The Impact of Diabetes Drugs on Cardiovascular Disease

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March 1, 2020
Learning Objectives

At the conclusion of this program the learner should be able to:

• List the anti-hyperglycemic medications which have data to support cardiovascular benefit.

• Identify 3 possible mechanisms of action by which anti-hyperglycemic medications provide cardiovascular benefit.
True/False: All anti-diabetes medications reduce cardiovascular risk

FALSE
Definitions

• Medications to treat diabetes: anti-hyperglycemic medications, hypoglycemic medications, anti-diabetes drugs

• Microvascular complications: retinopathy, nephropathy and neuropathy

• Macrovascular complications: cardiovascular disease including heart attack and stroke

Background

- Cardiovascular disease (CVD) is the leading cause of death in patients with diabetes mellitus.
- CV risk increases with diabetes duration and is affected by other comorbidities like hypertension, dyslipidemia, metabolic syndrome, and chronic kidney disease (CKD).
- Diabetic patients with existing CVD have the highest risk of a subsequent CV events.
- Secondary prevention of CV events is a main outcome for which the efficacy of anti-diabetic therapies is evaluated.

Type 2 diabetes is increasingly prevalent

- Globally, 387 million people are living with diabetes\(^1\)
- At least 68% of people >65 years with diabetes die of heart disease\(^2\)

This will rise to 592 million by 2035\(^1\)

Mortality risk associated with diabetes
\((n=820,900)^3\)


Zinman, et al. NEJM. 2015
Meta-analysis of intensive glucose control in T2DM: major CV events including heart failure

<table>
<thead>
<tr>
<th>Event</th>
<th>Number of events</th>
<th>Difference in HbA1c (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>378</td>
<td>-0.88</td>
<td>0.96 (0.83, 1.10)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>730</td>
<td>-0.88</td>
<td>0.85 (0.76, 0.94)</td>
</tr>
<tr>
<td>Hospitalization for or death from heart failure</td>
<td>459</td>
<td>-0.88</td>
<td>1.00 (0.86, 1.16)</td>
</tr>
</tbody>
</table>

- Meta-analysis of 27,049 participants and 2370 major vascular events from:
  - ADVANCE
  - UKPDS
  - ACCORD
  - VADT

Turnbull FM et al. Diabetologia 2009;52:2288–2298

Zinman, et al. NEJM. 2015
# Meta-analysis of intensive glucose control in T2DM: mortality

<table>
<thead>
<tr>
<th></th>
<th>Number of events</th>
<th>Difference in HbA1c (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>More intensive</td>
<td>Less intensive</td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>980</td>
<td>884</td>
<td>-0.88</td>
</tr>
<tr>
<td>CV death</td>
<td>497</td>
<td>441</td>
<td>-0.88</td>
</tr>
<tr>
<td>Non-CV death</td>
<td>476</td>
<td>432</td>
<td>-0.88</td>
</tr>
</tbody>
</table>

- Meta-analysis of 27,049 participants and 2370 major vascular events from
  - ADVANCE
  - UKPDS
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  - VADT

HR, hazard ratio; CV, cardiovascular

Turnbull FM et al. Diabetologia 2009;52:2288-2298

Zinman, et al. NEJM. 2015
Recent trials of newer glucose-lowering agents have been neutral on the primary CV outcome.

- **SAVOR-TIMI 53**: HR: 1.0 (95% CI: 0.89, 1.12)
- **EXAMINE**: HR: 0.96 (95% CI: UL ≤1.16)
- **TECOS**: HR: 0.98 (95% CI: 0.88, 1.09)
- **ELIXA**: HR: 1.02 (95% CI: 0.89, 1.17)
- **EMPA-REG OUTCOME**: HR: 1.02 (95% CI: 0.89, 1.17)

CV, cardiovascular; HR, hazard ratio; DPP-4, dipeptidyl peptidase-4

*Saxagliptin, alogliptin, sitagliptin

Adapted from Johansen OE. World J Diabetes 2015;6:1092-96

Zinman, et al. NEJM. 2015
Background

- Previous a lack of large prospective randomized clinical trials (RCTs) in diabetic patients with CVD
- 2008 FDA mandate to demonstrate safety of all new antihyperglycemic agents prior to seeking approval
- As a result, several new hypoglycemic medications have recently undergone randomized placebo-controlled CV outcome trials (CVOT) focused on patients with preexisting CVD or are at high risk of developing CVD

Microvascular vs Macrovascular Complications

• Traditional anti-hyperglycemic medications reduce BOTH blood sugar AND microvascular complications
• Microvascular complications: retinopathy, nephropathy and neuropathy
• There was NOT evidence to support that traditional anti-diabetes medications reduced macrovascular complications
• Macrovascular complications: cardiovascular disease including MI and stroke
• Episodes of hypoglycemia can actually INCREASE CV risk

Increased CV risk with traditional anti-diabetes drugs

• Some hypoglycemic drugs can paradoxically INCREASE CV events

• Thiazolidinediones (TZDs): An increased risk of heart failure and concerns about myocardial infarction with the use of thiazolidinediones, rosiglitazone and pioglitazone.

• Clinical use of TZDs decreased dramatically due to awareness of potential CV effects.

• DPP4 inhibitors: Increased risk of HF with Saxagliptin, alogliptin

• FDA and other regulatory agencies mandated all new diabetes drugs to demonstrate CV safety.

• All new drugs be approved for marketing only after adequately-powered RCTs could demonstrate that such treatment would not be associated with unacceptably high rates of CV events.

• Post-approval, a CV safety outcome trial in patients with preexisting CVD would need to further demonstrate a significantly elevated CV event.

• Over the past 5 years a steady stream of CV safety trials in patients with preexisting CVD have been performed. And although designed to demonstrate safety, some of trials have shown unprecedented CV benefit in secondary prevention of CVD and related outcomes.
Question Break

• Which anti-diabetes medications have cardiovascular benefits?
  • GLP-1 agonists
  • Metformin
  • DPP4 inhibitors
  • SGLT2 agonists
  • Sulfonylureas
  • Thiazolidinediones
Cardiovascular benefits

• Two classes of medication for T2DM decrease the incidence of heart attack, stroke, hospitalization for heart failure

• SGLT-2 inhibitors
  • Empagliflozin (Jardiance®)
  • Canagliflozin (Invokana®)
  • Ertugliflozin (Steglatro®)

• GLP-1 agonists
  • Exenatide (Byetta®)
  • Liraglutide (Victoza®)
  • Exenatide ER (Bydureon®)
  • Dulaglutide (Trulicity®)
SGLT-2 Inhibitors

Dapagliflozin

Canagliflozin

Empagliflozin
SGLT-2 Inhibitor Background

• Empagliflozin (Jardiance®), Canagliflozin (Invokana®), Dapagliflozin (Farxiga®), Ertugliflozin (Steglatro®)

• A1c lowering: 0.5-0.8% A1c lowering

• No previous RCT had demonstrated a reduction in cardiovascular events or death by an antihyperglycemic medication until the 2015 EMPA-REG OUTCOME study
SGLT-2 Inhibitor MOA

• Sodium-glucose co-transporter 2 (SGLT2) is a low affinity, high capacity sodium-glucose co-transporter in the proximal renal tubules and is responsible for glucose reabsorption

• Medication prevents glucose reabsorption into the blood stream and facilitating elimination of glucose in the urine. As a result, these agents also have a diuretic effect and promote weight and blood pressure reduction by sodium and water loss.

• Daily oral medication

SGLT-2 Inhibitor MOA

Renal glucose reabsorption

Increased urinary glucose excretion with JARDIANE

Proximal tubule

SGLT2

JARDIANE

Glucose

Increased urinary glucose excretion

hcp.jardiance.com
Liakos A et al. Diabetes Obes Metab 2014;16:984-93
EMPA-REG

• Randomized, double-blind, placebo-controlled CV outcomes trial

• Objective: To examine the long-term effects of empagliflozin versus placebo, in addition to standard of care, on CV morbidity and mortality in patients with type 2 diabetes and high risk of CV events

• September 2010-April 2015

Empagliflozin modulates several factors related to CV risk

- Blood pressure without increasing HR
- Weight
- Oxidative stress
- LDL, HDL
- Triglycerides
- Uric acid
- Albuminuria
- Sympathetic nervous system activity
Study Outcomes

• Primary outcome:
  • 3 point MACE: Time to first occurrence of death from CV causes, nonfatal myocardial infarction (MI) or nonfatal stroke

• Secondary outcome:
  • 4 point MACE: Primary outcome plus hospitalization for unstable angina

*MACE: Major adverse cardiac event
Zinman, et al. EMPA-REG OUTCOME study
Summary

EMPA-REG showed Absolute Risk Reduction (ARR) of 1.9% for Primary outcome (CV death, MI, nonfatal stroke)

- Risk for 3 point MACE by 14%
- Cardiovascular death by 38%
- Hospitalization for heart failure by 35%
- All cause mortality by 37%

• NNT 39 to prevent 1 death from CV causes for treatment with empagliflozin for 3 years

CANVAS

• Canagliflozin was the second SGLT2 inhibitor to undergo a CV safety trial, and consistent with results of EMPA-REG OUTCOME, showed reduction in HF hospitalization (5.5% vs 8.7%).

• Canagliflozin was shown to be superior to placebo in reducing the primary combined outcome of CV death, MI, and stroke (26.9% vs. 31.5%; P = 0.02) but did not improve any of these outcomes individually.

• However, the reduction in the HF related outcome was identical to that observed with empagliflozin in the EMPA-REG OUTCOME trial.

Figure 3. Effects of Canagliflozin on Cardiovascular, Renal, Hospitalization, and Death Events in the Integrated CANVAS Program.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Canagliflozin (N=5795)</th>
<th>Placebo (N=4347)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke</td>
<td>26.9</td>
<td>31.5</td>
<td>0.86 (0.75–0.97)</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>11.6</td>
<td>12.8</td>
<td>0.87 (0.72–1.06)</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>9.7</td>
<td>11.6</td>
<td>0.85 (0.69–1.05)</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>7.1</td>
<td>8.4</td>
<td>0.90 (0.71–1.15)</td>
</tr>
<tr>
<td>Fatal or nonfatal myocardial infarction</td>
<td>11.2</td>
<td>12.6</td>
<td>0.89 (0.73–1.09)</td>
</tr>
<tr>
<td>Fatal or nonfatal stroke</td>
<td>7.9</td>
<td>9.6</td>
<td>0.87 (0.69–1.09)</td>
</tr>
<tr>
<td>Hospitalization for any cause</td>
<td>118.7</td>
<td>131.1</td>
<td>0.94 (0.88–1.00)</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>5.5</td>
<td>8.7</td>
<td>0.67 (0.52–0.87)</td>
</tr>
<tr>
<td>Death from cardiovascular causes or hospitalization for heart failure</td>
<td>16.3</td>
<td>20.8</td>
<td>0.78 (0.67–0.91)</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>17.3</td>
<td>19.5</td>
<td>0.87 (0.74–1.01)</td>
</tr>
<tr>
<td>Progression of albuminuria</td>
<td>89.4</td>
<td>128.7</td>
<td>0.73 (0.67–0.79)</td>
</tr>
<tr>
<td>40% reduction in eGFR, renal-replacement therapy, or renal death</td>
<td>5.5</td>
<td>9.0</td>
<td>0.60 (0.47–0.77)</td>
</tr>
</tbody>
</table>
Figure 5. Rates of Hospitalization for Heart Failure, Death from Any Cause, and Renal Outcomes in the Integrated CANVAS Program.
CREDENCE

- CREDENCE Trial: Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation, reported on April 14, 2019, that canagliflozin cut the risk of renal failure or death by 30% in patients with type 2 diabetes and chronic kidney disease.

Adverse effects

- Genital mycotic infections
- UTI and sepsis due to UTI
- Euglycemic diabetic ketoacidosis
- Increased amputation and bone fractures with canagliflozin in the CANVAS trial. The FDA has issued a warning to avoid canagliflozin in patients that may be at a higher risk for amputations.
- Contraindicated if GFR<30mL/min

Future directions

• More renal and heart failure outcomes trials are underway
• Various dedicated trials exploring the therapeutic value of SGLT2 inhibitors are ongoing
Question Break

What are 3 ways SGLT2 inhibitors reduce cardiovascular risk?

- Blood pressure without increasing HR
- Weight
- Albuminuria
Glucagon-Like Peptide-1 Agonists

• Liraglutide (Victoza), Byetta and Bydureon (Exenatide and Lisixenatide), Trulicity (Dulaglutide), Tanzeum (Albiglutide), Semaglutide (Ozempic)

• A1c lowering: 0.5-1.5%

• Daily or weekly injectable, one oral daily pill newly available

• Approved as second agent to metformin, as add on to basal insulin, in clinical practice also used in addition to basal/bolus insulin

GLP-1 agonist MOA

- Glucagon-like peptide-1 (GLP-1) is one 'satiety peptide' known to stimulate insulin release in the context of elevated blood glucose levels, reduce prandial glucagon, and delay gastric emptying.

GLP-1 Agonist CV Risk Reduction

• Initial GLP-1 agonist trials showed non-inferiority

• LEADER Trial (Liraglutide) showed ARR for Primary Outcome (CV death, nonfatal stroke, MI) was 1.9%. Mainly driven by reduction in CV death. Liraglutide reduced all-cause mortality as well (8.2% vs. 9.6%; P = 0.02).

• SUSTAIN-6 Trial (Semaglutide as Ozempic) showed ARR Primary Outcome (CV death, nonfatal stroke, MI) was 2.3%. Mainly driven by reduction in nonfatal stroke, 1.6% vs. 2.7%.

• PIONEER-6 Trial (Semaglutide as oral Rybelsus) Demonstrated non-inferiority but event driven trial halted too early to demonstrate superiority

• NOT a class effect

Liraglutide and Semaglutide effect on CV Risk

• No reduction in admissions for heart failure, suggesting a different mechanism of action than SGLT2 inhibitors.

• Mechanism of reduction in CV risk not completely understood

• Anti-atherothrombotic effect.

• Blood pressure
  • The mean pulse rate increased by 2 and 2.5 bpm with 0.5 and 1.0 mg dose of semaglutide in SUSTAIN 6, and by 4 bpm in PIONEER 6

• Weight

• Avoidance of hypoglycemia

GLP-1 agonist and renal insufficiency

• PIONEER-5 trial revealed no decline in renal function during treatment with 3, 7, and 14mg doses of oral semaglutide in patients with GFR 30-59

• Granted indication for patients with T2DM and CKD
GLP-1 Agonist Adverse Effects

- Gastrointestinal side effects
- Pancreatitis
- Increased C cell tumors in rat studies – do not use in patients with PMH or FH of medullary thyroid cancer or MEN2

LEADER TRIAL:
- Liraglutide: Increased gallstones, cholecystitis, nausea, vomiting, diarrhea
- No increase in benign or malignant neoplasms

- Hypoglycemia: Rare
- Other than Dulaglutide and Semaglutide do not recommend use in GFR<30
- Increase in diabetic retinopathy with oral semaglutide, dedicated study ongoing

Question Break

• True or False: All GLP-1 agonists cause cardiovascular risk reduction.

FALSE
DPP4 inhibitors

- Sitagliptin (Januvia), Saxagliptin (Onglyza), Linagliptin (Tradjenta), Alogliptin (Takeda)
- A1c lowering: 0.5-1.0%
- TECOS, SAVOR-TIMI, and EXAMINE Trials: None of the DPP4 inhibitors were found to increase adverse CV events, CV mortality, or all-cause mortality. Neither was there a signal of CV benefit.
- Heart failure was a different story
DPP4 inhibitors MOA

Incretin-Based Therapies
MOA

DPP-4 enzyme inactivates GLP-1

DPP-4 inhibitors block the DPP-4 enzyme

Stimulates insulin secretion
Suppresses glucagon secretion

GLP-1 effects on insulin and glucagon are glucose-dependent

Drucker DJ, Nauck MA. Lancet. 2006;368:1696-1705.
DPP4 Inhibitor Adverse Effects

• Class effect: Increased incidence of pancreatitis
• Saxagliptin and Alogliptin: Heart failure
  • SAVOR-TIMI 53 Study found a 27% increased relative risk of hospitalization for heart failure in patients assigned to saxagliptin compared with placebo. No MOA has been determined.
  • EXAMINE Study: Not initially apparent with alogliptin in the main report of the study. But a subsequent post-hoc analysis suggested increased HF hospitalizations (2.2% vs 1.3%) in patients without a history of HF, but no increase in those with preexisting HF
  • In 2015, the FDA issued a safety warning for the risk of HF with saxagliptin and alogliptin. No signal of HF hospitalizations was seen with sitagliptin in TECOS Trial.

Some medications in the class of DPP4 inhibitors have been found to:

a) Increase risk of cardiovascular events
b) Cause hypoglycemia
c) Increase hospitalization from heart failure
d) Reduce hemoglobin A1c by 2%
Metformin

• Decreases hepatic gluconeogenesis
• A1c lowering 0.5-1.0%
• Cardiovascular benefits: 1-2% weight loss, improved lipoprotein metabolism
• Adverse effects: Diarrhea, vitamin B12 deficiency, very rare lactic acidosis (incidence rate of lactic acidosis 8 or 9 per 100,000 person-years). Do not use in decompensated heart failure or liver disease.

Sulfonylureas

• Glipizide, glimepiride, glyburide
• MOA: Enhanced insulin release
• Cardiovascular benefits: Reduction in hyperglycemia
• Adverse effects: Increase in hypoglycemia, INCREASED cardiovascular risk
• A1c lowering 1-1.25%
• In 1970, the UGPD study, cardiovascular mortality rates of type 2 diabetic patients treated with the sulfonylurea tolbutamide exceeded those of patients treated with placebo or insulin
• UKPDS: decreased CV disease with sulfonylureas
• Reduction in ischemic preconditioning: Sulfonylureas bind also to cardiovascular $K_{ATP}$ channels, although less well than to $\beta$-cell $K_{ATP}$ channels in pancreas, presumably promoting closure of the channel and opposing ischemic preconditioning. This property of sulfonylureas has the potential to increase cardiovascular risk in patients with diabetes.
• Ischemic preconditioning occurs with glimepiride but is blocked by glyburide

Thiazolidinediones

- Rosiglitazone, Pioglitazone
- MOA: Enhanced sensitivity to insulin, reduced hepatic gluconeogenesis, reduced inflammation
- A1c lowering 1-1.25%
- Cardiovascular benefits: Reduction in BP, fat redistribution to subcutaneous sites and reduction in lipotoxicity
- Adverse effects: Weight gain, fractures, edema, INCREASED CV risk- increased HF and concerns about increased MI

TZDs

Insulin

• Basal and bolus
• If A1c > 9, this is the recommended medication
• Cardiovascular benefits: Reduction in hyperglycemia
• Adverse effects: Increase in hypoglycemia, weight gain, no increased risk of cardiovascular event
• DEVOTE trial demonstrated non-inferiority for Insulin degludec (Tresiba) vs insulin glargine (Lantus) in the risk of cardiovascular event. Decreased hypoglycemia with degludec compared to glargine.
Question break

What class of medication increases cardiovascular disease by blocking ischemic preconditioning?

a) SGLT2 inhibitors

b) Sulfonylurea

c) GLP-1 agonists

d) Thiazolidinediones
Learning Objectives

Here we are at the conclusion of this program, you should be able to:

• List the anti-hyperglycemic medications which have data to support cardiovascular benefit.
  • GLP-1 agonists Semaglutide and Liraglutide
  • SGLT2 inhibitors

• Identify 3 possible mechanisms of action by which anti-hyperglycemic medications provide cardiovascular benefit.
  • Decrease BP without increasing heart rate
  • Weight loss
  • Decreased albuminuria
Bibliography

5. ADA Standards of Care 2016