Diabetes & Stable Chronic Ischemic Heart Disease; Update 2018

Prof. Adel El-Etriby
Professor of Cardiology – Ain Shams University
President of the Working Group of Interventional Cardiology

Prevalence of diabetes in 2030

IDF diabetes atlas, 4th edition, 2009
• The International Diabetes Federation (IDF) has identified Egypt as the ninth leading country in the world for the number of patients with T2D.

• The prevalence of T2D in Egypt was almost tripled over the last 2 decades

There were over 7.8 million cases of diabetes in Egypt in 2015.
Diabetes and CV Disease

- Pts with diabetes are 2-4 times more likely to develop CVD than those without diabetes
- 80% of pts with T2DM will develop CVD
- The Worst CVD outcome after ACS events
- >60% will die of CVD.
- The CVD risk in DM is greater among women (3.5) than in men (2.06)
- In addition, diabetes increases the risks of stroke (2x) and PAD
- Other diabetic complications add additional morbidity and risk for diabetics with CVD

Diabetics have abnormalities

- The Endothelium
- Platelets
- Clotting Factors
- Natural Anticoagulants
- The Fibrinolytic System
Insulin resistance is as strong a risk factor for cardiovascular disease as smoking.

Diagnosis of CAD in DM

- CAD is often silent in DM (on Holter monitoring: 35% - 58%)
- Up to 60% of MI may be asymptomatic diagnosed by ECG screening
- Stress testing:
  - Blunted response of BP ad HR
  - Painless ST depression is common
  - Diminished diagnostic specificity of ST depression
- Stress echo:
  - Presence of SWMA from myopathy
  - Blunted adrenergic enhancement of contractility
- Nuclear testing images:
  - False positive defects from LVH, myopathy, decrease coronary vasodilator response
Pharmacologic Targets of Current Drugs Used in the Treatment of T2DM

- **GLP-1 analogs**: Improve pancreatic islet glucose sensing, slow gastric emptying.
- **Biguanides**: Increase glucose uptake in fat & muscle (IR) and decreases hepatic glucose production + GLP-1 secretion.
- **Sulfonylureas**: Increase insulin secretion from pancreatic β-cells.
- **Glinides**: Increase insulin secretion from pancreatic β-cells.
- **DPP-4 inhibitors**: Prolong GLP-1 action leading to improved pancreatic islet glucose sensing, increase glucose uptake (IR).
- **Thiazolidinedione**: Decrease lipolysis in adipose tissue, increase glucose uptake in skeletal muscle and decrease glucose production in liver.
- **α-glucosidase inhibitors**: Delay intestinal carbohydrate absorption.

**Amylin Analogs**


---

Support for Metformin 1957 - 2008

- **1957**: First used in clinical practice.
- **1958**: UGDP findings for Phenformin.
- **1968**: Lactic Acidosis withdrawal of Phenformin from US.
- **1995**: Approval of Metformin in US.
- **1998**: UKPDS mortality/morbidity in Metformin treated patients.
- **2001**: Prevention of complications Approved in Europe.
- **2002**: Use in children.
- **2004**: PCOS.
- **2005**: NASH.
- **2005**: MS.

---

New Millennium
Metformin Use Among Patients With T2D and Atherothrombosis

No deleterious CV effect of SUs vs insulin or conventional therapy observed in UKPDS 33¹

In addition, in the ADVANCE study, intensive glucose control involving gliclazide was not associated with deleterious CV effects²

Coronary death rate according to the insulin-secreting agents associated with metformin in T2DM (Florence Register)

Gliclazide/Glimepiride

OR 2.09 [1.07;4.11]

Glibenclamide


Ongoing CAROLINA® Trial

<table>
<thead>
<tr>
<th>Study</th>
<th>CAROLINA®</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP-4-I</td>
<td>Linagliptin</td>
</tr>
<tr>
<td>Comparator</td>
<td>Sulfonylurea</td>
</tr>
<tr>
<td>N</td>
<td>6000</td>
</tr>
<tr>
<td>Estimated completion date</td>
<td>Sep 2018</td>
</tr>
</tbody>
</table>

In 2007, separate meta-analyses suggested differing CV effects of drugs within the TZD class.

**Rosiglitazone meta-analysis**
- MI
  - OR 1.43 (95% CI: 1.03–1.96)
  - p = 0.02
- CV death
  - OR 1.84 (95% CI: 0.94–2.74)
  - p = 0.06

**Pioglitazone meta-analysis**
- MI
  - HR 0.81 (95% CI: 0.64–1.02)
  - p = 0.08
- Death
  - HR 0.92 (95% CI: 0.78–1.11)
  - p = 0.38

No clinical trial directly compares the CV effects of pioglitazone and rosiglitazone.

---

**Evolution of the FDA CV Safety Requirements and CV Safety Concerns**

<table>
<thead>
<tr>
<th>Year</th>
<th>Drug</th>
<th>Safety concerns and response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992</td>
<td>Human proinsulin</td>
<td>Trials and development suspended CV issues and ↑ risk of acute MI&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>2005</td>
<td>Muroglitazar</td>
<td>↑ Risk of death, major CV adverse events, CHF&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>2007</td>
<td>Rosiglitazone</td>
<td>CV risk; withdrawn from market in many countries&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>2008</td>
<td>—</td>
<td>FDA issues guidance document for the evaluation of CV risk.&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>FDA has reversed its stance on REMS for rosiglitazone.<br>
For a diabetic patient with CVD or at risk of CVD using old traditional antidiabetics it is better to use metformin and new generation sulphonarylureas as gliclazide (Diamicron) or glimepride (Amaryl) as first choice. Second options include acarbose (glucobay) if tolerated plus pioglitazone cautiously except in heart failure patients.

Cardiac Effects of New Treatments of T2DM
Agenda

• GLP-1 Agonists.
• DPP-4 inhibitors.
• SGLT2 Inhibitor.
Liraglutide and Weight Loss: LEAD Trials

- **LEAD-3 trial:**
  - Weight reduction of up to 2.5 kg with liraglutide compared with a weight gain of 1.1 kg with glimepiride ($P = 0.0001$)
  - Weight loss sustained throughout a 52-week study

- **LEAD-5 trial:**
  - Liraglutide produced a greater reduction in A1c and body weight (loss of 1.8 kg) than insulin glargine (gain of 1.6 kg)

- **LEADER trial:**
  - Compared with placebo, liraglutide treatment resulted in:
    - 13% risk reduction for MACE (non-fatal MI, non-fatal stroke, and CV death)
    - 22% risk reduction for CV death
    - 15% reduction in all-cause mortality


Cardiovascular Risk Reduction: Lipids

- Major vascular events reduced by 21% with every 39 mg/dL reduction in LDL-C in people with T2DM (RR 0.79 [99% CI 0.72–0.86]; $P < 0.0001$)

- All-cause mortality reduced by 9% with every 39 mg/dL reduction in LDL-C (RR 0.91 [99% CI 0.82–1.01]; $P = 0.02$)

Summary

- GLP-1 agonists not only help reduce plasma glucose levels in type-2 diabetics, but also help improve markers of cardiovascular function including blood pressure, cholesterol, and weight loss.
- GLP-1 agonists are shown to have positive effects on cardiovascular outcomes and reduce the risk for heart failure.
- These benefits to cardiovascular health are independent of GLP-1 agonists’ effect on glucose control and add important cardiocascular effects for type-2 diabetics.

Agenda

- GLP-1 Agonists.
- DPP-4 inhibitors.
- SGLT2 Inhibitor.
SAVOR-TIMI 53: Hospitalization for HF

Hospitalization for HF

Baseline | Saxagliptin (n=8280) | Placebo (n=8212)
---|---|---
Prior HF no. (%) | 1056 (12.8) | 1049 (12.8)

P=0.007
Hazard ratio=1.27
95% CI: 1.07-1.51

Saxagliptin (n=8280) Placebo (n=8212)

3.5% | 2.8% | 27%

Prior HF no. (%) | 1056 (12.8) | 1049 (12.8)


FDA Drug Safety Communication: FDA adds warnings about heart failure risk to labels of type 2 diabetes medicines containing saxagliptin and alogliptin

This is an update to the FDA Drug Safety Communication: FDA to review heart failure risk with diabetes drugs saxagliptin (marketed as Onglyza) and Kombiglyze XR issued on February 11, 2014.

Safety Announcement [4-6-2016] A U.S. Food and Drug Administration (FDA) safety review has found that type 2 diabetes medicines containing saxagliptin and alogliptin may increase the risk of heart failure, particularly in patients who already have heart or kidney disease. Heart failure can result in the heart not being able to pump enough blood to meet the body's needs. As a result, we are adding new warnings to the drug labels about this safety issue.

Saxagliptin and alogliptin are part of the class of dipeptidyl peptidase-4 (DPP-4) inhibitor drugs, which are used with diet and exercise to lower blood sugar in adults with type 2 diabetes. Untreated, type 2 diabetes can lead to serious health problems, including blindness, nerve and kidney damage, and heart disease (see List of saxagliptin- and alogliptin-containing Medicines).

Patients taking these medicines should contact their health care professionals right away if they develop signs and symptoms of heart failure such as:
Unusual shortness of breath during daily activities
**TECOS: Effect of Sitagliptin vs Placebo on CV Outcomes in T2DM**

**Primary Composite CV Outcome**

<table>
<thead>
<tr>
<th>Month</th>
<th>Sitagliptin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>12</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>24</td>
<td>14</td>
<td>18</td>
</tr>
<tr>
<td>36</td>
<td>16</td>
<td>20</td>
</tr>
<tr>
<td>48</td>
<td>18</td>
<td>22</td>
</tr>
</tbody>
</table>

Hazard ratio = 0.98
95% CI: 0.89-1.08
P = 0.65


---

**TECOS: Secondary Outcomes**

<table>
<thead>
<tr>
<th>Secondary Outcome</th>
<th>Sitagliptin</th>
<th>Placebo</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death</td>
<td>380 (5.2)</td>
<td>366 (5.0)</td>
<td>1.03 (0.89-1.19)</td>
<td>.71</td>
</tr>
<tr>
<td>Hospitalization for UA</td>
<td>116 (1.6)</td>
<td>129 (1.8)</td>
<td>0.90 (0.70-1.16)</td>
<td>.42</td>
</tr>
<tr>
<td>Fatal or nonfatal MI</td>
<td>300 (4.1)</td>
<td>316 (4.3)</td>
<td>0.95 (0.81-1.11)</td>
<td>.49</td>
</tr>
<tr>
<td>Fatal or nonfatal stroke</td>
<td>178 (2.4)</td>
<td>183 (2.5)</td>
<td>0.97 (0.79-1.19)</td>
<td>.76</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>547 (7.5)</td>
<td>537 (7.3)</td>
<td>1.01 (0.90-1.14)</td>
<td>.88</td>
</tr>
<tr>
<td>Hospitalization for HF</td>
<td>228 (3.1)</td>
<td>229 (3.1)</td>
<td>1.00 (0.83-1.20)</td>
<td>.98</td>
</tr>
</tbody>
</table>

Identical HF event rates

Agenda

• GLP-1 Agonists.
• DPP-4 inhibitors.
• SGLT2 Inhibitor.

Primary outcome: 3-point MACE

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

1.4%

Cumulative incidence function. MACE, Major Adverse Cardiovascular Event; HR, h
* Two-sided tests for superiority were conducted (statistical significance was indicated if \( p \leq 0.0498 \) )
CV death

Cumulative incidence function. HR, hazard ratio

MACE + UA and MACE, CV Meta-Analysis

Results showed no increase in the primary CV composite endpoint (MACE + hospitalization for unstable angina) or MACE with DAPA overall and in separate subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Events, n</th>
<th>Favours</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MACE+UA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>N=5699</td>
<td>N=3240</td>
<td>0.824 (0.497, 1.365)</td>
</tr>
<tr>
<td>CVD History</td>
<td>N=1826</td>
<td>N=1333</td>
<td>0.806 (0.562, 1.156)</td>
</tr>
<tr>
<td>Elderly patients with CVD risk</td>
<td>N=533</td>
<td>N=535</td>
<td>0.824 (0.497, 1.365)</td>
</tr>
<tr>
<td><strong>MACE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>N=5418</td>
<td>N=3101</td>
<td>0.772 (0.543, 1.097)</td>
</tr>
<tr>
<td>CVD History</td>
<td>N=1799</td>
<td>N=1325</td>
<td>0.802 (0.527, 1.221)</td>
</tr>
<tr>
<td>Elderly patients with CVD risk</td>
<td>N=533</td>
<td>N=535</td>
<td>0.802 (0.527, 1.221)</td>
</tr>
</tbody>
</table>

HRs were not tested for statistical significance

Data presented for the overall population, the subgroup of patients with a history of CVD (CVD history) and the subgroup of elderly patients aged ≥65 years with a history of CVD and hypertension (Elderly patients with CVD risk).

CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; DAPA, dapagliflozin; HR, hazard ratio; MACE, major adverse cardiac event; UA, unstable angina. Sonesson et al., Cardiovasc Diabetol. 2018;17(3):1-12.
If the goal is to avoid hypoglycemia...

If the goal is to avoid hypoglycemia and weight gain...

*Dapagliflozin is not indicated for the management of obesity; weight change was a secondary endpoint in clinical trials.

Inzucchi SE, et al. Diabetes Care 2015;38:140-149
If the goal is to avoid hypoglycemia, lose weight and reduce the risk of CV events*…

**Healthy eating, weight control, increased physical activity and diabetes education**

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>DPP-4 inhibitor</th>
<th>GLP-1 receptor agonist</th>
<th>SGLT2 inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>Side effects</td>
<td>Costs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*As demonstrated by the EMPA-REG study and emerging data from the LEADER trial; neither class is currently approved by any health authority for this indication and not reflected on respective labels.

---

If the goal is to avoid hypoglycemia, lose weight, reduce blood pressure, and reduce the risk of CV events*…

**Healthy eating, weight control, increased physical activity and diabetes education**

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>DPP-4 inhibitor</th>
<th>GLP-1 receptor agonist</th>
<th>SGLT2 inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>Side effects</td>
<td>Costs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*As demonstrated by the EMPA-REG study; currently not approved by any health authority for this indication and not reflected on empagliflozin label.
Conclusions

- CV disease is a common complication in people with T2D.
- Optimal multiple risk factor intervention is required to improve long-term outcomes.
- The ischemic diabetic patients have peculiar coronary anatomy and higher risk for CV complications.
- When treating diabetic patients with chronic stable angina, you should use the drugs with known cardiovascular safety profile.
- The new anti-diabetic drugs offers the ischemic patients the best outcomes by reducing both mortality and HF hospitalization.