Diabetes drugs and cardiovascular outcomes trials

2017

Karol E. Watson, MD, PhD, FACC
Professor of Medicine/Cardiology
Co-director, UCLA Program in Preventive Cardiology
Director, UCLA Barbra Streisand Women’s Heart Health Program
David Geffen School of Medicine at UCLA

John Mazziotta, M.D., Ph.D. Term Chair in Medicine
Disclosures

- Research grants: NHLBI, NIDDK, NIH BD2K
- Consultant: Amarin, Amgen, Behringher Ingelheim
- Speaker’s Bureau: Behringher Ingelheim
Diabetes Drugs and CVOT - 2017

• Approval process for diabetes drugs
• Rationale for Cardiovascular Outcomes trials (CVOT)
• CVOT results
  – DPP-4 inhibitors
  – GLP-1 receptor agonists
  – SGLT2 inhibitors
• Mechanisms?
Diabetes Drugs and CVOT - 2017

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• Mechanisms?
HTN & Diabetes meds through the years

Number of Medication Classes

- insulin
- sulfonylureas
- Biguanides
- angiotensin II receptor blockers
- ACE Inhibitors
- Ca\(^{2+}\) channel blockers
- peripheral \(\alpha-1\) blockers
- \(\beta\)-blockers
- central \(\alpha-2\) agonists
- adrenergic neuronal blockers
- diuretics
- renin inhibitors
- SGLT-2 inhibitors
- \(\text{glucosidase inhibitors}
- thiazolidinediones
- meglitinides
- GLP-1 analogues
- DPP-4 inhibitors
- amylin mimetics
- bile acid sequestrants
- dopamine agonists

Courtesy of Silvio Inzucchi, MD, Yale University
FDA Approval Process for glucose lowering drugs

• Diabetes drugs are approved for the primary indication of improving glycemic control

• HbA1c is the primary efficacy endpoint

• But the primary cause of death for people with diabetes is cardiovascular disease

• The effects of diabetes medications on cardiovascular (CV) endpoints or outcomes was not assessed

There is an epidemiologic association between HbA1c and CVD

Sabin et al. NEJM March 2010
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  – GLP-1 receptor agonists
  – SGLT2 inhibitors
• Mechanisms?
Anti-diabetes medication and cardiovascular outcomes


<table>
<thead>
<tr>
<th>Study</th>
<th>More glucose control</th>
<th>Less glucose control</th>
<th>Weight</th>
<th>Heart failure risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998 UK Prospective Diabetes Study</td>
<td>80/2729</td>
<td>36/1138</td>
<td>5.5%</td>
<td>0.91 (0.62-1.34)</td>
</tr>
<tr>
<td>2005 PROactive</td>
<td>281/2605</td>
<td>198/2633</td>
<td>9.5%</td>
<td>1.43 (1.21-1.71)</td>
</tr>
<tr>
<td>2006 ADOPT</td>
<td>22/1456</td>
<td>28/2895</td>
<td>3.6%</td>
<td>1.56 (0.90-2.72)</td>
</tr>
<tr>
<td>2006 DREAM</td>
<td>14/2635</td>
<td>2/2634</td>
<td>0.7%</td>
<td>7.03 (1.60-30.90)</td>
</tr>
<tr>
<td>2008 ACCORD</td>
<td>152/5128</td>
<td>124/5123</td>
<td>8.3%</td>
<td>1.18 (0.93-1.49)</td>
</tr>
<tr>
<td>2008 ADVANCE</td>
<td>220/5571</td>
<td>231/5569</td>
<td>9.3%</td>
<td>0.95 (0.79-1.14)</td>
</tr>
<tr>
<td>2009 BARi2D</td>
<td>248/1183</td>
<td>218/1185</td>
<td>9.7%</td>
<td>1.14 (0.97-1.34)</td>
</tr>
<tr>
<td>2009 RECORD</td>
<td>61/2220</td>
<td>29/2227</td>
<td>4.8%</td>
<td>2.10 (1.35-3.27)</td>
</tr>
<tr>
<td>2009 VADT</td>
<td>76/892</td>
<td>82/899</td>
<td>6.7%</td>
<td>0.91 (0.66-1.25)</td>
</tr>
<tr>
<td>2012 ORIGIN</td>
<td>310/6264</td>
<td>343/6273</td>
<td>9.8%</td>
<td>0.90 (0.77-1.05)</td>
</tr>
<tr>
<td>2013 EXAMINE</td>
<td>106/2701</td>
<td>89/2679</td>
<td>7.3%</td>
<td>1.19 (0.90-1.58)</td>
</tr>
<tr>
<td>2013 Look-AHEAD</td>
<td>99/2570</td>
<td>119/2575</td>
<td>7.7%</td>
<td>0.80 (0.62-1.04)</td>
</tr>
<tr>
<td>2013 SAVOR-TIMI 53</td>
<td>289/8280</td>
<td>228/8212</td>
<td>9.5%</td>
<td>1.27 (1.07-15.1)</td>
</tr>
<tr>
<td>2014 AleCardio</td>
<td>122/3616</td>
<td>100/3610</td>
<td>7.7%</td>
<td>1.22 (0.94-1.59)</td>
</tr>
</tbody>
</table>

Total: 2080/47850 | 1827/47652 | 100% | 1.14 (1.01-1.30)

Heterogeneity: Tau$^2$=0.04; $\chi^2$=45.56, df=13; p<0.0001; I$^2$=71%
Test for overall effect: $Z$=2.04; p=0.041

Favors diabetic med Favors placebo
“Although cardiovascular disease is the cause of death in 75% of diabetics, there exist no well-designed, adequately-powered comparative effectiveness trials evaluating macrovascular outcomes for diabetes drugs”

Steve Nissen, MD - Cleveland Clinic

glu-co-cen-tricity |ˈɡlʊʊkəʊ senˈtrɪsɪtɪ

noun

The irrational belief that lowering blood sugar using virtually any pharmacological means will produce a reliable reduction in adverse outcomes
In 2008 the FDA offered guidance to industry on cardiovascular safety of diabetes drugs

• FDA recommendation: “To establish safety of a new antidiabetic therapy to treat Type 2 diabetes, sponsors should demonstrate that the therapy will not result in an unacceptable increase in cardiovascular risk.”

• The CV outcomes trials are characterized by:
  – Inclusion of high-risk patients
  – Non-inferiority design
  – If the non-inferiority threshold is met, these trials can also assess for superiority.

• Due to their long duration and large numbers, these trials can generate an enormous amount of data on other safety endpoints (pancreatitis, cancer, and hypoglycemia).

• FDA still approves diabetes drugs on the basis of HbA1c

Diabetes Drugs and CVOT - 2017

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  – DPP-4 inhibitors
  – GLP-1 receptor agonists
  – SGLT2 inhibitors
• Mechanisms?
CV Outcomes Trials in Type 2 DM

More than 200,000 T2DM patients

The DPP-4 inhibitor Studies

Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes

William B. White, M.D., Christopher P. Cannon, M.D., Simon R. Heller, M.D., Steven E. Nissen, M.D., Valentin Fuster, M.D., Flournoy Stallings, M.D., M.B.A., Cyrus R. Mehta, Ph.D., Stuart Kupta, M.D., Craig Wilson, Ph.D., William C. Cushman, M.D., and Faiez Zannad, M.D., Ph.D., for the EXAMINE Investigators*

Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus


Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes

Clinical Outcomes with Alogliptin: EXAMINE

**Study Design**
- N=5380 patients with T2D and ACS
  - Randomization
    - Alogliptin: n=2701
    - Placebo: n=2679
  - Noninferiority study:
    - Primary composite endpoint: CV death, nonfatal MI, or nonfatal stroke

**Key Results**
- Median follow-up: 18 months
- A1C: -0.36% for alogliptin vs placebo
- Noninferior to placebo for cardiovascular outcomes
- Also no difference in pancreatitis, cancer, renal impairment, angioedema, or severe hypoglycemia

EXAMINE, Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; HR, hazard ratio; MI, myocardial infarction.

Clinical Outcomes with Saxagliptin: SAVOR

**Study Design**
- N=16,492 patients with T2D and CVD or CVD risk
- Randomization
  - Saxagliptin: n=8280
  - Placebo: n=8212
- Superiority study with noninferiority provision
- Primary composite endpoint: CV death, nonfatal MI, or nonfatal ischemic stroke

**Key Results**
- Median follow-up: 2.1 years
- A1C -0.36% for saxagliptin vs placebo
- Noninferior to placebo for cardiovascular outcomes
- **Higher incidence of HF hospitalization w/ saxagliptin**
- No difference in pancreatitis; fewer cases of pancreatic cancer in saxagliptin group; more cases of nonfatal angioedema in saxagliptin group (8 vs 1)

Clinical Outcomes with Sitagliptin: TECOS

• **Study Design**
  - N=14,671 patients with T2D and CVD
  - Randomization
    - Sitagliptin: n=7332
    - Placebo: n=7339
  - Noninferiority study:
    - Primary composite outcome: cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina

• **Key Results**
  - Median follow-up: 3.0 years
  - A1C: -0.29% for sitagliptin vs placebo
  - **Noninferior** to placebo for cardiovascular outcomes
  - Also no difference infections, cancer, renal failure, hypoglycemia, or noncardiovascular death

TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin.
Modest HbA1c Response

Saxagliptin vs Placebo

HbA1c (%)

Saxagliptin: 8.0, 7.9, 7.8, 7.6
Placebo: 8.0, 7.9, 7.8, 7.5

*p<0.001

Difference between the Alogliptin and Placebo Groups at the Last Visit: −0.36%; P<0.001


Green JB et al. *NEJM* 2015;

Comparison of Primary Endpoint Rates

All Trials met non-inferiority boundary of <1.3

Green JB et al. *NEJM* 2015;
SAVOR-TIMI 53, EXAMINE, and TECOS: Hospitalization for Heart Failure

<table>
<thead>
<tr>
<th>Trial</th>
<th>HR (95% CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAVOR-TIMI</td>
<td>1.27 (1.07–1.51)</td>
<td>0.007</td>
</tr>
<tr>
<td>EXAMINE</td>
<td>1.19 (0.89–1.59)</td>
<td>0.235</td>
</tr>
<tr>
<td>TECOS</td>
<td>1.00 (0.84–1.20)</td>
<td>0.99</td>
</tr>
<tr>
<td>SAVOR-TIMI + EXAMINE + TECOS</td>
<td>1.14 (0.97–1.34)</td>
<td>0.102</td>
</tr>
</tbody>
</table>

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

FDA April 5, 2016
DPP-4 inhibitors and CV safety

- Dipeptidyl peptidase (DPP)-4 inhibitors do not increase or reduce the risk of major CV events.
  - Increased HF events with saxagliptin and per FDA, alogliptin
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  - DPP-4 inhibitors
  - GLP-1 receptor agonists
  - SGLT2 inhibitors
- Mechanisms?
Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome

Marc A. Pfeffer, M.D., Ph.D., Brian Claxton, Ph.D., Rafael Diaz, M.D., Kenneth Dickstein, M.D., M.D., Lars V. Kober, M.D., Francesca C. Lawson, M.D., Lin Ping, M.D., Xiaodan Wei, Ph.D., Eldrin F. Lewis, M.D., M.D., Alda R. Maggioni, M.D., John J.V. McMurray, M.D., Matthew C. Riddle, M.D., Scott D. Solomon, for the ELIXA investigators.

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Steven P. Marso, M.D., Gilbert H. Daniels, M.D., Kirstine Brown-Frandsen, M.D., Per E. Christiansen, M.D., Johannes F.E. Mann, M.D., Michael E.次要, M.D., Steven D. Nissen, M.D., Stuart Pocock, Ph.D., Neil R. Poultor, F.C.Med.Sc., Lasse S. Ravn, M.D., Ph.D., William M. Steinberg, M.D., Mette Stockner, M.D., Bernard Zinman, M.D., Richard M. Bergenstal, M.D., for the LEADER investigators.

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

Clinical Outcomes with Lixisenatide: ELIXA

• Study Design
  • N=6,068 patients with T2D and recent ACS (<180 days)
  • Randomization
    – Lixisenatide: n=3034
    – Placebo: n=3034
  • Noninferiority study:
  • Primary composite outcome: cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina

• Key Results
  • Median follow-up: 25 months
  • A1C: -0.27% for lixisenatide vs placebo
  • Noninferior to placebo for cardiovascular outcomes
  • Also no difference in severe hypoglycemia, pancreatitis, pancreatic cancer, or allergic reactions
GLP -1: ELIXA TRIAL

Hazard ratio, 1.02 (95% CI, 0.89–1.17)

805 Events
Clinical Outcomes with Liraglutide: LEADER

- **Study Design**
  - N=9,340 patients with T2D and high CV risk
  - Randomization
    - Liraglutide: n=4,668
    - Placebo: n=4,672
  - Noninferiority study:
  - Primary composite outcome: cardiovascular death, nonfatal myocardial infarction, nonfatal stroke

- **Key Results**
  - Median follow-up: 3.8 years
  - A1C: -0.40% for liraglutide vs placebo
  - 13% RRR in CV events with liraglutide \([p<0.001 \text{ for noninferiority}; \ p<0.01 \text{ for superiority}]\)
  - Liraglutide was also associated with a NS increase in pancreatic cancer (13 vs 5), a NS decrease in prostate cancer (26 vs 47) and leukemia (5 vs 14); no difference in severe hypoglycemia or pancreatitis

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LEADER, Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes.
LEADER Trial

Primary Endpoint
- 13% RRR
- NNT = 66

CV Death
- 22% RRR
- NNT = 98

Myocardial Infarction
- NS

Stroke
- NS
Clinical Outcomes with Semaglutide: SUSTAIN 6

• **Study Design**
  - N=3,297 patients with T2D and CVD, CKD or both
  - Randomization
    - Semaglutide: n=1,648
    - Placebo: n=1,649
  - Noninferiority study:
    - Primary composite outcome: cardiovascular death, nonfatal myocardial infarction, nonfatal stroke

• **Key Results**
  - Median follow-up: 3.8 years
  - A1C: -1.1% for .5 mg semaglutide and -1.4% for 1 mg semaglutide
  - 26% RRR in 1° outcome with semaglutide [p<0.001 for noninferiority; p=0.04 for superiority]
  - Semaglutide was also associated with more retinopathy complications (HR 1.76 p=0.02), fewer nephropathy complications (HR .64 p=0.005), and a greater # of discontinuations due to GI side effects

SUSTAIN 6, Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes
SUSTAIN 6 Trial

Primary Endpoint

- **26% RRR**
- **NNT = 43**

CV Death

- **NS**
- **0.65–1.48**

Myocardial Infarction

- **NS**
- **0.51–1.08**

Stroke

- **39% RRR**
- **NNT = 91**
The Glucagon-Like Peptide-1 Receptor Agonist lixisenatide does not increase or reduce the risk of major CV events (including no increase in heart failure events).

The GLP-1 receptor agonists liraglutide and semaglutide reduce the risk of major CV events.
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• Approval process for diabetes drugs
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• CVOT results
  – DPP-4 inhibitors
  – GLP-1 receptor agonists
  – SGLT2 inhibitors
• Mechanisms?
Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erik Rudeknoll, Ph.D., Stefan Hantel, Ph.D., Michaela Mattei, M.D., Susana Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woolf, M.D., Jill C. Buse, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-R...
Clinical Outcomes with Empagliflozin: EMPA-REG

• **Study Design**
  - N=7,020 patients with T2D and CVD
  - Randomization
    - Empagliflozin: n=4,687
    - Placebo: n=2,333
  - Noninferiority study:
  - Primary composite outcome: cardiovascular death, nonfatal myocardial infarction, nonfatal stroke

• **Key Results**
  - Median follow-up: 3.1 years
  - A1C: -.54% for 10 mg empagliflozin and -.60% for 25 mg
  - 14% RRR in 1° outcome with empagliflozin [p=0.04]
  - Empagliflozin was also associated with 38% RRR in CV death (p<0.001), but no significant change in nonfatal MI or nonfatal stroke.
  - There were significantly more genital infections with empagliflozin but no other AEs

EMPA-REG, Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes
**EMPA-REG Primary outcome:**

(CV death, MI, stroke)

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

- **14% RRR**
- **NNT = 63**

772 Events

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### CV death, MI and stroke

<table>
<thead>
<tr>
<th>Event</th>
<th>Patients with event/analysed</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-point MACE</td>
<td>490/4687, 282/2333</td>
<td>0.86 (0.74, 0.99)*</td>
<td>0.0382</td>
</tr>
<tr>
<td>CV death</td>
<td>172/4687, 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, 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, 60/2333</td>
<td>1.24 (0.92, 1.67)</td>
<td>0.1638</td>
</tr>
</tbody>
</table>

*Favours empagliflozin*  
*Favours placebo*  

EMPA-REG OUTCOME: Cardiovascular Mortality

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

38% RRR  
NNT = 45
EMPÁ-REG OUTCOME:
Hospitalization for heart failure

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

35% RRR
NNT = 71

EMPA-REG OUTCOME: Renal Outcomes

- **eGFR**
- **Doubling of serum Cr**
- **Worsening nephropathy**

Clinical Outcomes with Canagliflozin: CANVAS

- **Study Design**
  - N=10,142 patients with T2D and high CV risk
  - Randomization
    - Canagliflozin: n=5,795
    - Placebo: n=4,347
  - Noninferiority study:
  - Primary composite outcome: cardiovascular death, nonfatal myocardial infarction, nonfatal stroke

- **Key Results**
  - Median follow-up: 3.6 years
  - A1C: -.58% for 100 mg 300 mg canagliflozin groups pooled
  - 14% RRR in 1° composite outcome with canagliflozin \([p=0.02]\)
  - None of the individual components was significantly reduced and a 17% RRR in progression of albuminuria.
  - With canagliflozin there were more genital infections, a 26% increase in fractures \((CI 1.04-1.52)\) and a significant increase in amputations \(HR 1.97 \ (CI 1.41-2.75)\)

CANVAS Trial: Primary Outcome components

**CV death, MI, Stroke**

- 13% RRR
- NNT = 200

**CV death**

- Placebo
- Canagliflozin

**Nonfatal stroke**

- Placebo
- Canagliflozin

**Nonfatal MI**

- Placebo
- Canagliflozin

CANVAS Trial: Secondary Outcomes

**Hospitalization for heart failure**

- 33% RRR
- NNT = 250

**Total mortality**

- NS

**Progression of albuminuria**

- NS

**Progression of renal failure or death**

- From renal causes
  - 40% RRR
  - NNT = 250

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Canagliflozin and Amputations

- 5/18/2016
- FDA warns of increase risk of leg and foot amputations, mostly affecting the toes, with the diabetes medicine canagliflozin
- CANVAS Trial Interim analysis showed higher risk of amputation (particularly toe) in canagliflozin than placebo
  - 7/1000 with canagliflozin 100mg daily
  - 5/1000 with canagliflozin 300mg daily
  - 3/1000 with placebo daily
  - Study permitted to continue
- Mechanism unclear
  - Volume depletion?
  - Higher risk of amputations has also been noted with diuretic use
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Renal glucose re-absorption in healthy individuals

Filtered glucose load
180 g/day

SGLT2
~ 90%

SGLT1
~ 10%

SODIUM

GLP-1 Modulates Numerous Functions in Humans

GLP-1: Secreted upon the ingestion of food

Promotes satiety and reduces appetite

Alpha cells:
↓ Glucose-dependent postprandial glucagon secretion

Beta cells:
Enhances glucose-dependent insulin secretion

Liver:
↓ Glucagon reduces hepatic glucose output

Stomach:
Helps regulate gastric emptying

Why CVOT are important

Controlled Phase 2b/3
Pooled Population
Saxagliptin Trials

HR 0.44
(95% CI 0.24-0.82)
41 total events

SAVOR-TIMI 53

CV Death, MI or Ischemic CVA (%)

Saxagliptin 7.3%
Placebo 7.2%

Conclusions

• DPP-4 inhibitors do not increase CV events.
  – Increased HF events with saxagliptin and alogliptin

• The GLP-1 RA lixisenatide does not increase or CV events

• The GLP-1 RAs liraglutide and semaglutide reduce the risk of CV events and CV death

• The SGLT2 inhibitors empagliflozin and canagliflozin reduce the risk of CV events and renal events
  – an outsized reduction in HF events

• Empagliflozin reduces CV death

• Canagliflozin increases amputation risk
Why we must prevent cardiovascular events in patients with diabetes

If we keep on doing what we've always done... we'll keep on getting what we've always gotten...