# Macrovascular Complications and Dyslipidemia

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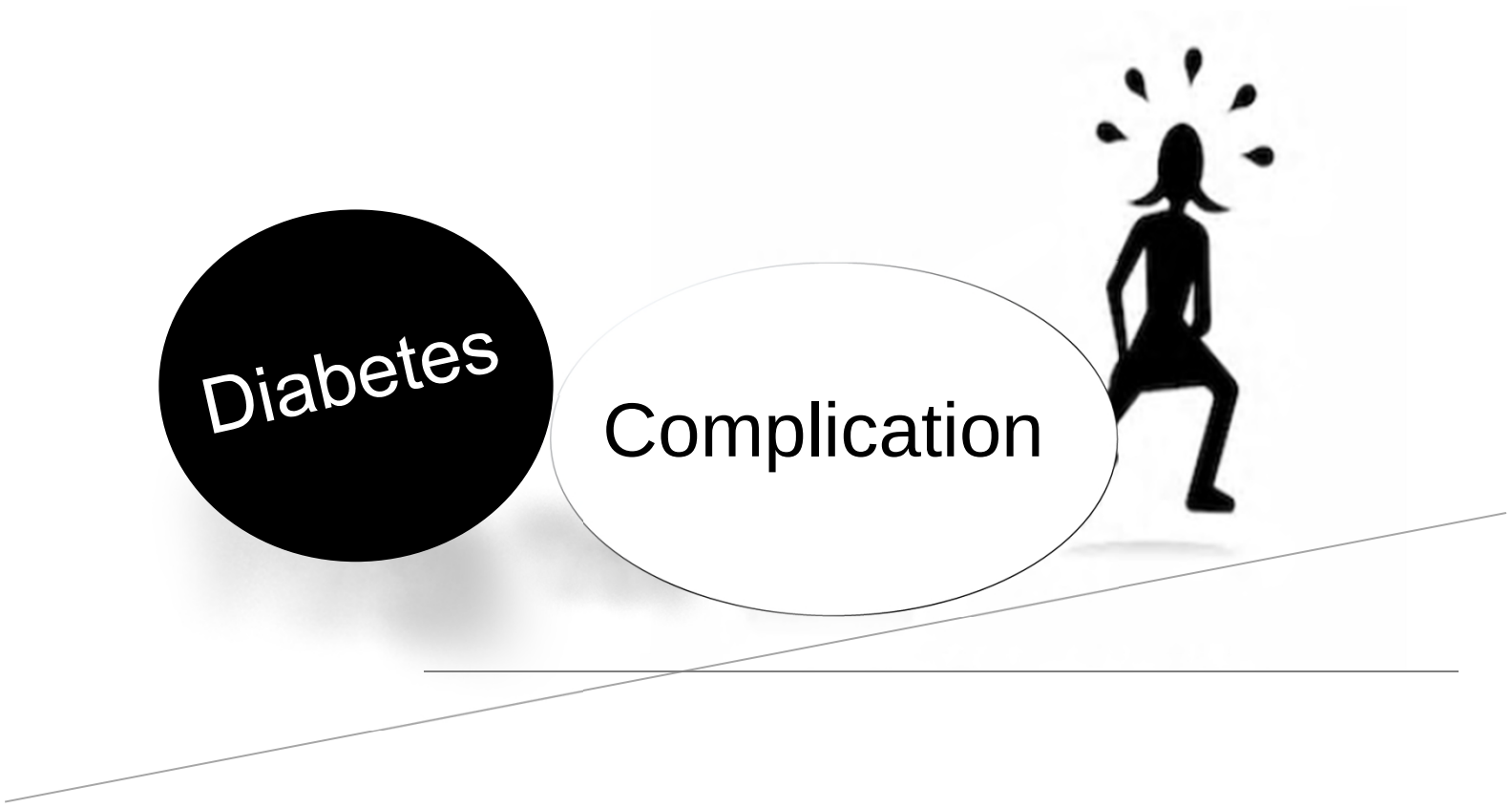
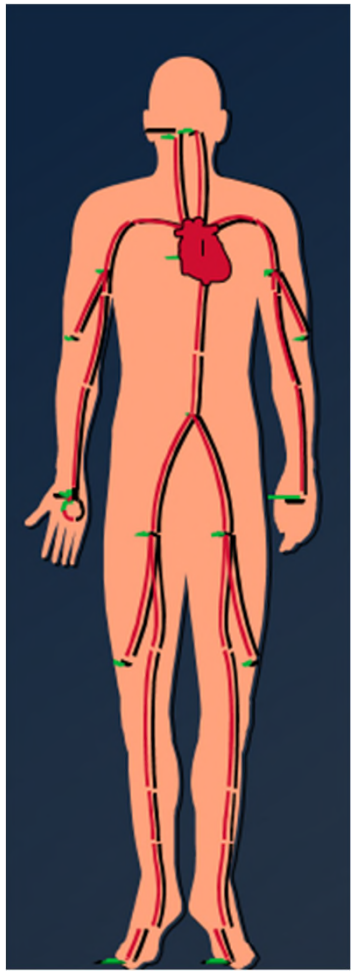
# Diabetes …



# Macrovascular Complications

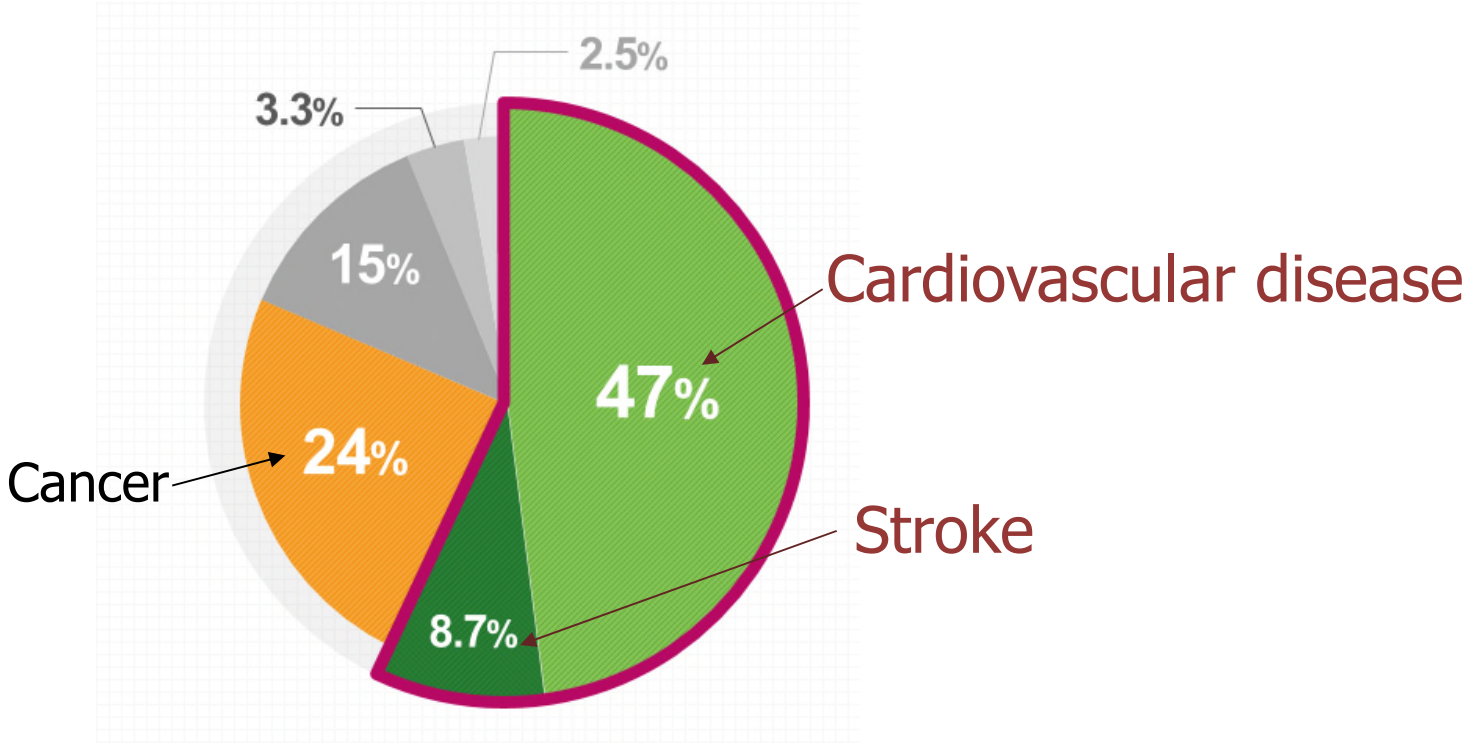
- Coronary heart disease
- Cerebrovascular disease
- Peripheral vascular disease



*Diabetes Care 42: S103-S123, 2019*

# Macrovascular Complications

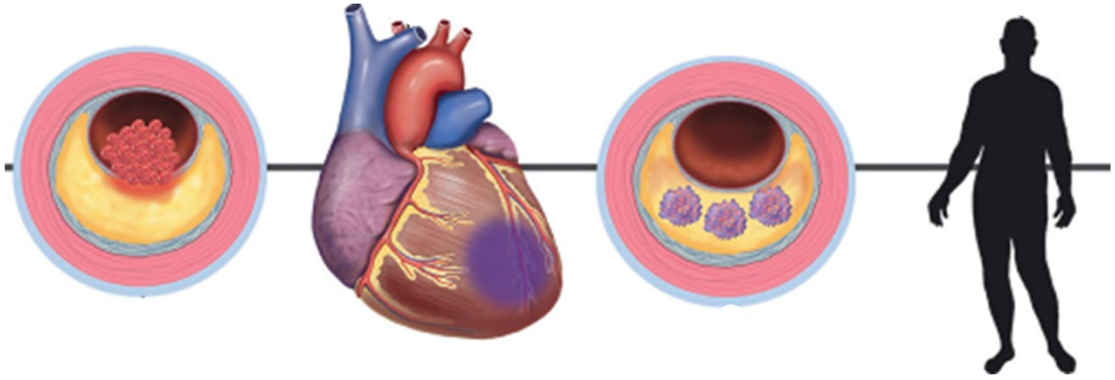
- Major cause of morbidity and mortality in diabetes




United Kingdom Prospective Diabetes Study (UKPDS) – 10 year follow up

*N Engl J Med 359:1577-89, 2008*

# Atherosclerotic cardiovascular disease (ASCVD)

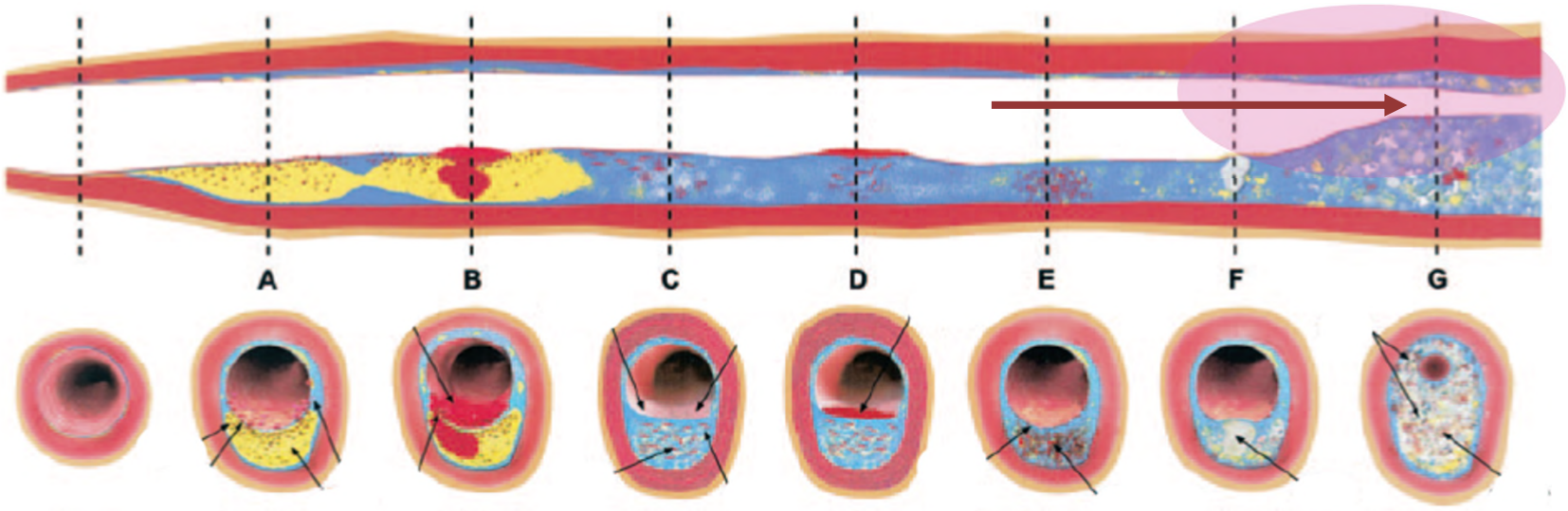


Underlying abnormality – **"Atherosclerosis"**

*Diabetes Care 42: S103-S123, 2019*

*J Am Coll Cardiol 74:1582-93, 2019*

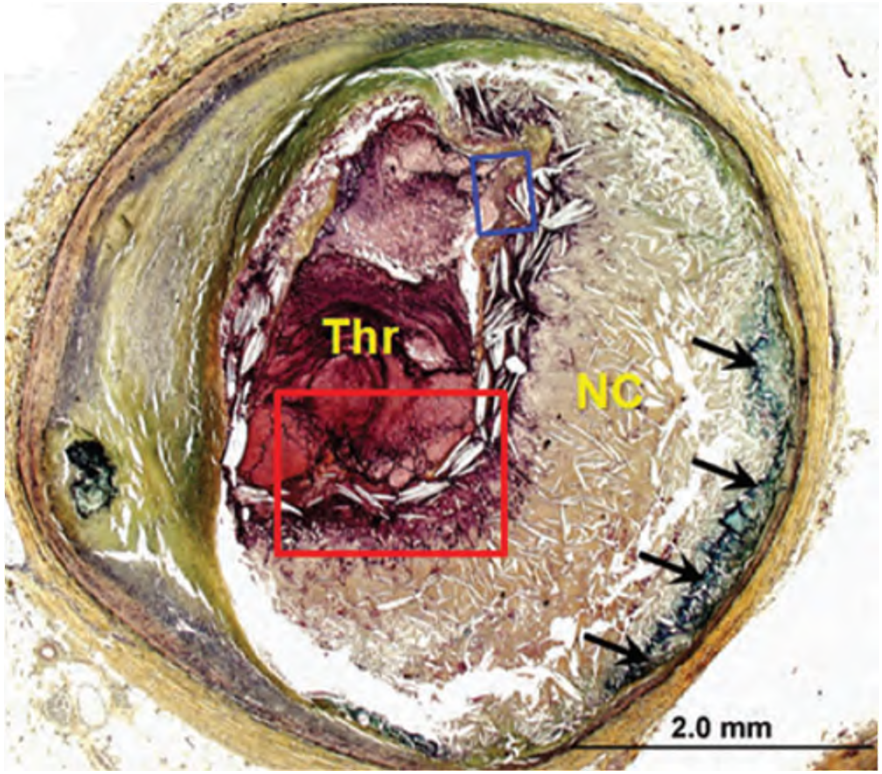
# What is Atherosclerosis ?




Cholesterol-containing fatty deposits
accumulate on the walls of arteries

*Circulation 108:1664-72, 2003*

# Someday…Plaque Rupture..




Thrombus

↓

Occlusion

↓

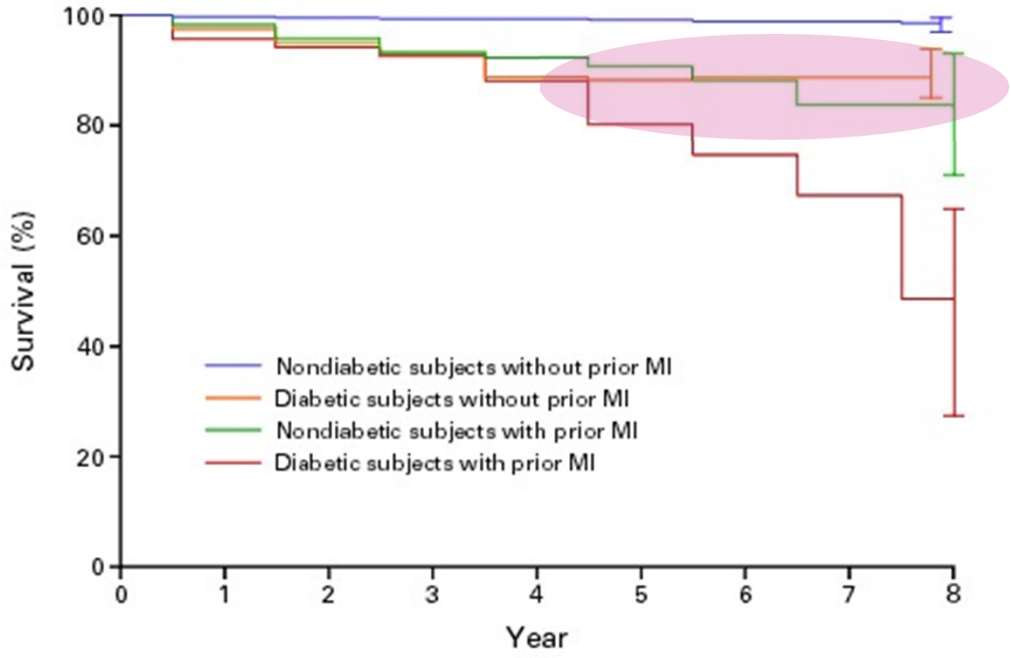
Block blood supply

*Eur Heart J 34:719-28, 2013*

# Coronary Heart Disease in Diabetes

**People with type 2 diabetes have**

the same risk of heart attack
as those who have already had a heart attack





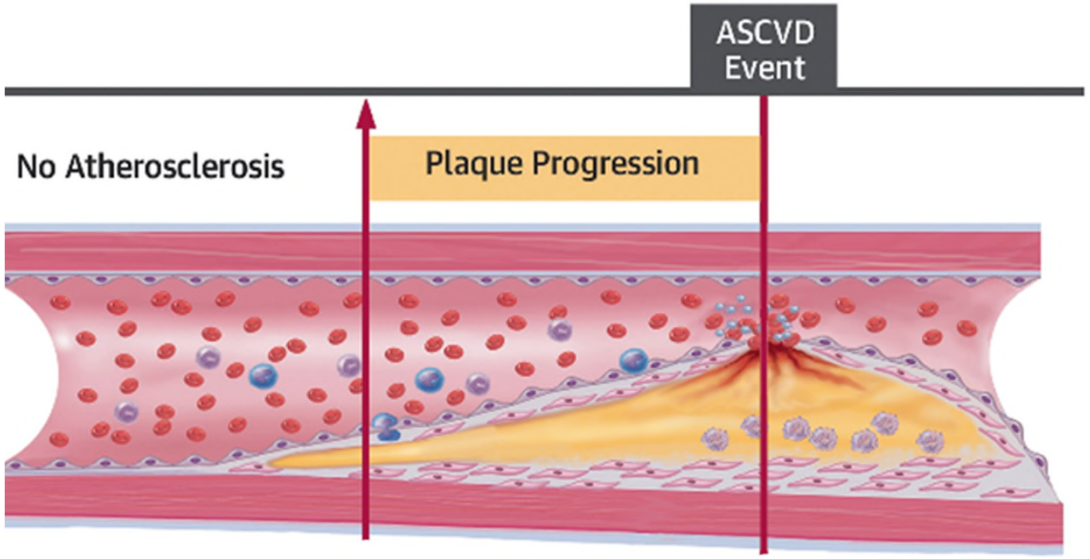

*N Engl J Med 339:229-34, 1998*

# Coronary Heart Disease in Diabetes

**Compared to people without diabetes, People with type 2 diabetes have**

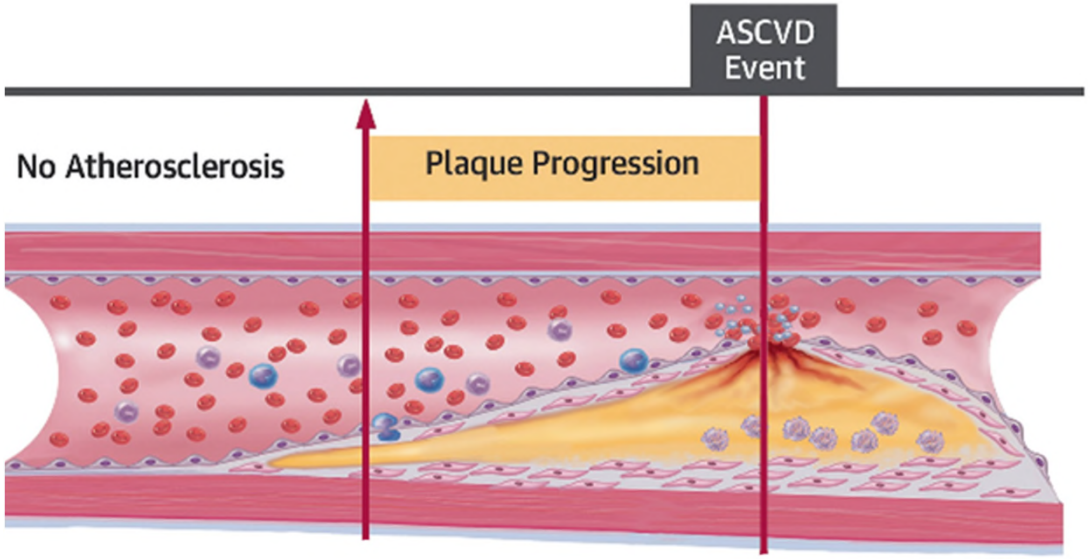
- Two- to three-fold higher risk of heart failure
- Sudden death occurs more commonly in people with diabetes than among peers without diabetes of the same age

# How to Prevent or Slow ASCVD in People with Diabetes?




*J Am Coll Cardiol 71:1781-96, 2018*

# How to Prevent or Slow ASCVD in People with Diabetes?

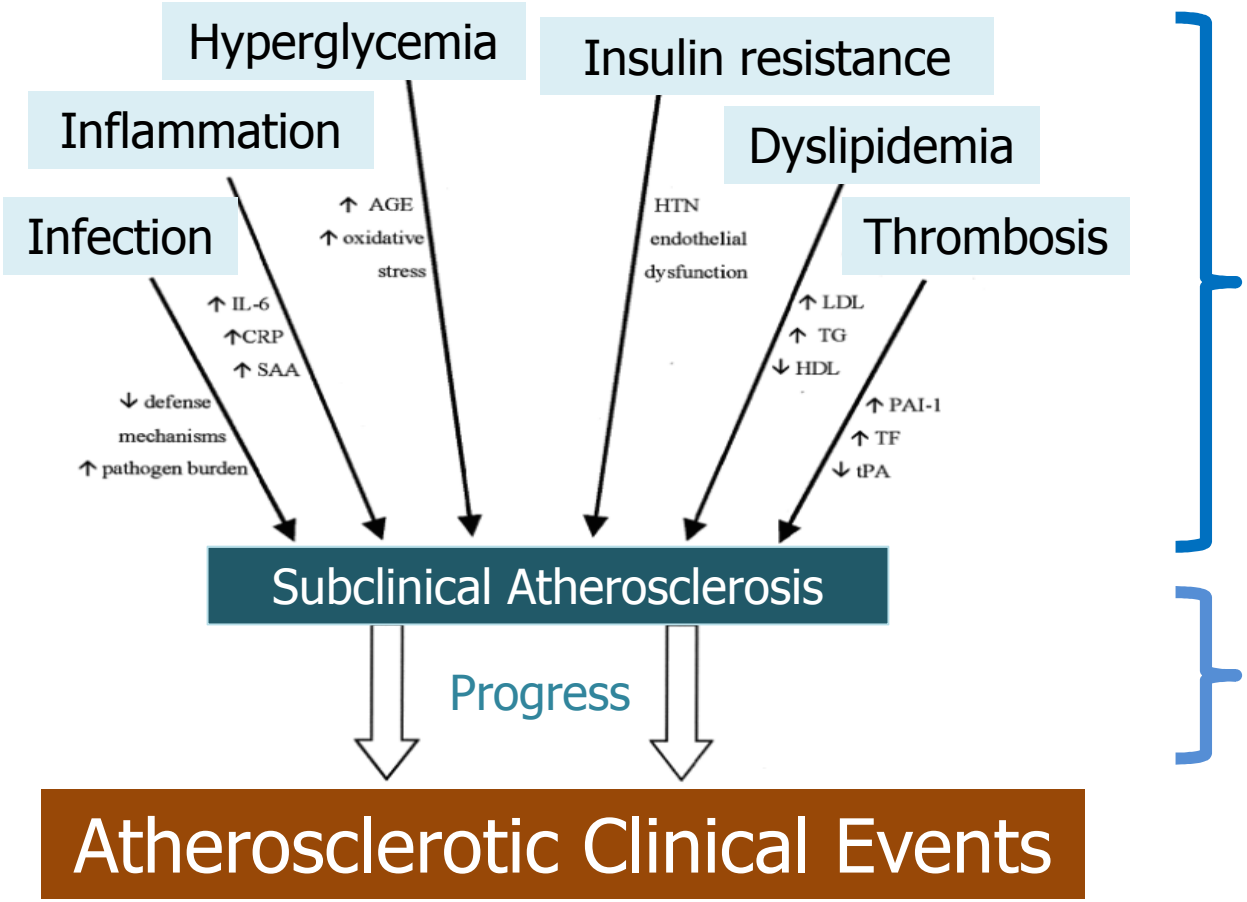



Primary Prevention
Based on Risk factor Assessment

Secondary Prevention

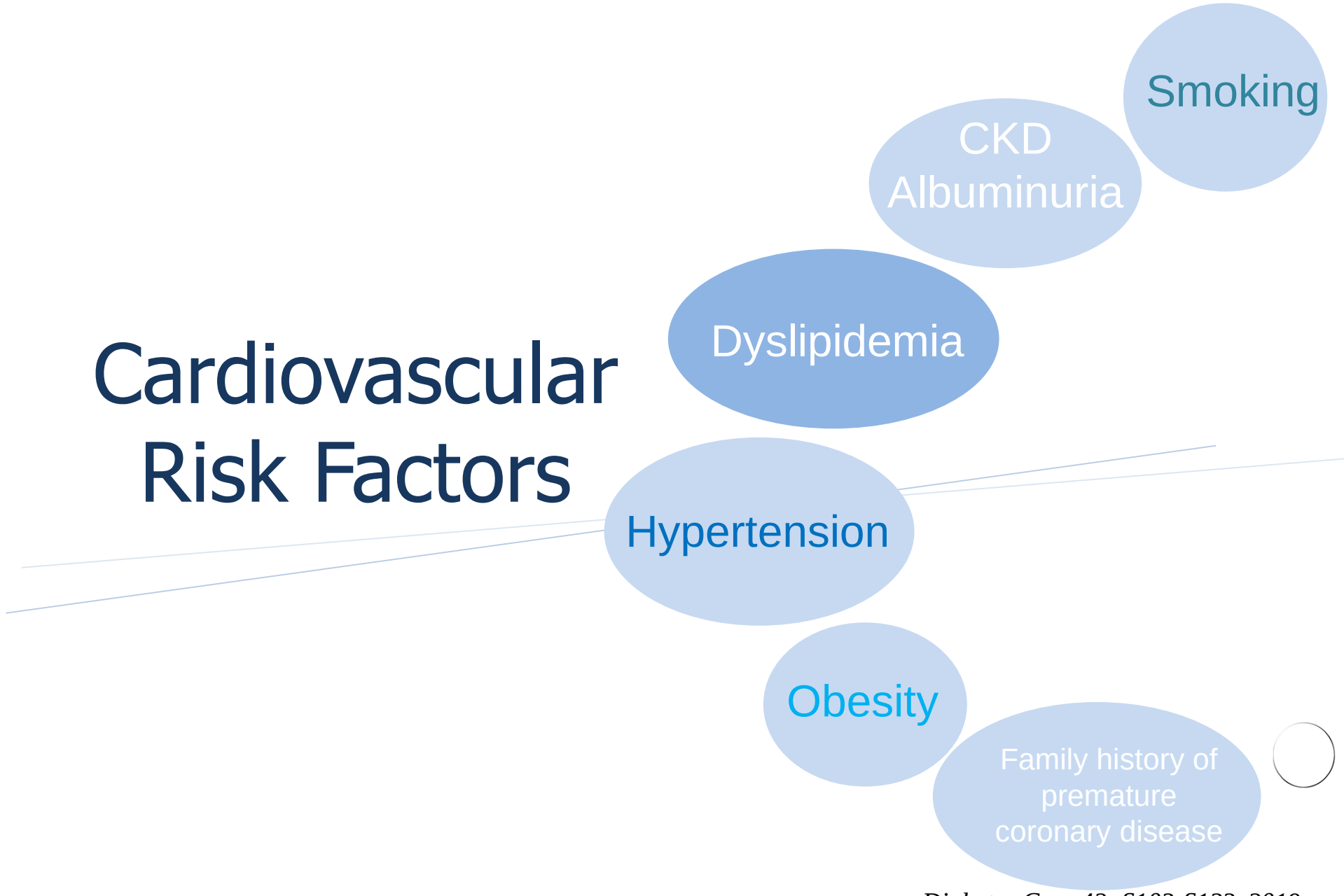
*J Am Coll Cardiol 71:1781-96, 2018*

# Atherothrombosis, inflammation, and Diabetes




*J Am Coll Cardiol 41:1071-1, 2003*

# Cardiovascular Risk Factors




*Diabetes Care 42: S103-S123, 2019*

# Prevention

- Cardiovascular risk factors should be systematically assessed at least annually in all patients with diabetes.
- Modifiable abnormal risk factors should be treated.

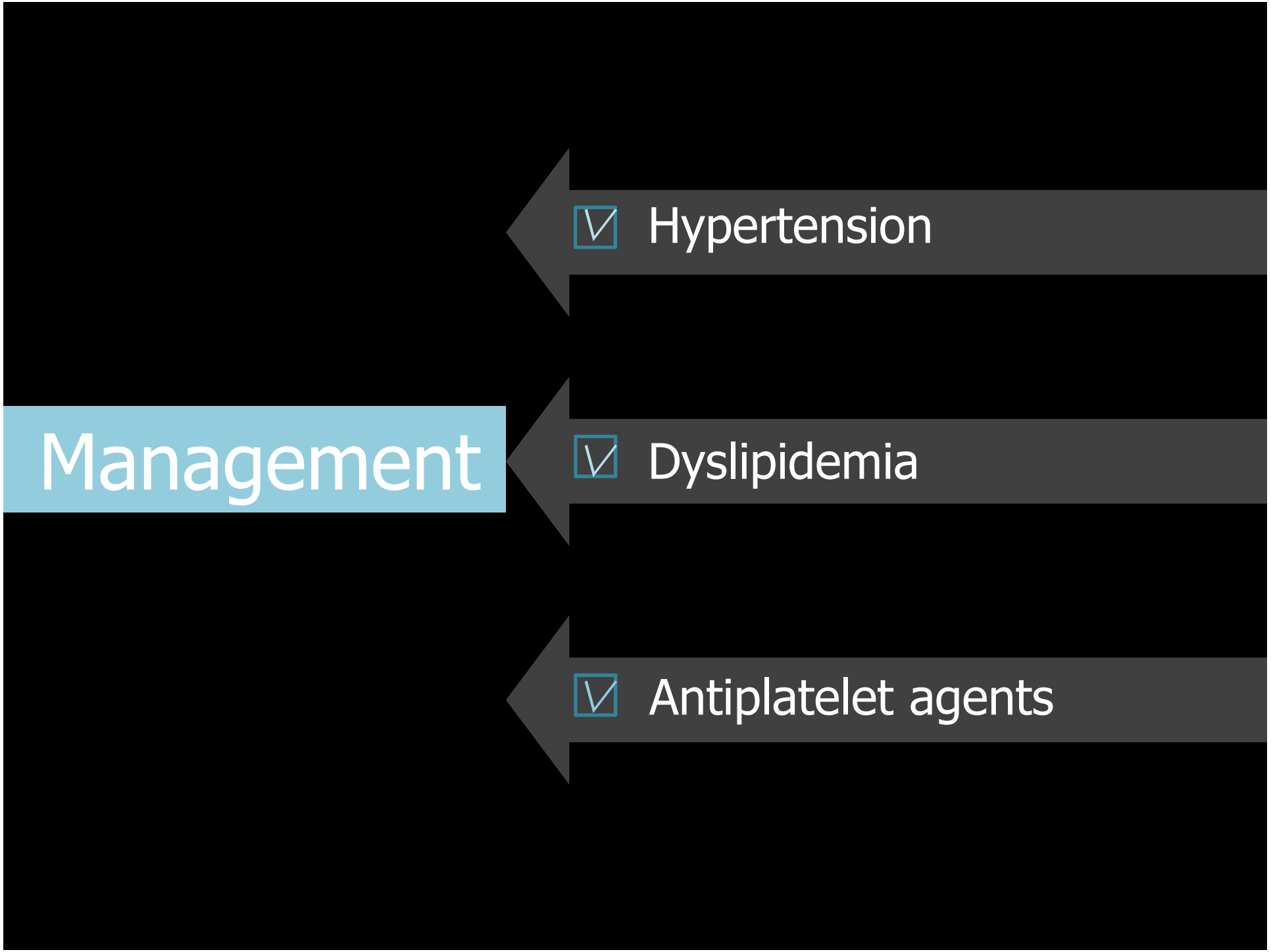
*Diabetes Care 42: S103-S123, 2019*

# Prevention

**Research shows the benefits of reducing the modifiable risk factors for atherosclerosis.**

**Modifiable risk factors are**

- Dyslipidemia
- Smoking and exposure to tobacco smoke
- High blood pressure
- Diabetes
- Central obesity
- Physical inactivity


Management
☑ Hypertension
☑ Dyslipidemia
☑ Antiplatelet agents

# Hypertension – Blood Pressure Control

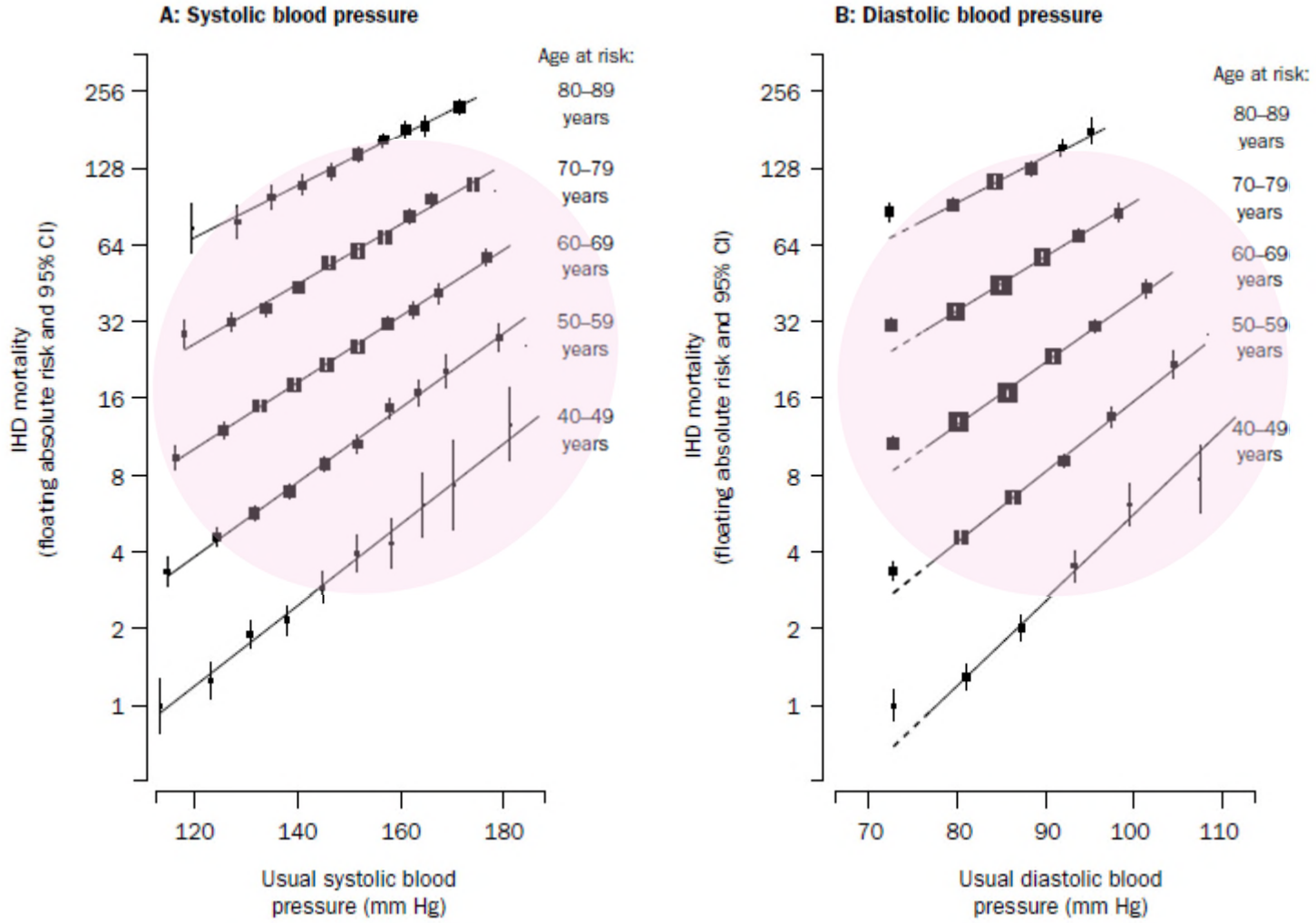
## Screening and Diagnosis

- Blood pressure (BP) should be measured at every routine clinical visit.

- Patients found to have elevated BP (≥140/90 mmHg) should have blood pressure confirmed using multiple readings, including measurements on a separate day, to diagnose hypertension. **B**

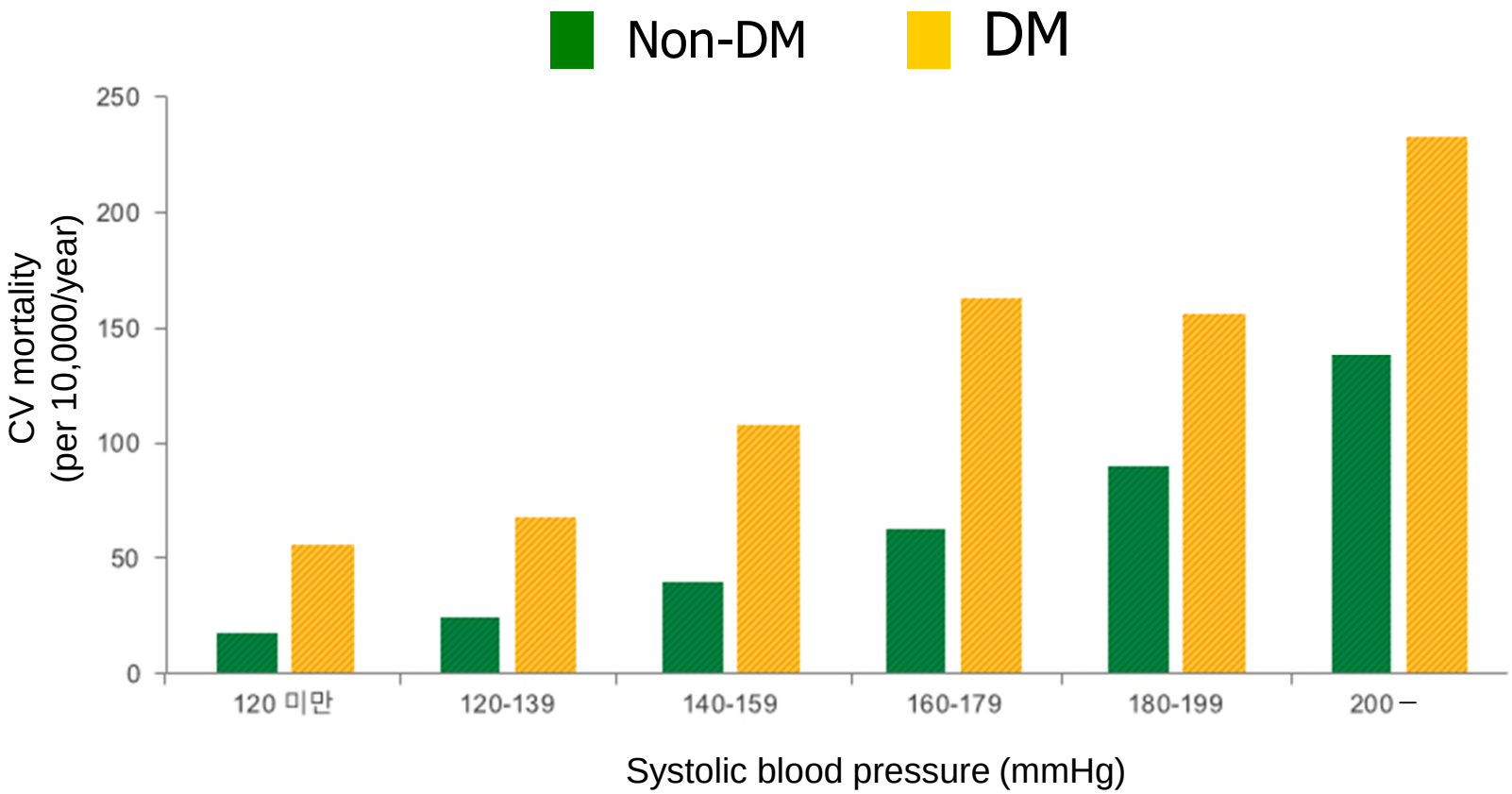
*Diabetes Care 42: S103-S123, 2019*

# Blood Pressure and Ischemic Heart disease mortality
## : Meta-Analysis of 61 Prospective Studies




*Lancet 360:1903-1913, 2002*

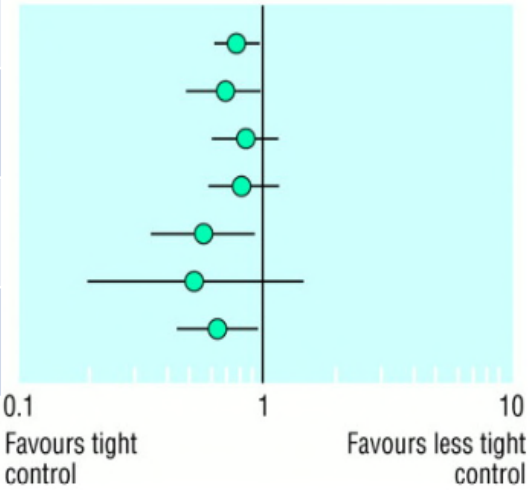
# Systolic Blood Pressure and CV Mortality




*Diabetes Care 16: 433-44, 1993*

# UKPDS – Tight vs. Less tight B.P control

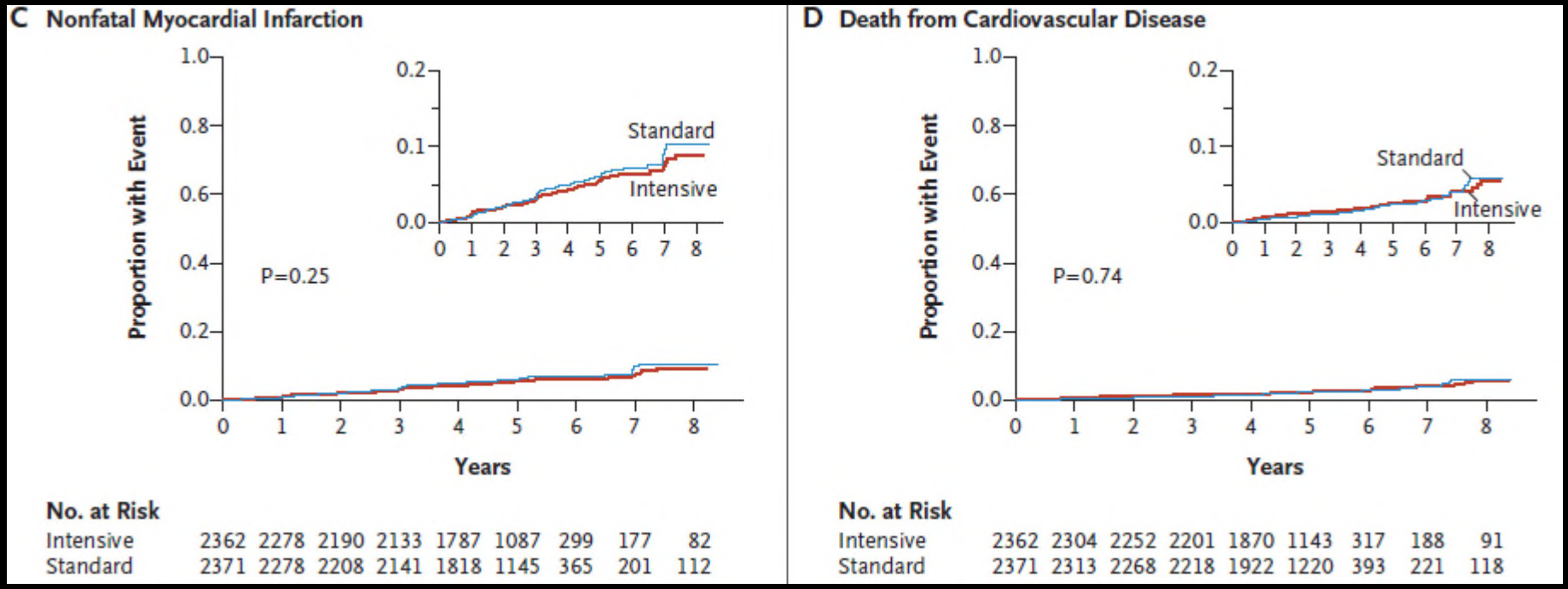
| | Risk (P value) |
|---|---|
| Any diabetes related end point | 24% ↓ (<0.05) |
| Deaths related to diabetes | 32% ↓ (<0.05) |
| Myocardial infarction | 21% ↓ (0.79) |
| Stroke | 44% ↓ (<0.05) |
| Peripheral vascular disease | 49% ↓ (0.51) |




- Type 2 diabetes (n = 1,148)
- Tight group: 144/82 mmHg vs. Less tight group: 154/87 mmHg

*BMJ 317:703-13, 1998*

# Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus




Intensive lowering of systolic B.P to a target of less than 120 mmHg has no effect on the rate of CV events in high-risk type 2 diabetes

ACCORD Study Groups. N Engl J Med 362:1575-85, 2010

# Treatment Goals

- BP targets should be individualized through a shared decision-making process that addresses cardiovascular risk, potential adverse effects of antihypertensive medications, and patient preferences. **C**

- For individuals with diabetes and hypertension at lower risk for cardiovascular disease (10-year atherosclerotic cardiovascular disease risk <15%), treat to a BP of <140/90 mmHg. **A**

*Diabetes Care 42: S103-S123, 2019*

# Treatment Goals

- For individuals with diabetes at higher cardiovascular risk (existing atherosclerotic cardiovascular disease or 10-year atherosclerotic cardiovascular disease risk >15%), a BP target of <130/80 mmHg may be appropriate, if it can be safely attained. **C**

*Diabetes Care 42: S103-S123, 2019*

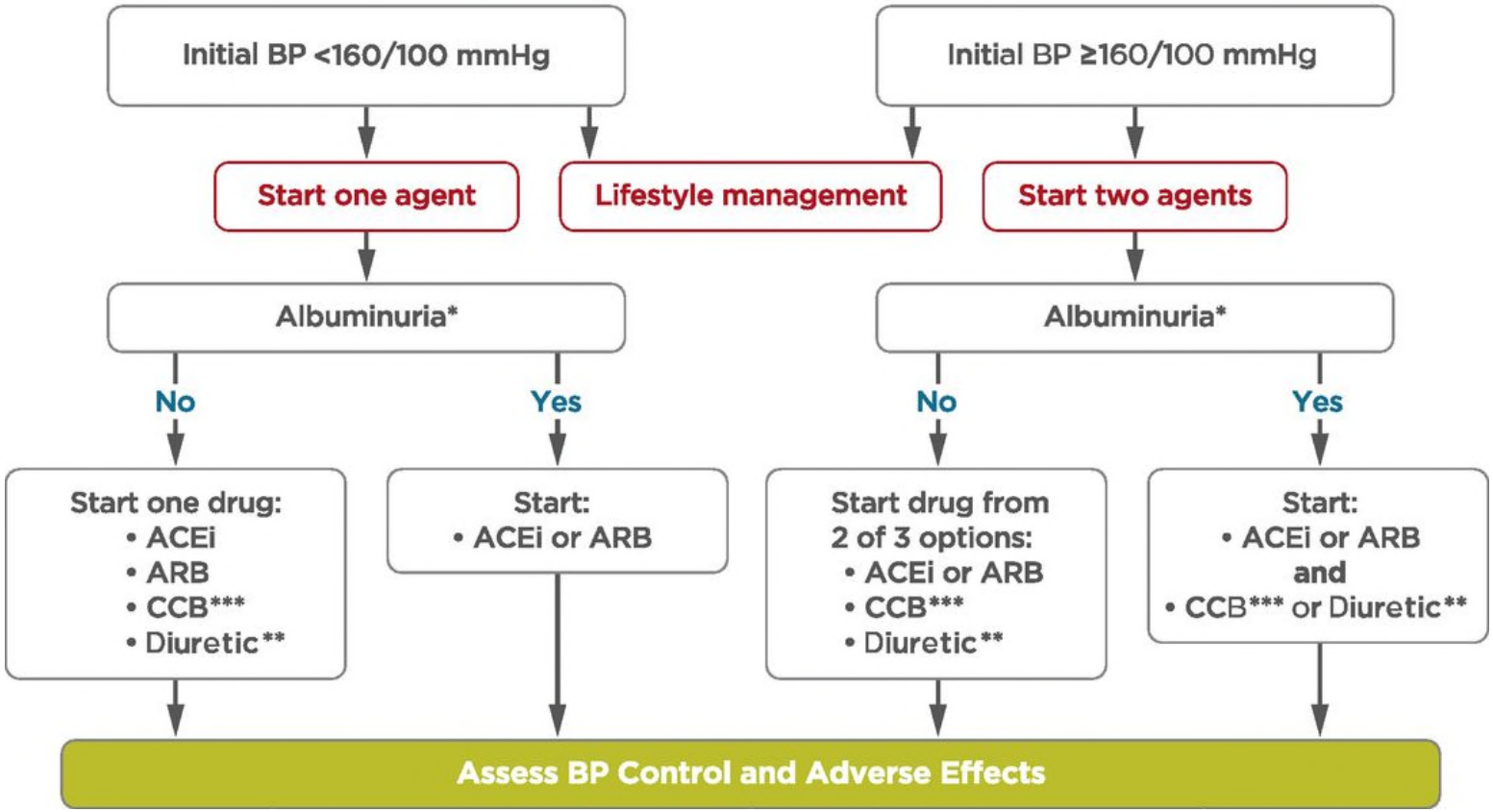
# Korean Diabetes Association 2019

| | Target goals |
|---|---|
| Diabetes | 140/85 mm Hg |
| Diabetes with CVD | 130/80 mm Hg |

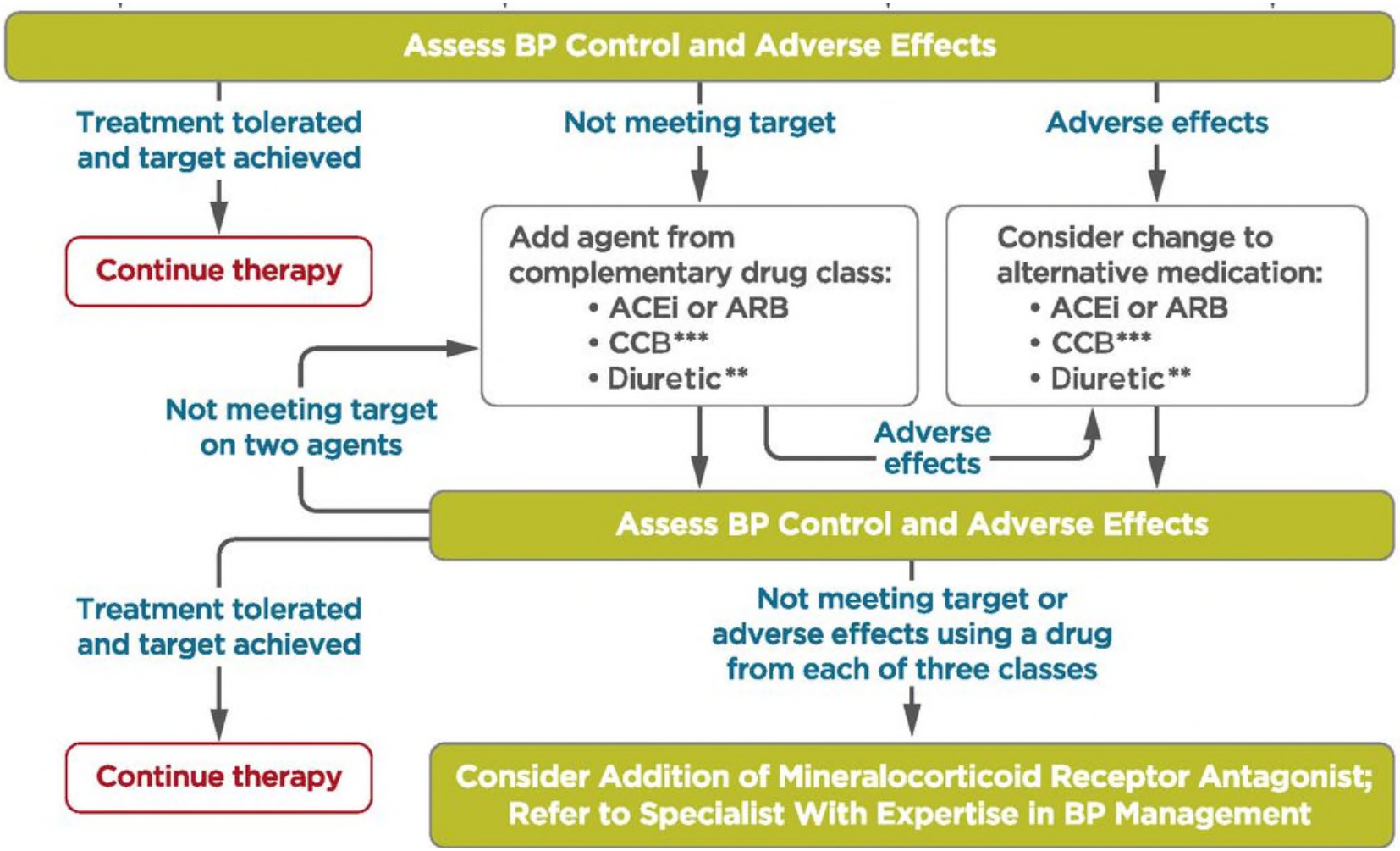
BP targets need to be individualized depending on level of glycemic control, duration of diabetes, level of complications, and comobidities.

*KDA treatment guideline for diabetes 2019*

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




*Diabetes Care 42: S103-S123, 2019*




*Diabetes Care 42: S103-S123, 2019*

# Potential side effects

| Anti-hypertensive Medications | Potential Side Effects |
|---|---|
| ACE-inhibitors | hyperkalaemia, cough, angioedema, rise in creatinine |
| A2 Receptor blockers | angioedema, rise in creatinine |
| Calcium antagonists<br>-Dihydropyridine<br><br>-Non-dihydropyridine | <br>fluid retention, flushing, tachycardia<br><br>fluid retention, constipation, bradycardia |
| Diuretics | dehydration, hypokalaemia, impotence |
| B-blockers | asthma, claudication, tiredness, impotence |

IDF Education module

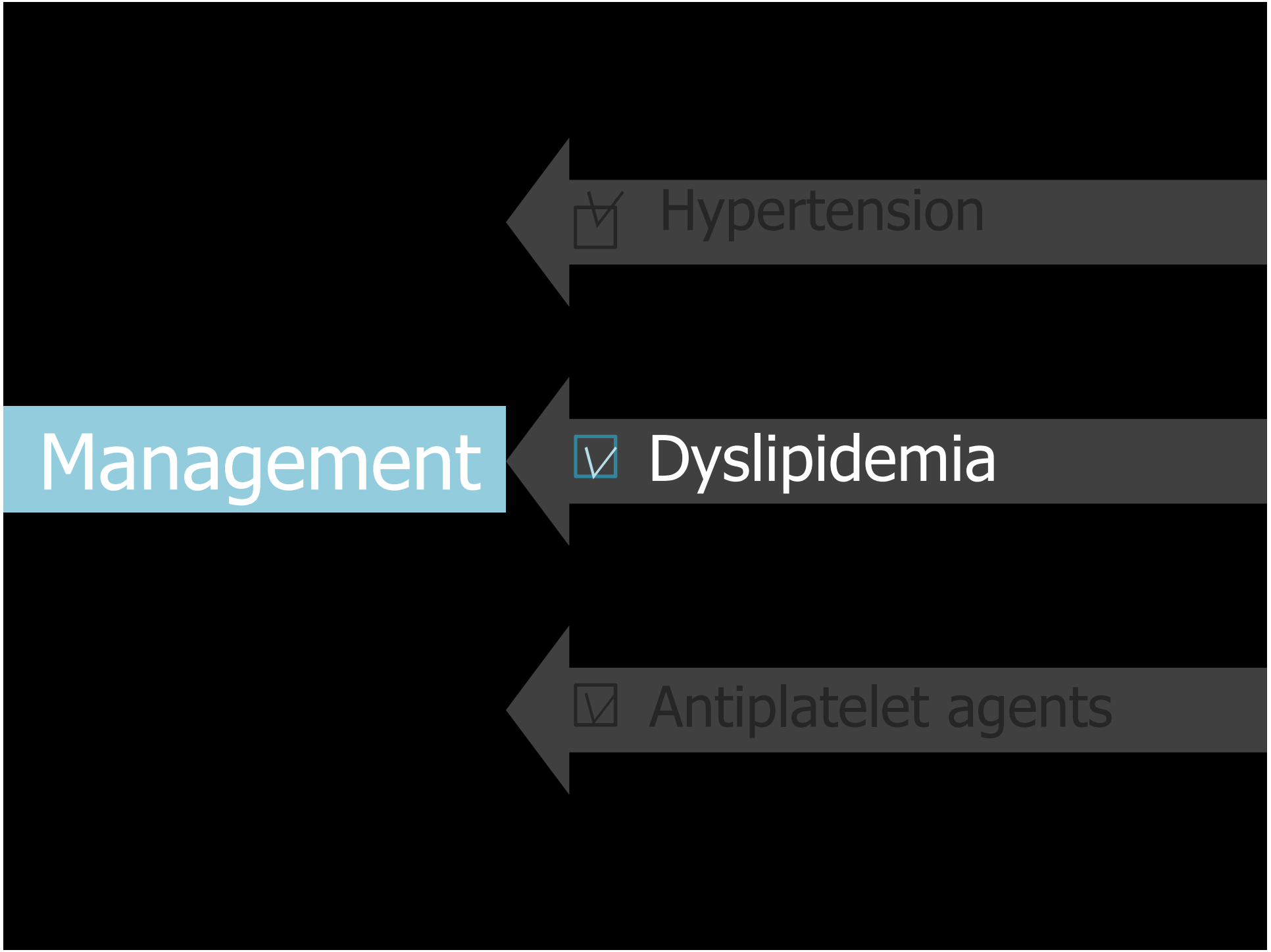
# Individualization of Treatment Targets

- Potential adverse effects
  - hypotension, syncope, falls, acute kidney injury, electrolyte abnormalities

- High risk patients
  - older age, chronic kidney disease, frailty orthostatic hypotension, substantial comorbidity, functional limitations, polypharmacy

- Patients at high risk should have a higher BP target.

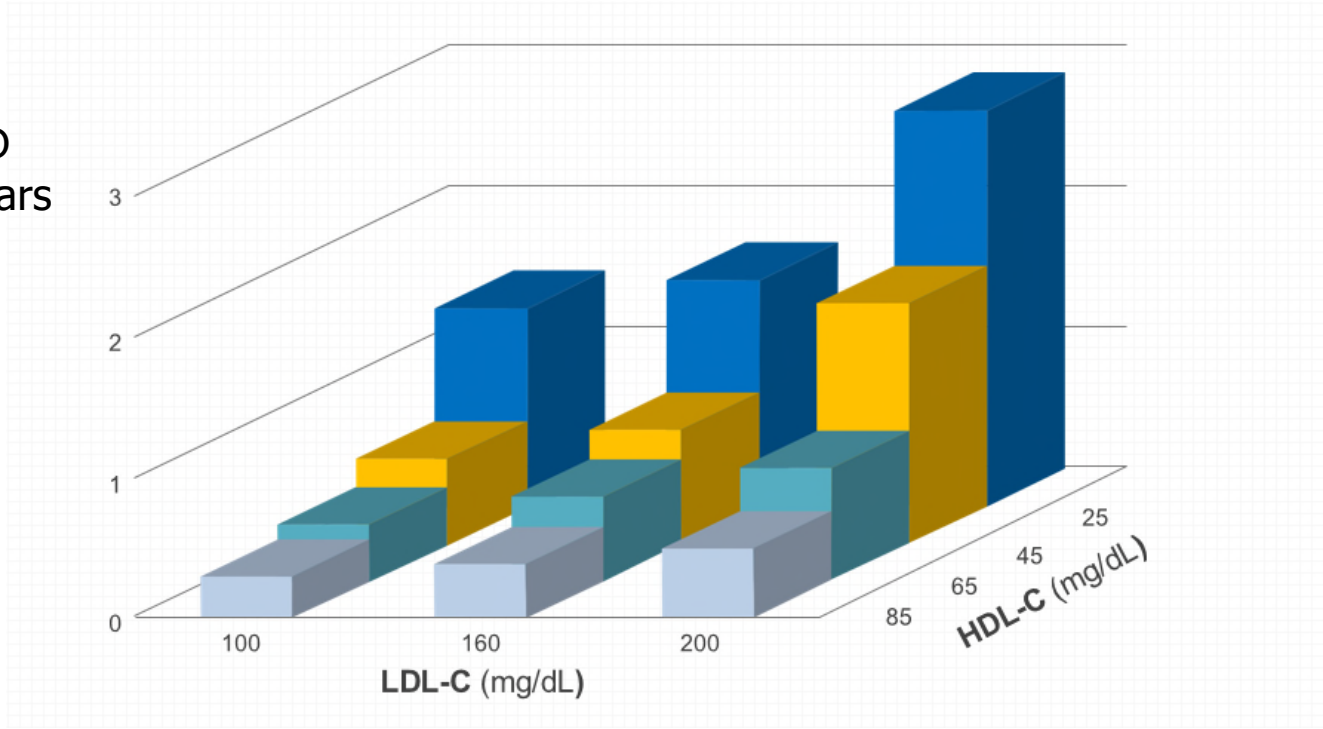
*Diabetes Care 42: S103-S123, 2019*


Hypertension
Management
Dyslipidemia
Antiplatelet agents

# Dyslipidemia and Cardiovascular Disease

## Framingham Heart Study

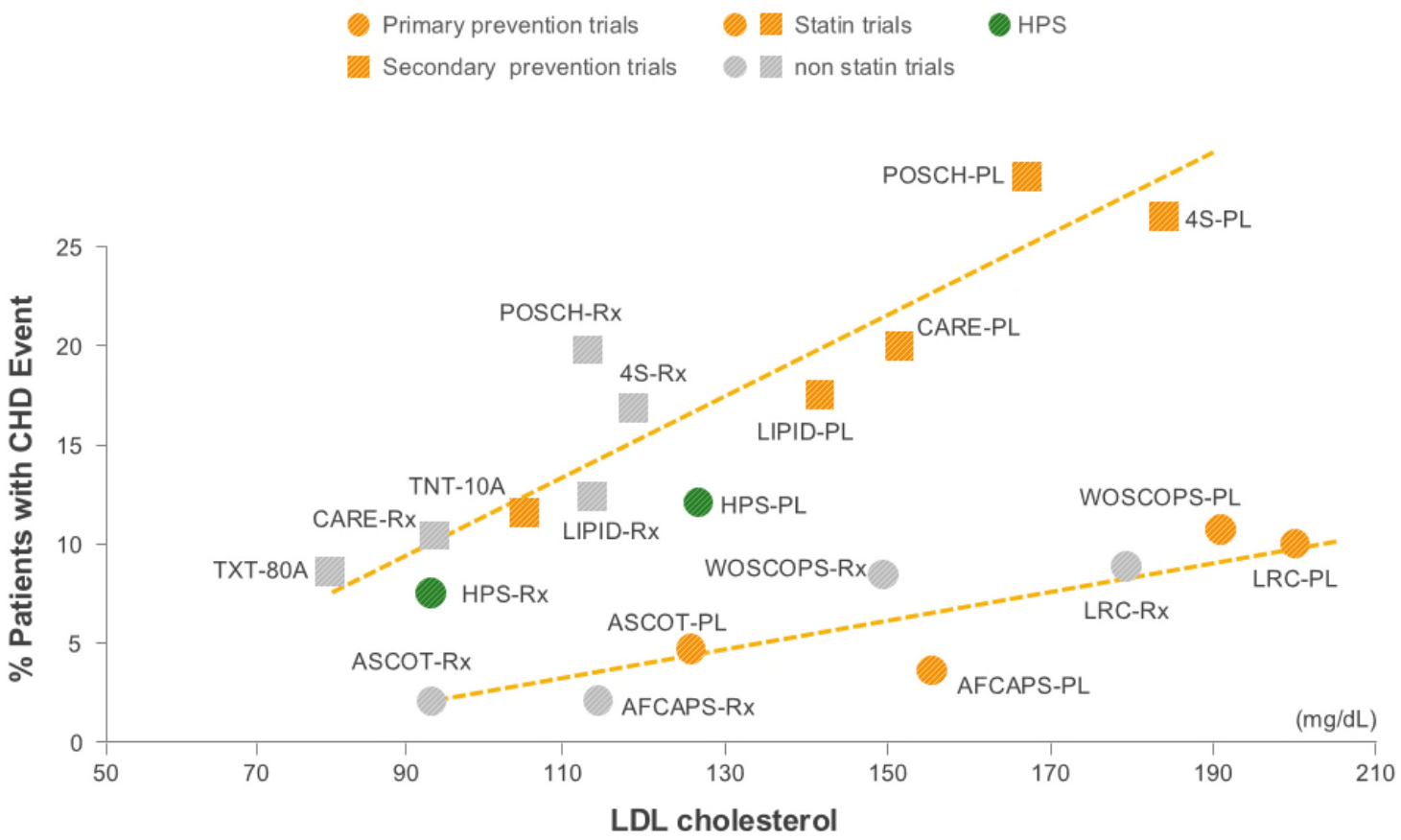
RR of CVD
after 4 years




**Main predictors of CVD mortality**

*Castelli WP. Can J Cardiol. 1988;4(suppl A):5A3*

# Reduced CHD Events with LDL Reduction



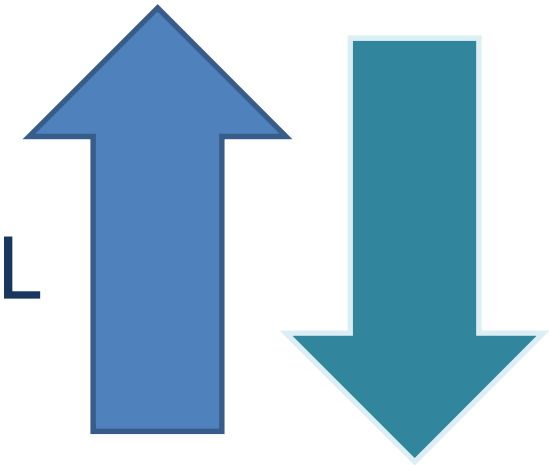

*LaRosa JC et al. NEJM 2005:352*

# CV Risk Reduction with Lipid-Lowering in type 2 Diabetes

| Agent | Study | Decreased Risk of CV events |
|---|---|---|
| • LDL Target | | |
| - Simvastatin | 4S/HPS | 28-42% |
| - Lovastatin | AFCAPS/TexCaps | 43% |
| - Pravastatin | CARE/LIPID | 19-27% |
| • TG/HDL Target | | |
| - Gemfibrozil | Heisnki | 24-71% |
| - Fenofibrate | DAIS | 23% |
| - Bezafibrate | BIP | 42% |

# Dyslipidemia in Diabetes

Triglyceride
Small dense LDL
Apo B



HDL
Apo A-I

**More Atherogenic**

# Ongoing Therapy and Monitoring

- In adults not taking statins or other lipid-lowering therapy, it is reasonable to obtain a lipid profile

  - at the time of diabetes diagnosis,
  - at an initial medical evaluation,
  - every 5 years thereafter if under the age of 40 years, or more frequently if indicated.

**E**

- Obtain a lipid profile at initiation of lipid-lowering therapy, 4–12 weeks after initiation or a change in dose, and annually thereafter as it may help to monitor the response to therapy and inform medication adherence. **E**

*Diabetes Care 42: S103-S123, 2019*

# Goal (Korean Diabetes Association 2019)

| | LDL cholesterol |
|---|---|
| CVD (+) | < 70 mg/dL |
| CVD (-), CV risk facrors (+)<br>or Target organ damage (+) | < 70 mg/dL |
| CVD (-), CV risk facrors (-)<br>or Target organ damage (-) | < 100 mg/dL |

- Target organ damage: albuminuria, CKD (GFR < 60 ml/min/1.73 $m^2$)
- CV risk factors: HTN, smoking, family history of premature coronary disease

*KDA treatment guideline for diabetes 2019*

# Lipids: treatment

- Use HMG-CoA Reductase Inhibitors (statins)
  -Effective for primary and secondary prevention
- Increase physical activity
- Attain and maintain a healthy weight
- Reduce total and saturated fat
- Increase monounsaturated fat and flavonoids

# Recommendations for statin in Diabetes

| Age | ASCVD or 10-year ASCVD risk >20% | Recommended statin intensity^ and combination treatment* |
|---|---|---|
| <40 years | No | None† |
| | Yes | High<br>• In patients with ASCVD, if LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)# |
| ≥40 years | No | Moderate‡ |
| | Yes | High<br>• In patients with ASCVD, if LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor) |

*Diabetes Care 42: S103-S123, 2019*

# High, Moderate-intensity statin therapy

| High-intensity statin therapy (lowers LDL cholesterol by ≥50%) | Moderate-intensity statin therapy (lowers LDL cholesterol by 30–50%) |
|---|---|
| Atorvastatin 40–80 mg<br>Rosuvastatin 20–40 mg | Atorvastatin 10–20 mg<br>Rosuvastatin 5–10 mg<br>Simvastatin 20–40 mg<br>Pravastatin 40–80 mg<br>Lovastatin 40 mg<br>Fluvastatin XL 80 mg<br>Pitavastatin 2–4 mg |

*Diabetes Care 42: S103-S123, 2019*

# Lipids: side effects of statins

- Muscle pain (with or without an increase in muscle enzymes)
- Increase of liver enzymes
- Rhabdomyolysis:
  - More common when statins and fibrates are used in combination
- Cluster nightmares and sleep disturbance

# Other Combination Therapy

- Combination therapy (statin/fibrate) has not been shown to improve atherosclerotic cardiovascular disease outcomes and is generally not recommended. **A**

- Combination therapy (statin/niacin) has not been shown to provide additional cardiovascular benefit above statin therapy alone, may increase the risk of stroke with additional side effects, and is generally not recommended. **A**

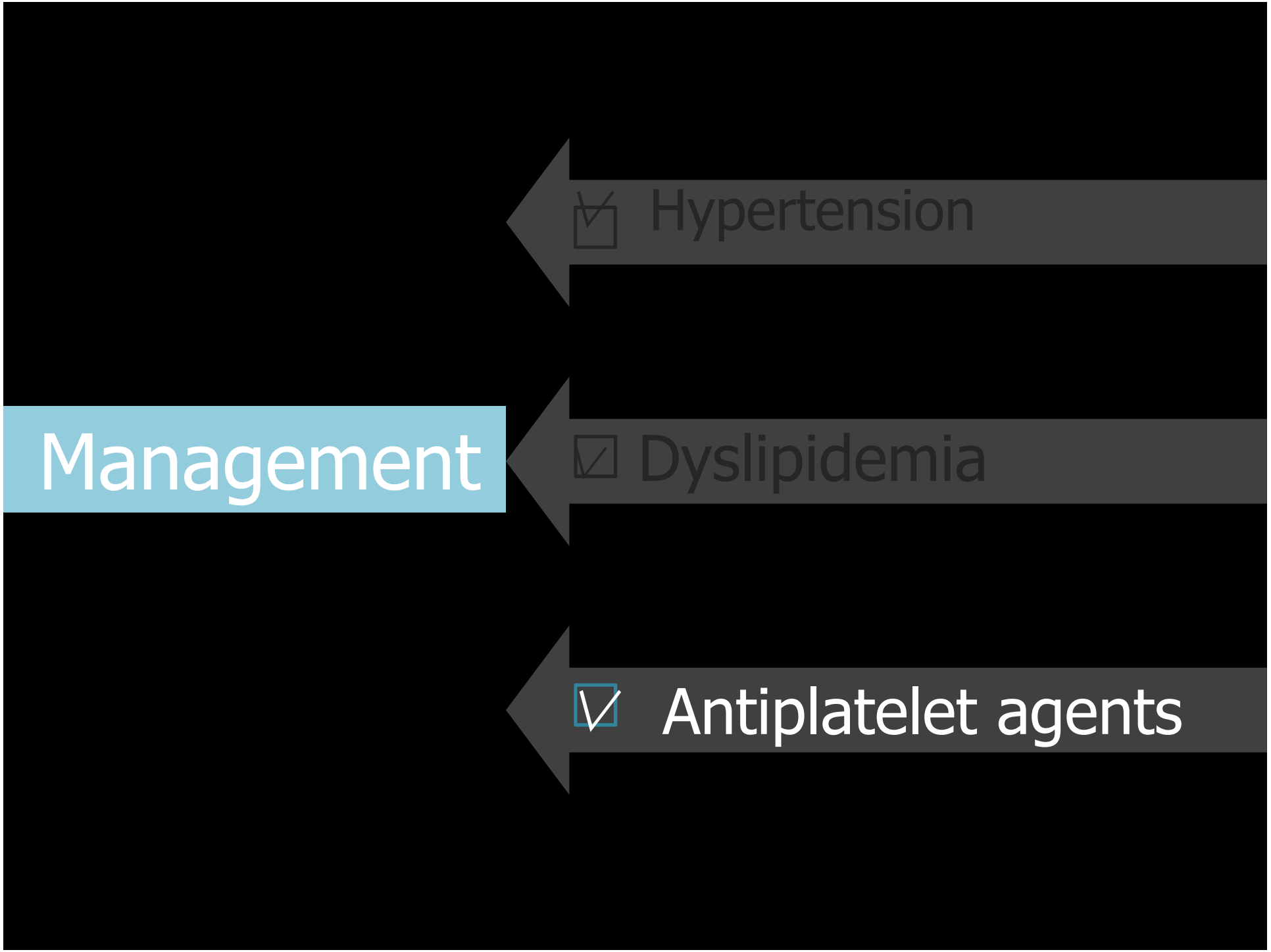
*Diabetes Care 42: S103-S123, 2019*

# Other Lipoprotein Fractions

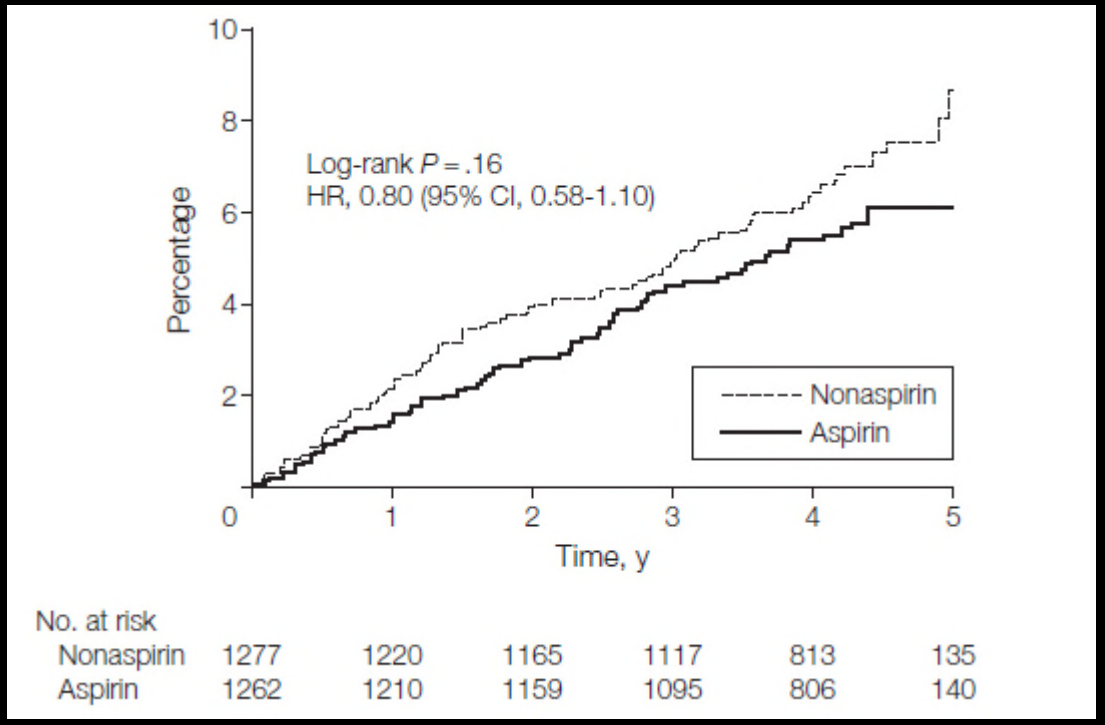
- For patients with fasting triglyceride levels ≥500 mg/dL, evaluate for secondary causes of hypertriglyceridemia and consider medical therapy to reduce the risk of pancreatitis. **C**

- In moderate hypertriglyceridemia (fasting or nonfasting triglycerides 175–499 mg/dL), clinicians should address and treat lifestyle factors (obesity and metabolic syndrome), secondary factors (diabetes, chronic liver or kidney disease and/or nephrotic syndrome, hypothyroidism), and medications that raise triglycerides. **C**

*Diabetes Care 42: S103-S123, 2019*


Management
Hypertension
Dyslipidemia
Antiplatelet agents

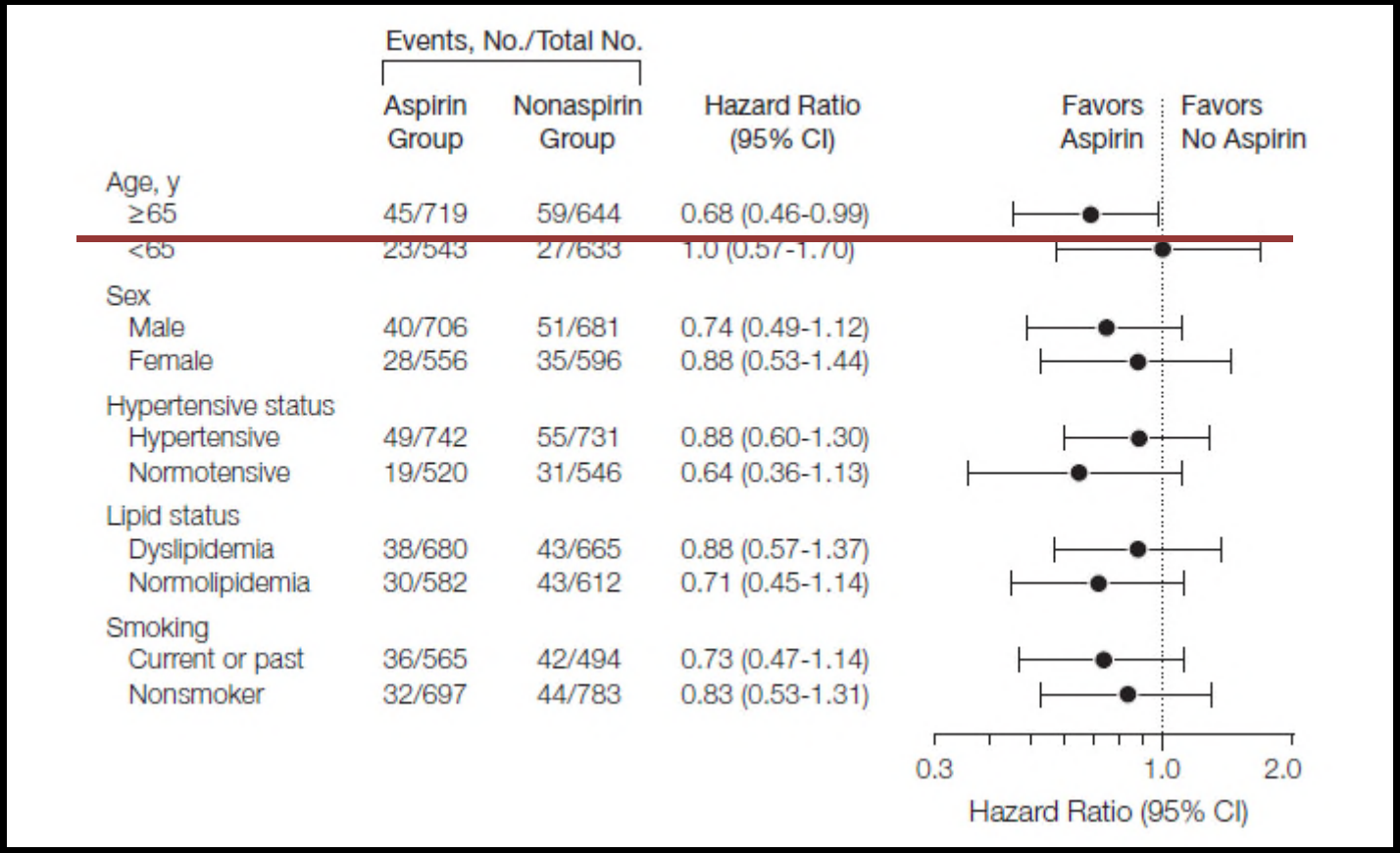
# Aspirin for Primary Prevention of Atherosclerotic Events in Type 2 Diabetes




| No. at risk | | | | | | |
|---|---|---|---|---|---|---|
| Nonaspirin | 1277 | 1220 | 1165 | 1117 | 813 | 135 |
| Aspirin | 1262 | 1210 | 1159 | 1095 | 806 | 140 |

JPAD Trial investigators. JAMA 300:2134-2141, 2008

# Aspirin for Primary Prevention of Atherosclerotic Events in Type 2 Diabetes




JPAD Trial investigators. JAMA 300:2134-2141, 2008

# Antiplatelet Agents – Secondary Prevention

- Use aspirin therapy (75–162 mg/day) as a secondary prevention strategy in those with diabetes and a history of atherosclerotic cardiovascular disease. **A**

- For patients with atherosclerotic cardiovascular disease and documented aspirin allergy, clopidogrel (75 mg/day) should be used. **B**

- Dual antiplatelet therapy (with low-dose aspirin and a P2Y12 inhibitor) is reasonable for a year after an acute coronary syndrome **A** and may have benefits beyond this period. **B**

*Diabetes Care 42: S103-S123, 2019*

# Antiplatelet Agents – Primary Prevention

• Aspirin therapy (75–162 mg/day) may be considered as a primary prevention strategy in those with diabetes who are at increased CV risk, after a discussion with the patient on the benefits versus increased risk of bleeding. **C**

## KDA 2019

• Aspirin therapy (100 mg/dL) may be considered

- aged 40-70 years who are at increased CV risk,

if they have not increased bleeding risk. **C, IIb**

*Diabetes Care 42: S103-S123, 2019*

*KDA treatment guideline for diabetes 2019*

# Cardiovascular Disease - Screening

• In asymptomatic patients, routine screening for coronary artery disease is not recommended as it does not improve outcomes as long as atherosclerotic cardiovascular disease risk factors are treated. **A**

• Consider investigations for coronary artery disease in the presence of any of the following: atypical cardiac symptoms (e.g., unexplained dyspnea, chest discomfort); signs or symptoms of associated vascular disease including carotid bruits, transient ischemic attack, stroke, claudication, or peripheral arterial disease; or electrocardiogram abnormalities (e.g., Q waves). **E**

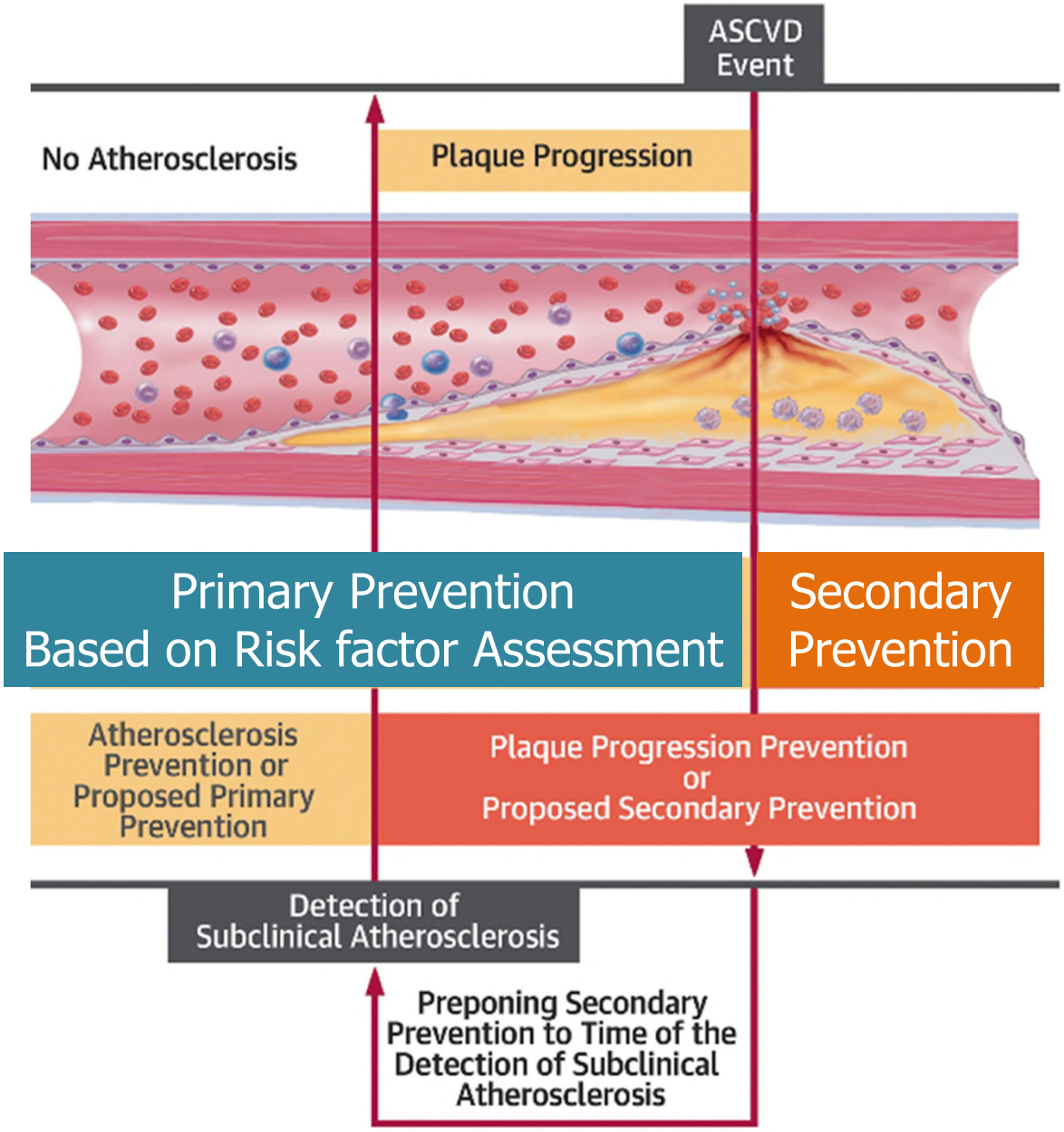
*Diabetes Care 42: S103-S123, 2019*

# Cardiovascular Disease - Treatment

- In patients with known atherosclerotic cardiovascular disease, consider ACE inhibitor or angiotensin receptor blocker therapy to reduce the risk of cardiovascular events. **B**

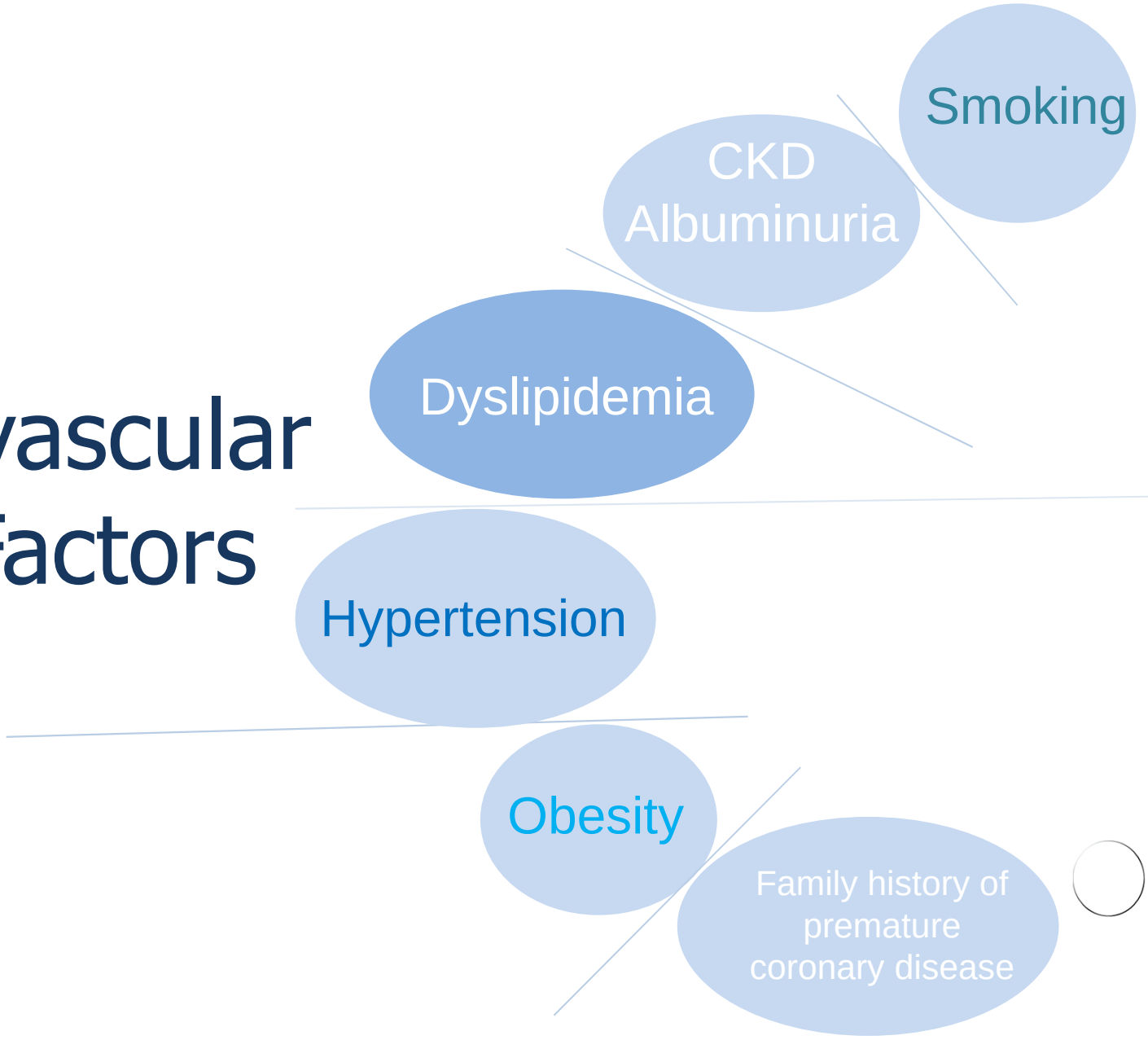
- In patients with prior myocardial infarction, β-blockers should be continued for at least 2 years after the event. **B**

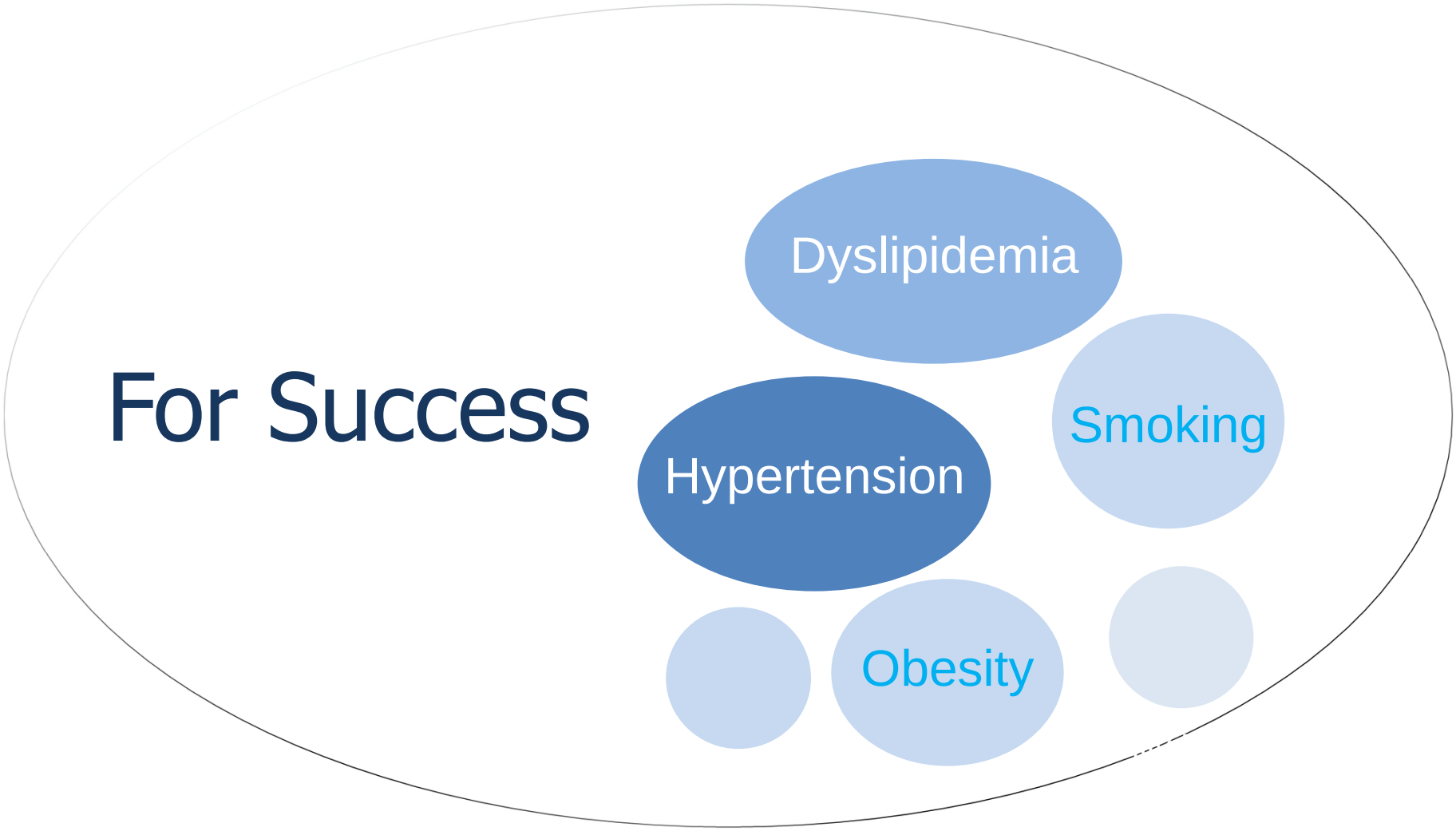
*Diabetes Care 42: S103-S123, 2019*




*J Am Coll Cardiol 71:1781-96, 2018*

# Cardiovascular Risk Factors




For Success
Dyslipidemia
Smoking
Hypertension
Obesity

Thank you for your attention.