

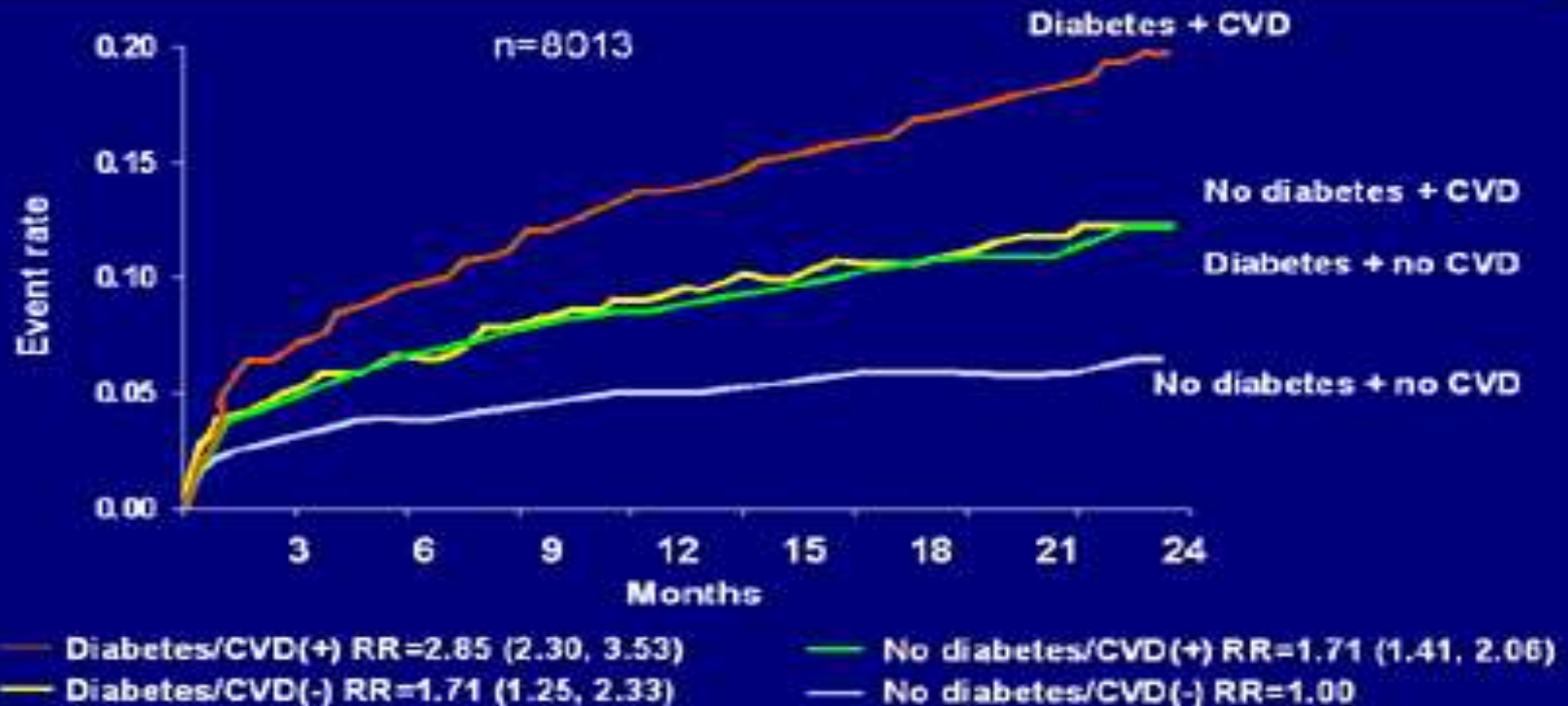
Long-Term Complications of  
Diabetes Mellitus  
**Macrovascular Complication**

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# Diabetes = CVD equivalent

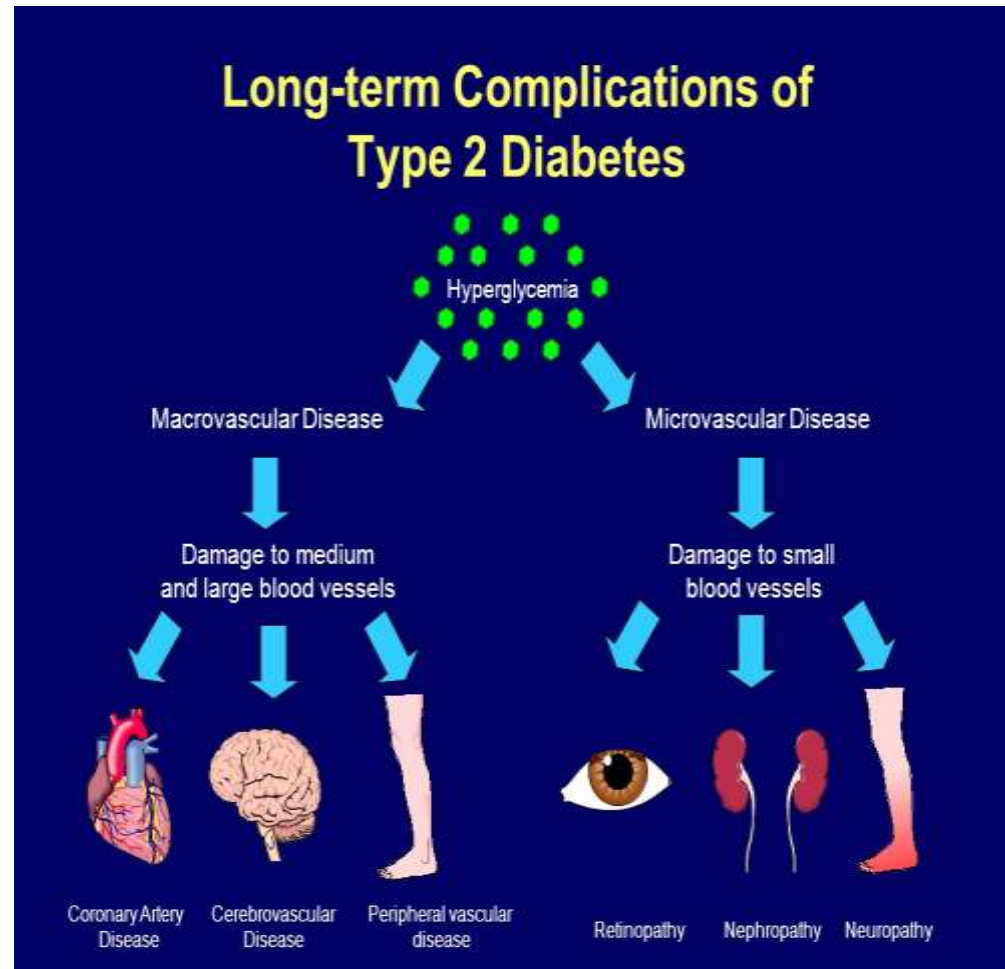
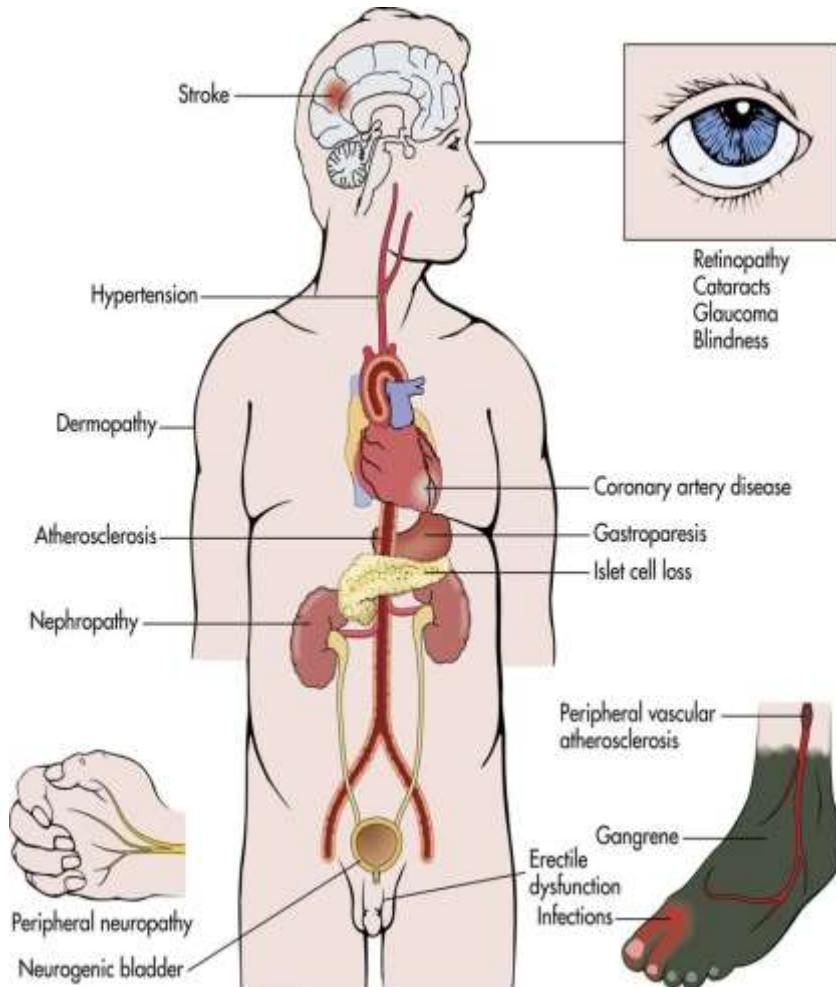
## Patients With Diabetes at High Risk of Cardiovascular Mortality: OASIS Registry



OASIS = Organization to Assess Strategies for Ischemic Syndromes

Adapted with permission from Malmberg K et al. *Circulation*. 2000;102:1014

# Long-term complications of diabetes mellitus



# Chronic complications of diabetes

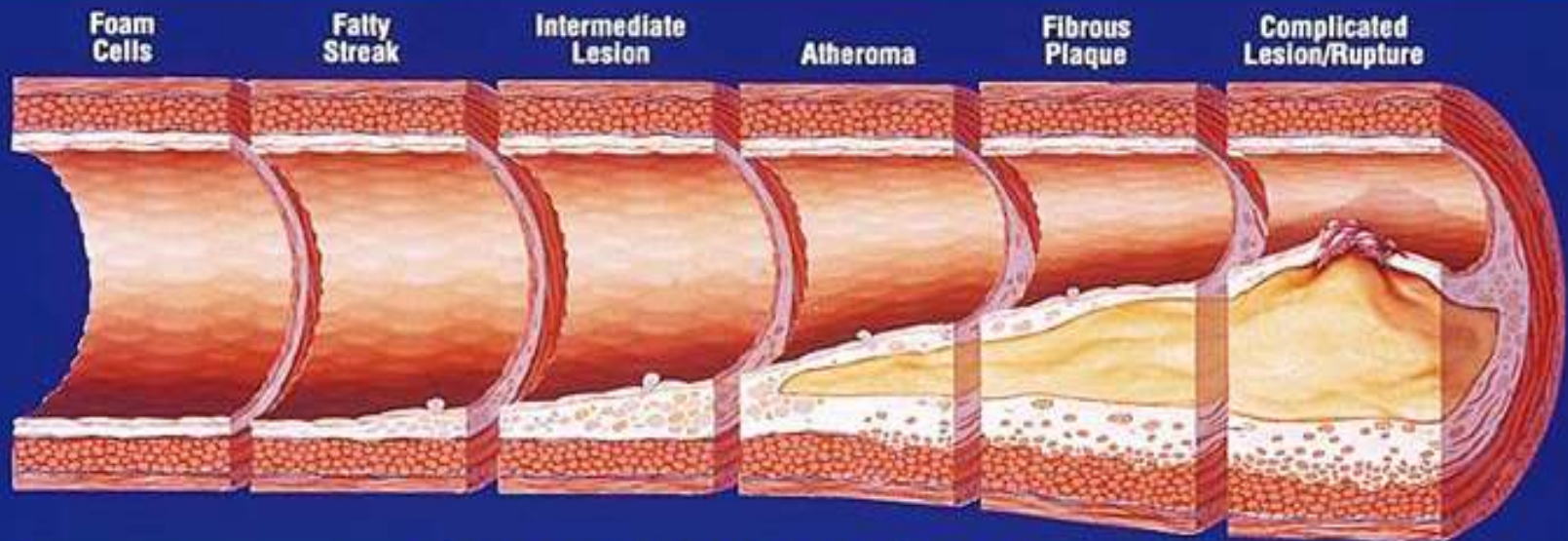
- Categories of long-term diabetic complications
  - macrovascular disease : Large to medium sized artery, Atherosclerosis
  - microvascular disease
  - neuropathy
- **Hypertension, Dyslipidemia**
  - major contributing factor especially in macrovascular disease



# Macrovascular Changes

VBWG

## Atherosclerosis Timeline



ENDOTHELIAL DYSFUNCTION

From first decade

From third decade

From fourth decade

Growth mainly by lipid accumulation

Smooth muscle  
and collagen

Thrombosis,  
hematoma

Adapted from Stary HC et al. *Circulation*. 1995;92:1355-1374.

Hypertension, Dyslipidemia, Platelet aggregation

# **Cardiovascular Disease and Risk Management 2017 standard care**

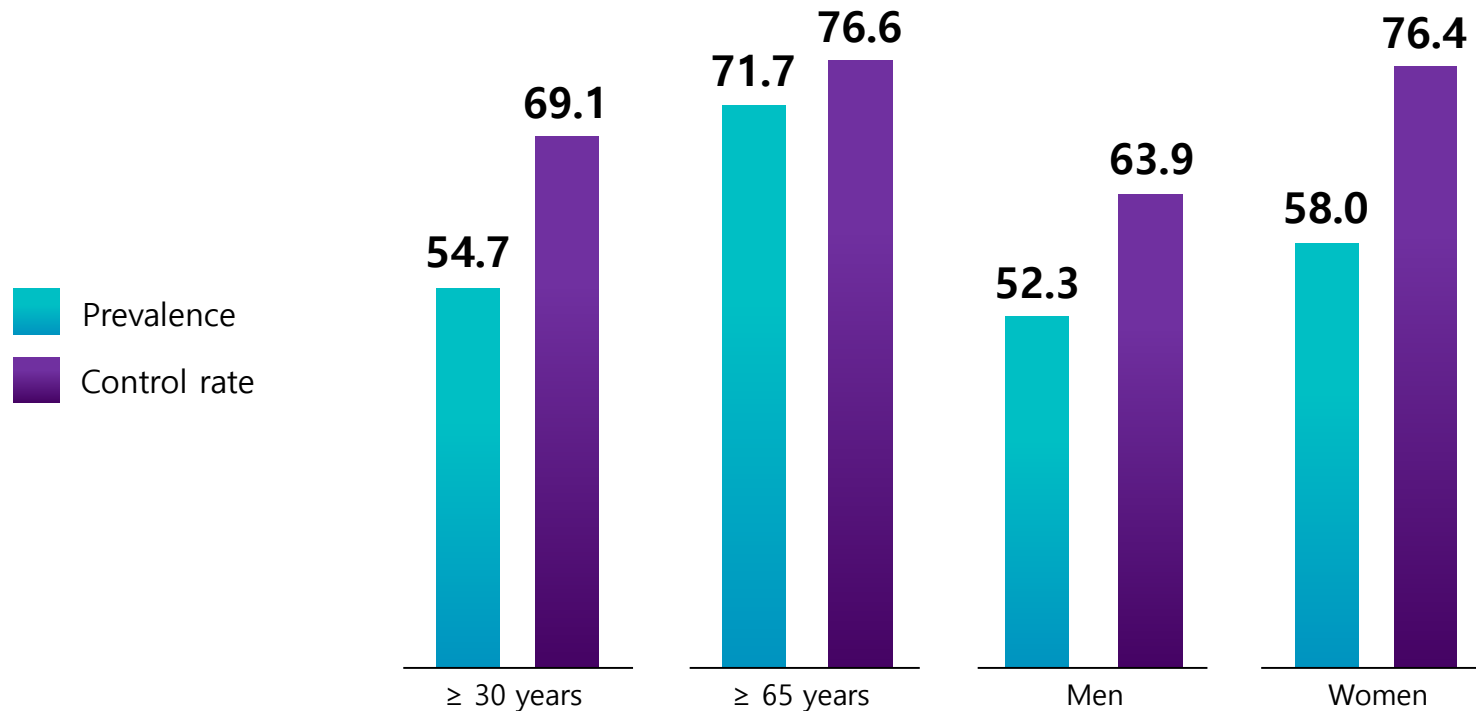
# Hypertension in Diabetes in Korea

The prevalence and control rate of hypertension in persons with diabetes are 54.7% and 69.1%, respectively.

“In men aged 40~49 years with diabetes, fewer than half do not reach the blood pressure goal of < 140/85 mmHg”



단위(%)



Hypertension is defined by systolic/diastolic blood pressure  $\geq 140/90$  mmHg and/or antihypertensive medications, and control rate is defined by blood pressure less than 140/85 mmHg based on the KDA guideline.

# Blood Pressure Control & T2DM

## Action to Control Cardiovascular Risk in Diabetes (ACCORD):

- Does SBP <120 provide better cardiovascular protection than SBP 130-140? **No.**

## ADVANCE-BP:

- Significant risk reduction



# Recommendations: Hypertension/ Blood Pressure Control

## Screening and Diagnosis:

- Blood pressure should be measured at every routine visit. **B**
- Patients found to have elevated blood pressure should have blood pressure confirmed on a separate day. **B**

## 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

- Patients with BP  $>120/80$  should be advised on lifestyle changes to reduce BP. **B**
- Patients with confirmed BP  $>140/90$  should, in addition to lifestyle therapy, have prompt initiation and timely subsequent titration of pharmacological therapy to achieve blood pressure goals. **A**

## 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**

당뇨병환자는 병원 방문 시마다  
혈압을 측정 [B]

Monitor BP at every OPD visit



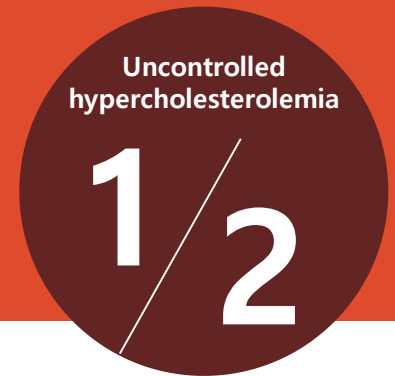
당뇨병환자의 목표혈압  
수축기 **140 mm Hg** 미만, 이완기 **85 mm Hg** 미만

Systolic < 140, Diastolic <85 mmHg

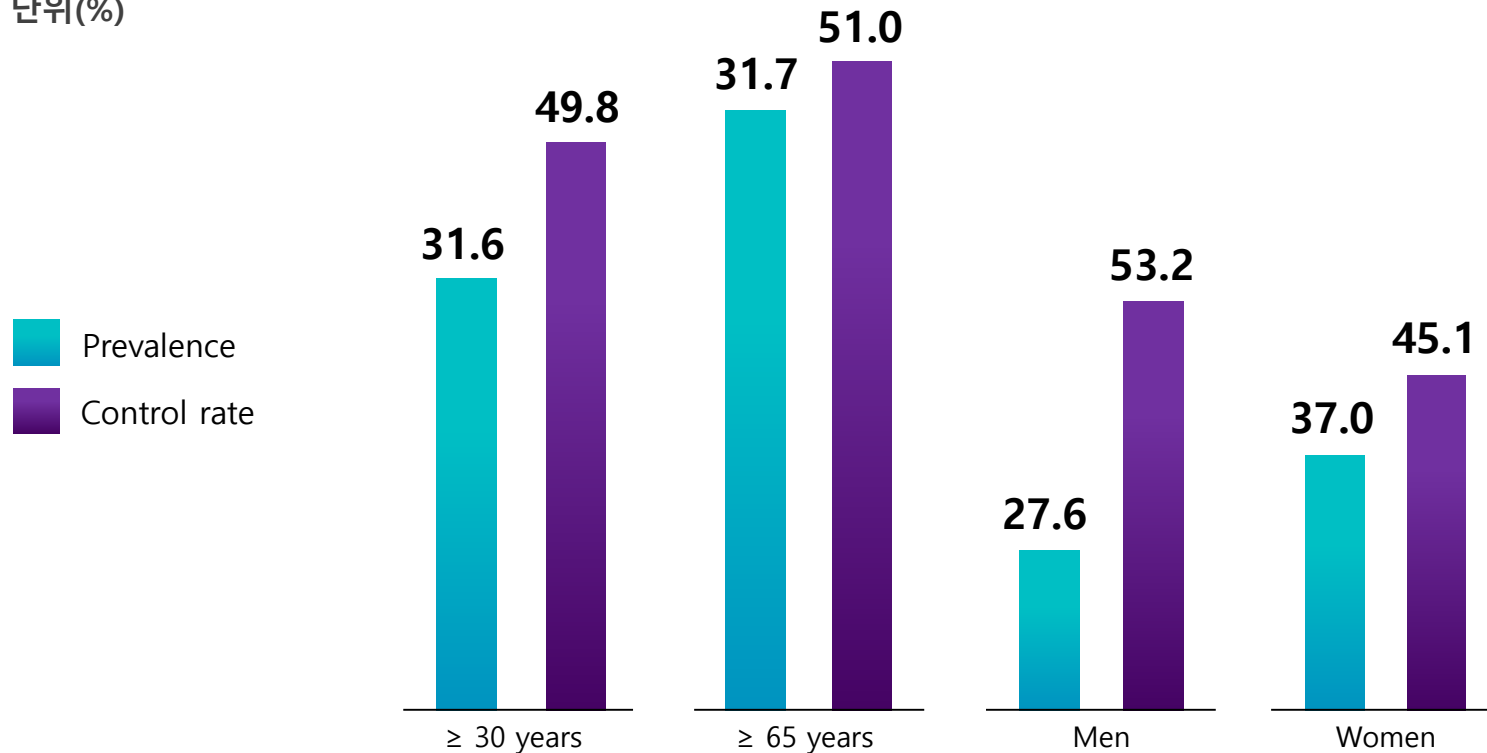
# Hypercholesterolemia in Diabetes

The prevalence and control rate of hypercholesterolemia in persons with diabetes are 31.6% and 49.8%, respectively.

**“More than half of persons with diabetes do not reach the LDL-C goal of < 100 mg/dL”**



단위(%)



Hypercholesterolemia is defined by total cholesterol  $\geq 240$  mg/dL or medication(s) and control rate is defined by low-density lipoprotein cholesterol (LDL-C)  $< 100$  mg/dL based on KDA guideline.

# Recommendations: Lipid Management

- In adults not taking statins, a screening lipid profile is reasonable (E):
  - At diabetes diagnosis
  - At the initial medical evaluation
  - And every 5 years, or more frequently if indicated
- Obtain a lipid profile at initiation of statin therapy, and periodically thereafter. E

# Recommendations: Lipid Management (2)

- To improve lipid profile in patients with diabetes, recommend lifestyle modification **A**, focusing on:
  - Weight loss (if indicated)
  - Reduction of saturated fat, trans fat, cholesterol intake
  - Increase of  $\omega$ -3 fatty acids, viscous fiber, plant stanols/sterols
  - Increased physical activity

# Recommendations: Lipid Management (3)

- Intensify lifestyle therapy & optimize glycemic control for patients with: **C**
  - Triglyceride levels  $\geq 150$  mg/dL (1.7 mmol/L) and/or
  - HDL cholesterol  $< 40$  mg/dL (1.0 mmol/L) in men and  $< 50$  mg/dL (1.3 mmol/L) in women
- For patients with fasting triglyceride levels  $\geq 500$  mg/dL (5.7 mmol/L), evaluate for secondary causes and consider medical therapy to reduce the risk of pancreatitis. **C**



# New ACC/AHA guideline

ACCEPTED MANUSCRIPT

Stone NJ, et al.  
2013 ACC/AHA Blood Cholesterol Guideline

## 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

### A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines

Endorsed by  
Pharmac  
Cardiologists, I

**Ultimate goals: prevent ASCVD and improve  
the management of patients with ASCVD**

n, American  
of Black  
tional Coalition

#### EXPERT PANEL MEMBERS

Neil J. Stone, MD, MACP, FAHA, FACC, *Chair*

Jennifer Robinson, MD, MPH, FAHA, *Vice Chair*

Alice H. Lichtenstein, DSc, FAHA, *Vice Chair*

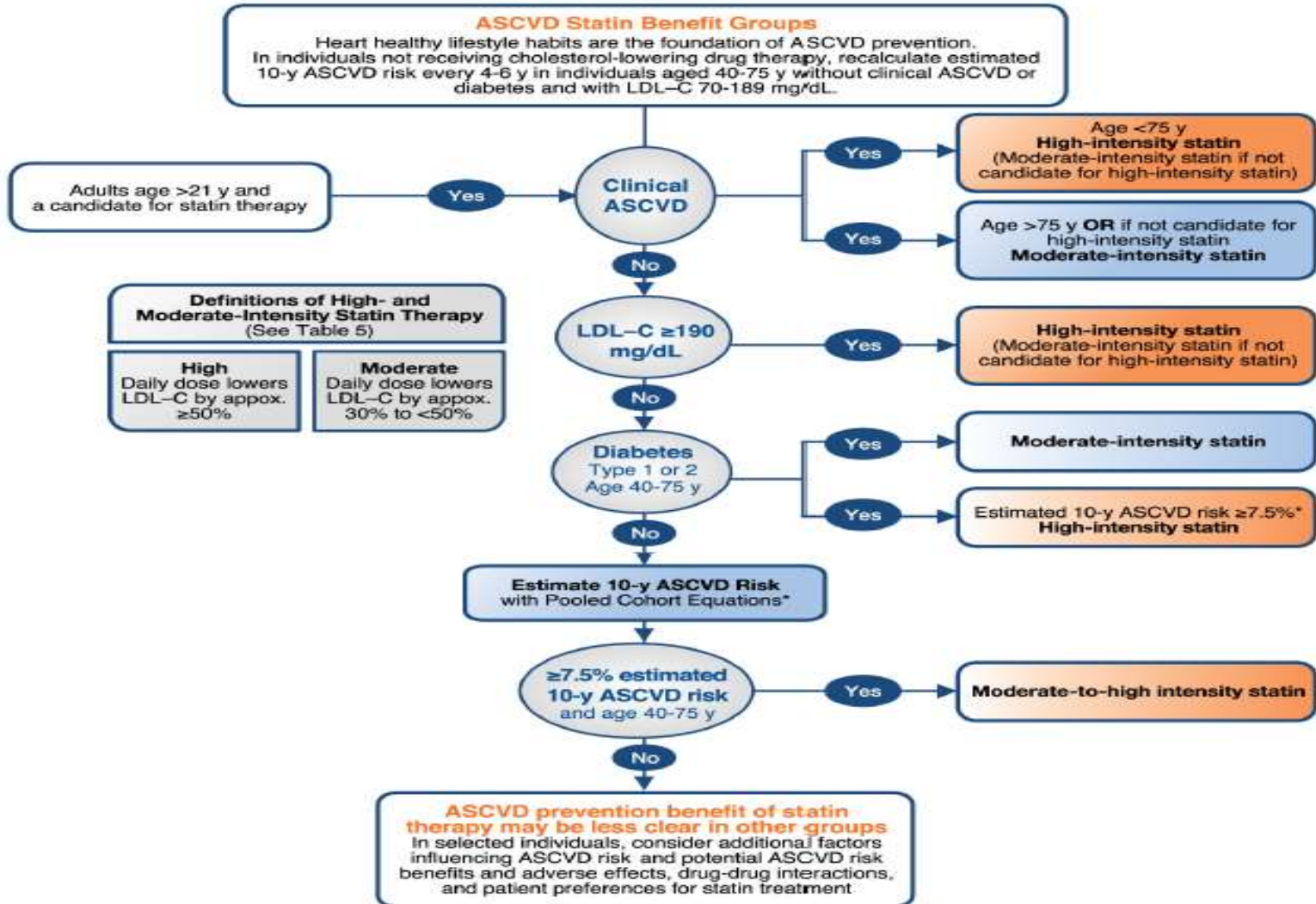
C. Noel Bairey Merz, MD, FAHA, FACC

Conrad B. Blum MD FAHA

Donald M. Lloyd-Jones, MD, ScM, FACC, FAHA

Patrick McBride MD MPH FAHA

# New ACC/AHA guideline



# Focus on ASCVD Risk Reduction: 4 statin benefit groups\*

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Clinical ASCVD<sup>†</sup>

LDL-C level  
≥190 mg/dL

Diabetes, aged 40-75  
years, with LDL-C  
70-189 mg/dL

Estimated 10-year risk of  
ASCVD of ≥7.5%,<sup>‡</sup> 40-75  
years of age, and with  
LDL-C 70-189 mg/dL

**\* Moderate- or high-intensity statin therapy recommended for these 4 groups**

<sup>†</sup> Clinical ASCVD defined as acute coronary syndromes, history of MI, stable or unstable angina, coronary or arterial revascularization, stroke, transient ischemic attacks, or peripheral artery disease

<sup>‡</sup> Estimated using Pooled Cohort Risk Assessment Equations

In Asian: can be considered lesser potent statin

# Intensity of Statin Therapy

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
LDL-C ↓ ≥50%	LDL-C ↓ 30% to <50%	LDL-C ↓ <30%
<b>Atorvastatin (40<sup>†</sup>)–80 mg</b> <b>Rosuvastatin 20 (40) mg</b>	<b>Atorvastatin 10 (20) mg</b> <b>Rosuvastatin (5) 10 mg</b> <b>Simvastatin 20–40 mg<sup>‡</sup></b> <b>Pravastatin 40 (80) mg</b> <b>Lovastatin 40 mg</b> <i>Fluvastatin XL 80 mg</i> <b>Fluvastatin 40 mg bid</b> <i>Pitavastatin 2–4 mg</i>	<i>Simvastatin 10 mg</i> <b>Pravastatin 10–20 mg</b> <b>Lovastatin 20 mg</b> <i>Fluvastatin 20–40 mg</i> <i>Pitavastatin 1 mg</i>

**Lifestyle modification remains a critical component of ASCVD risk reduction, both prior to and in concert with the use of cholesterol lowering drug therapies.**

Statins/doses that were not tested in randomized controlled trials (RCTs) reviewed are listed in *italics*

<sup>†</sup>Evidence from 1 RCT only: down-titration if unable to tolerate atorvastatin 80 mg in IDEAL

<sup>‡</sup>Initiation of or titration to simvastatin 80 mg not recommended by the FDA due to the increased risk of myopathy, including rhabdomyolysis.

# Recommendations for Statin Treatment in People with Diabetes

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

# Recommendations: Lipid Management (4)

- In clinical practice, providers may need to adjust intensity of statin therapy based on individual patient response to medication (e.g., side effects, tolerability, LDL cholesterol levels). **E**
- Ezetimibe + moderate intensity statin therapy provides add'l CV benefit over moderate intensity statin therapy alone; consider for patients with a recent acute coronary syndrome w/ LDL  $\geq$  50mg/dL **A** or in patients with a history of ASCVD who can't tolerate high-intensity statin therapy. **E**



# Recommendations: Lipid Management (5)

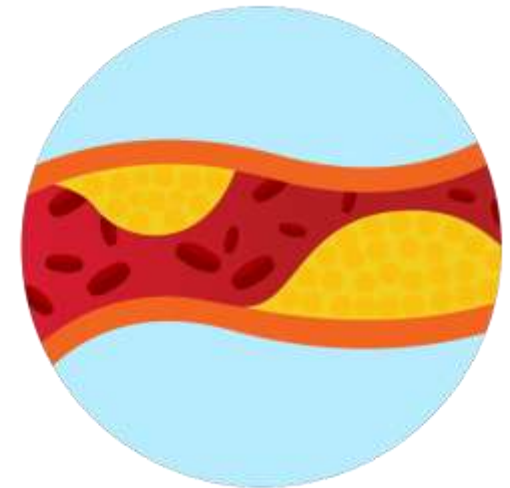
- Combination therapy (statin/fibrate) doesn't improve ASCVD outcomes and is generally not recommended **A**. Consider therapy with statin and fenofibrate for men with *both* trigs  $\geq 204$  mg/dL (2.3 mmol/L) and HDL  $\leq 34$  mg/dL (0.9 mmol/L). **B**
- Combination therapy (statin/niacin) hasn't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

# 이상지질혈증 관리

Dyslipidemia management in  
Korea : NCEP + AHA

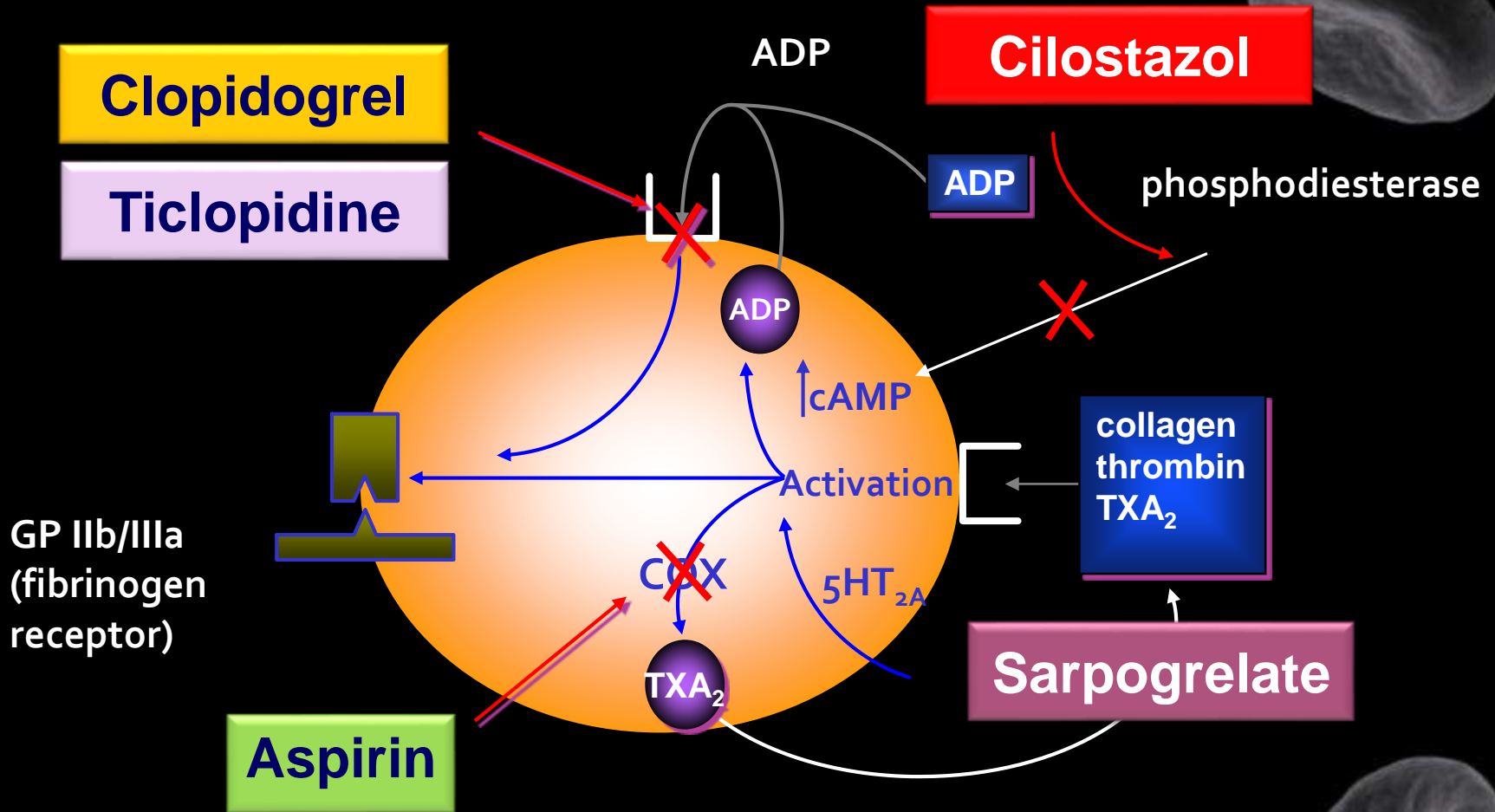


- 지질검사 : 매년 1회 이상 시행 [E]
- 일차목표 : LDL 콜레스테롤 100 mg/dL 미만
- 심혈관질환이 있거나 심혈관질환 고위험 당뇨병환자의 경우 LDL 콜레스테롤이 70 mg/dL 미만 [B]
- 일차 치료약제 : 스타틴 [B]
- 최대 스타틴 용량에서도 목표치에 도달하지 못할 경우  
기저 LDL콜레스테롤의 30-40%감소를 또 다른 목표치로 사용 [B]
- 중성지방 150 mg/dL 미만, HDL 콜레스테롤은 남자 40 mg/dL 초과,  
여자 50 mg/dL 초과로 조절 [C]



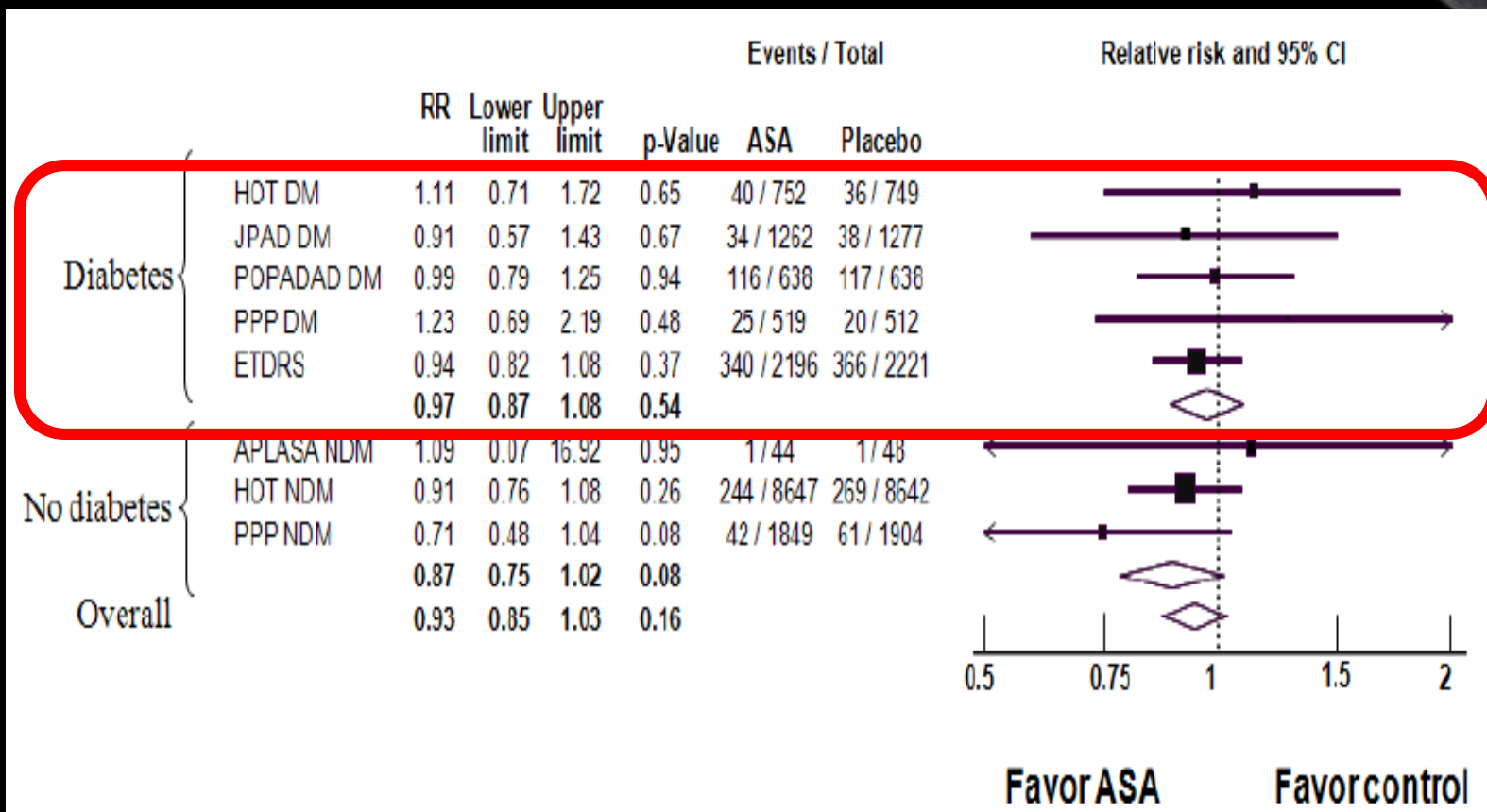
# Mechanisms of Action

## Oral Antiplatelet Therapies



ADP = adenosine diphosphate, TXA<sub>2</sub> = thromboxane A<sub>2</sub>, COX = cyclooxygenase.

# Aspirin for the primary prevention of cardiovascular events



Overall effect in patients with diabetes not significant.

# 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**

# Recommendations: Coronary Heart Disease

## Screening

- In asymptomatic patients, routine screening for CAD isn't recommended & doesn't improve outcomes provided ASCVD risk factors are treated. **A**
- Consider investigations for CAD with:
  - Atypical cardiac symptoms (e.g. unexplained dyspnea, chest discomfort)
  - Signs or symptoms of associated vascular disease incl. carotid bruits, transient ischemic attack, stroke, claudication or PAD
  - EKG abnormalities (e.g. Q waves) **E**

Treadmill test, Multi-detector CT, SPECT, or Coronary angiography

# Recommendations: Coronary Heart Disease (2)

## Treatment

- In patients with known ASCVD, use aspirin and statin therapy (if not contraindicated) **A** and consider ACE inhibitor therapy **C** to reduce risk of cardiovascular events.
- In patients with a prior MI,  $\beta$ -blockers should be continued for at least 2 years after the event. **B**

# Conclusion

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- To prevent macrovascular complication of diabetes mellitus (in Type 1 or Type2 DM)
  - Glycemic control & management of Multiple CV risk factors
    - Hypertension: <140/90 mmHg (but, we should modify the target for considering the degree of target organ damage)
    - Dyslipidemia: over 40 yrs of diabetes, CV risk factors
      - Statin therapy (intensified) is essential
    - Low dose anti-platelet therapy
      - Not for the primary prevention in DM patients with low ASCVD risk
      - Definitely Yes!!! For the secondary prevention of CVD