The most common cause of death in patients with type 2 diabetes (T2DM) is cardiovascular disease (CVD.). However, to date, intensive control of the most obvious metabolic abnormality in this disease, namely hyperglycemia, has had little effect on reducing CV complications. Moreover, until recently, no individual diabetes medication has been convincingly proven to reduce overall macrovascular events in high-risk T2DM patients. This is despite the fact that several of these have been proposed to have beneficial effects on CV risk factors or markers of CV disease. In 2008, the FDA presented a Guidance to Industry, mandating the demonstration of CV safety in any new glucose lowering therapy. This has led to a series of large CV outcome trials initially set up to rule out any undue CV risk from these medications. This guidance was initially roundly criticized as futile and resulting in an inefficient use of financial resources. However, over the past 2 years, several of these outcome trials have demonstrated not only safety but actual effectiveness in reducing CV complications in these high-risk patients. The results of these trials will be reviewed and placed in historical context. Specific attention will be paid to EMPA-REG OUTCOME, IRIS, LEADER and SUSTAIN-6. Based on their results, the approach to glucose lowering in patients with T2DM and established CVD is apt to change dramatically over the next few years.

References:


**Update on Diabetes Drugs and CVD Risk**

Silvio E. Inzucchi MD
Yale School of Medicine
News Haven, Connecticut

---

**DISCLOSURES**

Research Support
- NIDDK (GRADE trial)
- NINDS (IRIS trial)
- Takeda* (IRIS trial)

*study drug & placebo for trial

Clinical Trial Steering Committees
- Boehringer Ingelheim
- Astra Zeneca
- Daiichi Sankyo

Clinical Trial DMCs
- Novo Nordisk
- Intarcia

Advisor / Consultant
- Novo Nordisk
- Intarcia
- Sanofi/Lexicon
- vTv Therapeutics

---

**25 Years of Outcome Trials in Diabetes**

1. More intensive glycemic control (HbA1c ~7%, perhaps lower) reduces microvascular complications in both T1DM and T2DM (RRR ~25-60%)

2. Impact of intensive glycemic control itself on macrovascular complications in T2DM is small (~15% RRR), solely on non-fatal MI, and, moreover, requires long-term efforts before it can be detected. (RRR in T1DM may be larger.)

3. There are some data to suggest an actual increased risk of CV mortality when overly stringent strategies are employed in high-risk T2DM patients.

4. Various diabetes drugs have been proposed to exert beneficial CV effects but, until recently, no individual agent has been conclusively shown to reduce events.

---

**The Puzzles of Diabetes & Its Complications**

**MACROVASCULAR COMPLICATIONS**

**MICROVASCULAR COMPLICATIONS**

---

**Multiple Complex Pathophysiological Abnormalities in T2DM**

**Major Pathophysiologically-Based Therapies for T2DM**
**DM Meds & CV Outcomes from RCTs pre-2015**

<table>
<thead>
<tr>
<th>Classes</th>
<th>Generic Names</th>
<th>A1c</th>
<th>Impact on MACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>Degludec, Glargine, Detemir, NPH, Lispro, Aspart, Glulisine</td>
<td>No limit</td>
<td><img src="image1" alt="Impact on MACE" /></td>
</tr>
<tr>
<td>SU’s</td>
<td>Glyburide, Glipizide, Glimepiride</td>
<td>1-1.5%</td>
<td><img src="image2" alt="Impact on MACE" /></td>
</tr>
<tr>
<td>Metformin</td>
<td>Metformin</td>
<td>1-1.5%</td>
<td><img src="image3" alt="Impact on MACE" /></td>
</tr>
<tr>
<td>TZD’s</td>
<td>Rosiglitazone, Pioglitazone</td>
<td>1-1.5%</td>
<td><img src="image4" alt="Impact on MACE" /></td>
</tr>
<tr>
<td>DPP-4 i’s</td>
<td>Sitagliptin, Saxagliptin, Alogliptin, Linagliptin</td>
<td>0.5-1%</td>
<td><img src="image5" alt="Impact on MACE" /></td>
</tr>
<tr>
<td>GLP-1 RA’s</td>
<td>Exenatide, Liraglutide, Albiglutide, Dulaglutide</td>
<td>1-1.5%</td>
<td><img src="image6" alt="Impact on MACE" /></td>
</tr>
<tr>
<td>SGLT2 i’s</td>
<td>Canagliflozin, Dapagliflozin, Empagliflozin</td>
<td>0.5-1%</td>
<td><img src="image7" alt="Impact on MACE" /></td>
</tr>
</tbody>
</table>

*S: small studies, low-no population, M: high - 2nd edition

---

**UKPDS 34 Substudy: Metformin Improves CVD Outcomes vs. Standard Therapy**

<table>
<thead>
<tr>
<th>Myocardial Infarction</th>
<th>Coronary Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=851</td>
<td>N=851</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Metformin</th>
<th>improvement per 1000 patient years</th>
</tr>
</thead>
<tbody>
<tr>
<td>39%</td>
<td>50%</td>
<td></td>
</tr>
</tbody>
</table>

* Names

---

**Long-term Effects of Metformin on Metabolism and Macrovascular & Microvascular Disease in Insulin-treated Patients with T2DM**

Survival functions for the primary (lower pair of curves) and the secondary, macrovascular (upper pair of curves) endpoints. Metformin treatment was associated with an end-point hazard ratio of 0.61 (95% confidence interval, 0.40-0.94, P=0.02). The number needed to treat to prevent 1 macrovascular end point was 16 (95% confidence interval, 9-67).

Mean A1c: 7.5 vs. 7.9%
Mean BMI: 31 vs. 30 kg/m²
Mean weight: 85 vs. 80 kg
Mean insulin dose: 67 vs. 84 units

---

**The “Common Soil” Hypothesis**

![Diabetes](image8) ![CVD](image9)

*Stern MF. Diabetes 1998; 44:960

---

**Pioglitazone & MACE: Principal 2° Endpoint from the PROactive trial**

![Hospitalization for heart failure](image10)

Kaplan-Meier event rate graph showing the comparison between placebo and pioglitazone. The graph shows a statistically significant reduction in hospitalization for heart failure with pioglitazone compared to placebo. The primary endpoint is HR 0.90 (p=0.095).

*Dornamdy JA et al. Lancet 2005;366:1279-89 (Primary Endpoint: HR 0.90 p=0.095)
**Heart Attack Risk Seen in Drug for Diabetes**

Tuesday, May 22, 2007

Heart Attack Risk Seen in Drug for Diabetes

**Figure 2. Kaplan-Meier plots of time to the primary endpoint (cardiovascular death or cardiovascular hospitalisation).**

**Home PD et al. Lancet 2009;373:2125-2135**

**RECORD Trial: CV Safety Trial of Rosiglitazone**

HR 0.99 (95% CI, 0.85-1.16)

**Bypass Angioplasty Revascularization Investigation in T2DM (BARI-2D)**

- 2368 T2DM patients with stable CAD
- Pre-assigned to CABG vs. PCI strata by cardiologist
- Subsequent comparison of 2 anti-hyperglycemic strategies:
  - "insulin sensitization" (met + rosi) vs. "insulin provision" (SU + insulin


**Bypass Angioplasty Revascularization Investigation in T2DM (BARI-2D)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Death from Any Cause</th>
<th>Major Cardiovascular Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>HR: 0.99 (95% CI, 0.85-1.16)</td>
<td>HR: 0.99 (95% CI, 0.85-1.16)</td>
</tr>
</tbody>
</table>

- **Mortality:** P=0.89
- **MACE:** P=0.13

**Large CV Outcomes Trials in Diabetes (Non-Insulin)**

- **DPP-4 inhibitor**
  - Saxagliptin
  - Sitagliptin
  - Alogliptin
  - Linagliptin

- **GLP-1 receptor agonist**
  - Liraglutide
  - Exenatide LR
  - Dulaglutide

- **SGLT-2 inhibitor**
  - Empagliflozin
  - Canagliflozin
  - Dapagliflozin
  - Ertugliflozin

**Study**

- **SAVOR-TIMI 53**
  - **result:** NEUTRAL

- **EXAMINE**
  - **result:** NEUTRAL

- **TECOS**
  - **result:** NEUTRAL

- **CAROLINA**
  - **result:** NEUTRAL

- **CARMELINA**
  - **result:** NEUTRAL

- **LEADER**
  - **result:** NEUTRAL

- **ELIXA**
  - **result:** NEUTRAL

- **SUSTAIN-6**
  - **result:** NEUTRAL

- **ERSEL**
  - **result:** NEUTRAL

- **REWIND**
  - **result:** NEUTRAL

- **EMPADA**
  - **result:** NEUTRAL

- **CANVAS**
  - **result:** NEUTRAL

- **DECLARE**
  - **result:** NEUTRAL

- **WESPE**
  - **result:** NEUTRAL

- **SGLT-2 inhibitor**
  - **result:** NEUTRAL

- **LUMIO**
  - **result:** NEUTRAL

- **LUMIO-2**
  - **result:** NEUTRAL

- **LEADER**
  - **result:** NEUTRAL

- **ELIXA**
  - **result:** NEUTRAL

- **SUSTAIN-6**
  - **result:** NEUTRAL

- **ERSEL**
  - **result:** NEUTRAL

- **REWIND**
  - **result:** NEUTRAL

- **EMPADA**
  - **result:** NEUTRAL

- **CANVAS**
  - **result:** NEUTRAL

- **DECLARE**
  - **result:** NEUTRAL

- **WESPE**
  - **result:** NEUTRAL

- **SGLT-2 inhibitor**
  - **result:** NEUTRAL

- **LUMIO**
  - **result:** NEUTRAL

- **LUMIO-2**
  - **result:** NEUTRAL

- **LEADER**
  - **result:** NEUTRAL

- **ELIXA**
  - **result:** NEUTRAL

- **SUSTAIN-6**
  - **result:** NEUTRAL

- **ERSEL**
  - **result:** NEUTRAL

- **REWIND**
  - **result:** NEUTRAL

- **EMPADA**
  - **result:** NEUTRAL

- **CANVAS**
  - **result:** NEUTRAL

- **DECLARE**
  - **result:** NEUTRAL

- **WESPE**
  - **result:** NEUTRAL

- **SGLT-2 inhibitor**
  - **result:** NEUTRAL

- **LUMIO**
  - **result:** NEUTRAL

- **LUMIO-2**
  - **result:** NEUTRAL
**Glucose (& Sodium) Transport via SGLT2 in the Renal Proximal Tubular Cell**

- **Tubular lumen**
- **Glucose**
- **SGLT2**
- **Interstitium**
- **GLUT2**
- **Na+**
- **K+**

**SGLT2 Inhibition Reduces Renal Glucose Reabsorption**

- **Glomerulus**
- **Proximal tubule**
- **Distal tubule**
- **Collecting duct**

**SGLT2 Inhibitors: Risk : Benefit Ratio pre-2015**

- **Benefits**: Genital mycotic infections, UTIs, Polyuria/Dehydration, Diabetic Ketoacidosis (DKA), Reversible ↓ GFR, Small ↑ LDL-C, ↓ Fractures
- **Risks**: ↓ HbA1c ~ 0.6-0.9% (insulin-independent, irrespective of disease duration), Low hypoglycemia risk, Modest ↓ weight, Modest ↓ BP, ↓ Albuminuria, Small ↓ TIs, Small ↑ HDL-C

**Empa-Reg Outcome® Trial design**

- **Placebo** (n=2333)
- **Empagliflozin 10 mg** (n=2345)
- **Empagliflozin 25 mg** (n=2342)

- **Screening** (n=11531)
- **Randomized and treated** (n=9028)

- **Primary outcome**: 3-point MACE
- **Analysis** Placebo vs. pooled empagliflozin groups
- **Key inclusion criteria**:
  - Adults with type 2 diabetes and established CVD
  - BMI ≤ 45 kg/m²; HbA1c 7-10%; eGFR ≥ 30 ml/min/1.73m² (MDRD)

**The New England Journal of Medicine**

**Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes**

Bernard Zinman, M.D., Christoph Werner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Matheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Ul C. Brodli, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

* Not approved for weight loss; BMI, WC, BP, TG, albuminuria reduction; or to increase HDL-C

**Trial design**

- **Age** ~63 yrs
- **BMI** ~31 kg/m²
- **eGFR<60** ~26%
- **CAD** ~76%
- **MI** ~46%
- **Stroke** ~23%
- **HF** ~10%

**Randomized and treated** (n=7020)

- Empagliflozin 10 mg (n=2345)
- Empagliflozin 25 mg (n=2342)
- Placebo (n=2333)

**Screening** (n=11531)

- Metformin ~74%
- Insulin ~48%
- ACEI or ARB ~81%
- Statins ~77%
- Aspirin ~83%

**Primary outcome**: 3-point MACE

- **HR 0.86** (95.02% CI 0.74, 0.99)  
  \( p = 0.0382^* \)

**Cumulative incidence function. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio.**

* Two-sided tests for superiority were conducted (statistical significance was indicated if \( p \leq 0.0498 \)).

**CV death, MI and stroke**

<table>
<thead>
<tr>
<th>Patients with event/analysed</th>
<th>Empagliflozin</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-point MACE</td>
<td>490/4687</td>
<td>282/2333</td>
<td><strong>0.86</strong> (0.74, 0.99)*</td>
<td>0.0382*</td>
</tr>
<tr>
<td>CV death</td>
<td>172/4687</td>
<td>137/2333</td>
<td><strong>0.62</strong> (0.49, 0.77)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>213/4687</td>
<td>121/2333</td>
<td><strong>0.87</strong> (0.70, 1.09)</td>
<td>0.2189</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>150/4687</td>
<td>60/2333</td>
<td><strong>1.24</strong> (0.92, 1.67)</td>
<td>0.1638</td>
</tr>
</tbody>
</table>

**Hospitalization for heart failure**

- **HR 0.65** (95% CI 0.50, 0.85)  
  \( p = 0.0017 \)

**Potential pathways to CV impact of SGLT2-inhibitors, based on clinical and mechanistic studies**

- Osmotic Diuresis / Natriuresis
- Ketonemia
- Increased arterial stiffness
- LDL-C, HDL-C
- Oxidative stress
- Adiposity
- Albuminuria
- SNS activity

**Novel Pathways (?)**

**Presented at**

- Ferrannini E et al. *Diabetes* 2016
- Weir M. *Postgrad Med* 2016
Increase in hematocrit with empagliflozin

- 75 subjects with T2DM (mean age 56 yrs, disease duration 6.3 yrs)
- Randomized to placebo, dapagliflozin 10 mg, or HCTZ 25 mg QD x 12 weeks
- Diuretic properties on BP, weight, plasma volume, eGFR

BP: D>H>P
Weight: D>H>P
eGFR: D>H>P


Pioglitazone after Ischemic Stroke or Transient Ischemic Attack


IRIS Baseline Features

<table>
<thead>
<tr>
<th>Pioglitazone (N=1939)</th>
<th>Placebo (N=1937)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean years</td>
<td>63.5</td>
</tr>
<tr>
<td>Male sex</td>
<td>67%</td>
</tr>
<tr>
<td>Black race</td>
<td>11%</td>
</tr>
<tr>
<td>Mean BMI, mean kg/m²</td>
<td>29.9±6.6</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>98±10</td>
</tr>
<tr>
<td>Impaired Fasting Glucose (IFG - ADA)</td>
<td>42%</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.8±0.4</td>
</tr>
<tr>
<td>Elevated HbA1c (25.7%)</td>
<td>65%</td>
</tr>
<tr>
<td>HOMA-IR (mean)</td>
<td>5.5±2.8</td>
</tr>
<tr>
<td>Statin therapy</td>
<td>82.5%</td>
</tr>
<tr>
<td>Anti-platelet therapy</td>
<td>62.6%</td>
</tr>
<tr>
<td>SBP/DBP</td>
<td>133±18 / 79±11</td>
</tr>
</tbody>
</table>

IRIS Primary Outcome

- Cumulative Event-Free Survival Probability
  - HR 0.76
  - 95% CI 0.62; 0.93, P=0.007
  - RRR 24%, ARR 2.9%

- Months in Trial
  - Pioglitazone: 9.0%
  - Placebo: 11.8%
**IRIS Secondary Outcomes**

<table>
<thead>
<tr>
<th>Outcome*</th>
<th>% (No.)</th>
<th>% (No.)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>6.5 (127)</td>
<td>8.0 (156)</td>
<td>0.82</td>
<td>0.19</td>
</tr>
<tr>
<td>ACS</td>
<td>5.0 (96)</td>
<td>6.6 (128)</td>
<td>0.75</td>
<td>0.11</td>
</tr>
<tr>
<td>Stroke/MI/HF</td>
<td>10.6 (206)</td>
<td>12.9 (249)</td>
<td>0.82</td>
<td>0.11</td>
</tr>
<tr>
<td>DM</td>
<td>3.8 (73)</td>
<td>7.7 (149)</td>
<td>0.48 &lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>7.0 (136)</td>
<td>7.5 (146)</td>
<td>0.93</td>
<td>0.52</td>
</tr>
</tbody>
</table>

*ACS=Acute coronary syndrome (unstable angina or MI).

**IRIS Serious Adverse Events**

<table>
<thead>
<tr>
<th>Event</th>
<th>% (N)</th>
<th>% (N)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone fracture†</td>
<td>5.1 (99)</td>
<td>3.2 (66)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Heart failure†</td>
<td>2.6 (51)</td>
<td>2.2 (42)</td>
<td>0.35</td>
</tr>
<tr>
<td>Incident cancer</td>
<td>6.9 (133)</td>
<td>7.7 (150)</td>
<td>0.29</td>
</tr>
</tbody>
</table>

†Previously reported to be associated with pioglitazone or drugs in its class.

**IRIS Secondary Outcomes**

<table>
<thead>
<tr>
<th>Outcome*</th>
<th>% (No.)</th>
<th>% (No.)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>6.5 (127)</td>
<td>8.0 (156)</td>
<td>0.82</td>
<td>0.19</td>
</tr>
<tr>
<td>ACS</td>
<td>5.0 (96)</td>
<td>6.6 (128)</td>
<td>0.75</td>
<td>0.11</td>
</tr>
<tr>
<td>Stroke/MI/HF</td>
<td>10.6 (206)</td>
<td>12.9 (249)</td>
<td>0.82</td>
<td>0.11</td>
</tr>
<tr>
<td>DM</td>
<td>3.8 (73)</td>
<td>7.7 (149)</td>
<td>0.48 &lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>7.0 (136)</td>
<td>7.5 (146)</td>
<td>0.93</td>
<td>0.52</td>
</tr>
</tbody>
</table>

*ACS=Acute coronary syndrome (unstable angina or MI).

**Primary and secondary CV outcomes**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of patients (%)</th>
<th>Hazard ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-point MACE</td>
<td></td>
<td>0.87 (0.78-0.97)</td>
<td>0.01</td>
</tr>
<tr>
<td>CV death</td>
<td></td>
<td>0.78 (0.66-0.93)</td>
<td>0.07</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td></td>
<td>0.88 (0.75-1.03)</td>
<td>0.11</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td></td>
<td>0.89 (0.72-1.11)</td>
<td>0.31</td>
</tr>
<tr>
<td>HF hospitalization</td>
<td></td>
<td>0.87 (0.73-1.05)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

**Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes**

Steven P. Marso, M.D., Stephen C. Bain, M.D., Agostino Consoli, M.D.,
Freddy G. Elaschewitz, M.D., Esteban Jódar, M.D., Lawrence A. Leiter, M.D.,
Ilkka Lingvay, M.D., M.P.H., M.S.C.S., Julio Rosenstock, M.D.,
Jochen Seufert, M.D., Ph.D., Mark L. Warren, M.D., Vincent Woo, M.D.,
Oluf Hansen, M.Sc., Anders G. Holst, Ph.D., Jonas Pettersson, M.D., Ph.D.,
and Tina Vilsbøll, M.D., D.M.Sc., for the SUSTAIN-6 Investigators

Presented at the American Diabetes Association 76th Scientific Sessions, June 13 2016, New Orleans, LA
Diabetes Drugs & CVD Risk

SUMMARY

1. In T2DM, the effect of glycemic control itself on CVD outcomes in clinical trials is little to non-existent.

2. As a specific treatment strategy, metformin may have CV benefits, but the data are far from robust.

3. SU’s, insulin & DPP4 inhibitors are likely neutral for CV outcomes.

4. In contrast over the past 18 months, 4 large RCTs have demonstrated significant CV benefits from a TZD, a SGLT2 inhibitor and two GLP-1 RA’s.

5. These data may result in the favoring of certain glucose-lowering agents after metformin in those with overt CVD.