Coronary Artery Disease in Diabetes

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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.

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\(^1\)

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

- 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\(^2,3\)

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.
Cardiovascular disease and diabetes

Coronary heart disease deaths 2- to 4-fold
Stroke risk 2- to 4-fold
Heart failure 2- to 5-fold

~65% of deaths are due to CV disease

T2DM = type 2 diabetes mellitus

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

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.
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.

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

Relative Risk of MI or Stroke

- No diabetes throughout the study: 1.00
- Risk of event before diagnosis of diabetes: 2.82
- Risk of event after diagnosis of diabetes: 3.71
- Diabetes at baseline: 5.02

MI=myocardial infarction.
Copyright © 2002 American Diabetes Association From Diabetes Care®, Vol. 25, 2002; 1129–1134
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<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Defining Level</th>
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<tbody>
<tr>
<td>Abdominal obesity (waist circumference)</td>
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<tr>
<td>Men</td>
<td>&gt;102 cm (&gt;40 in)</td>
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<tr>
<td>Women</td>
<td>&gt;88 cm (&gt;35 in)</td>
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<td>Triglycerides</td>
<td>≥150 mg/dL or on drug treatment for high TG’s</td>
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<tr>
<td>HDL-C</td>
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<td>Men</td>
<td>&lt;40 mg/dL</td>
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<tr>
<td>Women</td>
<td>&lt;50 mg/dL</td>
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<tr>
<td></td>
<td>or on drug treatment for low HDL</td>
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<tr>
<td>Blood pressure</td>
<td>≥130/≥85 mm Hg or on antihypertensive therapy</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>≥100 mg/dL or on antidiabetes</td>
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<tr>
<td>therapy</td>
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</table>

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

% of Population =

- No MS/No DM: 54.2%
- MS/No DM: 28.7%
- DM/No MS: 2.3%
- DM/MS: 14.8%

CHD Prevalence

- No MS/No DM: 8.7%
- MS/No DM: 13.9%
- DM/No MS: 7.5%
- DM/MS: 19.2%

The Metabolic Syndrome: 
Current Perspective

Body Size
\[\uparrow\text{Central Adiposity}\]

Insulin Resistance

Hyperinsulinemia

Glucose Metabolism

Uric Acid Metabolism

Dyslipidemia

Hemodynamic

Novel Risk Factors

Coronary Heart Disease

Adapted from Reaven G. *Drugs* 1999;58(suppl):19-20 with permission from WoltersKluwer Health.
Increased Visceral Fat Induces Increased Insulin resistance in Liver and Muscle

- Increased body fat
  - Large, insulin resistant adipocytes, TNF
  - Increased lipolysis of triglycerides
  - Increased free fatty acid (FFA) levels

Muscle
- Increased FFA oxidation
- Decreased glucose utilization

Liver
- Increased FFA oxidation
- Increased gluconeogenesis
- Increased very low density lipoprotein (VLDL) cholesterol
- Increased triglycerides
- Decreased high density lipoprotein (HDL) cholesterol
- Increased small, dense low density lipoprotein (LDL)

Hyperglycemia
Atherogenic Lipid Profile

References:
- 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

Endothelial dysfunction is common to microvascular and macrovascular events

Normal conditions | Risk factors | Subclinical organ factors | Clinical events
Endothelial function

Figure 1. The adverse effects of DM on cardiovascular system

- oxidative
- hypertension
- hyperglycaemia
- RAAS activation ET-1
- dyslipidaemia
- disinsulinemia
- increase in mitogen cytotoxins
- rapid and extensive atherosclerosis
- platelet activation
- advanced glycosylation products
- tendency to thrombosis

Endothelial dysfunction, thrombosis, inflammation of prol smooth muscle cells

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

DIABETES
HIGH BLOOD SUGAR

Free radical
Increases production of free radicals
Missed Electron
Can cause mutation which leads to ROS (reactive oxygen species) production

Nitric Oxide
Reduces (NO) nitric oxide
N O
Decreased blood flow, allows fatty deposit to stick to the blood vessel wall, and the blood vessel wall becomes stiff and too thick.

Damaged Cell Structure
Damage cell structure
Can cause individual cell death

Fatty Deposit Build Up

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

AGEs: consequences

AGEs → RAGE

- Crosslinking collagen → Directly ↓ function
- Binding lipoproteins
  - Inflammation
  - Oxidative stress
  - Atherosclerosis

Lennert Van Putte¹, Sofie De Schrijver¹, Peter Moortgat² ¹ University of Antwerp, Faculty of Medicine and Health science, Antwerp, Belgium
Glucose fluctuations correlate with oxidative stress

n = 21 with T2DM

MAGE = mean amplitude of glycemic excursions
PG = prostaglandin

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

$r = 0.86$
$P < 0.001$

MAGE (mg/dL) vs. Urinary 8-iso PGF$_{2\alpha}$ excretion rate (pg/mg creatinine)

Atherogenic Effects of AngII Are Enhanced by Hyperglycemia

Hyperglycemia

Tissue AngII

Oxidative stress

Endothelial dysfunction

- Endothelin
- Catecholamines
- PAI-1
- Tissue Factor
- VCAM
- ICAM

Growth Factors
Cytokines–Matrix
Metalloproteinases

Proteolysis
Inflammation

Vascular Lesion
Vascular Remodeling

Vasoconstriction
Thrombosis
Inflammation
Plaque Formation
Plaque Rupture

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

The Role of Aldosterone in Cardiovascular Disease

Deleterious Effects of Aldosterone

- Prothrombotic effects
- Vascular inflammation and injury
- Potassium and magnesium loss
- Myocardial fibrosis
- Catecholamine potentiation
- Sodium retention
- Ventricular arrhythmias
- Central hypertensive effects
- Endothelial dysfunction

Cardiovascular Disease

Impact of hyperglycemia on platelet function

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

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-\(\alpha\), IL-6)
- Hyperhomocysteinemia
- Hypercoagulation

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

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
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
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**.

Unmet Clinical Need associated with Abdominal Obesity

General vs Visceral Obesity

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

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

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

• Insulin resistance
• Hyperinsulinemia
• Glucose intolerance
• Impaired fibrinolysis
• Endothelial dysfunction
Medicamentos y cirugías
Cambiari estilo de vida
Abdominal obesity is associated with increased risk of both diabetes and CVD

Population of 168,000 primary care patients across 63 countries
## Overweight/Obesity Treatment Options in T2DM

<table>
<thead>
<tr>
<th>Treatment</th>
<th>25.0-26.9 (or 23.0-26.9*)</th>
<th>27.0-29.9</th>
<th>30.0-34.9 (or 27.5-32.4*)</th>
<th>35.0-39.9 (or 32.5-37.4*)</th>
<th>≥40 (or ≥37.5*)</th>
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</thead>
<tbody>
<tr>
<td>Diet, physical activity &amp; behavioral therapy</td>
<td>+</td>
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<tr>
<td>Pharmacotherapy</td>
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<tr>
<td>Metabolic surgery</td>
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<td></td>
<td>+</td>
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</tr>
</tbody>
</table>

* 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

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>B-R</td>
<td>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).</td>
</tr>
<tr>
<td>IIa</td>
<td>B-NR</td>
<td>2. Replacement of saturated fat with dietary monounsaturated and polyunsaturated fats can be beneficial to reduce ASCVD risk (S3.1-12, S3.1-13).</td>
</tr>
<tr>
<td>IIa</td>
<td>B-NR</td>
<td>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).</td>
</tr>
<tr>
<td>IIa</td>
<td>B-NR</td>
<td>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).</td>
</tr>
<tr>
<td>III: Harm</td>
<td>B-NR</td>
<td>5. As a part of a healthy diet, the intake of <em>trans</em> fats should be avoided to reduce ASCVD risk (S3.1-12, S3.1-17, S3.1-25–S3.1-27).</td>
</tr>
</tbody>
</table>
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 (1.28 mg)
- Polyphenols (1780 mg)

Average reduction in LDL cholesterol by 6.6 mg/dL

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

## Study
<table>
<thead>
<tr>
<th>Study</th>
<th>Control n</th>
<th>Intervention n</th>
<th>Mean difference in LDL cholesterol (mg/dL) (95% CI, n=10)</th>
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</thead>
<tbody>
<tr>
<td>Albers et al.</td>
<td>19</td>
<td>6</td>
<td>-0.68 (1.17 to -0.33) (0.06)</td>
</tr>
<tr>
<td>Albers et al.</td>
<td>39</td>
<td>20</td>
<td>0.22 (-0.24 to 0.68)</td>
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<tr>
<td>Anderson et al.</td>
<td>5</td>
<td>5</td>
<td>-0.11 (1.27 to 1.22)</td>
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<td>Anderson et al.</td>
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<td>Anderson et al.</td>
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<td>-0.43 (1.81 to 0.77)</td>
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<td>Anderson et al.</td>
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<td>9</td>
<td>-0.30 (1.21 to 0.81)</td>
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<td>Anderson et al.</td>
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<td>10</td>
<td>-0.15 (1.39 to 0.89)</td>
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<td>Aoki et al.</td>
<td>47</td>
<td>46</td>
<td>0.03 (1.07 to 0.00)</td>
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<td>Colace et al.</td>
<td>10</td>
<td>10</td>
<td>-0.02 (1.07 to 0.10)</td>
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<td>Davenport et al.</td>
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<td>Frayley et al.</td>
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<td>Frayley et al.</td>
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<tr>
<td>Groot et al.</td>
<td>48</td>
<td>46</td>
<td>0.12 (1.07 to 0.84)</td>
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<td>Hachicha et al.</td>
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<td>Almers et al.</td>
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<td>Mashayekhi et al.</td>
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<td>-0.12 (1.21 to 0.83)</td>
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<tr>
<td>Zhang et al.</td>
<td>28</td>
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<td>-0.14 (1.21 to 0.83)</td>
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<td>Zhang et al.</td>
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<td>-0.14 (1.21 to 0.83)</td>
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<tr>
<td>Overall heterogeneity P = 0.36</td>
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</table>

Mean difference (95% CI, n=10) from Albers et al. 2015, 288-292
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

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).
Statin therapy has a pivotal role in reducing CV risk

<table>
<thead>
<tr>
<th>Trial</th>
<th>Secondary prevention</th>
<th>High risk</th>
<th>Primary prevention</th>
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<td>ALLHAT-LLT\textsuperscript{8}</td>
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</table>

\text{RR reduction or hazard ratio (\%)}


N 4444 9014 4159 10,001 20,536 6595 6605 17,802 2838 10,355

Conclusions

**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**

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

Placebo

59% mean decline
P<0.00001

Absolute ↓ 56 mg/dL
(95% CI: 55-57)

Evolocumab
Median 30 mg/dL
IQR [19-46 mg/dL]

KM Rate (%) at 3 Years

<table>
<thead>
<tr>
<th></th>
<th>CV death, MI, stroke, UA, cor revasc</th>
<th>CV death, MI, stroke</th>
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</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>14.6</td>
<td>12.6</td>
</tr>
<tr>
<td>Evolocumab</td>
<td>9.9</td>
<td>7.9</td>
</tr>
</tbody>
</table>

HR 0.85 (0.79-0.92)
P<0.00001

HR 0.80 (0.73-0.88)
P<0.000001
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

Schwartz CG, NEJM 2018;379:2097-107
Hyperglycemia is an independent risk factor for adverse CV outcomes

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

UKPDS: Intensive glycemic control reduced microvascular but not macrovascular outcomes

- All-cause mortality: 6% p = 0.44
- Diabetes-related death: 10% p = 0.34
- Myocardial infarction: 16% p = 0.052
- Microalbuminuria: 33% p = 0.000054
- Retinopathy progression: 21% p = 0.015
- Microvascular complications: 25% p = 0.0099
- Any diabetes-related endpoint: 12% p = 0.029

*Median follow-up, 10 years; †assessed as surrogate endpoints; follow-up, 12 years.
UKPDS: Long-term follow-up revealed significant reduction in MI associated with previous intensive glycemic control

Fatal or non-fatal MI: Intensive treatment

<table>
<thead>
<tr>
<th>Year</th>
<th>Conventional therapy</th>
<th>Sulphonylurea–insulin</th>
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<tbody>
<tr>
<td>1997</td>
<td>186</td>
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<td>1999</td>
<td>212</td>
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<td>2003</td>
<td>271</td>
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<tr>
<td>2005</td>
<td>296</td>
<td>636</td>
</tr>
<tr>
<td>2007</td>
<td>319</td>
<td>678</td>
</tr>
</tbody>
</table>

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

ADVANCE: intensive glycemic control reduced microvascular but not macrovascular events

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

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

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

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

**Primary outcome**

<table>
<thead>
<tr>
<th>Years</th>
<th>0.00</th>
<th>0.20</th>
<th>0.40</th>
<th>0.60</th>
<th>0.80</th>
<th>1.00</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.00</td>
<td>0.80</td>
<td>0.60</td>
<td>0.40</td>
<td>0.20</td>
<td>0.00</td>
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<td>2</td>
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<td>4</td>
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<td>6</td>
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<td>8</td>
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<tr>
<td>10</td>
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</tbody>
</table>

HR 0.88 (95% CI 0.74–1.05)
p = 0.14

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

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

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

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, dialysis or kidney transplantation during the follow-up study), death from cardiovascular causes, and death from any cause.
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”
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.

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

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

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.

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

![Graph showing cumulative incidence of any cardiovascular event (%)](image)

Conventional therapy

Intensive therapy

p < 0.001

STENO-2: Dramatic ↓ in Cardiovascular Events

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

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Goal(^1)</th>
<th>Recommendation(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raised blood pressure</td>
<td>&lt; 140/90 mmHg(^*)</td>
<td>ACE inhibitor or ARB</td>
</tr>
<tr>
<td>Abnormal blood lipids</td>
<td>LDL cholesterol &lt; 100 mg/dL (&lt; 2.6 mmol/L)</td>
<td>Lifestyle modification and statin therapy</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>Smoking cessation</td>
<td>Counselling and pharmacological therapy</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>HbA(_1c) &lt; 7%(^\dagger) (&lt; 53 mmol/mol)</td>
<td>Lifestyle modification and then metformin as initial monotherapy</td>
</tr>
<tr>
<td>Raised CV risk: 10-year risk &gt; 10%</td>
<td>Antiplatelet use</td>
<td>ASA (75–162 mg/day)(^\ddagger)</td>
</tr>
</tbody>
</table>

- 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. \(^\dagger\)More or less stringent goals may be appropriate for individuals. \(^\ddagger\)Not recommended for those at low CV risk.
From CRP to IL-6 to IL-1: Moving Upstream to Identify Novel Targets for Atheroprotection
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)

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

Primary Outcome
Myocardial infarction, stroke, or CV death (per 100 person-year)
HR 0.86; 95% CI 0.74 - 0.98; P=0.02

Secondary Outcome
- MI, stroke, hospitalization for UA that led to unplanned revascularization, or CV death
  HR 0.83; 95% CI 0.73 - 0.96; P=0.005
- MI, stroke, or death from any cause
  HR 0.85; 95% CI 0.75 - 0.96; P=0.01

Antinflammatory 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.
Bleeding risk vs. Cardiovascular benefit
New Trials: Aspirin for Primary Prevention

ASCEND
- 15,480 with diabetes and no evident CVD.
- 100 mg aspirin vs. placebo
- Reduction in vascular events was counterbalanced by bleeding

ARRIVE
- 12,546 with Moderate CVD risk w/o DM or high risk of GI bleeding
- 100 mg aspirin vs. placebo
- No difference in a composite of CV death, MI, UA, CVA, or TIA. With increased risk of bleeding

ASPREE, 2018
- 19,114 adults > 70 yr with no cardiovascular disease.
- 100 mg aspirin vs. placebo
- Aspirin did not prolong disability free survival but increased major hemorrhage

Lancet. 2018;392:1036-46
Slide Courtesy: Dr. Abdulhamied Al Faddagh
ASCEND Aspirin

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

Prescribing based on totality of evidence

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

ASCVD benefit

Bleeding Risk

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

Patient-clinician preference
Shared-decision making

Low dose ASA (Class IIb)

Avoid ASA (Class III)
Focus on other risk factors

Slide Courtesy: Dr. Abdulhamied Al Fakiagh
2019 ACC/AHA Guidelines

Recommendations for Aspirin Use
Referenced studies that support recommendations are summarized in Online Data Supplements 17 and 18.

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIb</td>
<td>A</td>
<td>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).</td>
</tr>
<tr>
<td>III</td>
<td>C-LD</td>
<td>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).</td>
</tr>
</tbody>
</table>
Summary

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

Thanks for your Attention!
References


