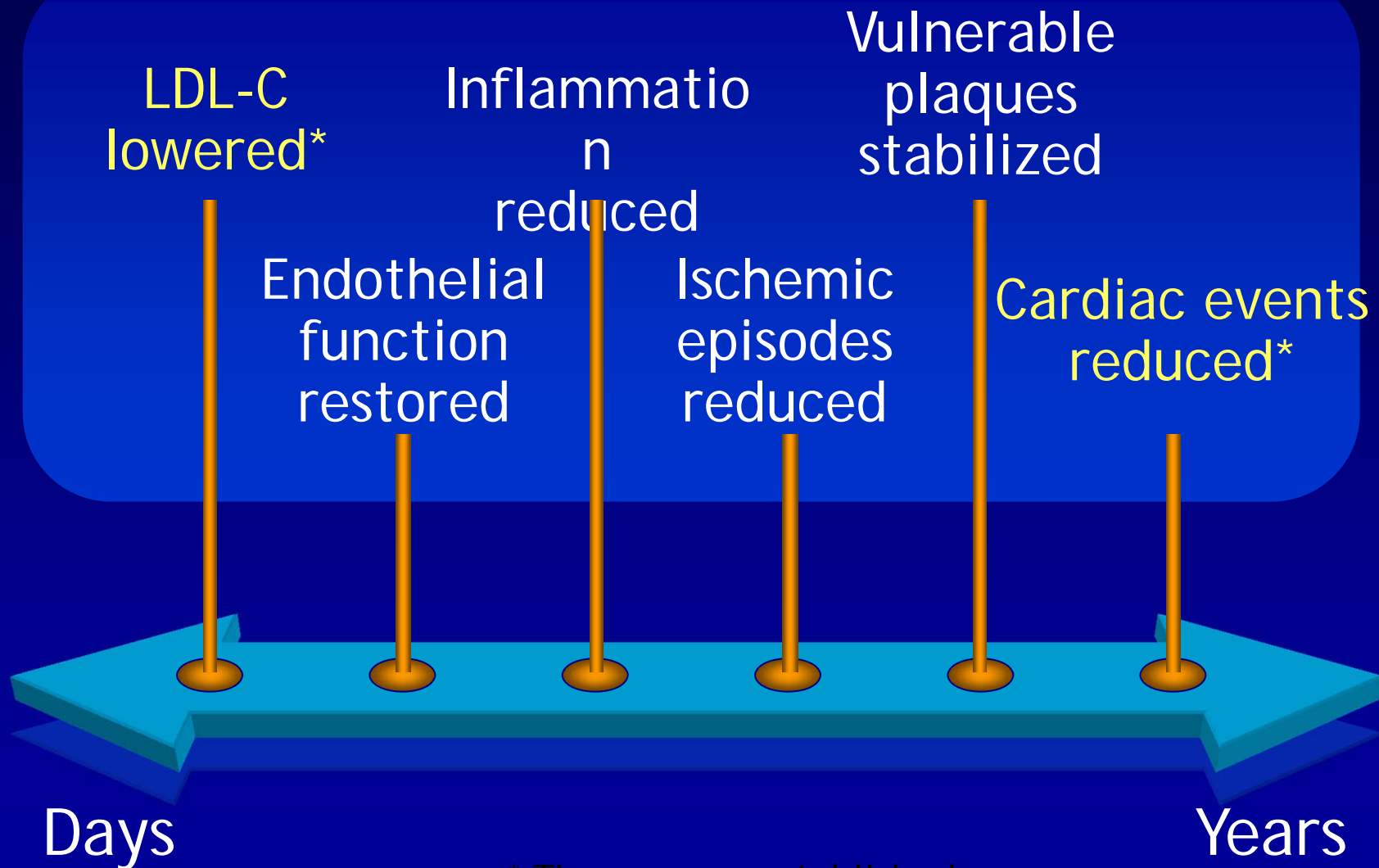


MMPs = matrix metalloproteinases

Liao JK. *Am J Cardiol.* 2005;96(suppl 1):24F-33F.

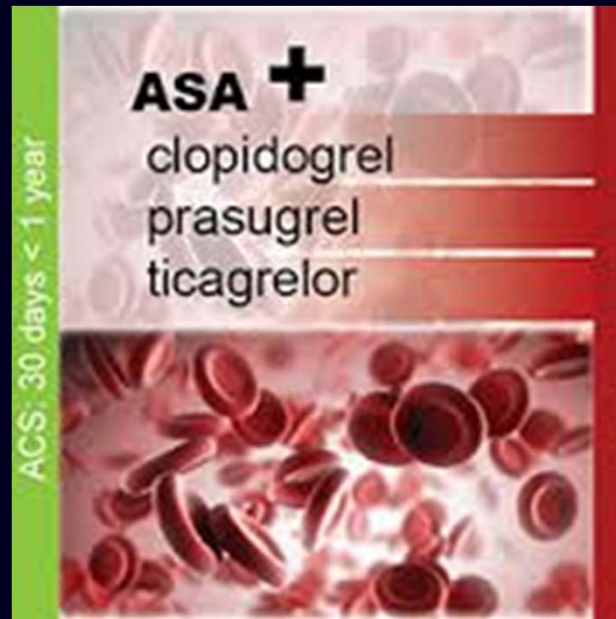


# Time course of Statin effects



\* Time course established

## Antiplatelet



# Recommendations: Antiplatelet Agents

Consider aspirin therapy (75–162 mg/day) **C**

- As a primary prevention strategy in those with type 1 or type 2 diabetes at increased cardiovascular risk
- Includes most men or women with diabetes age  $\geq 50$  years who have at least one additional major risk factor, including:
  - Family history of premature ASCVD
  - Hypertension
  - Smoking
  - Dyslipidemia
  - Albuminuria

# Recommendations: Antiplatelet Agents (2)

- Aspirin is not recommended for ASCVD prevention for adults with DM at low ASCVD risk, since potential adverse effects from bleeding likely offset potential benefits. **C**
  - Low risk: such as in men or women with diabetes aged <50 years with no major additional ASCVD risk factors)
- In patients with diabetes <50 years of age with multiple other risk factors (e.g., 10-year risk 5–10%), clinical judgment is required. **E**

# Recommendations: Antiplatelet Agents (3)

- Use aspirin therapy (75–162 mg/day) as secondary prevention in those with diabetes and history of ASCVD. **A**
- For patients w/ ASCVD & aspirin allergy, clopidogrel (75 mg/day) should be used. **B**
- Dual antiplatelet therapy is reasonable for up to a year after an acute coronary syndrome. **B**



# **ASA Not Routinely Recommended for 1<sup>o</sup> Prevention for CVD Among Patients with DM**

**Insufficient evidence to support use of ASA  
for primary prevention**

Risk of bleeding

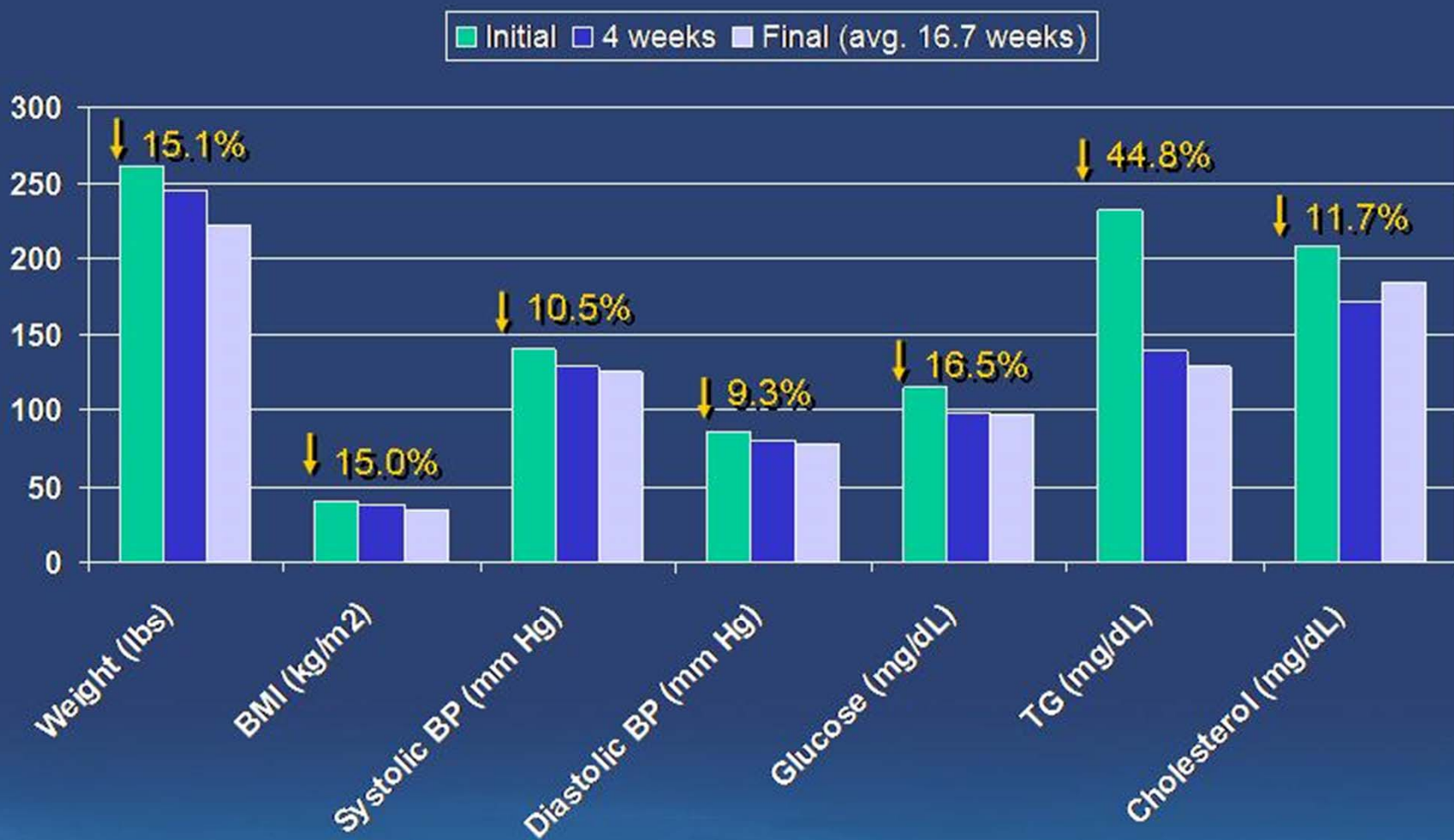


CVD

protection

## Cardiometabolic Risk

### Effect of Moderate Weight Loss On Cardiometabolic Risk Factors



## Q13. How is obesity managed in patients with diabetes?

# Diagnosis of Obesity and Staging of for Management

- Diagnose obesity according to body mass index (BMI)
  - Overweight: BMI 25-29.9 kg/m<sup>2</sup>
  - Obese\*: BMI  $\geq 30$  kg/m<sup>2</sup>
- Consider waist circumference measurement for patients with BMI between 25 and 35 kg/m<sup>2</sup>
  - Larger waist circumference = higher risk for metabolic disease
    - Men: >102 cm (40 in)
    - Women: >88 cm (35 in)
- Evaluate patients for obesity-related complications to determine disease severity and appropriate management

\*BMI 23-24.9 may be considered obese in certain ethnicities; perform waist circumference and use ethnicity-specific criteria in risk analysis.

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# Recommendations: Smoking Cessation

- Advise all patients not to smoke (A)
- Include smoking cessation counseling and other forms of treatment as a routine component of diabetes care (B)

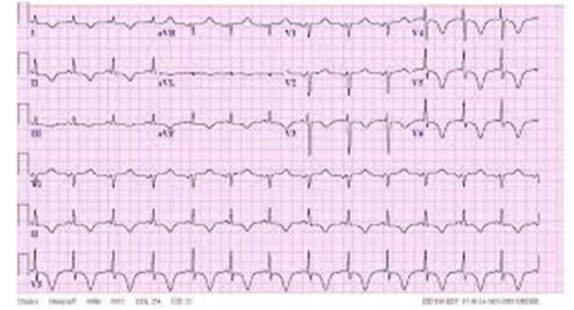


\*If not contraindicated.



## CASE

- Mr A, 50 years, c/o chest pain
- Type 2 DM for 7 years,
- Hypertension for 4 years
- Smoke 10 cigarette/day
- BMI 30
- ECG IHD, Heart rate 90/min
- FBS 120mg%, HbA1c 7%, BP 150/90,
- On metformin 500mg BD, losartan 50 mg od
- Any more treatment?



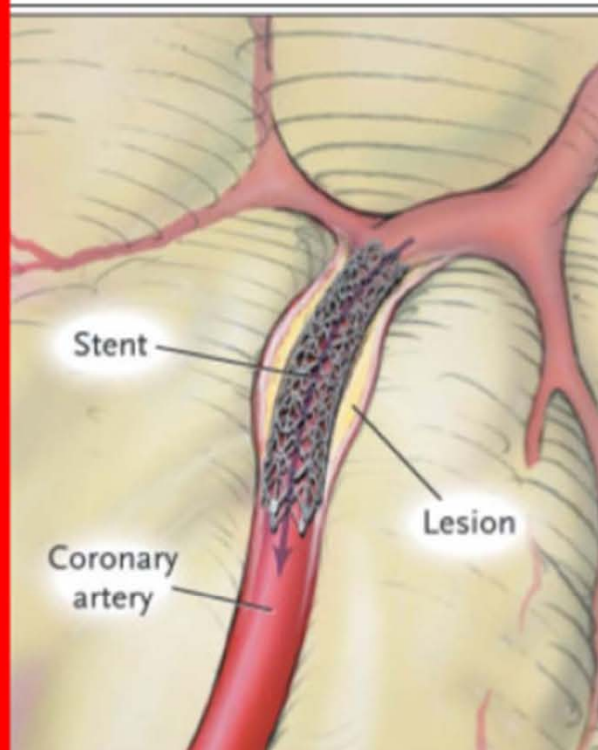


# Treatment Options in Patients with Angina

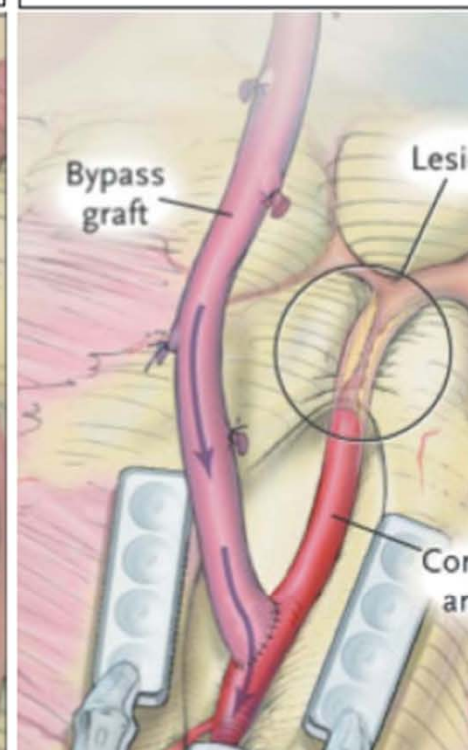
## Optimal Medical Therapy (OMT)



## Percutaneous Coronary Intervention



## Aorto-Coronary Bypass (ACB)



Speaker

## Treatment

- Lifestyle Management
- Metformin 500mg BD
- Stop smoking
- ACEI, Beta blocker(carvidolol ,metoprolol,omit losartan,)
- Atovastatin 40 mg od
- Aspirin 75 mg od
- Monotrate,if HR cannot controlled with beta blocker---Ivabradine
- Obesity management

# Goals in the Management of Stable Angina

- To Decrease Anginal Symptoms
    - Medical treatment  
( $\beta$ -blockers, CCBs, nitrates, metabolic agent ( Trimetazidine) , ivabradine)
    - Revascularization procedures (PCI, CABG)
  - To Improve Prognosis (Mortality reduction)
    - Modification of risk factors
    - Aspirin
    - Lipid-lowering therapy
    - ACE-Inhibitor
  - Effect on natural history
-



# Risk factor Modification

- Smoking
- Diabetes Mellitus- HbA1c ( 7%)
- Obesity- BMI between 18.5 and 24.9 kg/m<sup>2</sup>.
  - gradually reduce body weight by approximately 10% from baseline
- Hypertension- BP < 140/90 mm Hg or <130/80 mm Hg
  - BB and/or ACEI
- Dyslipidemia- LDL-C should be <100 mg/dL
  - statin therapy is reasonable.
- Stress
- Physical activity- 30 to 60 minutes, 7d/wk (minimum 5d/wk)



# ACS Discharge management

➡ NSTEMI-ACS pt should be hospitalized for at least 24 h after successful stenting of the culprit lesion

|  |   |
|--|---|
| <b><i>Aspirin</i></b>                                | Continue life long  |
| <b><i>P2Y<sub>12</sub> inhibitor</i></b>             | Continue for 12 months (unless at high risk of bleeding)  |
| <b><i>β-Blocker</i></b>                              | Consider for all especially if LV function depressed  |
| <b><i>ACEI/ARB</i></b>                               | Consider for all especially if LV function depressed  |
| <b><i>Aldosterone antagonist/<br/>Eplerenone</i></b> | If depressed LV function (LVEF ≤35%) and either DM or HF, without significant renal dysfunction |
| <b><i>Statin</i></b>                                 | Titrate to achieve target LDL-C levels < 1.8 mmol/L (<70 mg/dL)                                 |
| <b><i>Lifestyle</i></b>                              | Cardiac rehabilitation<br>Risk-factor modification and secondary prevention                     |



# Non-Insulin Therapy for Hyperglycemia in Type 2 Diabetes, Match Patient Characteristics to Drug Characteristics

## A. $\beta$ -Cell-Centric Construct: Egregious Eleven The $\beta$ -Cell is the **FINAL COMMON DENOMINATOR** Of the Mechanisms of $\beta$ -Cell Damage

### 8. Colon/Biome

Probiotics  
Incretins



### 9. Immune Dysregulation/ Inflammation

Incretins,  
Anti-Inflammatories  
Immune modulators



↓Amylin

### 10. Stomach/ Small intestine

GLP-1 Agonists  
Pramlintide  
AGI



### 1. Pancreatic $\beta$ -cells

↓  $\beta$ -Cell function  
↓  $\beta$ -Cell mass  
↓ **Insulin** Incretins,  
Ranolazine

**FINAL COMMON  
DENOMINATOR**

2. ↓ Incretin  
Effect

3.  $\alpha$ -Cells  
defect

↑ Glucagon  
Incretins  
Pramlintide

**HYPERGLYCEMIA**

11. Kidney  
SGLT2 inhibitors



### 7. Brain

Incretins  
Dopamine agonist-QR  
Appetite Suppressants



### INSULIN RESISTANCE

#### 6. Liver

Metformin  
TZDs



#### 5. Muscle

TZDs  
Metformin



#### 4. Adipose

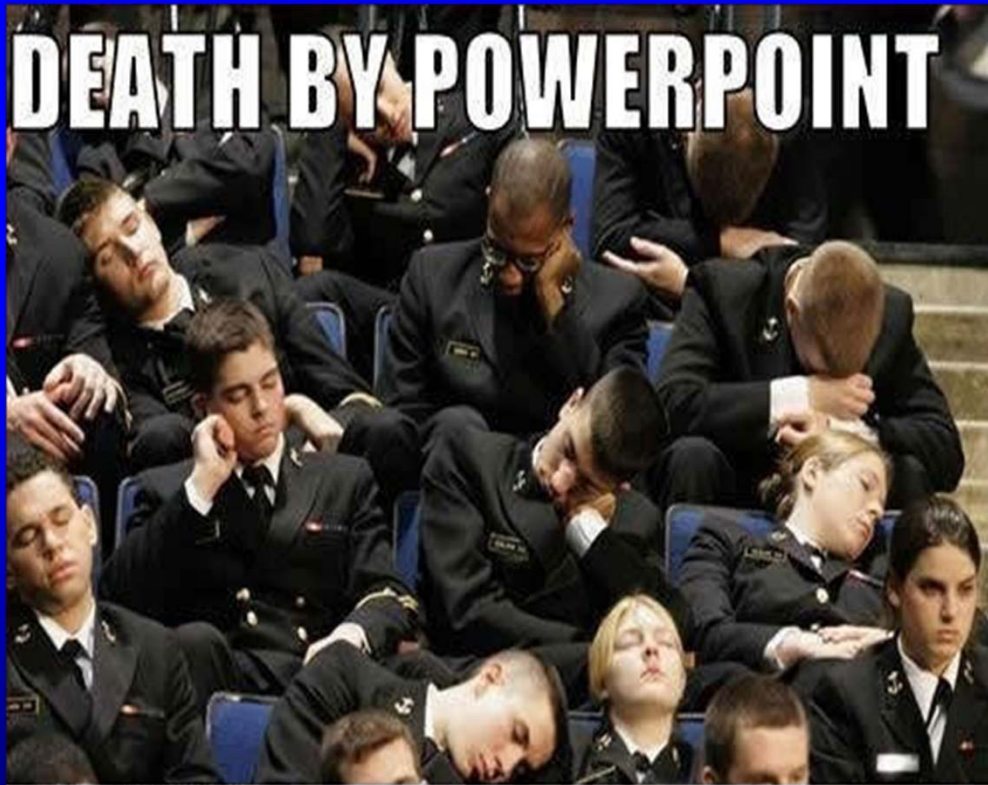
TZDs  
Metformin



# Summary of Care: ABC's for Providers

|          |   |
|----------|---|
| <b>A</b> | <b>A1c Target<br/>Aspirin Daily</b>                           |
| <b>B</b> | <b>Blood Pressure Control</b>                                 |
| <b>C</b> | <b>Cholesterol Management<br/>Cigarette Smoking Cessation</b> |
| <b>D</b> | <b>Diabetes and Pre-Diabetes<br/>Management</b>               |
| <b>E</b> | <b>Exercise</b>   |
| <b>F</b> | <b>Food Choices</b>   |

Thank you  
drkoko@gmail.com



more awesome pictures at [THEMETAPICTURE.COM](http://THEMETAPICTURE.COM)

