Cardiodiabetology: Evidence and Strategies for Optimizing Cardiovascular Risk Reduction

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Presenter Disclosures

- Research support through institution from Amarin, Amgen, Boehringer-Ingelheim, Novo Nordisk, Gilead, and Pfizer
- Speaker, Sanofi
Estimated number of people with diabetes worldwide and per region in 2015 and 2040 (20-79 years)

North America and Caribbean
- 2015: 44.3 million
- 2040: 60.5 million

Europe
- 2015: 59.8 million
- 2040: 71.1 million

Middle East and North Africa
- 2015: 35.4 million
- 2040: 72.1 million

South and Central America
- 2015: 29.6 million
- 2040: 48.8 million

South East Asia
- 2015: 78.3 million
- 2040: 140.2 million

Western Pacific
- 2015: 153.2 million
- 2040: 214.8 million

Africa
- 2015: 14.2 million
- 2040: 34.2 million

World
- 2015: 415 million
- 2040: 642 million
## Rank by Country/Territory 2015 vs. 2040 in Number of People with Diabetes: China, India and USA the Top 3

<table>
<thead>
<tr>
<th>Rank</th>
<th>Country/territory</th>
<th>2015 Number of people with diabetes</th>
<th>2040 Number of people with diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>China</td>
<td>109.6 million (99.6-133.4)</td>
<td>150.7 million (138.0-179.4)</td>
</tr>
<tr>
<td>2</td>
<td>India</td>
<td>69.2 million (56.2-84.8)</td>
<td>123.5 million (99.1-150.3)</td>
</tr>
<tr>
<td>3</td>
<td>United States of America</td>
<td>29.3 million (27.6-30.9)</td>
<td>35.1 million (33.0-37.2)</td>
</tr>
<tr>
<td>4</td>
<td>Brazil</td>
<td>14.3 million (12.9-15.8)</td>
<td>23.3 million (21.0-25.9)</td>
</tr>
<tr>
<td>5</td>
<td>Russian Federation</td>
<td>12.1 million (6.2-17.0)</td>
<td>20.6 million (11.4-24.7)</td>
</tr>
<tr>
<td>6</td>
<td>Mexico</td>
<td>11.5 million (6.2-13.7)</td>
<td>16.2 million (14.3-17.7)</td>
</tr>
<tr>
<td>7</td>
<td>Indonesia</td>
<td>10.0 million (8.7-10.9)</td>
<td>15.1 million (7.3-17.3)</td>
</tr>
<tr>
<td>8</td>
<td>Egypt</td>
<td>7.8 million (3.8-9.0)</td>
<td>14.4 million (10.6-20.4)</td>
</tr>
<tr>
<td>9</td>
<td>Japan</td>
<td>7.2 million (6.1-9.6)</td>
<td>13.6 million (10.7-24.6)</td>
</tr>
<tr>
<td>10</td>
<td>Bangladesh</td>
<td>7.1 million (5.3-12.0)</td>
<td>12.4 million (6.4-17.1)</td>
</tr>
</tbody>
</table>

IDF Atlas 2015
Causes of Mortality in Patients With Diabetes

- Malignant Neoplasms: 13%
- Diabetes: 13%
- Cerebrovascular Disease: 10%
- Pneumonia/Influenza: 4%
- Other: 5%
- Heart Disease: 55%

Metabolic Syndrome and Diabetes in Relation to CHD, CVD, and Total Mortality: U.S. Men and Women Ages 30-74
(Risk-factor Adjusted Cox Regression) NHANES II Follow-up (n=6255)

Persons with both DM and CVD represent an extreme risk condition


* p<.05, ** p<.01, **** p<.0001 compared to none
## Risk of Cardiovascular Events in Diabetics

### Framingham Study

<table>
<thead>
<tr>
<th>Cardiovascular Event</th>
<th>Age-adjusted Biennial Rate Per 1000</th>
<th>Age-adjusted Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>Coronary Disease</td>
<td>39</td>
<td>21</td>
</tr>
<tr>
<td>Stroke</td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td>Peripheral Artery Dis.</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Cardiac Failure</td>
<td>23</td>
<td>21</td>
</tr>
<tr>
<td>All CVD Events</td>
<td>76</td>
<td>65</td>
</tr>
</tbody>
</table>

Subjects 35-64  36-year Follow-up  **P<.001,***P<.0001
Most Cardiovascular Patients Have Abnormal Glucose Metabolism

GAMI: n = 164
- Normoglycemia: 34%
- Prediabetes: 31%
- Type 2 Diabetes: 35%

EHS: n = 1920
- Normoglycemia: 45%
- Prediabetes: 18%
- Type 2 Diabetes: 37%

CHS: n = 2263
- Normoglycemia: 36%
- Prediabetes: 37%
- Type 2 Diabetes: 27%

GAMI = Glucose Tolerance in Patients with Acute Myocardial Infarction study; EHS = Euro Heart Survey; CHS = China Heart Survey

Initial Presentations of CVD in DM: CALIBER UK Cohort (Shah et al, Lancet Diab Endocrinol 2015) n=1.9 M

PAD (16.2%) and Heart Failure (14.7%) were the most common first manifestations of CVD in DM, followed by angina and nonfatal MI.

Suggests the need for earlier screening of subclinical PAD/HF and consideration of newer therapies to address these conditions.
Diabetes: A CHD Equivalent?

DM without prior MI has a 43% lower risk of developing total CHD events compared to those without DM with prior MI, suggesting DM is not a coronary risk equivalent.

Role of Duration of Diabetes

Rana J et al., J Gen Intern Med 2015
Annual CHD Event Rates (in %) by Calcium Score Events by CAC Categories in Subjects with DM, MetS, or Neither Disease (Malik and Wong et al., Diabetes Care 2011)

Coronary Heart Disease

Coronary Artery Calcium Score

ACCF/AHA 2010 Guideline: CAC Scoring for CV risk assessment in asymptomatic adults aged 40 and over with diabetes (Class IIa-B)
ACC/AHA Guidelines: ASCVD Risk Estimator

- Provides 10-year ASCVD risk for persons aged 40-79 years and lifetime risk estimate for people aged 20-59 years without known ASCVD
- Compared to Caucasians, the risk of ASCVD is generally lower among Asian populations—further research needed to stratify risk in this population
- Intended to drive discussion of greater adherence to heart-healthy lifestyle
- Not an automatic prescription for a statin or other therapy
- **NOT** appropriate for use in those with known ASCVD who are by definition at high risk.

Those with DM and ≥7.5% 10-year risk eligible for high intensity statin
Premature family Hx, hs-CRP, CAC, and ABI can further risk stratify and inform the treatment decision when uncertain from global risk assessment

UKPDS Risk Engine for Diabetes

- T2DM specific risk calculator
- Based on 53,000 patients years of data from the UK Prospective Diabetes Study
- Risk estimates and 95% confidence intervals in individuals with type 2 diabetes not known to have heart disease, for:
  - Non-fatal and fatal coronary heart disease
  - Fatal coronary heart disease
  - Non-fatal and fatal stroke
  - Fatal stroke

http://www.dtu.ox.ac.uk/riskengine/
Clinical Trial and Epidemiologic Evidence Inform the Value of Multiple Risk Factor Control: Treating ABCs Reduces Diabetes Complications

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Complication</th>
<th>Reduction of Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood glucose control</td>
<td>Heart attack</td>
<td>↓ 39%&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
| Blood pressure control | ▪ Cardiovascular disease  
                                   ▪ Heart failure  
                                   ▪ Stroke  
                                   ▪ Diabetes-related deaths | ↓ 51%<sup>2</sup>  
                                   ↓ 56%<sup>3</sup>  
                                   ↓ 44%<sup>3</sup>  
                                   ↓ 32%<sup>3</sup> |
| Lipid control | ▪ Coronary heart disease mortality  
                                   ▪ Major coronary heart disease event  
                                   ▪ Any atherosclerotic event  
                                   ▪ Cerebrovascular disease event | ↓ 35%<sup>4</sup>  
                                   ↓ 55%<sup>5</sup>  
                                   ↓ 37%<sup>5</sup>  
                                   ↓ 53%<sup>4</sup> |


A = Assess risk  
Antiplatelet therapy  
Atrial fibrillation  
B = BP  
C = Cholesterol  
Cigarette cessation  
D = Diet + weight management  
Diabetes prevention + treatment  
E = Exercise  
F = Heart failure
CVD Risk Factor Control in DM Remains Poor and We Can do Better!

Analysis of 2009-2010 US National Health and Nutrition Examination Survey (NHANES) data: Adults with Type 2 DM

Only 25% at goal for HbA1c, BP, LDL-C

Only 4% at goal for all 4 measures

56% HbA1C <7%
53% BP <130/80mmHg
54% LDL-C <100 mg/dL
10% BMI <25 kg/m²

Steno-2: Effects of Multifactorial Intervention on CV Outcomes

N = 160 with type 2 diabetes and microalbuminuria

53% risk reduction
P = 0.01

Follow-up (months)

Primary composite outcome* (%)

Conventional

Intensive

*CV death, MI, stroke, revascularization, amputation

Steno-2: 13 year mortality 40% lower

Multivariable adjusted risks of CVD events 62% lower and CHD events 60% lower with all 3 risk factors controlled (versus none at control)

Wong ND, Zhao Y et al. *Diabetes Care.* 2016;39:668-676
Risk of total mortality, MI, and stroke when all 5 RFs at target similar to controls; only HF still significantly higher in DM eve when 5 RFs at target

271,174 DM Ptss and Matched Controls in the Swedish National Diabetes Registry (Rawshani et al., NEJM 2018)

RFs include HbA1c, LDL-C, BP, Smoking, Albuminuria
The shape of things to come

Cardiometabolic Risk
Effect of Moderate Weight Loss

Percent changes from initial visit to final visit

2013 AHA/ACC Lifestyle Management Recommendations

*Diet: DASH, USDA, AHA

Physical activity: 150 min x 3 days/week moderate intensity

Resistance training at least 3X/week

BP + lipid control

*Class Ia Recommendation: Consume a dietary pattern that emphasizes intake of vegetables, fruits, and whole grains; includes low-fat dairy products, poultry, fish, legumes, nontropical vegetable oils and nuts; and limits intake of sweets, sugar-sweetened beverages, and red meats.

Eckel RH, et al. J Am Coll Cardiol. 2014;63(25_PA) and ADA Standards of Care 2018
ADA Standards of Care 2018: Prevention or Delay of T2DM: Recommendations

1) At least annual monitoring for the development of diabetes in those with prediabetes is suggested. E

2) Patients with prediabetes should be referred to an intensive behavioral lifestyle intervention program modeled on the Diabetes Prevention Program to achieve and maintain 7% loss of initial body weight and increase moderate-intensity physical activity (such as brisk walking) to at least 150 min/week. A

Prevention or Delay of Type 2 Diabetes: Standards of Medical Care in Diabetes - 2018. Diabetes Care 2018; 41 (Suppl. 1): S51-S54
PREDIMED STUDY

Primary Prevention of High Risk Pts with DM or 3+ Risk Factors Randomized to Mediterranean Diet with Extra Virgin Olive Oil or Nuts vs. AHA Diet

Risk of composite CVD end point was reduced by 30% in both Mediterranean diet groups

Diabetes Mellitus: Effect of Aspirin

Consider daily ASA 75-162 mg for patients with DM at high risk for CVD (10-year risk >10%)

2. ETDRS Investigators. JAMA 1992;268:1292
5. Sacco M et al. Diabetes Care 2003;26:3264
7. Ogawa H et al. JAMA 2008; 300: 2134

NS=Not Significant
ASCEND Trial: Effect of aspirin on Serious Vascular Events in Diabetes (ESC, NEJM 2018)

15480 pts with DM and no prior CVD in UK, randomized to 100 mg aspirin vs. placebo.

In primary prevention pts with DM, the benefit of low dose aspirin on serious vascular events is largely counterbalanced by the risk of major bleeding. Also see in subgroup with baseline risk ≥10%
UKPDS

Effects of Tight vs. Less-Tight Blood Pressure Control

% Risk Reduction

-75 -50 -25 0

Any Diabetes-Related Endpoint
Diabetes-Related and All-Cause Mortality
Microvascular Disease
Retinopathy Progression
Vision Deterioration
Stroke
Heart Failure

-24* -32† -37‡ -34§ -47¶ -44‖ -56**

*P=0.0046; †P=0.019; ‡P=0.0092; §P=0.0038; ¶P=0.0036; ‖P=0.013; **P=0.0043

UK Prospective Diabetes Study Group. BMJ. 1998;317:703-713.
Diabetes Mellitus: Effect of Blood Pressure Control in ACCORD

4,733 diabetic patients randomized to intensive BP control (target SBP <120 mm Hg) or standard BP control (target SBP <140 mm Hg) for 4.7 years

Intensive BP control in DM does not reduce a composite of adverse CV events, but does reduce the rate of stroke

ACCORD study group. NEJM 2010  BP=Blood pressure, DM=Diabetes mellitus, HR=Hazard ratio, SBP=Systolic blood pressure
# Recommendations for Treatment of Hypertension in Patients With DM

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>SBP: B-R&lt;sup&gt;SR&lt;/sup&gt;</td>
<td>In adults with DM and hypertension, antihypertensive drug treatment should be initiated at a BP of 130/80 mm Hg or higher with a treatment goal of less than 130/80 mm Hg.</td>
</tr>
<tr>
<td>I</td>
<td>DBP: C-EO</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>A&lt;sup&gt;SR&lt;/sup&gt;</td>
<td>In adults with DM and hypertension, all first-line classes of antihypertensive agents (i.e., diuretics, ACE inhibitors, ARBs, and CCBs) are useful and effective.</td>
</tr>
<tr>
<td>IIb</td>
<td>B-NR</td>
<td>In adults with DM and hypertension, ACE inhibitors or ARBs may be considered in the presence of albuminuria.</td>
</tr>
</tbody>
</table>

SR indicates systematic review.
Tobacco Cessation Algorithm

**Ask** and document tobacco use status
- Recent Quitter (<6 months)
- Current User

**Advise** Provide a strong, personalized message
- Prevent Relapse
  - Congratulate successes
  - Encourage
  - Discuss benefits experienced by patient
  - Address weight gain, negative mood, lack of support

**Assess** Readiness to quit in next 30 days
- Ready
- Not Ready

**Assist:** Negotiate plan
- STAR**
  - Discuss pharmacotherapy
  - Social support
  - Provide educational materials

**Arrange** Follow-up to check plan or adjust meds
- Call right before and after quit date
- Weekly follow-up x 2 weeks, then monthly x 6 months
- Ask about difficulties (withdrawal, depressed mood)
- Build upon successes
- Seek commitment to stay tobacco-free

**Recent Quitter (≤6 months)**

**Increase Motivation**
- Relevance to personal situation
- Risks: short and long-term, environmental
- Rewards: potential benefits of quitting
- Roadblocks: identify barriers and solutions
- Repetition: repeat motivational intervention
- Reassess readiness to quit

**Not Ready**

**Current User**

**STAR**
- Set quit date
- Tell family, friends, and coworkers
- Anticipate challenges: withdrawal, breaks
- Remove tobacco from the house, car etc.

Advise all patients not to use cigarettes and other tobacco products or e-cigarettes. Include smoking cessation counseling and other forms of treatment as a routine component of diabetes care.
Statins in Type 2 Diabetes

Effect of lipid lowering analyzed in 14 randomized statin trials (N=18,686 people with diabetes)

Mean duration of follow-up: 4.3 years

2013 ACC/AHA Cholesterol Guideline Recommendations for Adults with Diabetes

- Adults aged 40-75 years without ASCVD but with DM + LDL-C 70-189 mg/dL
  - Moderate-intensity statin

- If 10-y ASCVD risk = ≥7.5%
  - Consider high-intensity statin

AACE Lipid Targets for Patients with Type 2 Diabetes

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Risk Factorsᵃ / 10-Year Riskᵇ</th>
<th>Treatment Goals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>LDL-C (mg/dL)</td>
</tr>
</tbody>
</table>
| Extreme Risk    | - Progressive ASCVD including unstable angina in patients after achieving an LDL-C <70 mg/dL  
- Established clinical cardiovascular disease in patients with DM, CKD 3/4, or HeFH  
- History of premature ASCVD (<55 male, <65 female) | <55            | <80            | <70          |
| Very High Risk  | - Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease  
- Diabetes or CKD 3/4 with 1 or more risk factor(s)  
- HeFH | <70            | <100           | <80          |
| High Risk       | ≥2 risk factors and 10-year risk >10% or CHD risk equivalentsᵃ, including diabetes or CKD 3, 4 with no other risk factors | <100           | <130           | <90          |

ᵃ Major independent risk factors are high LDL-C, polycystic ovary syndrome, cigarette smoking, hypertension (blood pressure ≥140/90 mm Hg or on hypertensive medication), low HDL-C (<40 mg/dL), family history of coronary artery disease (in male, first-degree relative younger than 55 years; in female, first-degree relative younger than 65 years), chronic renal disease (CKD) stage 3/4, evidence of coronary artery calcification and age (men≥45; women≥55 years years). Subtract 1 risk factor if the person has high HDL-C.

ᵇ Framingham risk scoring is applied to determine 10-year risk.

Abbreviations: ACS = acute coronary syndrome; ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; DM = diabetes mellitus; HDL-C = high-density lipoprotein cholesterol; HeFH = heterozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; MESA = Multi-Ethnic Study of Atherosclerosis; NR = not recommended; UKPDS = United Kingdom Prospective Diabetes Study.

Non-Statin therapies may be used in selected high risk patients if \( \geq 50\% \) LDL-C reduction (or LDL-C < 70 mg/dl or non-HDL-C < 100 mg/dl) not achieved on maximal tolerated statin therapy including:

1) ezetimibe (if ASCVD w/o comorbidities or <25% addl LDL-C lowering needed), or
2) then alirocumab or evolocumab (all with ASCVD or LDL-C \( \geq 190 \) at baseline)
Improve-IT : Primary Endpoint — ITT

Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke

HR 0.936 CI (0.887, 0.988)
p=0.016

Simva — 34.7%
2742 events

EZ/Simva — 32.7%
2572 events

NNT= 50

6% relative risk reduction,
but 2% absolute risk reduction

7-year event rates
IMPROVE-IT Diabetes Subgroup Analyses

Impact of an PCSK9 mAb on LDL Receptor Expression
LDL-C Reduction with Evolocumab

Patients w/o Diabetes at Baseline

- Evolocumab: 0.8 mmol/L
- Placebo: 2.2 mmol/L
- 57% mean reduction, P<0.00001

Patients w/ Diabetes at Baseline

- Evolocumab: 0.8 mmol/L
- Placebo: 2.4 mmol/L
- 60% mean reduction, P<0.00001

Sabatine et al., Lancet Endocrinology, 2017
Effect of Evolocumab on Primary Endpoint

Patients w/o Diabetes at Baseline

- Hazard Ratio 0.83 (95% CI 0.75-0.93)
- P=0.0008
- ∆ 2.7%
- NNT 37

Patients w/ Diabetes at Baseline

- Hazard Ratio 0.87 (95% CI 0.79-0.96)
- P=0.0052
- ∆ 1.6%
- NNT 62

P_{interaction} = 0.60

Sabatine et al., Lancet Endocrinology, 2017
ADA Standards of Diabetes Care 2018
- A reasonable HbA1c target for most adults with diabetes is <7%
- Target of <6.5% may be considered if can be done without undue side effects or adverse events
- A less stringent target of 8% may be appropriate for those with hx of advanced microvascular or macrovascular complications or severe hypoglycemia
ADA Guidelines Recommend a 2nd Agent of Proven CVD Benefit in DM and CVD

Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes - 2018. Diabetes Care 2018; 41 (Suppl. 1): S73-S85
<table>
<thead>
<tr>
<th>Drugs with ASCVD Benefit:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin (potential benefit)</td>
</tr>
<tr>
<td>Canagliflozin</td>
</tr>
<tr>
<td>Empagliflozin</td>
</tr>
<tr>
<td>Liraglutide</td>
</tr>
<tr>
<td>Pioglitazone (potential benefit)</td>
</tr>
</tbody>
</table>

**ADA 2018**

### Table 8.1—Drug-specific and patient factors to consider when selecting antihyperglycemic treatment in adults with type 2 diabetes

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Hypoglycemia</th>
<th>Weight Change</th>
<th>CV Effects</th>
<th>Cost</th>
<th>Oral/SQ</th>
<th>Renal Effects</th>
<th>Additional Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>High</td>
<td>No</td>
<td>Neutral (Potential for Moderate)</td>
<td>Potential benefit</td>
<td>Neutral</td>
<td>Low</td>
<td>Oral</td>
</tr>
<tr>
<td>SGLT2 Inhibitors</td>
<td>Intermediate</td>
<td>No</td>
<td>Less</td>
<td>Benefit: canagliflozin, empagliflozin¹</td>
<td>Benefit: canagliflozin, empagliflozin</td>
<td>High</td>
<td>Oral</td>
</tr>
<tr>
<td>GLP-1 RAs</td>
<td>High</td>
<td>No</td>
<td>Less</td>
<td>Neutral: liraglutide, exenatide extended release, benefit: liraglutide</td>
<td>Neutral</td>
<td>High</td>
<td>SQ</td>
</tr>
<tr>
<td>DPP-4 Inhibitors</td>
<td>Intermediate</td>
<td>No</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Potential Risk: saxagliptin, alogliptin</td>
<td>High</td>
<td>Oral</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>High</td>
<td>No</td>
<td>Gain</td>
<td>Potential Benefit: pioglitazone</td>
<td>Increased Risk</td>
<td>Low</td>
<td>Oral</td>
</tr>
<tr>
<td>Sodium-葡萄糖共载体1抑制剂 (第二代)</td>
<td>High</td>
<td>Yes</td>
<td>Gain</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Low</td>
<td>Oral</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>High</td>
<td>Yes</td>
<td>Gain</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Low</td>
<td>SQ</td>
</tr>
</tbody>
</table>

¹See ref. 31 for description of efficacy. FDA approved for CV benefit. CVD, cardiovascular disease; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; NASH, nonalcoholic steatohepatitis; RAs, receptor agonists; SQ, subcutaneous; TZDM, type 2 diabetes.
UKPDS 34: Evidence for Beneficial CV Effects of Metformin in Overweight Patients

Risk of MI is 39% Lower with Metformin vs. Conventional Therapy in Obese Patients

Significant Reduction in MI Maintained Over 10 Years’ Post-trial Follow-up

1. All surviving patients entered the post-trial monitoring program after completion of the interventional trial

**Metformin vs. conventional**

- Conventional (n=411; events=73)
- Intensive (n=951; events=139)
- Metformin (n=342; events=39)

**Proportion of Patients With MI**

- 0 3 6 9 12 15
- 0 10 20 30

**Time from Randomization (Years)**

**HR (95% CI)**

- RR 0.61 (p=.01)
- RR 0.67 (p=.005)

**No. of events:**

<table>
<thead>
<tr>
<th>Year</th>
<th>Conventional therapy</th>
<th>Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997</td>
<td>73</td>
<td>39</td>
</tr>
<tr>
<td>1999</td>
<td>83</td>
<td>45</td>
</tr>
<tr>
<td>2001</td>
<td>92</td>
<td>55</td>
</tr>
<tr>
<td>2003</td>
<td>106</td>
<td>64</td>
</tr>
<tr>
<td>2005</td>
<td>118</td>
<td>68</td>
</tr>
<tr>
<td>2007</td>
<td>126</td>
<td>81</td>
</tr>
</tbody>
</table>

*All surviving patients entered the post-trial monitoring program after completion of the interventional trial*
## No ASCVD Benefit from DPP4-Inhibitors

### Design and Outcomes of SAVOR-TIMI 53, EXAMINE, and TECOS Trials

<table>
<thead>
<tr>
<th>Variable</th>
<th>SAVOR-TIMI 53</th>
<th>EXAMINE</th>
<th>TECOS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of patients</strong></td>
<td>16,492</td>
<td>5380</td>
<td>14,671</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>T2DM patients with CVD or high CV risk</td>
<td>T2DM with an acute MI or UA requiring hospitalization within the previous 15-90 d</td>
<td>T2DM patients with CVD or high CV risk</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>Saxagliptin vs placebo</td>
<td>Alogliptin vs placebo</td>
<td>Sitagliptin vs placebo</td>
</tr>
<tr>
<td><strong>Mean age (y)</strong></td>
<td>65</td>
<td>61</td>
<td>65</td>
</tr>
<tr>
<td><strong>Diabetes duration (y)</strong></td>
<td>10</td>
<td>7</td>
<td>11.6</td>
</tr>
<tr>
<td><strong>Established CVD (%)</strong></td>
<td>78</td>
<td>100</td>
<td>74</td>
</tr>
<tr>
<td><strong>Mean HbA1c (%)</strong></td>
<td>8 ± 1.4</td>
<td>8 ± 1.1</td>
<td>7.2 ± 0.5</td>
</tr>
<tr>
<td><strong>Mean BMI (kg/m²)</strong></td>
<td>31</td>
<td>28.7</td>
<td>30.2</td>
</tr>
<tr>
<td><strong>Prior HF (%)</strong></td>
<td>12.8</td>
<td>28</td>
<td>18</td>
</tr>
<tr>
<td><strong>Median follow-up (y)</strong></td>
<td>2.1</td>
<td>1.5</td>
<td>3.0</td>
</tr>
<tr>
<td><strong>Hypoglycemia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>15.3</td>
<td>6.7</td>
<td></td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td>13.4</td>
<td>6.5</td>
<td></td>
</tr>
<tr>
<td><strong>Definition of primary outcome</strong></td>
<td>CV death, nonfatal MI, nonfatal ischemic stroke</td>
<td>CV death, nonfatal MI, nonfatal stroke</td>
<td>CV death, nonfatal MI, nonfatal stroke, or UA hospitalization</td>
</tr>
<tr>
<td><strong>HR for primary outcome (95% CI)</strong></td>
<td>1.00 (0.89-1.12)</td>
<td>0.96 (≤1.16)</td>
<td>0.98 (0.88-1.09)</td>
</tr>
<tr>
<td><strong>Definition of secondary outcome</strong></td>
<td>CV death, MI, stroke, hospitalization for UA, HF, or coronary revascularization</td>
<td>Primary outcome + urgent revascularization due to UA within 24 hours after hospital admission</td>
<td>CV death, nonfatal MI, or nonfatal stroke</td>
</tr>
<tr>
<td><strong>HR for secondary outcome (95% CI)</strong></td>
<td>1.02 (0.94-1.11)</td>
<td>0.95 (≤1.14)</td>
<td>0.99 (0.84-1.11)</td>
</tr>
<tr>
<td><strong>Hospitalization for HF, HR (95% CI)</strong></td>
<td>1.27 (1.07-1.51)</td>
<td>1.19 (0.89-1.59)</td>
<td>1.00 (0.83-1.20)</td>
</tr>
<tr>
<td><strong>CV mortality, HR (95% CI)</strong></td>
<td>1.03 (0.87-1.22)</td>
<td>0.85 (0.66-1.00)</td>
<td>1.02 (0.90-1.15)</td>
</tr>
<tr>
<td><strong>All-cause mortality, HR (95% CI)</strong></td>
<td>1.11 (0.96-1.27)</td>
<td>0.88 (0.71-1.09)</td>
<td>1.01 (0.90-1.14)</td>
</tr>
<tr>
<td><strong>Comments</strong></td>
<td>Subjects at greatest risk of HF hospitalization had previous HF, an eGFR ≤60 mL/min/1.73 m², or elevated baseline levels of NT-proBNP</td>
<td>Post hoc analyses showed that alogliptin increased HF incidence in patients who had signs of HF at the time of randomization (HR 1.76; 95% CI, 1.07-2.90)</td>
<td>A recent post hoc analysis confirmed that sitagliptin does not increase HF hospitalization even after adjustment for pre-existing HF</td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td>The rate of any hypoglycemic event (minor and major) was significantly increased with saxagliptin as compared with placebo (15.3% vs 13.4%, P &lt; .001)</td>
<td>Incidences of hypoglycemia, cancer, pancreatitis, and initiation of dialysis were similar with alogliptin and placebo</td>
<td>There was no significant difference between sitagliptin and placebo with respect to the overall incidence of infections, cancer, site-reported renal failure, or severe hypoglycemia</td>
</tr>
</tbody>
</table>

---

Paneni, F & Luscher, TF. Am J Cardiol 2017;120[suppl];S17-S27.
Primary outcome was composite of all-cause mortality, nonfatal MI, stroke, acute coronary syndrome, coronary or leg revascularization, leg amputation

Primary outcome: HR, 0.90 (95% CI, 0.80-1.02); p=.095
Secondary outcome: HR, 0.84 (95% CI, 0.72-0.98); p=.027

Data from Dormandy JA et al. Lancet 2008;366:1279-89
PROactive: Pioglitazone Significantly Reduced the Incidence of Macrovascular Events

**MACE**
- Composite of nonfatal MI (excluding silent MI), coronary revascularization, acute coronary syndrome, and cardiac death in patients with prior MI
- Change in Risk: **-19%**
  - *p*=.033

**Myocardial Infarction**
- Fatal and nonfatal MI in patients with prior MI
- Change in Risk: **-28%**
  - *p*=.045

**Stroke**
- Fatal and nonfatal stroke in patients with prior stroke
- Change in Risk: **-47%**
  - *p*=.009

---

Pioglitazone ↓ MACE (NFMI, NF CVA & CVD Mortality)

IRIS Trial of Pioglitazone after Ischemic Stroke or TIA.
Kernan, WN. NEJM, 2016;374:1321-31
SGLT2 Inhibition

CV Risk Factor Reduction
- Lowers blood glucose levels
- Lowers BP via osmotic diuresis
- Increases urinary caloric loss with reductions in body weight
- Reduces albuminuria possibly due to alterations in tubuloglomerular feedback
Sodium Glucose CoTransporter 2 (SGLT2) Inhibition in the Kidney

- **BP**
- **Arterial stiffness**
- **Albuminuria**
- **Sympathetic nervous system activity**
- **Glucose**
- **Insulin**
- **Weight**
- **Visceral adiposity**
- **Oxidative stress**
- **Uric acid**
- **LDL-C**
- **HDL-C**
- **Triglycerides**
- **Other**
**Study design:** Multicenter, randomized, double-blind, placebo-controlled study

**Primary objective:** To assess the effects of empagliflozin vs. placebo on CV morbidity and mortality in patients with T2DM who were at high risk for CV events and were receiving standard care.

---

**Eligibility Criteria:**
- T2DM with HbA1c 7.0%-10.0%\(^a\)
- Age ≥18 years
- BMI ≤45 kg/m\(^2\)
- GFR ≥30 mL/min/1.73 m\(^2\)
- Had established CV disease

---

**Empagliflozin (10 mg or 25 mg QD) + Standard Care**
- N=4687\(^b\)

**Placebo + Standard Care**
- N=2333

---

**Primary Outcome:**
- Composite of CV death, nonfatal MI, or nonfatal stroke

**Key Secondary Outcome**
- Composite of CV death, nonfatal MI, nonfatal stroke, or hospitalization for UA

---

\(^a\)HbA1c 7.0%-9.0% in patients who did not receive any glucose lowering agents ≥12 weeks prior to randomization

\(^b\)Pooled empagliflozin group

**Empa-REG: Cardiovascular Outcomes and Death from Any Cause**

**Empagliflozin:**

- **A Primary Outcome**
  - Reduced risk for 3-point MACE by 14%
    - Hazard ratio, 0.86 (95.02% CI, 0.74–0.99)
    - P = 0.04 for superiority

- **B Death from Cardiovascular Causes**
  - Reduced CV death by 38%
    - Hazard ratio, 0.62 (95% CI, 0.49–0.77)
    - P < 0.001

- **C Death from Any Cause**
  - Improved survival by reducing all-cause mortality by 32%
    - Hazard ratio, 0.68 (95% CI, 0.57–0.82)
    - P < 0.001

- **D Hospitalization for Heart Failure**
  - Reduced hospitalization for heart failure by 35%
    - Hazard ratio, 0.65 (95% CI, 0.50–0.85)
    - P = 0.002

* 3-Point MACE = CV Death, Non-Fatal MI, Non-Fatal Stroke

DOI: 10.1056/NEJMoa1504720
**Study design:** Multicenter, randomized, double-blind, placebo-controlled, parallel group study

**Primary objective:** To determine the effects of canagliflozin compared to placebo (against a background of standard care) on the risk of CV disease and to provide data on safety and tolerability

**Study start - expected completion:** December 2009 - February 2017

---

**Eligibility Criteria:**
- T2DM with HbA1c 7.0%-10.5%
- Elevated risk for CV disease

**Randomization and Groups:**
R 1:1:1

<table>
<thead>
<tr>
<th>Group</th>
<th>Canagliflozin (100 mg)</th>
<th>Canagliflozin (300 mg)</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>1445</td>
<td>1441</td>
<td>1441</td>
</tr>
</tbody>
</table>

**Primary Outcome:**
- Composite of CV death, nonfatal MI, or nonfatal stroke

**Key Secondary Outcome:**
- Composite of CV death, nonfatal MI, nonfatal stroke, hospitalization for UA

---

Primary MACE Outcome
CV Death, Nonfatal Myocardial Infarction or Nonfatal Stroke

Hazard ratio 0.86 (95% CI, 0.75-0.97)
p < 0.0001 for noninferiority
p = 0.0158 for superiority

No. of patients
Placebo  4347  4153  2942  1240  1187  1120  789
Canagliflozin  5795  5566  4343  2555  2460  2363  1661
Summary

Hazard ratio (95% CI)

**Primary cardiovascular outcome**
- CV death: 0.87 (0.72-1.06)
- Nonfatal myocardial infarction: 0.85 (0.69-1.05)
- Nonfatal stroke: 0.90 (0.71-1.15)

Hospitalization for heart failure: 0.67 (0.52-0.87)
CV death or hospitalization for heart failure: 0.78 (0.67-0.91)
All-cause mortality: 0.87 (0.74-1.01)
Primary effects of increased beta cell response to insulin secretion, suppressed glucagon secretion by alpha cells, reduced appetite, slowed gastric emptying.

Secondary effects of reduced glucagon-stimulated hepatic glucose production, insulin-stimulated increased peripheral utilization of glucose, reduced postprandial glucose excursions.
GLP-1 has multifactorial effects

Pancreas
- ↑ Beta-cell function
- ↓ Beta-cell apoptosis
- ↑ Insulin biosynthesis
- ↑ Glucose-dependent insulin secretion
- ↓ Glucose-dependent glucagon secretion

Brain
- ↓ Body weight
- ↓ Food intake
- ↑ Satiety

Stomach
- ↓ Gastric emptying

Heart
- ↓ Cardiovascular risk
- ↓ Fatty acid metabolism
- ↑ Cardiac function
- ↓ Systolic blood pressure
- ↓ Inflammation

Liver
- ↓ Endogenous glucose production
- ↑ Hepatic insulin sensitivity
- ↓ De novo lipogenesis
- ↓ Lipotoxicity
- ↓ Steatosis

Adapted from Campbell JE, Drucker DJ. *Cell Metab.* 2013;17:819–837; Pratley RE, Gilbert M. *Rev Diabet Stud.* 2008;5:73–94. A full reference list for this slide can be found in the slide notes.

GLP-1 RA, glucagon-like peptide-1 receptor agonist.

# results shown in *in-vitro* and animal studies
GLP-1 has multifactorial effects

- Pancreas:
  - ↑ Beta-cell function\(^1\)
  - ↓ Beta-cell apoptosis\(^1\)
  - ↑ Insulin biosynthesis\(^1\)
  - ↑ Glucose-dependent insulin secretion\(^1\)
  - ↓ Glucose-dependent glucagon secretion\(^1\)

- Brain:
  - ↓ Body weight\(^5\)
  - ↓ Food intake\(^6\)
  - ↑ Satiety\(^7,8\)

- Stomach:
  - ↓ Endogenous glucose production\(^10\)
  - ↑ Hepatic insulin sensitivity\(^10\)
  - ↓ De novo lipogenesis\(^10\)
  - ↓ Lipotoxicity\(^10\)
  - ↓ Steatosis\(^11\)

- Heart:
  - ↓ Cardiovascular risk\(^2\)
  - ↓ Fatty acid metabolism\(^3\)
  - ↑ Cardiac function\(^3\)
  - ↓ Systolic blood pressure\(^3\)
  - ↓ Inflammation\(^4\)

- Liver:

But Decreases in ASCVD Appear Not to be a Class-Effect

Adapted from Campbell JE, Drucker DJ. *Cell Metab.* 2013;17:819-837; Pratley RE, Gilbert M. *Rev Diabet Stud.* 2008;5:73-94. A full reference list for this slide can be found in the slide notes. GLP-1 RA, glucagon-like peptide-1 receptor agonist.

\# results shown in in-vitro and animal studies
**Study design:** International, randomized, placebo-controlled study

**Primary objective:** To evaluate the effect of liraglutide compared to placebo on the incidence of CV events in adults with type 2 diabetes

- **Eligibility Criteria:**
  - T2DM with HbA1c ≥7.0%
  - Age ≥50 years with ≥1 coexisting CV condition
  - Age ≥60 years with ≥1 CV risk factor
  - Coronary heart disease, cerebrovascular disease, peripheral vascular disease, CKD stage ≥3, chronic heart failure NYHA class II/III
  - Microalbuminuria or proteinuria, hypertension and left ventricular hypertrophy, left ventricular systolic or diastolic dysfunction, or an ankle-brachial index (the ratio of the systolic BP at the ankle to the systolic BP in the arm) of <0.9
  - Liraglutide was administered at 0.6 mg daily for 1 week, 1.2 mg/day for an additional week, and a potential maximum dosage of 1.8 mg/day thereafter

**Primary Outcomes:**
- Composite of CV death, nonfatal MI, or nonfatal stroke

**Key Secondary Outcome:**
- Composite of CV death, nonfatal MI, nonfatal stroke, revascularization, hospitalization for UA, or heart failure

LEADER: Primary Outcome
CV Death, Nonfatal MI, or Nonfatal Stroke

The primary composite outcome in the time-to-event analysis was the first occurrence of CV death, nonfatal MI, or nonfatal stroke. The cumulative incidences were estimated with the use of the Kaplan-Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses were truncated at 54 months, because <10% of the patients had an observation time beyond 54 months.

1. **Study design:** Multicenter, randomized, placebo-controlled, double-blind study

2. **Primary objective:** To evaluate cardiovascular and other long-term outcomes with semaglutide in subjects with type 2 diabetes

---

**Eligibility Criteria:**
- T2DM with HbA1c ≥7.0%
- Age ≥50 years with evidence of CVD or ≥60 years with subclinical evidence of CVD
- Drug naïve or treated with 1-2 OADs or insulin

**Primary Outcome:**
- Composite of CV death, nonfatal MI, or nonfatal stroke

**Key secondary Outcome**
- Expanded composite CV outcome

---

**Semaglutide (0.5 mg or 1.0 mg once a week) + Standard Care**

**Placebo + Standard Care**
SUSTAIN-6: Semaglutide Reduces Cardiovascular Outcomes in DM2

CV safety trial showed 24% reduction in primary composite outcome and 39% reduction in stroke

Marso, SP. NEJM 2016;375:1834-44.
The Cardiodiabetes Care Team

- Cardiologist
- Diabetologist
- Primary Care Physician
- Nurse / nurse practitioner
- Lifestyle Interventionalists: exercise physiologists, dietitians, stress management
- Pharmacist
- Other Specialists: Nephrologists, Podiatrists, Cardio-thoracic and vascular surgeons

Wong ND, Rosenblit PD, Lepor N, Acc.org 12/16 and Cardiovasc Endocrinol 2016
The ACC Diabetes and Cardiometabolic Clinical Community

Diabetes and Cardiometabolic Disease
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(Launched in 2014)
Most people with DM remain suboptimally treated for CVD risk and will die of CVD-related consequences.

The risk for CVD events is heterogeneous in people with DM: Risk assessment is key.

Screening for subclinical atherosclerosis may improve risk factors and motivate patients.

Evidence points to combined BP, lipid, and glycemic control to in people with DM to reduce CVD events.

Newer antiglycemic agents hold promise in reducing CVD risk:
- SGLT2i appear to have hemodynamic effects benefitting HF and CVD death
- GLP1-RA may have more antiatherosclerotic effects vs. HF benefits
Thank you for your attention

www.heart.uci.edu

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www.lipid.org