11th Annual Orange County Symposium on Cardiovascular Disease Prevention: 
*The Need to Know*

Saturday, Nov. 9, 2019

UCI School of Medicine
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11th Annual Orange County Symposium on Cardiovascular Disease Prevention: ‘The Need to Know’

Cardio-Diabetology

Cardio-Renal-Diabetology

Paul D. Rosenblit MD

Saturday, November 9, 2019,
UCI Health – UCI Medical Center – UCI School of Medicine
Doubletree Hotel by Hilton Anaheim, Orange County
100 City Drive South, Orange, CA 92868

Endorsed by: The American Society for Preventive Cardiology
Dr. Paul D. Rosenblit reported the following relevant financial relationships with commercial interests:

<table>
<thead>
<tr>
<th>Speaker / Teaching Faculty:</th>
<th>Akcea, Amarin, Amgen, Merck</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Research Site Trials:</td>
<td>Amgen, Dexcom, GlaxoSmithKline, Ionis, Lilly, Mylan, Novo Nordisk</td>
</tr>
<tr>
<td>Advisory / Consultant:</td>
<td>Akcea, Esperion, Novo Nordisk</td>
</tr>
</tbody>
</table>

* 12 months: July 1, 2018 – June 30, 2019
Cardio-Renal-Diabetology

Objectives:

• Review the natural history, the microvascular and cardiovascular (CV) complication(s) burden of diabetes.

• Recognize the conventional global risk factors, co-morbidities and multi-morbidities, that influence levels of risk and aggressiveness of management.

• Appraise the multidisciplinary collaboration and simultaneous multi-therapeutic, comprehensive strategies that are obligatory to adequate primary and secondary vascular disease prevention.

• Describe the impact of anti-diabetes agents, with properties beyond glycemia effects, on the burden of microvascular and CV outcomes,
Natural History of T2DM: Insulin Resistance, Progressing from Impaired Glucose Tolerance to Overt Type 2 Diabetes.

Years from Diagnosis: -10 -5 0 5 10 15 20

- Insulin resistance
- Insulin secretion
- Hepatic Glucose production
- Postprandial glucose
- Fasting glucose

Pre-diabetes: NGT → IGT → IFG

Type 2 Diabetes: Microvascular complications

Macrovascular complications

- 'Insulin resistance' persists (muscle, adipose, and liver)
- 'Incretin (GLP-1, GIP) resistance'
  - Beta cell unresponsiveness
  - Alpha cell unresponsiveness → Glucagon hypersecretion
- Beta cell insulin secretion progressively declines.
- By time of T2DM Dx 50-80% loss of beta-cell function

Modified from:
And Modified by Kendall DM, Bergenstall RM. 2005 International Diabetes Center. Minneapolis
Defronzo RA. Diabetes. 2009;58:773-795
“More than 100 million Americans have Diabetes or Prediabetes”

- Diagnosed Diabetes: 23.1%
- Undiagnosed Diabetes: 7.2%
- Prediabetes: 70%

30.3 million people have Diabetes (9.4% of US population)

Percent US adult population, with Prediabetes:
- 21.6% ≥18 yrs
- 48% ≥60 yrs

CDC.gov. 2017
Natural History of Type 2 Diabetes
Clustered Pre-Diabetes (Cardiovascular) Risks and Progression of Complications

Pre-Diabetes:
- Genetic susceptibility
- Environmental factors: Nutrition, Physical inactivity, Abdominal obesity
- Insulin resistance
- Hyperinsulinemia
- Hypertension
- Triglycerides and TG-rich remnant-C particles
- ↑ Small dense LDL particles
- ↓ Small dense HDL₂ particles
- Coagulopathy (PAI-1)

Diabetes:
- Hyperglycemia
- Vascular Complications: Macrovascular / Microvascular
- Atherosclerosis: Glomerulosclerosis
- CAD
- Carotid Artery Disease
- CVD
- PVD
- Retinopathy
- CKD / Nephropathy
- Neuropathy

Disability:
End Stage-Blindness
Renal Failure
Coronary Heart Disease
Heart Failure
Amputation

Death

Onset
Type 2 Diabetes Mellitus (T2DM) Associated with Serious Complications

**Microvascular and Neuropathic**

- Diabetic Retinopathy
  - Leading cause of blindness in adults

- Diabetic Nephropathy
  - CKD
  - Major cause of End-stage kidney disease/failure

- Diabetic Neuropathy
  - Peripheral, Painful, Autonomic

**Major cause of non-traumatic lower extremity amputations**

**Macrovascular ASCVD**

- CV Disease & Stroke
  - Account for ~65% of deaths in T2D patients; 2-to 4-fold increase risk

- Stroke
- Multi-infarct Dementia
- Carotid arterial disease

- Cardiovascular Disease
  - Coronary artery disease
  - Heart failure

- Peripheral Arterial Disease
  - Abdominal aorta, Renal arterial, Erectile dysfunction
  - Lower Extremity arterial

CV = cardiovascular.

Considerable (70%) prevalence of dysglycemia in patients presenting with acute MI and leads to increased death rates

CDC (2017) 65% of US Adults were Overweight or Obese

AHA (2014) 38% of US Adults were Obese

Relative to BMI <25 kg/m², the risk of Diabetes is 93 times greater if Severe (Morbid) Obesity the BMI ≥35 kg/m²

Approximately 80% of Patients with Diabetes are Overweight or Obese: Co-Morbidities

- Migraines
- Pseudotumor cerebri
- Dyslipidemia and Hypercholesterolemia
- Non-Alcoholic Fatty Liver Disease
- Metabolic syndrome
- Type 2 Diabetes Mellitus
- Polycystic Ovarian Syndrome: hirsutism, infertility, menstrual dysfunction
- Venous Stasis disease
- Gout
- Depression
- Obstructive Sleep Apnea
- Asthma
- ASCVD
- Hypertension
- GERD
- Stress urinary incontinence
- Degenerative Joint Disease
- Quality of Life
- Mortality


Cleveland Clinic Center. Accessed on 1/22/2012 at https://weightloss.clevelandclinic.org/index.aspx
US 2008–2009: Rate of New Cases of T1DM and T2DM, Among People < 20 years old, by Age & Race/Ethnicity

NHW=non-Hispanic whites; NHB=non-Hispanic blacks; H=Hispanics; API=Asians/Pacific Islanders; AIAN=American Indians/Alaska Natives

Rate (per 100,000 per year)

Distribution of ‘Markers of CKD’ in NHANES Participants with Diabetes, Hypertension, Self-reported Cardiovascular Disease, and Obesity, 2013–2016, ≥20 Years of Age

Data Source: National Health and Nutrition Examination Survey (NHANES), 2013-2016 participants age 20 & older. Single-sample estimates of eGFR & ACR; eGFR calculated using the CKD-EPI equation. Abbreviations: ACR, urine albumin/creatinine ratio; BMI, body mass index; CKD, chronic kidney disease; SR CVD, self-reported cardiovascular disease; eGFR, estimated glomerular filtration rate; HTN, hypertension.
Diabetes is the Leading Cause of Kidney Failure in US

Despite 103 Million US Adults with HTN vs. 23 Million US Adults with T2DM

Number of Patients

Age-Standardized Rates of ‘Cardiovascular Events’ According to the Estimated GFR among 1,120,295 Ambulatory Adults.

Age-standardized Rate of Cardiovascular Events* (per 100 persons-years)

*hospitalization for coronary heart disease (CHD), heart failure, ischemic stroke, and peripheral arterial disease (PAD).

No. of Events 73,108 34,690 18,580 8,809 3,824

10-Year **Mortality*** in T2DM by Kidney Disease Manifestation

The dashed line → indicates mortality in persons without diabetes or CKD (the reference group).

*NHANES III Third National Health and Nutrition Examination Survey

Cardio-Renal-Metabolic (CaReMe) Condition / Disease Prevalence (Adjusted Based on Distribution of ‘Diabetes’ by Age in the US Population)

Patients ≥18 yrs, with T2DM, Jan 1, 2013-June 30, 2016, total = 530,747 patients met criteria for inclusion in the study, from 271 sites [155 (57%) primary care, 96 (35%) cardiology, 20 (7%) endocrinology]. 9 CaReMe conditions examined.

Disease Prevalence
Age-Adjusted Estimate

≥3

HTN 83
Hyperlipidemia 80.8
CKD ≥3 19.6
CAD 31.9
CerebroVD 14.5
PAD 13.6
Atrial Fib/Flut 11.5
Heart Failure 12.2
Gout or Hyperuricemia 5.9

DCR is a USA-based, real-world, quality-oriented outpatient registry of patients with diabetes which includes primary care, endocrinology and cardiology practices.

Cardio-Renal-Metabolic (CaReMe) Condition / Disease Prevalence (Adjusted Based on Distribution of ‘Diabetes’ by Age in the US Population)

DCR is a USA-based, real-world, quality-oriented outpatient registry of Patients ≥18 yrs, with T2DM, Jan 1, 2013-June 30, 2016, total = 530,747 patients met criteria for inclusion in the study, from 271 sites (155 [57%] primary care, 96 [35%] cardiology, 20 [7%] endocrinology). Nine (9) CaReMe conditions examined.

End-Stage Renal Disease (ESRD) Patients in the United States
Number of ‘New ESRD patients’ and ‘Total ESRD patients’, 1980-2015

Mode of Treatment for ‘ESRD Patients’:
Number of prevalent ESRD patients treated with dialysis or a kidney transplant, 1980-2015


U.S. Renal Data System, Figure 1.8 and Table D.1., chapter 1 in Annual Data Report 2017, vol. 2
Mean Annualized Costs by Medical Service Category and CKD Stage by Commercial Group (A) and Medicare Group (B).
Incidence of Heart Failure (HF) Hospitalization from 3.25 million people in the National Health Service (NHS) Registry Information Services, Scotland

10-year incident HF rates in T1DM>T2DM>No Diabetes

Crude 10-year HF rates
Per 1000 person years
T1DM 12.4
T2DM 5.6
No DM 2.4

Of 689,300 participants, 24,677 (3.6%) had a history of diabetes at enrollment, 8583 (1.2%) had stroke, 21,591 (3.1%) had MI, 3233 (0.5%) had a history of both diabetes and MI, 1321 (0.2%) had both diabetes and stroke, 1836 (0.3%) had both stroke and MI, and 541 (0.1%) had diabetes, stroke, and MI.

A Perspective on Secondary Prevention ‘Guideline’ Nomenclature:

*Non-fatal MI, CV Death*  *Non-fatal MI, non-fatal stroke, CV Death*

2001 NCEP ATP-III

- “Very High” Risk
- 10-year CHD Risk* >20%

2017 AACE/ACE

- “Extreme” Risk
- 10-year ASCVD Risk** >30%

2018 AHA/ACC

- “Very High” Risk

AACE/ACE: DM, no major risks, ‘High Risk’, 10-20%

AHA/ACC: DM, >40, <75 yrs, no need to calculate risk

Very Low Risk

“ASCVD Not at Very High Risk” Unless multiple high-risk conditions

CHD Risk Equivalent

Stroke, PAD Included Diabetes with multiple ‘major’ risks

DM, no major risks ‘High Risk’, 10-20%

T2DM and Multi-Morbidities

- 20% to 44% of patients with T2DM have CKD
- 60% of patients with HF and T2DM have CKD
- 35 to 45% of patients with HF have CKD
- 12 to 45% of patients with T2DM have HF
- 32% of patients with T2DM have established CAD
- 14% of the US population have DM
- Of the US population, 33.9% ≥18 years of age and 48.3% ≥65 years of age have Pre-DM

- 60% of patients with HF and T2DM have CKD

Sources:
- Packer M. Diabetes Care. 2018;41:11-13
- Wanner C. Amer J Cardiology 2017;120:S59-S56
- Mendola ND, et al. NCHS Data brief. 2018;319:1-8

Accessed April 30, 2019
Mechanisms by which Metabolic Disorders (Obesity &/or T2DM) may Simultaneously Cause Atrial and Ventricular Myopathy, Leading to Atrial Fibrillation and to Heart Failure (with Preserved Ejection Fraction)

Type 2 diabetes

Epicardial adipose tissue expansion and inflammation

Obesity

Atrial myopathy

Atrial fibrillation

Microcirculatory dysfunction and fibrosis in adjoining myocardium

Ventricular myopathy

Heart failure with a preserved ejection fraction

Risk of New-onset Atrial Fibrillation (AF) Stratified by Diabetic Stage & BMI in 196,136 patients with newly developed Atrial fibrillation

a. The incidence of new-onset AF increased significantly according to diabetic stage. The risk also differed significantly within same diabetic stage according to BMI.

b. Adjusted hazard ratio for developing new-onset AF was significantly increased as diabetic stage was aggravated.

Obese patients who had diabetes for more than 5 years showed highest risk of AF.

AF atrial fibrillation, BMI body mass index, IFG impaired fasting glucose

Progression of Cardio-Renal Vascular Complications in T2DM:

Pre-Diabetes
- ASCVD Risk Factors Only
- CIMT

Diabetes
- ASCVD
- CKD 1, 2 (Nephropathy)
- Microalbuminuria
- Macroalbuminuria
- CKD 3
- Asymptomatic LV Dysfunction, HFpEF
- Established MACE
- Hx MI
- Hx HF, acute post-MI
- Hx PAD
- Hx Stroke
- Recent ACS
- Chronic Symptomatic HFpEF, HFrEF
- End-Stage HF
- Atrial Fibrillation
- End-Stage KD
- Death

Diabetes is a Cardio-Renal-Vascular Disease

Multidisciplinary Management Issues
Rising Healthcare Expenditure

In 2017, 54 billion USD more spent on diabetes than 2015

*Billion USD
Total healthcare expenditure by people with diabetes (20-79 years of age)
Adequately Manage the Cardio-Renal-Metabolic-Diabetes Risks: Sources of Residual Risk

Cardio-Renal Metabolic Risk
[Global Risk: Diabetes / ASCVD / CKD / Heart Failure / All-Cause Mortality]

- Overweight / Obesity
- Abnormal Lipid Metabolism
  - LDL ↑
  - ApoB ↑
  - HDL ↓
  - Triglycerides ↑
- Insulin Resistance
  - Lipids ↑
  - BP ↑
  - Glucose ↑
- Smoking
- Physical Inactivity
- Unhealthy Eating
- Hypertension
- Inflammation
- Hypercoagulation
- Age, Race, Gender, Family History
- Genetics
- Lipids
- BP
- Glucose
- Insulin Resistance Syndrome
- Age

Modified from
At baseline, mean age 54 years, 55% were women, 26% were African American.

Ideal Levels of AHA’s Life’s Simple 7 Health Factors
1. Nonsmoker* or quit >1 yr ago
2. BMI* <25 kg/m2
3. Physical activity* ≥150 mins/wk
4. Healthy dietary pattern
   a. high in fruits, vegetables, fish, fiber-rich whole grains
   b. low in Na and sugar-sweetened beverages
5. TChol <200 mg/dL
6. BP* <120/80 mm Hg
7. FBG* <100 mg/dL

*all p<0.01

Rebholz CM, Anderson CAM, Grams ME, J Am Heart Assoc. 2016;5:e003192
doi: 10.1161/JAHA.116.003192
Ideal Cardiovascular Health (CVH) Metrics

Higher ideal CVH metrics score strongly associated with lower prevalence of Coronary Artery Calcium (CAC) and with lower progression of CAC (males & females).

Incidence rates of myocardial infarction and stroke by the number of ideal health metrics in the total cohort, whites, blacks, and Caribbean Hispanics.


PREDIMED (Prevención con Dieta Mediterránea) Study: Primary Prevention of Cardiovascular Disease with a Mediterranean Diet

Multicenter trial in Spain, High CV risk participants (n=7,447, age 55-80, 57% women, mean BMI ~30, ~40% hx smoking ~48% diabetes, ~82% HTN, ~72% Dyslipidemia, 232% Fam Hx premature CAD), randomized to one of three diets. A control (low fat advice) diet or a ‘Mediterranean diet’ supplemented with either **mixed nuts** per day (30 g = 15 g of walnuts, 15 gm; hazelnuts, 7.5 gm; and almonds, 7.5 gm) or **extra-virgin olive oil**, EVOO, (approximately 1 liter per week) follow-up 4.8 years, 299 primary outcome events.

### Primary end point = 3-point Composite of Stroke, MI or CV Death

<table>
<thead>
<tr>
<th>Mediterranean diets (combined) vs. Control</th>
<th>Primary end point</th>
<th>Stroke</th>
<th>MI</th>
<th>CV death</th>
<th>Death from any cause</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0%</td>
<td>-30%</td>
<td>-23%</td>
<td>-17%</td>
<td>-11%</td>
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<tr>
<td>Relative Risk Reduction</td>
<td></td>
<td></td>
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<tr>
<td>-10%</td>
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<td>-40%</td>
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<tr>
<td>-50%</td>
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</tr>
</tbody>
</table>

The Fundamental Cause of ASCVD: Movement of Apolipoprotein B (Apo B)-containing Cholesterol Particles into the Arterial Wall.

A Gradient-Driven Process

Thus, a large concentration, or ‘number’ of, all atherogenic Apo B-containing particles [LDL, Lp(a), TG-rich lipoprotein cholesterol (chylomicron remnants, VLDL-remnants ~ IDL)] is most predictive of IHD
What about Targeting Blood Glucose to an Aggressive Goal to Reduce Cardiovascular (CV) Outcomes?

- Hypoglycemic and antihyperglycemic agents prior to Regulatory CV Randomization and Safety Mandate
  - Insulin / Sulfonylureas
  - Biguinides: Phenformin / Metformin
  - Alpha-Glucosidase Inhibitors
  - TZDs: Rosiglitazone / Pioglitazone
  - Meglitinides
  - Amylin mimetics
  - Bromocriptin QR
  - Bile Acid Sequestrants

- ‘Cardiovascular Outcome (safety) trials (CVOTs) with newer blood glucose-lowering agents
  - GLP-1 receptor agonists
  - DPP-4 inhibitors
  - SGLT2 inhibitors
UKPDS CVD (Diabetes-Related Deaths) and Trial Duration at Curve Separation: What are your expectations for ACCORD, ADVANCE and VADT

UKPDS 15 yrs, mean F/U 10 yrs

- Conventional (n=411)
- Intensive (n=951)
- Metformin (n=342)

Proportion of patients with events

Years from randomization

Patients in UKPDS:
- Newly diagnosed diabetes
- No CVD

Standard A1c

Between group A1c difference

Trial

Intensive A1c


I vs C
P=0.029
M vs C
P=0.017

Metformin in a subgroup of overweight patients (n =342)
UKPDS: Conclusions From Intensive Glucose Control Study in Patients with Type 2 Diabetes Mellitus

- Glycemic control deteriorated with time regardless of initial therapy.
- Intensive glycemic control reduced HbA$_1c$ (difference 0.9%) over 10 years, resulting decrease in clinical complications:

<table>
<thead>
<tr>
<th>Any diabetes-related endpoint</th>
<th>Risk Reduction *</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>16%</td>
<td>0.052</td>
</tr>
<tr>
<td>Microvascular disease</td>
<td>25%</td>
<td>0.0099</td>
</tr>
<tr>
<td>Retinopathy progression†</td>
<td>21%</td>
<td>0.015</td>
</tr>
<tr>
<td>Cataract extraction</td>
<td>24%</td>
<td>0.046</td>
</tr>
<tr>
<td>Microalbuminuria†</td>
<td>33%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Compared with conventional therapy. †At 12 years.

UKPDS: Between-Group A1c Difference (d) was Relatively Small (0.9%)

A 0.9% A1C between-group difference is equivalent to an approximate between-group difference in average Blood glucose of 27 mg/dL.

Prospective Observational Study: Glycemia Association with Myocardial Infarction & Microvascular Disease

n = 4,585 White, Asian Indians, Afro-Caribbean UKPDS patients whether randomized to treatment or not, followed 10 yrs

- 37% decrease for 1% HbA1c decrement, p < 0.0001
- Microvascular disease

- 14% decrease for 1% HbA1c decrement, p < 0.0001

- 2% HbA1c drop = 28% RRR in MI
- 3% HbA1c drop = 42% RRR in MI

The lower the HbA1c, the better with no indication of threshold.

UKPDS: Risk Reduction (Per 1% HbA1c Decrement) in Diabetes-Related Complications (Updated HbA1c)

- Microvascular Disease
- PAD
- MI
- Stroke
- Heart Failure
- Cataract extraction

-37 $p<0.0001$
-14 $p<0.0001$
-12 $p=0.035$
-16 $p=0.021$
-19 $p<0.0001$

* Lower extremity amputation or fatal peripheral vascular disease (PVD).

UKPDS CVD (Diabetes-Related Deaths) and Trial Duration at Curve Separation: What are your expectations for ACCORD, ADVANCE and VADT

ACCORD, ADVANCE and VADT trials were much shorter than 10 years; likely far too short to show reduction in CVD with intensive glycemic control.
Meta-analysis of RCTs of Intensive Glycemic Control in T2DM

HbA1c Concentration (%) at Follow-up

<table>
<thead>
<tr>
<th>Trial</th>
<th>Standard Therapy</th>
<th>Intensive Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS</td>
<td>7.9</td>
<td>7</td>
</tr>
<tr>
<td>PROactive</td>
<td>7.6</td>
<td>7</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>7.3</td>
<td>6.8</td>
</tr>
<tr>
<td>VADT</td>
<td>8.4</td>
<td>6.9</td>
</tr>
<tr>
<td>ACCORD</td>
<td>7.5</td>
<td>6.4</td>
</tr>
<tr>
<td>MEAN</td>
<td>7.5</td>
<td>6.6</td>
</tr>
</tbody>
</table>

N: 4620  5238  11,140  1791  10,251  33,040
Years: 10.1  2.9  5.0  5.6  3.5  4.95
Patient-Years: 46,237  15,059  55,700  10,030  35,879  162,905

Between-Group A1C difference: 0.9%  0.6%  0.5%  1.5%  1.1%  0.9%


Mean Between-Group A1C Difference 0.9%
Effect Of Intensive Control of Glucose on Cardiovascular Outcomes and Death in Patients with Diabetes Mellitus: A Meta-analysis of Randomised Controlled Trials

**Figure 1:** Probability of events of non-fatal myocardial infarction with intensive glucose-lowering versus standard treatment

<table>
<thead>
<tr>
<th>Intensive treatment/standard treatment</th>
<th>Weight of study size</th>
<th>Odds ratio (95% CI)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS41</td>
<td>307/1549</td>
<td>12.8%</td>
<td>0.78 (0.62-0.98)</td>
</tr>
<tr>
<td>PROactive18–22</td>
<td>266/2653</td>
<td>13.4%</td>
<td>0.83 (0.64-1.06)</td>
</tr>
<tr>
<td>ADVANCE3</td>
<td>557/5566</td>
<td>15.2%</td>
<td>0.98 (0.88-1.10)</td>
</tr>
<tr>
<td>VAIDT12</td>
<td>89/890</td>
<td>3.6%</td>
<td>0.81 (0.58-1.15)</td>
</tr>
<tr>
<td>ACCORD5</td>
<td>5112/5033</td>
<td>28.9%</td>
<td>0.78 (0.64-0.95)</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>17267/15773</td>
<td>100%</td>
<td>0.83 (0.75-0.93)</td>
</tr>
</tbody>
</table>

**Figure 3:** Probability of events of stroke with intensive glucose-lowering versus standard treatment

17% RRR Non-fatal MI HR 0.83 (0.75-0.93)

7% RRR Stroke HR 0.93 (0.81-1.06)

NS 2% Risk All-Cause mortality HR 1.02 (0.87-1.19)

**Figure 2:** Probability of events of coronary heart disease with intensive glucose-lowering versus standard treatment

<table>
<thead>
<tr>
<th>Intensive treatment/standard treatment</th>
<th>Weight of study size</th>
<th>Odds ratio (95% CI)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS41</td>
<td>307/1549</td>
<td>8.6%</td>
<td>0.75 (0.54-1.04)</td>
</tr>
<tr>
<td>PROactive18–22</td>
<td>266/2653</td>
<td>20.2%</td>
<td>0.81 (0.65-1.00)</td>
</tr>
<tr>
<td>ADVANCE3</td>
<td>557/5566</td>
<td>36.5%</td>
<td>0.92 (0.78-1.07)</td>
</tr>
<tr>
<td>VAIDT12</td>
<td>89/890</td>
<td>9.9%</td>
<td>0.85 (0.62-1.17)</td>
</tr>
<tr>
<td>ACCORD5</td>
<td>5112/5033</td>
<td>25.7%</td>
<td>0.82 (0.68-0.99)</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>17267/15773</td>
<td>100%</td>
<td>0.85 (0.77-0.93)</td>
</tr>
</tbody>
</table>

**Figure 4:** Probability of events of all-cause mortality with intensive glucose-lowering versus standard treatment

15% RRR CHD events HR 0.85 (0.77-0.93)

# Legacy Effect of Earlier Glucose Control

*After median 8.5 years post-trial follow-up*

<table>
<thead>
<tr>
<th>Aggregate Endpoint</th>
<th>1997</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any diabetes related endpoint</td>
<td>RRR: 12%</td>
<td>9%</td>
</tr>
<tr>
<td></td>
<td>( P: 0.029 )</td>
<td>( P: 0.040 )</td>
</tr>
<tr>
<td>Microvascular disease</td>
<td>RRR: 25%</td>
<td>24%</td>
</tr>
<tr>
<td></td>
<td>( P: 0.0099 )</td>
<td>( P: 0.001 )</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>RRR: 16%</td>
<td>15%</td>
</tr>
<tr>
<td></td>
<td>( P: 0.052 )</td>
<td>( P: 0.014 )</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>RRR: 6%</td>
<td>13%</td>
</tr>
<tr>
<td></td>
<td>( P: 0.44 )</td>
<td>( P: 0.007 )</td>
</tr>
</tbody>
</table>

\( RRR = \text{Relative Risk Reduction}, \ P = \text{Log Rank} \)
Impact of Intensive Glucose-Lowering Therapy in Diabetes: Summary of Major RCTs

<table>
<thead>
<tr>
<th>Study</th>
<th>Microvasc</th>
<th>CVD</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCCT</td>
<td>↓</td>
<td>←</td>
<td>←</td>
</tr>
<tr>
<td>(A1c 7.2 vs. 9.1%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UKPDS 33</td>
<td>↓</td>
<td>←</td>
<td>←</td>
</tr>
<tr>
<td>(A1c 7.0 vs. 7.9%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACCORD</td>
<td>↓</td>
<td>←</td>
<td>↑</td>
</tr>
<tr>
<td>(A1c 6.4% vs. 7.5%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADVANCE</td>
<td>↓</td>
<td>←</td>
<td>←</td>
</tr>
<tr>
<td>(A1c 6.3% vs. 7.0%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VADT</td>
<td>↓</td>
<td>←</td>
<td>←</td>
</tr>
<tr>
<td>(A1c 6.9% vs. 8.4%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

`Metabolic Memory’ or ‘Legacy Effect’ : Good early metabolic (Blood glucose) control mediates long-term benefit

Structural and functional changes in the microcirculation interact within the vascular continuum with larger arteries; such interaction may lead to subsequent upstream endothelial dysfunction, atherosclerosis and vascular complications ("Micro/Macro Interaction"). The underlying microvascular structural changes may be more long-term and possibly mediate the “metabolic memory”.

## Oldie by Goodie Metformin
### Pharmacologic Effects of Metformin in T2DM

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Effect of Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hyperglycemia</strong></td>
<td>Improves glycemic control in T2DM; reduces progression of IGT and IFG to T2DM (4 studies)</td>
</tr>
<tr>
<td><strong>Insulin resistance (IR)</strong></td>
<td>Counters IR by several insulin-dependent and –independent actions that reduce hepatic glucose output, improve peripheral glucose disposal, increase intestinal anaerobic glucose metabolism and assist endothelial function. In PCOs, metformin decreases the serum lipids, androgen and insulin; induces ovulation and regular</td>
</tr>
<tr>
<td><strong>Hyperinsulinemia</strong></td>
<td>Reduces fasting hyperinsulinemia</td>
</tr>
<tr>
<td><strong>Abdominal obesity</strong></td>
<td>Usually stabilizes body weight; can facilitate reduction in excess adiposity</td>
</tr>
<tr>
<td><strong>Dyslipidemia</strong></td>
<td>Modestly improves lipid profile in some individuals with high TG and high LDL-C</td>
</tr>
<tr>
<td><strong>Blood Pressure</strong></td>
<td>No significant effect except if weight loss results</td>
</tr>
<tr>
<td><strong>Proinflammatory state</strong></td>
<td>May reduce hsCRP and some adipocytokines</td>
</tr>
<tr>
<td><strong>Procoagulant state</strong></td>
<td>Modest antithrombotic activity; decrease in PAI-1, fibrinogen, platelet aggregation; improved capillary perfusion</td>
</tr>
<tr>
<td><strong>Atherosclerosis</strong></td>
<td>Reduced MI and increased survival in T2DM; reduced CIMT and reduced levels of adhesion molecules; other evidence from animal studies</td>
</tr>
</tbody>
</table>

**Diabetes, Metformin, Heart Failure and All-Cause Mortality (2013)**

Systematic Review and a Metaanalysis of ‘Observational’ Studies, n=34,000 patients, including preserved or reduced LVEF and CKD (10% moderate to severe renal impairment)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Risk Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>IV, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evans</td>
<td>-0.5108</td>
<td>0.25</td>
<td>2.6%</td>
<td>0.60 [0.37, 0.98]</td>
<td>2005</td>
</tr>
<tr>
<td>Eurich</td>
<td>-0.4156</td>
<td>0.2</td>
<td>4.1%</td>
<td>0.66 [0.45, 0.98]</td>
<td>2005</td>
</tr>
<tr>
<td>Masoudi</td>
<td>-0.1393</td>
<td>0.06</td>
<td>29.0%</td>
<td>0.87 [0.77, 0.98]</td>
<td>2005</td>
</tr>
<tr>
<td>Inzucchi</td>
<td>-0.0834</td>
<td>0.13</td>
<td>8.9%</td>
<td>0.92 [0.71, 1.19]</td>
<td>2005</td>
</tr>
<tr>
<td>Shah</td>
<td>-0.2357</td>
<td>0.4</td>
<td>1.1%</td>
<td>0.79 [0.36, 1.73]</td>
<td>2010</td>
</tr>
<tr>
<td>MacDonald</td>
<td>-0.4308</td>
<td>0.15</td>
<td>6.9%</td>
<td>0.65 [0.48, 0.87]</td>
<td>2010</td>
</tr>
<tr>
<td>Roussel</td>
<td>-0.3711</td>
<td>0.13</td>
<td>8.9%</td>
<td>0.69 [0.53, 0.89]</td>
<td>2010</td>
</tr>
<tr>
<td>Andersson</td>
<td>-0.1625</td>
<td>0.0682</td>
<td>24.6%</td>
<td>0.85 [0.74, 0.97]</td>
<td>2010</td>
</tr>
<tr>
<td>Aguilar</td>
<td>-0.2744</td>
<td>0.1</td>
<td>13.9%</td>
<td>0.76 [0.62, 0.92]</td>
<td>2011</td>
</tr>
</tbody>
</table>

**Total (95% CI)**

100.0%  
0.80 [0.74, 0.87]

**Heterogeneity**: Tau² = 0.00; Chi² = 9.45, df = 8 (P = 0.31); I² = 15%

**Test for overall effect**: Z = 5.35 (P < 0.000001)

---

**Metformin demonstrated favorable effects on all-cause mortality**

Metformin is at least as safe as other glucose-lowering treatments in patients with DM and HF, and even in those with reduced left ventricular ejection fraction (HFrEF) or concomitant CKD. Until trial data become available, metformin should be considered the treatment of choice for patients with DM and HF.

Comparative Safety of Sulfonylurea (SU) and Metformin Monotherapy on the Risk of Heart Failure: A Cohort Study

Cumulative incidence of ‘heart failure (HF) hospitalization’ or ‘cardiovascular (CV) death’ over time

Initiating treatment for T2DM with sulfonylurea had a higher risk of HF and CV death compared to similar patients initiating metformin.

Matched weighted cohort was formed using matching weights, derived using propensity scores, and up or down weighting patients to more closely resemble each other.

Eligible Patients in the Veterans Health Administration


Patients were followed up from reduced kidney function threshold until MACE, treatment change, loss to follow-up, death, or to study end (December 2016)
Competing Risk Cumulative MACE Incidence Match-Weighted Cohort

For metformin, the adjusted cause-specific HR for MACE was 0.80 (0.75-0.86), compared with sulfonylureas, yielding an adjusted rate difference of 5.8 (4.1-7.3) fewer events per 1000 person-years of metformin use compared with sulfonylurea use.

Cumulative Probability of Incident MACEs = [acute MI, ischemic or hemorrhagic stroke, transient ischemic attack (TIA), or CV death]

Pioglitazone (the only true ‘Insulin Sensitizer’); part 1

Considerations and practical use:

• Easy to prescribe and use as one tablet daily; no relation to food.

• A generic; not usually expensive.

• Adverse Effects are dose dependent (45 > 30 >15 mg/day); safest at 7.5 to ≤30 mg/day)

• Adverse Effects/Cautions: Risks related to change from insulin resistance in direction of normal insulin sensitization:
  • Sodium/water renal retention edema; NYHA class III or IV HF contraindication. Caution
  • Increase in weight (subcutaneous fat weight and water) – instruct patient to inform
  • Hypoglycemia risk with hypoglycemic agents (i.e. insulin or sulfonylureas).
  • No Hypoglycemia risk as monotherapy or in combination with anti-hyperglycemic agents;
  • Increased fracture risk in women, not men; [distal (wrist, ankle); not Lumbar spine or hips], 1.9 fractures vs. 1.1 per 100-patient-years.
  • Macular edema is common to DM; pioglitazone may increase risk.

• Can be combined with any therapy; caution with insulin as both increase sodium and fluid.
**Pioglitazone** (the only proven/true ‘Insulin Sensitizer’); part 2

Benefits are multiple:

- Lowers A1C ~0.9-1.3% with durable responsiveness
- Beta-cell function preservation
- Reduces conversion from pre-diabetes to diabetes by ~75%.
- Use is independent of renal status (no dose adjustment at any eGFR); reduces proteinuria.
- Reduction in abdominal (visceral fat)-liver (NASH, NAFLD), pancreas (Beta cell), renal, mesenteric; and muscle fat.
- Lipid/Lipoprotein profile is less atherogenic [↓ TG, ↑ HDL-C (HDL-P), with slight ↑ LDL-C (elevated numbers of small dense LDL particles → fewer large LDL particles, and fewer TG-rich lipoprotein remnant cholesterol particles).
- Atherosclerotic Plaque volume reduced (CIMT, CHICAGO; IVUS, PERISCOPE).
- Reduced ASCVD Composite (nonfatal MI, nonfatal stroke, CV death) events (PROACTIVE, IRIS (pre-diabetes patients with stroke).
European Medicines Agency (EMA) and US Food and Drug Administration (FDA): Need for CV Outcomes Studies

- ‘Demonstrate that a new anti-diabetic therapy is not associated with unacceptable increase in cardiovascular risk’

*Regulatory Requirements*

FDA Criteria for Requiring a CV Outcome Trial


# Incretin Therapies (US Market)

<table>
<thead>
<tr>
<th>DPP-IV Inhibitors</th>
<th>Generic</th>
<th>Trade Names</th>
</tr>
</thead>
<tbody>
<tr>
<td>sitagliptin</td>
<td></td>
<td>Januvia</td>
</tr>
<tr>
<td>saxagliptin</td>
<td></td>
<td>Onglyza</td>
</tr>
<tr>
<td>alogliptin</td>
<td></td>
<td>Nesina</td>
</tr>
<tr>
<td>linagliptin</td>
<td></td>
<td>Tradjenta</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GLP-1 Receptor Agonists</th>
<th>mimetics</th>
<th>analogs</th>
</tr>
</thead>
<tbody>
<tr>
<td>exenatide</td>
<td></td>
<td>liraglutide</td>
</tr>
<tr>
<td>exenatide-ER</td>
<td></td>
<td>albiglutide</td>
</tr>
<tr>
<td>lixisenatide</td>
<td></td>
<td>dulaglutide</td>
</tr>
</tbody>
</table>

- **DPP-IV Inhibitors**
  - Sitagliptin (Januvia)
  - Saxagliptin (Onglyza)
  - Alogliptin (Nesina)
  - Linagliptin (Tradjenta)

- **GLP-1 Receptor Agonists**
  - Exenatide (Byetta)
  - Exenatide-ER (Bydureon)
  - Lixisenatide (Adlyxin)
  - Liraglutide (Victoza)
  - Albiglutide (Tanzeum)
  - Dulaglutide (Trulicity)
Incretin therapies: DPP-IV Inhibitor CVOTs (3P-MACE): \( CV \) death, nonfatal MI, or nonfatal stroke.

**TECOS**
- CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina

**SAVOR-TIMI 53**
- 2-yr Kaplan-Meier rate: Saxagliptin, 7.3%; Placebo, 7.2%

**CARMELINA**
- HR, 1.02; 95% CI, 0.89-1.17; \( P < .001 \) for noninferiority
- \( P = .74 \) for superiority

CVOTs with DPP-IV inhibitors: MACE Endpoint and Hospitalization for Heart Failure

CARdiovascular Outcome Study of LINAgliptin vs Glimepiride in Type 2 Diabetes (CAROLINA)

Non-inferiority clinical trial; n=6,033 patients, early (~6.2 yrs)-duration) T2DM, Hx ASCVD event (34%), Multiple CV risk factors (37%) Microvascular damage (8.5%)

Follow-up: median of 6.3 yrs

The use of linagliptin demonstrated noninferiority, relative to glimepiride.

Extrapolated 10-year 3-Point MACE Risk for entire cohort = 19.0% ~ AACE ‘High risk’; just shy of AACE ‘Very High’ risk
CAROLINA: Moderate or Severe Hypoglycemia Over Time by Treatment Groups


≥1 Investigator-reported episode of Severe hypoglycemia:
- Glimepiride (65 / 3,010) = 2.2%
- Linagliptin (10 / 3,023) = 0.3%

≥1 Episode of hospitalized hypoglycemia
- Glimepiride (27 / 3,010) = 0.9%
- Linagliptin (2 / 3,023) = 0.1%

-92% RRR
HR 0.18
0.15-0.21
P<0.001

37.7%
10.6%
Incretin Therapies (GLP-1 RA): Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER)

SUSTAIN-6: GLP-1 RA (Semaglutide) and Cardiovascular Outcomes in Patients with T2DM

New or worsening nephropathy

SUSTAIN-6: GLP-1 RA (Semaglutide) and Microvascular Outcomes in Patients with T2DM

Diabetic retinopathy complications

Dulaglutide and cardiovascular outcomes in T2DM (REWIND): a double-blind, randomized placebo-controlled trial

Primary Outcome
Composite 3-point MACE = CV death non-fatal MI or Non-fatal stroke

12% RRR
1.4% ARR
5.4-yr NNT 71

Cumulative incidence of cardiovascular outcomes (%)

http://dx.doi.org/10.1016/S0140-6736(19)31149-3
GLP-1 RA ‘Mimetic’ (Exenatide derivatives) Effects on Primary Outcome

Primary Endpoint: 4-Point MACE
[CV Death, MI, stroke, or Hospitalization for unstable angina]

Kaplan–Meier Plots of the First Confirmed

Primary Endpoint: 3-Point Composite MACE
[CV Death, Non-fatal MI and Non-fatal stroke]

Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA)

EXenatide Study of Cardiovascular Event Lowering (EXSCEL)
Pharmaco-Kinetics and Peak Drug Levels Differ Among the GLP-1 RAs May Explain in part Differences in CVOT Results

EXSCEL Prespecified Analysis: Clinical Endpoints in Patients with Known CV Disease at Baseline (Once-weekly Exenatide vs. Placebo)

**Most ‘point estimates’ favor once-weekly Exenatide**

None meet the nominal level of statistical significance

Parameters Determining the Efficacy of GLP-1R Agonists and Corresponding Clinical Trial Results.

Drug-specific differences that contribute to differential GLP-1R activation in target tissues.

Trial-specific differences that impact clinical trial results examining the efficacy and safety of GLP-1R agonists.

Drucker DJ. The Ascending GLP-1 Road From Clinical Safety to Reduction of Cardiovascular Complications. Diabetes. 67(9):1710-1719. doi: 10.2337/dbi18-0008
GLP-1 RA ‘Analogs’ Effects on Primary Outcome 3-Point Composite MACE ‘Hardest End Point’ Cardiovascular Events

CV Death, non-Fatal MI, non-Fatal Stroke

<table>
<thead>
<tr>
<th></th>
<th>LEADER</th>
<th>SUSTAIN-6</th>
<th>REWIND</th>
<th>HARMONY Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liraglutide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Semaglutide</td>
<td>-13%</td>
<td></td>
<td>-12%</td>
<td></td>
</tr>
<tr>
<td>HR 0.87</td>
<td>0.78–0.97</td>
<td>HR 0.88</td>
<td>0.79–0.99</td>
<td>HR 0.78</td>
</tr>
<tr>
<td></td>
<td>(p=0.01)</td>
<td>(p=0.026)</td>
<td></td>
<td>0.68–0.90</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>-26%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR 0.74</td>
<td>0.58–0.95</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(p=0.02)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albiglutide</td>
<td></td>
<td></td>
<td>-22%</td>
<td></td>
</tr>
<tr>
<td>HR 0.78</td>
<td>0.68–0.90</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(p=0.0006)</td>
<td></td>
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</tr>
</tbody>
</table>
PIONEER 6: CVOT with Oral Semaglutide (14 mg) in Patients with T2DM

N = 3,183 patients
Mean age 66 yrs, 85% ≥ 50 yrs of age
Median F/U = 15.9 mos. = 1.3 yrs

Primary Outcome:
3-point Hard MACE Composite= CV Death, Non-fatal MI, Non-fatal Stroke.

~ 0.8% ↓ A1C
~ 4.5 kg (10 lb) wt. loss

Death from any Cause
49% RRR
HR 0.51
(0.31-0.84)
ARR 1.4%

45/1592 = 2.8%
23/1591 = 1.4%

GLP-1 Modifies CV Risk through Direct and Indirect Actions in Multiple Organs

The targets for GLP-1 that may impact risk of developing CV disease, and the consequences of GLP-1 action in specific tissues and cell types with CV implications.

http://dx.doi.org/10.1016/j.cmet.2016.06.009
## Sodium-Glucose Co-Transporters 2 (SGLT2) Antagonists / Inhibitors

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>empagliflozin</td>
<td>Jardiance</td>
</tr>
<tr>
<td>canagliflozin</td>
<td>Invokana</td>
</tr>
<tr>
<td>dapagliflozin</td>
<td>Farxiga</td>
</tr>
<tr>
<td>ertigliflozin</td>
<td>Steglatro</td>
</tr>
</tbody>
</table>
Sodium-Glucose Co-Transporters 2 (SGLT2) Inhibitors Block SGLT2 and Reduce Glucose and Na+ Reabsorption ¹,²

EMPA-REG: Empagliflozin, CV Outcomes, Mortality, Heart Failure in T2DM

Primary Outcome

Time to first occurrence of CV death, non-fatal MI or non-fatal stroke

- Hazard ratio, 0.86 (95% CI, 0.74–0.99)
- P=0.04 for superiority

Death from Cardiovascular Causes

- Hazard ratio, 0.62 (95% CI, 0.49–0.77)
- P<0.001

- 14% RRR
- 38% RRR

Death from Any Cause

- Hazard ratio, 0.68 (95% CI, 0.57–0.82)
- P<0.001

- 32% RRR

Hospitalization for Heart Failure

- Hazard ratio, 0.65 (95% CI, 0.50–0.85)
- P=0.002

- 35% RRR
The CANVAS Program: Effects on Cardiovascular Outcomes

**Primary Composite: MACE**
- CV Death, Nonfatal Myocardial Infarction, or Nonfatal Stroke

![Graph showing the hazard ratio and RRR for MACE](image1)

- Hazard ratio 0.86 (95% CI, 0.75-0.97)
- p < 0.0001 for noninferiority
- p = 0.0158 for superiority
- 14% RRR
- P=0.16

**Primary Component - Nonfatal Myocardial Infarction**

![Graph showing the hazard ratio and RRR for Nonfatal MI](image2)

- Hazard ratio 0.85 (95% CI, 0.69-1.05)
- Placebo
- Canagliflozin
- 15% RRR
- NS

**Primary Component - CV Death**

![Graph showing the hazard ratio and RRR for CV Death](image3)

- Hazard ratio 0.87 (95% CI, 0.72-1.06)
- Placebo
- Canagliflozin
- 13% RRR
- NS

**Primary Component - Nonfatal Stroke**

![Graph showing the hazard ratio and RRR for Nonfatal Stroke](image4)

- Hazard ratio 0.90 (95% CI, 0.71-1.15)
- Placebo
- Canagliflozin
- 10% RRR
- NS

---

CANVAS Program: CV Outcomes


Graph A: Cardiovascular Death, Nonfatal MI, or Nonfatal Stroke
- Secondary prevention: Hazard ratio 0.82 (95% CI: 0.72-0.95)
- Primary prevention: Hazard ratio 0.96 (95% CI: 0.74-1.30)
- Placebo vs. Canagliflozin
- 18% RRR

Graph B: Cardiovascular Death
- Secondary prevention: Hazard ratio 0.81 (95% CI: 0.70-1.06)
- Primary prevention: Hazard ratio 0.93 (95% CI: 0.63-1.43)
- Placebo vs. Canagliflozin
- 14% RRR
CANVAS Program: Heart Failure Hospitalization

CANVAS Program: All-Cause Mortality

CANNAS Program: Microvascular Disease (Nephropathy)

Change in Albumin:Creatinine Ratio (UACR)

Percent Change in UACR per Albuminuria Class (inset)

Mean % difference
-18%
(95% CI, -16 to -20)

No. of patients
Placebo 4084 3775 2556 753 652 594 618
Canagliflozin 5500 5103 3565 1689 1541 1408 1534

## CANVAS (Canagliflozin Cardiovascular Assessment Study)

### Table: Hazard ratios (95% CI) for the primary and secondary outcomes

<table>
<thead>
<tr>
<th>Outcome Description</th>
<th>Hazard ratio (95% CI)</th>
<th>Interaction P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression of albuminuria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of participants, Canagliflozin: 1615, Placebo: 136.3</td>
<td>0.74 (0.67–0.82)</td>
<td>0.48</td>
</tr>
<tr>
<td>840 participants, Canagliflozin: 77.7, Placebo: 116.0</td>
<td>0.69 (0.60–0.79)</td>
<td></td>
</tr>
<tr>
<td>2455 participants, Canagliflozin: 89.4, Placebo: 128.7</td>
<td>0.73 (0.67–0.79)</td>
<td></td>
</tr>
<tr>
<td>40% reduction in eGFR, renal replacement therapy, or renal death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>179 participants, Canagliflozin: 6.4, Placebo: 10.5</td>
<td>0.59 (0.44–0.79)</td>
<td>0.73</td>
</tr>
<tr>
<td>70 participants, Canagliflozin: 4.1, Placebo: 6.6</td>
<td>0.63 (0.39–1.02)</td>
<td></td>
</tr>
<tr>
<td>249 participants, Canagliflozin: 5.5, Placebo: 9.0</td>
<td>0.60 (0.47–0.77)</td>
<td></td>
</tr>
<tr>
<td>40% reduction in eGFR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>174 participants, Canagliflozin: 6.3, Placebo: 10.1</td>
<td>0.60 (0.44–0.81)</td>
<td>0.85</td>
</tr>
<tr>
<td>65 participants, Canagliflozin: 3.8, Placebo: 6.2</td>
<td>0.61 (0.37–1.00)</td>
<td></td>
</tr>
<tr>
<td>239 participants, Canagliflozin: 5.3, Placebo: 8.7</td>
<td>0.60 (0.47–0.78)</td>
<td></td>
</tr>
<tr>
<td>Renal replacement therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 participants, Canagliflozin: 0.4, Placebo: 0.5</td>
<td>0.70 (0.18–2.64)</td>
<td>0.92</td>
</tr>
<tr>
<td>9 participants, Canagliflozin: 0.6, Placebo: 0.8</td>
<td>0.93 (0.25–3.53)</td>
<td></td>
</tr>
<tr>
<td>18 participants, Canagliflozin: 0.4, Placebo: 0.6</td>
<td>0.77 (0.30–1.97)</td>
<td></td>
</tr>
</tbody>
</table>

---

## Summary of Completed SGLT2 inhibitor CVOTS

<table>
<thead>
<tr>
<th></th>
<th>EMPA-REG</th>
<th>CANVAS</th>
<th>DECLARE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SGLT2 inhibitor</strong></td>
<td>Empagliflozin</td>
<td>Canagliflozin</td>
<td>Dapagliflozin</td>
</tr>
<tr>
<td><strong>Percent Entire Cohort with Baseline ASCVD</strong></td>
<td>99%</td>
<td>66%</td>
<td>40%</td>
</tr>
<tr>
<td><strong>Placebo Extrapolated 10-year 3-point MACE</strong></td>
<td>40% (AACE Extreme)</td>
<td>28% (AACE Very high)</td>
<td>22% (AACE Very-high)</td>
</tr>
<tr>
<td><strong>CV safety endpoint</strong></td>
<td>Achieved (non-inferior to placebo)</td>
<td>Achieved (non-inferior to placebo)</td>
<td>Achieved (non-inferior to placebo)</td>
</tr>
<tr>
<td>3-P MACE</td>
<td>0.86 (95% CI 0.74-0.99), p=0.04</td>
<td>0.86 (95% CI 0.75-0.97), p&lt;0.02</td>
<td>0.93 (95% CI 0.84-1.03), p=0.17</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>0.62 (95% CI 0.49-0.77), p=&lt;0.001</td>
<td>0.87 (95% CI 0.72-1.06), p=0.04</td>
<td>0.98 (95% CI 0.82-1.17), p=</td>
</tr>
<tr>
<td>Heart Failure Hospitalization</td>
<td>0.65 (95% CI 0.50-0.85), p&lt;0.001</td>
<td>0.67 (95% CI 0.52-0.87), p&lt;0.001</td>
<td>0.73 (95% CI 0.61-0.88), p=0.005</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>0.68 (95% CI 0.57-0.82), p&lt;0.001</td>
<td>0.87 (95% CI 0.74-1.01), p=0.04</td>
<td>0.93 (95% CI 0.82-1.04), p=0.17</td>
</tr>
</tbody>
</table>

SGLT2i trials on the 3-Point Composite of CV Death, Non-Fatal MI, Non-Fatal Ischemic Stroke and (MACE) Stratified by the Presence or Absence of Established ASCVD: Meta-analysis

### Patients with atherosclerotic cardiovascular disease

<table>
<thead>
<tr>
<th>Patients</th>
<th>Events</th>
<th>Events per 1000 patient-years</th>
<th>Weight (%)</th>
<th>HR</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment (n)</td>
<td>Placebo (n)</td>
<td></td>
<td></td>
<td>Treatment</td>
<td>Placebo</td>
</tr>
<tr>
<td>EMPA-REG OUTCOME</td>
<td>4687</td>
<td>2333</td>
<td>37.4</td>
<td>43.9</td>
<td>29.4</td>
</tr>
<tr>
<td>CANVAS Program</td>
<td>3756</td>
<td>2900</td>
<td>34.1</td>
<td>41.3</td>
<td>32.4</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>3474</td>
<td>3500</td>
<td>36.8</td>
<td>41.0</td>
<td>38.2</td>
</tr>
</tbody>
</table>

Fixed effects model for atherosclerotic cardiovascular disease (p=0.0002)

### Patients with multiple risk factors

<table>
<thead>
<tr>
<th>Patients</th>
<th>Events</th>
<th>Events per 1000 patient-years</th>
<th>Weight (%)</th>
<th>HR</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment (n)</td>
<td>Placebo (n)</td>
<td></td>
<td></td>
<td>Treatment</td>
<td>Placebo</td>
</tr>
<tr>
<td>CANVAS Program</td>
<td>2039</td>
<td>1447</td>
<td>15.8</td>
<td>15.5</td>
<td>25.9</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>5108</td>
<td>5078</td>
<td>13.4</td>
<td>13.3</td>
<td>74.1</td>
</tr>
</tbody>
</table>

Fixed effects model for multiple risk factors (p=0.98)

In these relative short CVOTs, MACE Risk Reduction was demonstrable in the secondary prevention patients, but **not** primary prevention patients.

Preservation of kidney function was demonstrable in both primary and secondary ASCVD prevention patients

**SGLT2i Trials on Hospitalization for Heart Failure and CV death stratified established ASCVD status: Meta-analysis**

<table>
<thead>
<tr>
<th>Patients with atherosclerotic cardiovascular disease</th>
<th>Events</th>
<th>Events per 1000 patient-years</th>
<th>Weight (%)</th>
<th>HR</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment (n)</td>
<td>Placebo (n)</td>
<td>Treatment</td>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMPA-REG OUTCOME</td>
<td>4687</td>
<td>2333</td>
<td>463</td>
<td>19.7</td>
<td>30.1</td>
</tr>
<tr>
<td>CANVAS Program</td>
<td>3756</td>
<td>2900</td>
<td>524</td>
<td>21.0</td>
<td>27.4</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>3474</td>
<td>3500</td>
<td>597</td>
<td>19.9</td>
<td>23.9</td>
</tr>
</tbody>
</table>

**Fixed effects model for atherosclerotic cardiovascular disease (p<0.0001)**

<table>
<thead>
<tr>
<th>Patients with multiple risk factors</th>
<th>Events</th>
<th>Events per 1000 patient-years</th>
<th>Weight (%)</th>
<th>HR</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment (n)</td>
<td>Placebo (n)</td>
<td>Treatment</td>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CANVAS Program</td>
<td>2039</td>
<td>1447</td>
<td>128</td>
<td>8.9</td>
<td>9.8</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>5108</td>
<td>5078</td>
<td>316</td>
<td>7.0</td>
<td>8.4</td>
</tr>
</tbody>
</table>

**Fixed effects model for multiple risk factors (p=0.0634)**

- **Reduced Hospitalization for HF & CV Death was demonstrable in patients with ASCVD (significantly) and primary prevention patients (as NS trend)**

## RECENT CardioVascular Outcome Trials (CVOTs)

<table>
<thead>
<tr>
<th>Study</th>
<th>SAVOR</th>
<th>EXAMINE</th>
<th>TECOS</th>
<th>CAROLINA</th>
<th>CARMELINA</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP-4i</td>
<td>Saxagliptin</td>
<td>Alogliptin</td>
<td>Sitagliptin</td>
<td>Linagliptin</td>
<td>Linagliptin</td>
</tr>
<tr>
<td>Comparator</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Glimepiride</td>
<td>Placebo</td>
</tr>
<tr>
<td>N; median F-U</td>
<td>16,492; 2.1 yrs</td>
<td>5,380; 1.5 yrs</td>
<td>14,671; 3.0 yrs</td>
<td>6,033; 6.3 yrs</td>
<td>6,979; 1.9 yrs</td>
</tr>
<tr>
<td>Results</td>
<td>2013</td>
<td>2013</td>
<td>2015</td>
<td>2017</td>
<td>2018</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>LEADER</th>
<th>ELIXA</th>
<th>SUSTAIN 6</th>
<th>EXSCEL</th>
<th>REWIND</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP-1 RA</td>
<td>Liraglutide</td>
<td>Lixisenatide</td>
<td>Semaglutide</td>
<td>Exenatide LR</td>
<td>Dulaglutide</td>
</tr>
<tr>
<td>Comparator</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td>N</td>
<td>9,340; 3.8 yrs</td>
<td>6,068; 2.1 yrs</td>
<td>3,297; 2.1 yrs</td>
<td>14,572; 2.4 yrs</td>
<td>9,901; 5.4 yrs</td>
</tr>
<tr>
<td>Results</td>
<td>2016</td>
<td>2015</td>
<td>2016</td>
<td>2018</td>
<td>2019</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>EMPA-REG</th>
<th>CANVAS</th>
<th>DECLARE</th>
<th>VERTIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGLT-2i</td>
<td>Empagliflozin</td>
<td>Canagliflozin</td>
<td>Dapagliflozin</td>
<td>Ertugliflozin</td>
</tr>
<tr>
<td>Comparator</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td>N</td>
<td>7,020; 3.1 yrs</td>
<td>10,142</td>
<td>17,160; 4.2 yrs</td>
<td>8,246; 6.1 yrs?</td>
</tr>
<tr>
<td>Results</td>
<td>2015</td>
<td>2017</td>
<td>2019</td>
<td>2020</td>
</tr>
</tbody>
</table>
2001 Trials: Proven Renoprotection in T2DM: RENAAL & IDNT

**RENAAL**

- Doubling of serum creatinine, ESKD, or death

**IDNT**

- Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan

- Irbesartan Diabetic Nephropathy Trial
ACEi/ARB Reduce Intraglomerular Pressure: Mechanism for Renal Protection


ACEi and ARB ↓ efferent arteriole tone and ↓ intraglomerular pressure

Initial ↓ in eGFR followed by stabilization ↓ albuminuria

Renal protection
CVOT results suggested possible attenuation of renal effects in patients with reduced kidney function. Composite outcome of ESKD, doubling of serum creatinine, or renal or CV death.

**CREDENCE Primary Aim:** To assess the effects of the SGLT2 inhibitor, canagliflozin, on clinically important renal outcomes in people with T2DM and established CKD.

### CVOT Results

<table>
<thead>
<tr>
<th>eGFR</th>
<th>CANVAS Program</th>
<th>EMPA-REG OUTCOME</th>
<th>DECLARE</th>
<th>Overall HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60</td>
<td>83</td>
<td>NA</td>
<td>59</td>
<td>0.67 (0.51–0.89)</td>
</tr>
<tr>
<td>60–&lt;90</td>
<td>118</td>
<td>NA</td>
<td>186</td>
<td>0.56 (0.46–0.70)</td>
</tr>
<tr>
<td>≥90</td>
<td>48</td>
<td>NA</td>
<td>120</td>
<td>0.44 (0.32–0.59)</td>
</tr>
</tbody>
</table>

Low Renal Risk Populations in CV Outcomes (D, C, E) Trials

**GFR categories (mL/min/1.73 m²)**
- ≥90
- 60-90
- 45-59
- 30-44
- <30

**Low Renal Risk Populations**
- Low
- Moderately increased
- High
- Very high

**Albuminuria categories (mg/g)**
- A1: <30
- A2: 30-300
- A3: >300

**DECLARE**
- Mean eGFR (mL/min/1.73 m²): 85
- Median UACR (mg/g): 13

**CANVAS Program**
- Mean eGFR (mL/min/1.73 m²): 76
- Median UACR (mg/g): 12

**EMPA-REG OUTCOME**
- Mean eGFR (mL/min/1.73 m²): 74
- Median UACR (mg/g): 18

**Sustained Renal Replacement Therapy (RRT) Events**
- DECLARE: Not reported
- CANVAS Program: 18
- EMPA-REG OUTCOME: 11

Total of 29 sustained RRT events reported across trials

**CREDENCE Primary Aim:** To assess the effects of the SGLT2 inhibitor, canagliflozin, on clinically important renal outcomes in people with T2DM and established CKD (macroalbuminuria and moderate renal impairment)
Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE):

Objectives
In people with T2DM, eGFR 30 to 90 mL/min/1.73 m², and UACR 300 to 5000 mg/g who are receiving standard-of-care including a maximum tolerated dose of an ACEi or ARB, to assess whether canagliflozin compared with placebo reduces

Primary:
• Composite outcome of ESKD, doubling of serum creatinine, or renal or CV death

Secondary:
• CV death or hospitalization for heart failure
• Major cardiovascular events (3-point MACE: CV death, MI, or stroke)
• Hospitalization for heart failure
• ESKD, doubling of serum creatinine, or renal death
• CV death
• All-cause mortality
• CV death, MI, stroke, hospitalization for heart failure, or hospitalization for unstable angina

Prespecified Hierarchical Testing
CREDENCE: A High Renal Risk Population

GFR categories (mL/min/1.73 m²)
- <30 Low
- 30-44 Moderately increased
- 45-59 High
- ≥60 Very high

Albuminurca categories (mg/g)
- A1: <30
- A2: 30-300
- A3: >300

<table>
<thead>
<tr>
<th></th>
<th>DECLARE</th>
<th>CANVAS Program</th>
<th>EMPA-REG OUTCOME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean eGFR</td>
<td>85</td>
<td>76</td>
<td>74</td>
</tr>
<tr>
<td>MedianU ACR</td>
<td>13</td>
<td>12</td>
<td>18</td>
</tr>
</tbody>
</table>

Sustained Renal Replacement Therapy (RRT) Events
- DECLARE: Not reported
- CANVAS Program: 18
- EMPA-REG OUTCOME: 11
### Effects on HbA1c

**Baseline (%)**
- Canagliflozin: 8.3
- Placebo: 8.3

**Mean difference over study**
- **-0.25%**  
  (95% CI: **-0.31, -0.20**)

**No. of participants**
- Placebo: 2150, 2103, 2066, 2181, 1882, 1728, 1172, 2088, 352
- Canagliflozin: 2154, 2108, 2074, 2024, 1609, 1817, 1254, 729, 274

**Months since randomization**
- 0, 6, 12, 18, 24, 30, 36, 42

### Effects on Systolic BP

**Baseline (mmHg)**
- Canagliflozin: 139.8
- Placebo: 140.2

**Mean difference over study**
- **-3.30 mmHg**  
  (95% CI: **-3.87, -2.73**)

**No. of participants**
- Placebo: 2188, 2131, 2066, 2027, 1923, 1766, 1187, 682, 245
- Canagliflozin: 2190, 2141, 2096, 2047, 1962, 1842, 1261, 731, 264

**Months since randomization**
- 0, 6, 12, 18, 24, 30, 36, 42

### Effects on Body Weight

**Baseline (kg)**
- Canagliflozin: 87.3
- Placebo: 86.9

**Mean difference over study**
- **-0.80 kg**  
  (95% CI: **-0.92, -0.69**)

**No. of participants**
- Placebo: 2187, 2126, 2092, 2005, 1917, 1750, 1179, 679, 244
- Canagliflozin: 2188, 2134, 2091, 2023, 1957, 1830, 1256, 731, 263

**Months since randomization**
- 0, 6, 12, 18, 24, 30, 36, 42

### Effects on Albuminuric UACR (mg/g)

**Median baseline**
- Canagliflozin: 914
- Placebo: 918

**Geometric mean (95% CI)**
- Canagliflozin: 790, 1200  
  Placebo: 790, 1200

**Mean % difference over study**
- **-32%**  
  (95% CI: **-36, -28**)

**No. of participants**
- Placebo: 2113, 2051, 1986, 1865, 1714, 1158, 685, 251
- Canagliflozin: 2114, 2070, 2010, 1917, 1819, 1245, 730, 271

**Months since randomization**
- 0, 6, 12, 18, 24, 30, 36, 42
Effects on eGFR

Acute eGFR slope (3 weeks)
Difference: $-3.17$ (95% CI, $-3.87$, $-2.47$)

Chronic eGFR slope
Difference: $2.74$/year (95% CI, $2.37$–$3.11$)

No. of Participants
- Placebo: 2178, 2084, 1985, 1882, 1720, 1536, 1006, 583, 210
- Canagliflozin: 2179, 2074, 2005, 1919, 1782, 1648, 1116, 652, 241

Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE): Summary

- Canagliflozin **reduced the risk of the primary outcome** of ESKD, doubling of serum creatinine, or renal or CV death by **30%** ($P = 0.00001$)
  - The results were consistent across a broad range of prespecified subgroups

- Canagliflozin also **reduced the risk of the secondary outcome** of ESKD, doubling of serum creatinine, or renal death by **34%** ($P < 0.001$)

- Similar risk reductions were seen for exploratory outcomes assessing components of the primary outcome
  - **ESKD:** 32% lower (95% CI, 14–46)
  - **Dialysis, transplantation, or renal death:** 28% lower (95% CI, 3–46)

- Canagliflozin **attenuated the slope of chronic eGFR decline** by 2.7 mL/min/1.73 m$^2$/year (1.9 vs 4.6)

### CANVAS¹ vs. CREDENCE²: Lower Extremity Amputation

<table>
<thead>
<tr>
<th></th>
<th>Participants with an event per 1000 patient-years (n/N)</th>
<th>IRD per 1000 patient-years (95% CI)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Canagliflozin</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>CREDEENCE</td>
<td>12.3  (70/2200)</td>
<td>11.2  (63/2197)</td>
<td>1.16 (−2.87, 5.18)</td>
</tr>
<tr>
<td>CANVAS Program¹</td>
<td>6.3  (140/5790)</td>
<td>3.4  (47/4344)</td>
<td>2.93 (1.50, 4.36)</td>
</tr>
</tbody>
</table>

Whether the increased risk of lower limb amputation in the CANVAS Program was due to differing trial populations or protocols, or to chance remains unclear.

**Primary Outcome: Benefits in eGFR 30 to <45 Subgroup**

<table>
<thead>
<tr>
<th>Screening eGFR</th>
<th>Hazard ratio (95% CI)</th>
<th>Interaction P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 to &lt;45 mL/min/1.73 m²</td>
<td>0.75 (0.59–0.95)</td>
<td>0.11</td>
</tr>
<tr>
<td>45 to &lt;60 mL/min/1.73 m²</td>
<td>0.52 (0.38–0.72)</td>
<td></td>
</tr>
<tr>
<td>60 to &lt;90 mL/min/1.73 m²</td>
<td>0.82 (0.60–1.12)</td>
<td></td>
</tr>
</tbody>
</table>

**NNT in patients with eGFR 30 to <45 mL/min/1.73 m²**

16

Many Renal Effects of SGLT2 Inhibition Have Been Proposed

- Glucose
- BP/arterial stiffness
- Volume
- Inflammation/fibrosis
- Intragenic pressure
- Albuminuria
- Oxidant stress
- Intrarenal angiotensinogen upregulation
- And many others…

Canagliflozin among adults with type 2 diabetes and diabetic kidney disease new indication for the SGLT2 inhibitor to reduce the risk for:
- end-stage renal disease,
- worsening of kidney function,
- cardiovascular death and
- hospitalization for heart failure.
### Class Effects of SGLT2 Inhibitors on Cardio-Renal Outcomes in T2DM: Composite Renal Outcome Relative Risk Reductions (RRRs)

<table>
<thead>
<tr>
<th>CVOT</th>
<th>Composite Renal Outcome</th>
</tr>
</thead>
</table>
| DECLARE-TIMI 58 (Dapagliflozin) |  -- eGFR deterioration (≥ 40%) to < 60,  
  -- end-stage renal disease (ESRD) (dialysis ≥ 90 days, transplant or sustained eGFR < 15), or  
  -- renal/cardiovascular (CV) death |
| CANVAS (Canagliflozin)        |  -- eGFR deterioration (≥ 40%),  
  -- renal-replacement therapy (RRT) (transplant, chronic dialysis, or sustained eGFR < 15), or  
  -- renal death |
| EMPA-REG OUTCOME (Empagliflozin) |  -- doubling of serum creatinine (Cr) with eGFR ≤ 45,  
  -- RRT, or  
  -- renal death |
| CREDENCE (Canagliflozin)      |  -- doubling of serum Cr,  
  -- ESRD (eGFR < 15, dialysis, or renal transplant), or  
  -- renal/CV death |

Class Effects of SGLT2 inhibitors on Cardio-Renal Outcomes in T2DM: “Composite Renal Outcome’ Relative Risk Reductions (RRRs)

<table>
<thead>
<tr>
<th>Baseline eGFR</th>
<th>Composite Renal Outcome</th>
<th>Relative Risk Reduction (RRR, %)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>85.1</td>
<td>76.5</td>
<td>-47</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>74</td>
<td>56.2</td>
<td>-40</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>-30</td>
<td></td>
<td></td>
<td>p&lt;0.00001</td>
</tr>
</tbody>
</table>

SGLT2 Inhibitor Trials: Differences in Baseline CVD and Renal Status

Percent Baseline CVD Status

<table>
<thead>
<tr>
<th>Study</th>
<th>ASCVD</th>
<th>No ASCVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>DECLARE-TIMI 58</td>
<td>59.4</td>
<td>40.6</td>
</tr>
<tr>
<td>CANVAS</td>
<td>34.5</td>
<td>65.5</td>
</tr>
<tr>
<td>EMPA-REG OUTCOMES</td>
<td>0.8</td>
<td>99.2</td>
</tr>
<tr>
<td>CREDENCE</td>
<td>49.6</td>
<td>50.4</td>
</tr>
</tbody>
</table>

Percent Baseline eGFR Status

<table>
<thead>
<tr>
<th>Study</th>
<th>eGFR &lt;60</th>
<th>eGFR &gt;60</th>
</tr>
</thead>
<tbody>
<tr>
<td>DECLARE-TIMI 58</td>
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<td>91</td>
</tr>
<tr>
<td>CANVAS</td>
<td>20</td>
<td>80</td>
</tr>
<tr>
<td>EMPA-REG OUTCOMES</td>
<td>26</td>
<td>74</td>
</tr>
<tr>
<td>CREDENCE</td>
<td>59.5</td>
<td>49.5</td>
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</table>

Class Effects of SGLT2 inhibitors on Cardio-Renal Outcomes in T2DM:
Heart failure Hospitalization (HHF), HHF and Cardiovascular (CV) Death, and
Major Adverse Cardiovascular Event (MACE) Rates per 1000 Patients

In Patients with ASCVD, or at High Risk, Guidelines have placed SGLT2i and GLP-1 RA (usually after Metformin) Recognizing the Improvements in CV Outcomes (MACE, Reduced Hospitalization for Heart Failure), and Renal Protection.

AACE / ACE, American Association of Clinical Endocrinologists / American College of Endocrinology 2015
ADA, American Diabetes Association 2018
EASD, European Association for the Study of Diabetes 2018
IDF, International Diabetes Federation
Canadian Diabetes Association
Endocrine Society
ACC, American College of Cardiology
AHA, American Heart Association
ESC, European Society of Cardiology
ESH, European Society of Hypertension
AAFP, American Academy of Family Physicians
WONCA, World Organization of Family Doctors
Heart Failure

• Chronic, degenerative, progressive disease \(^1,2,3,4\)
  • Affects approximately \textbf{64 million people worldwide}.\(^1\)
  • Half of which have a reduced ejection fraction.
  • Half of patients will die within five years of diagnosis.\(^1,2,3,4\)

• As ‘malignant’ as some of the most common cancers\(^5\)
  • in both men (prostate and bladder cancers)
  • in women (breast cancers).

• It is the \textbf{leading cause of hospitalization for those over the age of 65}.\(^6\)

• A significant clinical and economic burden. \(^6\)

# SGLT2 Inhibitor Trials and Hospitalization for Heart Failure (HF) and CV Death Stratified by History of HF: Meta-analysis

<table>
<thead>
<tr>
<th>Patients with history of heart failure</th>
<th>Events</th>
<th>Events per 1000 patient-years</th>
<th>Weight (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment (n)</td>
<td>462</td>
<td>124</td>
<td>63.6</td>
<td>0.72 (0.50-1.04)</td>
</tr>
<tr>
<td>Placebo (n)</td>
<td>244</td>
<td>85.5</td>
<td>23.6</td>
<td></td>
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<tr>
<td>EMPA-REG OUTCOME</td>
<td>803</td>
<td>203</td>
<td>35.4</td>
<td>0.61 (0.46-0.80)</td>
</tr>
<tr>
<td>CANVAS Program</td>
<td>658</td>
<td>56.8</td>
<td>34.1</td>
<td></td>
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<tr>
<td>DECLARE-TIMI 58</td>
<td>852</td>
<td>55.5</td>
<td>42.4</td>
<td>0.79 (0.63-0.99)</td>
</tr>
<tr>
<td>Fixed effects model for history of heart failure (p&lt;0.0001)</td>
<td></td>
<td></td>
<td></td>
<td>0.71 (0.61-0.84)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients with no history of heart failure</th>
<th>Events</th>
<th>Events per 1000 patient-years</th>
<th>Weight (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment (n)</td>
<td>4225</td>
<td>339</td>
<td>15.5</td>
<td>0.63 (0.51-0.78)</td>
</tr>
<tr>
<td>Placebo (n)</td>
<td>2089</td>
<td>24.9</td>
<td>30.0</td>
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<tr>
<td>EMPA-REG OUTCOME</td>
<td>4992</td>
<td>449</td>
<td>13.6</td>
<td>0.87 (0.72-1.06)</td>
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<tr>
<td>CANVAS Program</td>
<td>3689</td>
<td>15.2</td>
<td>32.4</td>
<td></td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>7730</td>
<td>599</td>
<td>8.9</td>
<td>0.84 (0.72-0.99)</td>
</tr>
<tr>
<td>Fixed effects model for no history of heart failure (p&lt;0.0001)</td>
<td></td>
<td></td>
<td></td>
<td>0.79 (0.71-0.88)</td>
</tr>
</tbody>
</table>

SGLT2 inhibitors ‘prevented’ hospitalization for HF in patients with known history of HF and in patients with no prior history of HF.

DAPA-HF: Background

• Based on CVOTs, sodium-glucose co-transporters (SGLT2) inhibitors can prevent the development of heart failure (HF) in patients with T2DM.
• Question: Can they be used to treat patients with established HF?
• Could the benefits of SGLT2 inhibitors may be glucose-independent?
• Can SGLT2 inhibitors be used to treat patients with established HF without T2DM?

DAPA-HF: Plan

• Utilize dapagliflozin, 10 mg once daily added to standard therapy, in a dedicated trial of patients with heart failure and reduced ejection fraction (HFrEF), both with and without T2DM

DAPA-HF [Dapagliflozin in Patients With Heart Failure (HF) and Reduced Ejection Fraction (HFrEF)]: Trial Design

• Patients with HFrEF (irrespective of diabetes status) were randomized to dapagliflozin 10 mg daily (n = 2,373) versus placebo (n = 2,371).
  • Total number of enrollees: 4,744
  • Duration of follow-up: 18.2 months
  • Mean patient age: 66 years
  • Percentage female: 24%
  • Percentage with diabetes: 42%

• Inclusion criteria:
  • Symptomatic heart failure
  • Left ventricular ejection fraction (LVEF) ≤40%
  • N-terminal pro–B-type natriuretic peptide (NT Pro-BNP ≥600 pg/ml (if hospitalized for HF within last 12 months ≥400 pg/ml; if atrial fibrillation/flutter ≥900 pg/ml)

• Exclusion criteria:
  • Estimated glomerular filtration rate <30 ml/min/1.73 m2
  • Symptomatic hypotension or systolic blood pressure <95 mm Hg
  • Type 1 diabetes mellitus

DAPA HF Primary Efficacy Endpoint: CV death, or Worsening HF event (= unplanned hospitalization for heart failure, or urgent heart failure visit requiring IV therapy.

- 26% RRR
- HR, 0.74 (0.65-0.85)
- P < 0.00001
- ARR 4.9
- NNT = 21

Post DAPA-HF: Dapagliflozin is indicated to reduce the risk of CV death and hospitalization for HF in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction (HFrEF).
DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure)

**Primary Outcome**

- Death from Cardiovascular Causes
  - Hazard ratio, 0.82 (95% CI, 0.69–0.98)
  - Cumulative incidence (%)
  - Months since Randomization
- Death from Any Cause
  - Hazard ratio, 0.83 (95% CI, 0.71–0.97)
  - Cumulative incidence (%)
  - Months since Randomization

**Hospitalization for Heart Failure**

- Hazard ratio, 0.70 (95% CI, 0.59–0.83)
- Cumulative incidence (%)
- Months since Randomization

**No. at Risk**

- Placebo: 2371, 2330, 2279, 2230, 2091, 1636, 1219, 664, 234
- Dapagliflozin: 2373, 2339, 2293, 2248, 2127, 1664, 1242, 671, 232

**ARR**

- 26% RRR
  - HR, 0.74 (0.65–0.85)
  - P<0.00001
- 18% RRR
  - HR, 0.82 (0.69–0.98)
- 30% RRR
  - HR, 0.70 (0.59–0.83)
- 17% RRR
  - HR, 0.83 (0.71–0.97)

**NNT=24.91**

Mechanism(s) Responsible for SGLT2i-associated Cardiovascular (Heart Failure) Benefits Remain Unclear

- Increased Hematocrit
- Reduced systolic BP
- Reduction in interstitial edema
- Reduction in LV wall stress
- Improved renal function and cardiorenal physiology
- Reverse remodeling and reduced left ventricular mass
- Inhibition of cardiac sodium-hydrogen exchange
- Ketone utilization
- Improved cardiac bioenergetics
- Glucuresis Natriuresis

SGLT2i for Prevention and Treatment of CHF

Modified from Farkouh ME, Verma S. J Am Coll Cardiol. 2018;71:2507-2510
Obesity Refractory to Lifestyle & Pharmaceutical Management: Effect of ‘Metabolic’ Surgery on MACE Outcomes in Patients With T2DM and Obesity

• Of 287,438 adult patients with diabetes in the Cleveland Clinic Health System in the United States between 1998 and 2017
  • 2,287 patients underwent metabolic surgery.

• In this retrospective cohort study, these patients were matched 1:5 to nonsurgical patients with diabetes and obesity (body mass index [BMI] ≥30), resulting in 11,435 control patients, with follow-up through December 2018.

Co-Morbidities of Obesity are Reduced with Bariatric Surgery

Migraines: 57% resolved
Pseudotumor cerebri: 96% resolved
Depression: 55% resolved
Obstructive Sleep Apnea: 74%-98% resolved
Asthma: 82% improved or resolved
Cardiovascular Disease: 82% risk reduction
Hypertension: 52%-92% resolved
GERD: 72%-98% resolved
Stress urinary incontinence: 44%-88% resolved
Degenerative Joint Disease: 41%-76% resolved
Venous Stasis disease: 95% resolved
Gout: 72% resolved
Mortality: 89% reduction in 5-year mortality; 30%-40% reduction in 10-year mortality
Quality of Life: improved in 95% of patients

Cleveland Clinic Center. Accessed on 1/22/2012 at https://weightloss.clevelandclinic.org/index.aspx
Eight-Year Cumulative Incidence Estimates (Kaplan-Meier) for 2 Composite End Points

**The primary end point**
was the incidence of extended composite of MACE 6 outcomes),
defined as 1st occurrence of:
1) coronary artery events, 2) cerebrovascular events,
3) heart failure, 4) atrial fibrillation,
5) nephropathy, and 6) all-cause mortality.

**The secondary composite end points** included 3-component MACE:
1) all-cause mortality,
2) myocardial infarction, and
3) ischemic stroke.

39% RRR  
HR, 0.61  
CI 0.55-0.69  
P<0.001

38% RRR  
HR, 0.61  
CI 0.53-0.72  
P<0.001

Effect of Metabolic Surgery on Cumulative Incidence Estimates (Kaplan-Meier) of:

Coronary Artery Disease and Cerebrovascular Disease

31% RRR
HR, 0.69
CI 0.54-0.89
P=0.002

32% RRR
HR, 0.67
CI 0.48-0.94
P=0.02

Effect of ‘Metabolic Surgery’ on Cumulative Incidence Estimates (Kaplan-Meier) of All Cause Mortality and Heart Failure.

**All Cause Mortality**
- **41% RRR**
- HR, 0.59
- CI, 0.48-0.72
- P<0.001

**Heart Failure**
- **63% RRR**
- HR, 0.38
- CI, 0.30-0.49
- P<0.001

Effect of Metabolic Surgery on Cumulative Incidence Estimates (Kaplan-Meier) for

Nephropathy

60% RRR
HR, 0.69
CI 0.31-0.52
P<0.001

Atrial Fibrillation

22% RRR
HR, 0.67
CI 0.62-0.97
P=0.03

Progression of Cardio-Renal Vascular Complications in T2DM: Therapeutic Strategies and Multidisciplinary Cooperation are Dependent on Co-Morbidities (Absence, Presence and Levels/Degrees)
Cardio-Renal-Diabetology: Summary

- Greater than 80% of patients with T2DM have HTN and dyslipidemia and 20% having CKD.
- Diabetes mellitus is the most common cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD); HTN is next most common.
- The prevalence of CKD increases coincident with other cardiovascular (CV) risk factors such as HTN, dyslipidemia, and heart failure (HF).
- Common underlying relationships and mechanisms between these diseases are increasingly being recognized.
- T2DM BG-lowering medication options have expanded “beyond A1C-centricity”.
- >20 randomized, mostly placebo-controlled, CVOTs of newer BG-lowering meds (DPP-4i, SGLT2i, GLP-1-RAs) have been published in the last 5 years.
- Clinicians must have comprehensive strategies targeting multiple risk factors simultaneously, to have an impact on progression to CKD, ASCVD and CV outcomes, including end stage chronic complications, including ESKD and Heart Failure.
- A paradigm shift has occurred in prescribing recommendations in patients with T2DM, emphasizing prevention / aggressive Tx of CKD, established ASCVD and HF; newer options offer opportunity to improve outcomes.
Thank You