Intersection of Diabetes and Atherosclerotic Cardiovascular Disease Prevention – Contemporary Management and New Therapies

Andrew Ahmann, MD  
Director, Harold Schnitzer Diabetes Health Center  
Professor of Medicine  
Oregon Health & Science University Foundation

Age-adjusted Prevalence of Diagnosed Diabetes Among US Adults

<table>
<thead>
<tr>
<th>Year</th>
<th>No Data</th>
<th>&lt;4.5%</th>
<th>4.5%–5.9%</th>
<th>6.0%–7.4%</th>
<th>7.5%–8.9%</th>
<th>&gt;9.0%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994</td>
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<td>2000</td>
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<td>2014</td>
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</tbody>
</table>

WM2  Dear Dr Ahmann, please could you include your presentation title?  
WM, 6/22/2012
Prevalence of Diabetes 2014
- 29.1 million people in US -


Natural History of Type 2 Diabetes

Severity of Diabetes

Frank Diabetes
Insulin Resistance
Hepatic Glucose Production
Endogenous Insulin

Prediabetes
Postprandial Blood Glucose
Fasting Blood Glucose

Microvascular Complications
Macrovascular Complications

Years to
Decades

Typical Diagnosis of Diabetes
The Road To Type 2 Diabetes

Normal blood glucose

About 86 million people in the US have prediabetes.

Prediabetes (often with the metabolic syndrome and insulin resistance)

Diabetes

> 25% of adults have the metabolic syndrome

Prediabetes

- 86 million in the US
  - 37% of those over age 20
  - 51% of those over age 65
- 5-10% progress to diabetes each year
- Some regress back to normal
- Evidence shows associations with:
  - Early nephropathy
  - Neuropathy
  - Retinopathy
  - Macrovascular disease

Risk of Macrovascular Disease by Blood Glucose

- Analysis of 50 studies
- Includes 15211 vascular deaths


Lessons From Studies of Prediabetes Progression and CV Risk

- Impaired Glucose Tolerance (IGT)
  - Represents insulin resistance in muscle and liver
  - Global β-cell dysfunction
- Impaired Fasting Glucose (IFG)
  - Associated with insulin resistance in liver
  - Impaired early secretion of insulin
- IGT may have higher risk of DM than IFG
- Individuals with IGT manifest greater CV risk
- Microvascular complications can occur in prediabetes and are more associated with IGT

### Diabetes Prevention: Lifestyle vs Medications

- Lifestyle intervention continues to have an effect; most drugs do not

#### Lifestyle

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Treatment</th>
<th>Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Da Qing</td>
<td>Lifestyle</td>
<td>6 years 20 years</td>
<td>34% - 69%</td>
</tr>
<tr>
<td>Finnish DPS</td>
<td>Lifestyle</td>
<td>3+ years 7 years</td>
<td>58%</td>
</tr>
<tr>
<td>DPP</td>
<td>Lifestyle</td>
<td>3 years</td>
<td>58%</td>
</tr>
</tbody>
</table>

#### Pharmacologic

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Treatment</th>
<th>Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP</td>
<td>Metformin</td>
<td>3 years</td>
<td>31%</td>
</tr>
<tr>
<td>DREAM</td>
<td>Rosiglitazone</td>
<td>3 years</td>
<td>60%</td>
</tr>
<tr>
<td>STOP-NIDDM</td>
<td>Acarbose</td>
<td>3 years</td>
<td>21%</td>
</tr>
<tr>
<td>ACT NOW</td>
<td>Pioglitazone</td>
<td>3 years</td>
<td>81%</td>
</tr>
<tr>
<td>CANOE</td>
<td>Metformin + Rosiglitazone</td>
<td>3.9 years</td>
<td>66%</td>
</tr>
</tbody>
</table>


### DPP: Impact of lifestyle intervention or metformin on diabetes

- N = 3234, no diabetes
- Age 50
- 207 lbs
- Glucose 107

- Placebo
- P < 0.001

- Metformin
- < 0.001

- Lifestyle

- Lose 5–10 lbs
- Exercise 2.5 hrs/wk

DPP = Diabetes Prevention Program

Diabetes Prevention Program

- Metformin, intensive lifestyle modification delayed or prevented type 2 diabetes
  - Placebo: 11%/year incidence
  - Metformin: 7.8%/year incidence*
  - Lifestyle intervention: 4.8%/year incidence*
- Risk reduction:
  - 31% by metformin
  - 58% by lifestyle
  - 39% lifestyle vs metformin

*P<0.001 vs placebo


DPP: Metformin Intervention

- Intensive lifestyle intervention more effective than either metformin or placebo in primary study period
- By subgroup, metformin more effective if:
  - FPG >110 mg/dL
  - Age <60 years
  - History of GDM
  - BMI >35 kg/m²
- Gender, ethnicity, 2-h PGG, NOT predictive of response
- Use metformin in high-risk individuals

**Diabetes Prevention Program 10-Year Cost-Effectiveness**

- Lifestyle cost-effective, metformin marginally cost-saving vs placebo
- Investment in lifestyle, metformin interventions for diabetes prevention in high-risk adults provides good value

<table>
<thead>
<tr>
<th>Societal Perspective*</th>
<th>Lifestyle vs Placebo</th>
<th>Metformin vs Placebo</th>
<th>Lifestyle vs Metformin</th>
<th>DPP Group Lifestyle vs Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undiscounted</td>
<td>11,274</td>
<td>Cost-saving</td>
<td>44,562</td>
<td>Cost-saving</td>
</tr>
<tr>
<td>Discounted†</td>
<td>14,365</td>
<td>Cost-saving</td>
<td>42,753</td>
<td>1,681</td>
</tr>
</tbody>
</table>

*Includes direct medical costs and direct nonmedical costs including participant time
†Both costs and QALYs are discounted at 3%


**DPP: Metformin Had Sustained Effect After Drug Washout**

- Brief (1-2 week) drug washout study at end of Diabetes Prevention Program trial
- After washout, diabetes was more frequently diagnosed in metformin vs. placebo (1.49; 0.93, 2.38; *P*=0.098)
- DPP primary analysis: metformin decreased diabetes risk by 31%
- Washout: 26% accounted for by pharmacological effect of metformin
- Postwashout: diabetes reduced by 25%

Rosiglitazone Had No Sustained Effect After Drug Washout: DREAM

- During rosiglitazone vs placebo washout
  - Primary outcome, new-onset diabetes or death: 10.5% vs 9.8% (P=0.59)
  - Secondary outcome, regression to normoglycemia: 21.5% vs 23.8% (P=0.33)
  - Median follow-up: 71 days (range, 63-86 days)
- Rosiglitazone substantially reduced incidence of type 2 diabetes (DREAM); however, when withdrawn, this effect is not sustained


Prediabetes Treatment Algorithm

- Weight-loss agents orlistat, lorcaserin, and phentermine/topiramate can prevent progression to T2DM
  - Improve BP, triglycerides, and insulin sensitivity
- Metformin and acarbose can reduce progression to T2DM by 25% - 30%
  - Use for prediabetes is off-label
  - Both are safe, confer CVD risk benefit; metformin is well tolerated
- TZDs prevented progression to T2DM in 60% - 75% of patients in clinical trials
  - Associated with adverse outcomes
- GLP-1 receptor agonists may be as effective as TZDs
  - Promote weight loss, but inadequate safety data
- TZDs and GLP-1 RAs reserved for patients not responding to conventional therapies or at highest risk for T2DM

TZDM = type 2 diabetes mellitus
BP = blood pressure
CVD = cardiovascular disease
TZD = thiazolidinedione
GLP-1 RA= glucagon-like peptide-1 receptor agonist

Conclusions

• We must identify patients at highest risk (prediabetes)
• Modest lifestyle changes are the primary intervention
• Metformin is the best accepted pharmacological choice
• Sustain interventions
• Increase opportunities for community programs to screen for diabetes and support prevention
• Delaying or preventing type 2 diabetes is cost-effective and will help turn the tide on the diabetes epidemic

What can we say about specific benefits of medications on CV disease in T2DM?
Cardiovascular Implications of Older Agents

- Metformin
  - Some evidence for decreased CV events
  - Probably OK for those with early CHF
- Sulfonylureas
  - A number of retrospective studies suggesting disadvantage but lack of good prospective evidence
- TZDs
  - Increase CHF (volume expansion)
  - Pioglitazone may have modest beneficial effects overall

UKPDS 10 Year Extension: Reduced Myocardial Infarction Relative Risk In patients Treated from Diagnosis

Metformin

<table>
<thead>
<tr>
<th>Year</th>
<th>1997</th>
<th>1999</th>
<th>2001</th>
<th>2003</th>
<th>2005</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazard Ratio</td>
<td>0.6</td>
<td>0.8</td>
<td>1.0</td>
<td>1.2</td>
<td>1.4</td>
<td></td>
</tr>
</tbody>
</table>

P = 0.01

Sulfonylurea-Insulin

<table>
<thead>
<tr>
<th>Year</th>
<th>1997</th>
<th>1999</th>
<th>2001</th>
<th>2003</th>
<th>2005</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazard Ratio</td>
<td>0.6</td>
<td>1.0</td>
<td>1.4</td>
<td>2.0</td>
<td>2.4</td>
<td></td>
</tr>
</tbody>
</table>

P = 0.052

Holman RR et al. NEJM 2008; 359: 1577
Thiazolidinediones
Pioglitazone, Rosiglitazone

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>↑ Insulin sensitivity, especially at muscle, lowers both FPG and PPG, but effect may be delayed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>Moderate (↓ A1C 1.0%-1.5%)</td>
</tr>
<tr>
<td>Advantages</td>
<td>No hypoglycemia, no reliance on renal excretion</td>
</tr>
<tr>
<td></td>
<td>Probable modest reduced CV events.</td>
</tr>
<tr>
<td></td>
<td>Possible beta cell preservation</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>Fluid retention, edema, heart failure, weight gain, slow onset of action, bone fractures,</td>
</tr>
<tr>
<td></td>
<td>macular edema, osteoporosis, anemia, and bladder cancer</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Class III or IV CHF or hepatic impairment w/ALT &gt;2.5 times upper normal limits</td>
</tr>
</tbody>
</table>


The New York Times
February 20, 2010

“Research Ties Diabetes Drug to Heart Woes”

“Rosiglitazone should be removed from the market,” one report, by Dr. David Graham and Dr. Kate Gelperin of the FDA, concludes. Both authors recommended that Avandia be withdrawn.
Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD)

• more CHF
• more CHF-related deaths

No difference in CV hospitalization or death.

Comparator was patients on metformin or sulfonylureas
Study was adversely affected by drop-outs after initial concerns

Results confirmed 2013 on review

FDA modified warnings on rosiglitazone

Home PD et al. Lancet 2009; 373:2125-2135
Pioglitazone vs Rosiglitazone

General Characteristics of TZDs

- Pioglitazone probably has marginal CV benefits other than CHF
  - Pro-active trial and Periscope trial
  - Lipid advantages previously demonstrated relative to rosiglitazone
- Rosiglitazone doesn’t have increased CV adverse events vs many other agents but is rarely used now
- Both have benefits:
  - Beta cell protection is likely
  - Quite effective in highly insulin resistant patients
- Both have adverse effects:
  - Most weight gain per A1c reduction
  - Edema, particularly when used with insulin
  - CHF rates at least doubled.
  - Bone density decreased and bone fractures increased in women

Graham et al JAMA 2010; 304:411-418
Historical Perspective

- Phenformin removed from U.S. market in 1977 because of risk lactic acidosis
  - As a result, approval of metformin in the U.S. likely delayed and use in some populations may have been overly restricted
- Troglitazone removed from U.K. market in 1997 and U.S. market in 2000 due to risk of hepatotoxicity
  - As a result, subsequent thiazolidinediones subject to close scrutiny for evidence of liver injury
- Rosiglitazone sales was suspended by EMA in 2010 and significantly restricted in U.S by the FDA
  - TIDE trial was halted and RECORD trial did not confirm CV concerns raised in 2007 NEJM meta-analysis
  - FDA removes restrictions December 2015


Regulatory Response

International regulatory agencies now require that all new antihyperglycemic agents demonstrate glucose lowering AND exclude clinically meaningful increases in major adverse cardiovascular events

FDA guidance to industry: December 17, 2008

Recommend...sponsors should demonstrate that the therapy will not result in an unacceptable increase in cardiovascular risk.”

- Premarket: Must demonstrate that the upper bound of the two-sided 95% CI for estimated RR <1.8
- Postmarket: Must demonstrate that the upper bound of the two-sided 95% CI for estimated RR <1.3

What can be said about new drug classes in patients with CVD?

**DPP4 Inhibitors, GLP-1 Receptor Agonists, SGLT-2 inhibitors**

- They aren’t associated with hypoglycemia when used alone
- They are weight neutral or promote weight loss
  - Weight loss with GLP-1 RA and SGLT2 inhibitors
- They are all subject to FDA CV safety studies
  - Large, controlled trials in patients with high CV risk
    - Size of study and duration depend on population
  - CV safety in all completed trials, benefits in some

---

**CV Outcome Trials in Type 2 DM**

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Study</th>
<th>Details</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP-IV Inhibitors</td>
<td>EXAMINE</td>
<td>Alogliptin vs PBO</td>
<td>Neutral</td>
</tr>
<tr>
<td></td>
<td>SAVOR-TIMI 56</td>
<td>Saxagliptin vs PBO</td>
<td>Neutral</td>
</tr>
<tr>
<td></td>
<td>TECOS</td>
<td>Sitagliptin vs PBO</td>
<td>Neutral</td>
</tr>
<tr>
<td></td>
<td>CARMELINA</td>
<td>Linagliptin vs PBO</td>
<td>Expected 2017</td>
</tr>
<tr>
<td></td>
<td>CAROLINA</td>
<td>Linagliptin vs SU</td>
<td>Expected 2017</td>
</tr>
<tr>
<td>GLP-1 Receptor Ag.</td>
<td>ELIXA</td>
<td>Lixisenatide vs PBO</td>
<td>Neutral</td>
</tr>
<tr>
<td></td>
<td>LEADER</td>
<td>Liraglutide vs PBO</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td>SUSTAIN 6</td>
<td>Semaglutide vs PBO</td>
<td>Positive (?)</td>
</tr>
<tr>
<td></td>
<td>EXSCEL</td>
<td>Exenatide LR vs PBO</td>
<td>Expected 2018</td>
</tr>
<tr>
<td></td>
<td>REWIND</td>
<td>Dulaglutide vs PBO</td>
<td>Expected 2019</td>
</tr>
<tr>
<td>SGLT2 Inhibitors</td>
<td>EMPA-REG</td>
<td>Empagliflozin vs PBO</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td>CANVAS</td>
<td>Canagliflozin vs PBO</td>
<td>Expected 2017</td>
</tr>
<tr>
<td></td>
<td>DECLARE</td>
<td>Dapagliflozin vs PBO</td>
<td>Expected 2019</td>
</tr>
<tr>
<td></td>
<td>NCT01986881</td>
<td>Ertugliflozin vs PBO</td>
<td>Expected 2020</td>
</tr>
</tbody>
</table>
### SAVOR-TIMI 53, EXAMINE, and TECOS: MACE Outcomes

Results essentially neutral – safety established

<table>
<thead>
<tr>
<th>Study Drug</th>
<th>Placebo</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SAVOR-TIMI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>saxagliptin vs placebo</td>
<td>613/6280 (7.4%)</td>
<td>609/6212 (7.4%)</td>
<td>1.00 0.89, 1.12</td>
<td>0.99</td>
</tr>
<tr>
<td><strong>EXAMINE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>alogliptin vs placebo</td>
<td>305/2701 (11.3%)</td>
<td>316/2679 (11.8%)</td>
<td>0.96 NA, 1.16</td>
<td>0.315</td>
</tr>
<tr>
<td><strong>TECOS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sitagliptin vs placebo</td>
<td>745/7332 (10.2%)</td>
<td>746/7339 (10.2%)</td>
<td>0.99 0.89, 1.10</td>
<td>0.844</td>
</tr>
<tr>
<td><strong>SAVOR + EXAMINE + TECOS</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>(saxagliptin vs placebo)</td>
<td>1663/18313 (9.1%)</td>
<td>1671/18230 (9.2%)</td>
<td>0.99 0.92, 1.06</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity for 3 trials: 

$\text{p}=0.877, I^2=0\%$

*Lower Confidence Limit not given for EXAMINE trial; MACE = major adverse cardiac events.


### SAVOR-TIMI 53, EXAMINE, and TECOS: Hospitalization for Heart Failure

<table>
<thead>
<tr>
<th>Study Drug</th>
<th>Placebo</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SAVOR-TIMI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>saxagliptin vs placebo</td>
<td>289/8280 (3.5%)</td>
<td>228/8212 (2.8%)</td>
<td>1.27 1.07, 1.51</td>
<td>0.009*</td>
</tr>
<tr>
<td><strong>EXAMINE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>alogliptin vs placebo</td>
<td>106/2701 (3.9%)</td>
<td>89/2679 (3.3%)</td>
<td>1.19 0.89, 1.58</td>
<td>0.238</td>
</tr>
<tr>
<td><strong>TECOS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sitagliptin vs placebo</td>
<td>228/7332 (3.1%)</td>
<td>229/7339 (3.1%)</td>
<td>1.00 0.83, 1.20</td>
<td>0.983</td>
</tr>
</tbody>
</table>

*Statistically significant increase in hospitalizations for heart failure associated with saxagliptin use in SAVOR-TIMI.

Some General Characteristics of GLP-1 Agonists

- **Shorter acting agents (exenatide and lixisenatide)**
  - Have greater effect on post-prandial glucose for the meals immediately after the dose
  - Generally lower efficacy
  - More nausea

- **Once daily agent (liraglutide)**
  - Intermediate effects on post-prandial for all three meals but also significant fasting glucose reduction

- **Once weekly agents (exenatide once weekly, albiglutide, dulaglutide)**
  - Effects on pp and fasting glucose
  - May have variable efficacy and weight loss
    - Albiglutide appears to have lower efficacy and less weight loss

ELIXA Study

**No benefit or detriment seen with lixisenatide**

- First trial to present CV outcomes data for an agent in the GLP-1 RA class
  - Lixisenatide is just recently approved in the U.S.
  - 6,068 subjects with T2DM and recent ACS event randomized to lixisenatide vs placebo

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Lixisenatide (n=3034)</th>
<th>Placebo (n=3034)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome (CV death, nonfatal MI, nonfatal stroke, or hospitalization for UA)</td>
<td>13.4%</td>
<td>13.2%</td>
<td>1.02 (0.89–1.17)</td>
</tr>
<tr>
<td>Primary outcome plus hospitalization for HF</td>
<td>15%</td>
<td>15.5%</td>
<td>0.97 (0.85–1.10)</td>
</tr>
<tr>
<td>Hospitalization for HF</td>
<td>4.0%</td>
<td>4.2%</td>
<td>0.96 (0.75–1.23)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>–</td>
<td>–</td>
<td>0.94 (0.78–1.13)</td>
</tr>
</tbody>
</table>

**ELIXA = Evaluation of Lixisenatide in Acute Coronary Syndrome; ACS = acute coronary syndrome; UA = unstable angina; HF = heart failure.**

Liraglutide and CV Outcomes In Type 2 DM
First study in class to show benefit of GLP-1 RA

Marson SP et al. NEJM 2016; 375:311-22

Death from Cardiovascular Causes

Marson SP et al. NEJM 2016; 375:311-22
Liraglutide and CV Outcomes In Type 2 DM

Marson SP et al. NEJM 2016; 375:311-22

Liraglutide and CV Outcomes In Type 2 DM

Marson SP et al. NEJM 2016; 375:311-22
LEADER Trial: Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Liraglutide (N = 4668)</th>
<th>Placebo (N = 4672)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Adverse Event</td>
<td>62.3%</td>
<td>60.8%</td>
<td>0.12</td>
</tr>
<tr>
<td>Confirmed Hypoglycemia</td>
<td>43.7%</td>
<td>45.6%</td>
<td>0.06</td>
</tr>
<tr>
<td>Acute Pancreatitis</td>
<td>0.4%</td>
<td>0.5%</td>
<td>0.44</td>
</tr>
<tr>
<td>Benign Neoplasms</td>
<td>3.6%</td>
<td>3.1%</td>
<td>0.18</td>
</tr>
<tr>
<td>Malignant Neoplasms</td>
<td>6.3%</td>
<td>6.0%</td>
<td>0.46</td>
</tr>
</tbody>
</table>

Marson SP et al.  NEJM  2016; 375:311-22

LEADER Trial: Conclusion

- Definitely no increase in CV events
- Significant but modest reduction in primary outcome composite of CV death, nonfatal MI or nonfatal stroke
- Reduced CV death and death from any cause
- No specific evidence for reduced nonfatal MI, nonfatal stroke, or CHF admissions
- Reduced nephropathy
- No evidence for increase frequency of acute pancreatitis
Stay Tuned!

SUSTAIN-6 Presented At EASD Next Week
Study of CV effects of Semaglutide
- Earlier Press Release Reports Positive Results -

EMPA-Reg Study Could Change Priorities

- 7020 patients randomized to 10 mg, 25 mg or placebo
- Study intended to prove empagliflozin CV safety
- Found relative risk reduction:
  - CV death - - 38%
  - Hospitalization for CHF - - 35%
  - Death from any cause - - 32%
- No difference in
  - Myocardial infarction
  - Stroke
- Small difference in A1c - - 0.24% by end of study

Zinman B, et al  NEJM published online 9/17/15
EMPA-REG OUTCOME Study

**7020 T2DM Patients with Established CVD**

Difference in A1C between empagliflozin and placebo groups range from 
-0.54% to 0.60% at week 12, 0.24% to 0.36% at week 206

<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>0.86 (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 (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>0.87 (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>1.24 (0.92, 1.67)</td>
<td>0.1638</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>269/4687</td>
<td>194/2333</td>
<td>0.68 (0.57, 0.82)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*CV death, MI or stroke.

CVD = cardiovascular disease; MACE = Major Adverse Cardiovascular Event; HR = hazard ratio; CV = cardiovascular; MI = myocardial infarction.


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EMPA-Reg Study Could Change Priorities

A. Primary Outcome

B. Death from Cardiovascular Causes

C. Death from Any Cause

D. Hospitalization for Heart Failure

Zinman B, et al. NEJM published online 9/17/15
**EMPA-REG Trial Concerns**

- Primary endpoint did not include silent MI
  - When silent MI was included empagliflozin was not superior to placebo for the composite primary endpoint
- There was significant missing data as 211 participants discontinued early
- Of 463 deaths in the trial, 124 were stated to be “fatal events not assessable” and were presumed to be CV deaths.
  - Accounted for 40.1% of all CV deaths

Zinman B, et al NEJM published online 9/17/15

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**EMPA-REG Follow-Up**

- FDA reviewing indication for secondary CV disease prevention in 2016
- FDA advisory panel recently voted 23-0 to say that empagliflozin does not result in an increase in CV events
- Advisory panel voted 12-11 in favor of expanded indication to reduce CV death in type 2 DM
- The panel did not support an indication for hospitalization for heart failure.
- Final FDA decision is pending

Zinman B, et al NEJM published online 9/17/15
Rules Beyond the Guidelines in DM Patients with CV Disease

• Metformin is first choice unless contraindicated
  – Some evidence of CV benefit, long-term safety

• Second Drug
  – DPP-4 inhibitor safe if close to goal, active (risk of hypo) or elderly
  – Liraglutide once daily if overweight and hasn’t had pancreatitis significant GI symptoms
    • May reduce CV events
  – SGLT2 inhibitor if CV benefit is confirmed (could be 1st)

• Third Drug
  – Basal insulin – long-acting basal insulin safer

Rules Beyond the Guidelines (cont)

• Special add on agents in specific cases
  – Colesevelam
    • Good add on when LDL reduction is indicated
  – Bromocriptine (rapid acting)
    • Evidence of decreased CV events in a relatively small study
    • Expensive and has significant side effects
Selected Nutrition Recommendations

• No specific recommendations for macronutrient proportions
  – Monitor carbohydrate intake
  – Emphasize carbohydrate from fruits, vegetables, whole grains, legumes and low-fat milk
• Monounsaturated fats are encouraged
  – Saturated fats and trans fats are discouraged
• Insufficient evidence to support the use of supplements or vitamins
• Limit intake of alcohol to ≤ 1/day for women and ≤ 2 per day for men
• Limit sodium to < 2300 mg/day

Physical Activity Recommendations

• Aerobic activity
  – At least 150 min/week moderate intensity
    • 50-70% maximal heart rate
  or
  – 90 min/week vigorous aerobic activity
    • > 70% maximal heart rate
  – At least 3 days/week
  – Do not miss more than 2 consecutive days
• Resistance exercise at least 2 times/wk
  – 8-10 repetitions at a weight that cannot be lifted
  > 8-10x