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:

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 is 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.
**Classes**

- **Insulin**: Degludec, Glargine, Detemir, NPH, Regular, Aspart, Glulisine
- **SU's**: Glyburide, Glipizide, Glimepiride
- **Metformin**: Metformin
- **TZD's**: Rosiglitazone, Pioglitazone
- **DPP-4 i's**: Sitagliptin, Saxagliptin, Alogliptin, Linagliptin
- **GLP-1 RA's**: Exenatide, Liraglutide, Albiglutide, Dulaglutide
- **SGLT2 i's**: Canagliflozin, Dapagliflozin, Empagliflozin

**A1c Impact on HF**

- No limit
- 1.5%

**SU's Glyburide, Glipizide, Glimepiride**

- 1.5%

**Metformin**

- 1.5%

**TZD's**

- Rosiglitazone, Pioglitazone
- 1.5%

**DPP-4 i's**

- 0.5–1%

**GLP-1 RA's**

- Exenatide, Liraglutide, Albiglutide, Dulaglutide
- 1.5%

**SGLT2 i's**

- Canagliflozin, Dapagliflozin, Empagliflozin
- 0.5–1%

---

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

Survival functions for the primary and secondary, macrovascular (upper pair of curves) end points. Metformin treatment was associated with a decrease in both primary and secondary macrovascular end points (hazard ratio, 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: 33 vs. 30 kg/m²
- Mean weight: 85 vs. 90 kg
- Mean insulin dose: 67 vs. 84 units

**HR 0.61 (0.40–0.94) p=0.02**

---

### The “Common Soil” Hypothesis

The “Common Soil” Hypothesis: Diabetes & CVD

- Insulin Resistance

---

### DM Meds & CV Outcomes from RCTs pre-2015

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

---

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

- Hospitalization for heart failure:
  - Pio 209 events in 149 pts (5.7%)
  - Placebo 152 events in 108 pts (4.1%)
  - HR 1.41 (95% CI 1.10–1.80)
  - p=0.007

---

### Heart Attack Risk Seen in Drug for Diabetes

- **The New York Times**
  - Tuesday, May 22, 2007
  - Heart Attack Risk Seen in Drug for Diabetes
  - ![image8.png](https://example.com/image8.png)

---

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

- **Myocardial Infarction**
  - ![chart1](image9.png)
  - ![chart2](image10.png)

- **Coronary Deaths**
  - ![chart3](image11.png)
  - ![chart4](image12.png)

- **HR 0.61 (0.40–0.94) p=0.02**
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

N=4447

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

Mortality: P=0.89

Insulin sensitivity 88.2%
Insulin provision 87.9%

MACE: P=0.13

Insulin sensitization 77.7%
Insulin provision 75.4%

• 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)
  - "insulin provision" (SU + insulin


20.3%
25.2%
P=0.059
18.7%
26.0%
P=0.066

Pre-marketing Analyses
Upper CL of 95% CI <1.8
For a HR=1.0
≈122 events

Post-marketing Analyses
Upper CL of 95% CI <1.3
For a HR=1.0
≈611 events

Large CV Outcomes Trials in Diabetes (Non-Insulin)

Glucose (& Sodium) Transport via SGLT2 in the Renal Proximal Tubular Cell

Studies

LEADER
EXAM
SUSTAIN-EHF
EXCEL
REWIND
GLP1-RA

dapagliflozin
dapagliflozin
dapagliflozin
dapagliflozin
dapagliflozin
dapagliflozin
dapagliflozin

dapagliflozin
dapagliflozin
dapagliflozin
dapagliflozin
dapagliflozin
dapagliflozin
dapagliflozin

Comparator
placebo
tablet
tablet
tablet
tablet
tablet
tablet

N
9,340
3,007
5,440
8,300

Results
2016
2015
2016
2018
2019

Studies

GLP1-RA
DPP4-i
SGLT-2-i

Comparator

dapagliflozin
dapagliflozin
dapagliflozin

dapagliflozin
dapagliflozin
dapagliflozin

N
7020

Results
2016
2017
2019
2020

Studies

NCT01986881
0123456

Comparator
placebo
placebo
placebo
placebo

N
16,492
5,380
14,671
6,000
8,300

Results
2013
2013
2015
2017
2017

Studies

EMPAR-REG
CANVAS
DECLARE

Comparator
placebo
placebo
placebo

N
7020
4300
22,200
3900

Results
2015
2017
2019
2020

Sovara should demonstrate that the therapy will not result in an unacceptable increase in CV risk.

Meta-analysis strategy using Phase 2/3 data
Blinded central adjudication of CVD events
Inclusion of high-risk subjects: advanced
Minimum exposure of 2 years in large CVOT
Approximately 15,000 pt-yrs

Glucose
SGLT2
Nutrient

Na+

Interstitium
Tubular lumen

K+

Na+

At-Risk Volume

Na+

GLUT2


• Glucose (and Sodium) Transport via SGLT2 in the Renal Proximal Tubular Cell

Large CV Outcomes Trials in Diabetes (Non-Insulin)
SGLT2 Inhibition Reduces Renal Glucose Reabsorption

![Diagram showing the mechanism of SGLT2 inhibition and its effects on glucose filtration and reabsorption across different segments of the nephron.]

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

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

**Risks**

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

Before CV outcomes trial(s)

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=7020)

- Study medication was given in addition to standard of care.
- 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/1.73 m² (MDRD)

**Primary outcome:**

**3-point MACE**

HR 0.86  
(95.0% CI 0.74, 0.99)  
P = 0.0382*

**CV death**

HR 0.62  
(95% CI 0.49, 0.77)  
P < 0.0001

<table>
<thead>
<tr>
<th>Event</th>
<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>0.86</td>
<td>(0.74, 0.99)</td>
<td>0.0382*</td>
</tr>
<tr>
<td>CV death</td>
<td>172/4687</td>
<td>137/2333</td>
<td>0.62</td>
<td>(0.49, 0.77)</td>
<td>&gt;0.0001</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>215/4687</td>
<td>127/2333</td>
<td>0.87</td>
<td>(0.70, 0.95)</td>
<td>0.2189</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>100/4687</td>
<td>60/2333</td>
<td>1.24</td>
<td>(0.93, 1.67)</td>
<td>0.1438</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**

- **Ketonemia**
- **Osmotic Diuresis / Natriuresis**
- **Glucose**
- **Insulin**
- **Albuminuria**
- **Uric Acid**
- **LDL-C**
- **HDL-C**
- **Triglycerides**
- **Oxidative stress**
- **SNS activity**

---

**Dapagliflozin a glucose-regulating drug with diuretic properties in subjects with type 2 diabetes**

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

**Eligibility:** Recent TIA or Ischemic Stroke
Non-Diabetic
Insulin-Resistant (HOMA > 3.0)
No CHF

**IRIS Baseline Features**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Pioglitazone (N=1939)</th>
<th>Placebo (N=1937)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean years</td>
<td>63.5</td>
<td>63.5</td>
</tr>
<tr>
<td>Male sex</td>
<td>67%</td>
<td>64%</td>
</tr>
<tr>
<td>Black race</td>
<td>11%</td>
<td>12%</td>
</tr>
<tr>
<td>Mean BMI, mean kg/m²</td>
<td>29.9 ±5.6</td>
<td>30.0 ±5.3</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>96 ±10</td>
<td>98 ±10</td>
</tr>
<tr>
<td>Impaired Fasting Glucose (IFG) - ADA</td>
<td>42%</td>
<td>41%</td>
</tr>
<tr>
<td>Elevated HbA1c (%)</td>
<td>5.8 ±0.4</td>
<td>5.8 ±0.4</td>
</tr>
<tr>
<td>HOMA-IR (mean)</td>
<td>5.5 ±2.8</td>
<td>5.4 ±2.7</td>
</tr>
<tr>
<td>Statin therapy</td>
<td>82.5%</td>
<td>82.4%</td>
</tr>
<tr>
<td>Anti-platelet therapy</td>
<td>92.0%</td>
<td>92.3%</td>
</tr>
<tr>
<td>SBP/DBP</td>
<td>133 ±19 / 79 ±11</td>
<td>133 ±17 / 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%

**IRIS Secondary Outcomes**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pioglitazone (N=1939)</th>
<th>Placebo (N=1937)</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 (154)</td>
<td>0.82 (0.65, 1.02)</td>
<td>0.19</td>
</tr>
<tr>
<td>ACS</td>
<td>5.0 (96)</td>
<td>6.6 (128)</td>
<td>0.75 (0.59, 0.95)</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 (0.65, 1.02)</td>
<td>0.11</td>
</tr>
<tr>
<td>DM</td>
<td>3.8 (73)</td>
<td>7.7 (149)</td>
<td>0.48 (0.27, 0.84)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Death</td>
<td>7.0 (136)</td>
<td>7.5 (146)</td>
<td>0.93 (0.67, 1.28)</td>
<td>0.52</td>
</tr>
</tbody>
</table>

**IRIS Serious Adverse Events**

<table>
<thead>
<tr>
<th>Event</th>
<th>Pioglitazone (N=1939)</th>
<th>Placebo (N=1937)</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>0.36</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.
Primary outcome
CV death, non-fatal MI, or non-fatal stroke

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>0.02</td>
</tr>
<tr>
<td>CV death</td>
<td></td>
<td>0.78 (0.66-0.93)</td>
<td>0.002</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td></td>
<td>0.88 (0.75-1.03)</td>
<td>0.071</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td></td>
<td>0.89 (0.72-1.11)</td>
<td>0.39</td>
</tr>
<tr>
<td>HF hospitalization</td>
<td></td>
<td>0.87 (0.73-1.05)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

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

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

Semaglutide & Cardiovascular Outcomes in Patients with Type 2 Diabetes

Large CV Outcomes Trials in Diabetes (Non-Insulin)
Metformin, if not contraindicated and if tolerated, is the preferred initial pharmacologic agent for the treatment of type 2 diabetes.

If noninsulin monotherapy at maximum tolerated dose does not achieve or maintain the A1C target after 3 months, add a second oral agent, a glucagon-like peptide 1 receptor agonist, or basal insulin.

In patients with long-standing suboptimally controlled type 2 diabetes and established atherosclerotic cardiovascular disease, empagliflozin or dapagliflozin should be considered as they have been shown to reduce cardiovascular and all-cause mortality when added to standard care. Ongoing studies are investigating the cardiovascular benefits of other agents in these drug classes.

1. In T2DM, the effects of glycemic control on CVD outcomes 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.