Evaluating the Cardiovascular Benefits of Antidiabetic Medications
Target Audience: Pharmacists
ACPE#: 0202-0000-18-054-L01-P
Activity Type: Application-based
Disclosures

- Stuart T. Haines has no relevant conflicts of interest to disclose related to the subject matter in this presentation.

The American Pharmacists Association is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.
This activity is supported by an independent educational grant from Novo Nordisk, Inc.
Learning Objectives

At the conclusion of this session, given a patient with diabetes, the participant should be able to:

1. Describe the evidence regarding the cardiac risks and benefits of antidiabetic agents.

2. Select antidiabetic agents to meet individual patient needs.
Assessment Question #1

BB is a 61 year old man with type 2 diabetes, HTN, dyslipidemia, and is morbidly obese. He had an MI 8 months ago and had two coronary stents placed. In addition to guideline recommended treatments for the prevention of recurrent atherosclerotic cardiovascular (ASCVD) events, BB is taking metformin and glyburide. His A1c today is 7.3%, BP = 124/62, and LDL-C = 52 mg/dL. What is BB’s risk for an ASCVD event in the next 10 years?

A. Less than 5% (Low)
B. 5-10% (Moderate)
C. More than 10% (High)
D. Unclear; need smoking and family ASCVD history
Assessment Question #2

BB is a 61 year old man with type 2 diabetes, HTN, dyslipidemia, and is morbidly obese. He had an MI 8 months ago and had two coronary stents placed. In addition to guideline recommended treatments for the prevention of recurrent atherosclerotic cardiovascular (ASCVD) events, BB is taking metformin and glyburide. Which of BB’s antidiabetic medications reduce BB’s ASCVD risk?

A. Glyburide
B. Metformin
C. Both glyburide and metformin
D. Neither glyburide or metformin
BB is a 61 year old man with type 2 diabetes, HTN, dyslipidemia, and is morbidly obese. He had an MI 8 months ago and had two coronary stents placed. In addition to guideline recommended treatments for the prevention of recurrent atherosclerotic cardiovascular (ASCVD) events, BB is taking metformin and glyburide. Which of the following antidiabetic agents, if added, would reduce BB’s ASVCD risk and lower his risk of death over the next few years?

A. Alogliptin  
B. Canagliflozin  
C. Exenatide LR  
D. Liraglutide
Patient Case

PG is a 69 year old woman who is recovering from an ischemic stroke.
Patient Case

History of Present Illness:
PG was discharged home after suffering an ischemic stroke 8 days ago. She was previously in “good health” but experienced sudden dysarthria and right-sided paralysis (right arm and leg). Atrial fibrillation and carotid artery disease were ruled out. Although she is now able to articulate words without difficulty, she continues to have some weakness and requires a walker to ambulate. She is receiving physical and occupational therapy.
Patient Case

Past Medical History:
- Hypertension for 10+ years
- Diabetes type 2 for 6 years
- Dyslipidemia for 6 years
- Obesity
- Osteoarthritis (hip, knee, and ankle)
Patient Case

Current Medications

- Clopidogrel 75mg daily (initiated in hospital; previously on ASA 81mg daily)
- Metformin 850mg BID
- Glyburide 5mg BID
- Ramipril 20mg daily
- Chlorthalidone 12.5mg daily
- Rosuvastatin 20mg daily
- Acetaminophen 1000mg TID
- Naproxen 220mg PRN for OA pain
Patient Case

Family Medical History
Father died at age 92 (unknown causes); Mother committed suicide (age 40)
Brother (66 years old) has DM type 2 and “heart problems”
Sister (70 years old) has HTN and suffered a “mini-stroke” 2 years ago

Social History
Widow – husband of 44 years died 8 years ago.
Children – 2 grown children (38 and 42 years old), 3 grandchildren
Lived independently until stroke; owns home
Wide circle of friends; very active in church
Medicare A/B and Part D – able to afford meds and health care visits
Drinks alcohol socially (1-2 mixed drinks < 5/month); never smoked
Patient Case

Review of Systems

**Endo:** Has had diabetes for several years. Does not check BG very often but will check if necessary. No hypoglycemic episodes “in years” and has been told diabetes control was “just fine”

**Neuro:** Continues to have right-sided weakness but able to lift limbs against gravity and small objects. Diminished sensory perception / numbness in feet.
Patient Case

Vital Signs
BP = 128 / 62 mmHg  Pulse = 84, bpm
Weight = 201 lbs      Height = 5’ 2”
Temp = 98.5 ºF        BMI = 36.8 kg/m²

Pain = 1 out of 10 in right knee/ankle, 2 out of 10 in left knee/ankle
Patient Case

**Labs (fasting) – drawn morning prior to hospital discharge**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na</td>
<td>141</td>
</tr>
<tr>
<td>K</td>
<td>4.4</td>
</tr>
<tr>
<td>Cl</td>
<td>101</td>
</tr>
<tr>
<td>CO₃</td>
<td>19</td>
</tr>
<tr>
<td>Gluc</td>
<td>136</td>
</tr>
<tr>
<td>A₁c</td>
<td>8.3%</td>
</tr>
<tr>
<td>SCr</td>
<td>1.3</td>
</tr>
<tr>
<td>BUN</td>
<td>17</td>
</tr>
<tr>
<td>CrCl</td>
<td>55 ml/min</td>
</tr>
<tr>
<td>AST</td>
<td>21</td>
</tr>
<tr>
<td>ALT</td>
<td>16</td>
</tr>
<tr>
<td>TChol</td>
<td>124</td>
</tr>
<tr>
<td>LDL-C</td>
<td>64</td>
</tr>
<tr>
<td>HDL-C</td>
<td>34</td>
</tr>
<tr>
<td>Trig</td>
<td>125</td>
</tr>
</tbody>
</table>
Key Clinical Questions

1) What factors place this patient at risk for a recurrent cardiovascular event?
2) What is the “optimal” (effective and safe) medication regimen for this patient?
Estimating CV Risk
Key Clinical Questions

- How do you determine a patient’s cardiovascular risk?
- What CV risk assessment tools are available?
Cardiovascular Risk

- **Prior ischemic cardiovascular event** (e.g. TIA/stroke or MI) or evidence of ASCVD (e.g. angina, revascularization procedure, peripheral arterial disease)

- **Risk Factors:**
  - **Traditional factors:** Age, sex, tobacco use, BP, lipids (TChol, HDL, and Non-HDL), diabetes, weight (BMI), abdominal obesity (waist circumference), physical activity, family history of premature CV event
  - **Emerging Factors:** hs-CRP, coronary artery calcification (CAC), small dense LDL-C (lipid sub-fraction analysis)
Cardiovascular Risk Calculators

**Risk calculators** (in those without pre-existing ASCVD)

- Mayo Clinic - Heart Disease Risk Calculator ([https://goo.gl/4O1uGd](https://goo.gl/4O1uGd))
- QRISK2 – 2017 and QRISK-3 ([https://qrisk.org/](https://qrisk.org/))
Diabetes Meds and CVD
Key Clinical Questions

- Do any of the available antidiabetic agents reduce cardiovascular (CV) risk?
- Increase CV risk?
- Should some antidiabetic agents be favored over others in patients at high-risk for CV events?
## Evolution of CV Safety Trials

<table>
<thead>
<tr>
<th>YEAR</th>
<th>DRUG</th>
<th>Safety Issue</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1971</td>
<td>Tolbutamide</td>
<td>UGDP Study: ↑ cardiovascular and all-cause mortality</td>
<td>FDA adds warning to package insert</td>
</tr>
<tr>
<td>1992</td>
<td>Pro-insulin</td>
<td>↑ risk of acute MI</td>
<td>Clinical trial suspended</td>
</tr>
<tr>
<td>1998</td>
<td>Metformin, SU, and Insulin</td>
<td>UKPDS: Cardiovascular benefit seen in metformin arm but not SU/Insulin treatment arms (neutral impact)</td>
<td>Metformin becomes drug of choice of patients with type 2 DM</td>
</tr>
<tr>
<td>2005</td>
<td>Muraglitazar</td>
<td>↑ risk of death, major CV event, CHF</td>
<td>Completed Phase III trials but never submitted for FDA approval</td>
</tr>
<tr>
<td>2005</td>
<td>Pioglitazone</td>
<td>PROactive Study: ↓ Composite CV endpoint but ↑ CHF</td>
<td>Emerging concerns regarding CHF and other ADEs led to decline in TZD use</td>
</tr>
<tr>
<td>2007</td>
<td>Rosiglitazone</td>
<td>↑ CV risk (based on meta-analysis)</td>
<td>Drug pulled from EU markets; FDA restricts access; all new drugs must have CV safety trial</td>
</tr>
<tr>
<td>2008</td>
<td>Intensive Treatment (A1c ≤ 6.0%)</td>
<td>ACCORD, ADVANCE, and VADT studies: No CV benefit, ↑ mortality in ACCORD</td>
<td>Glycemic control is only part of the CV risk puzzle</td>
</tr>
</tbody>
</table>

# UKPDS Study

## Relative Risk Reduction in Metformin Group vs Usual Care

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>1997$^1$</th>
<th>2007$^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any diabetes related endpoint</td>
<td>12% (0.029)</td>
<td>9% (0.040)</td>
</tr>
<tr>
<td>Microvascular complications</td>
<td>25% (0.01)</td>
<td>24% (0.001)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>16% (0.052)</td>
<td>15% (0.014)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>6% (0.44)</td>
<td>13% (0.007)</td>
</tr>
</tbody>
</table>

Metformin versus Sulfonylurea

Figure 2. Cumulative incidence (95% CIs) of cardiovascular disease or death.

Retrospective cohort study of 253,690 patients initiating treatment

Comparative Effectiveness of Sulfonylurea and Metformin Monotherapy on Cardiovascular Events in Type 2 Diabetes Mellitus
Antidiabetes Drugs

Cardiovascular Studies

- SAVOR-TIMI 53 (Saxagliptin)
- EXAMINE (Alogliptin)
- ELIXA (Lixisenatide)
- TECOS (Sitagliptin)
- EMPA-REG OUTCOME (Empagliflozin)
- LEADER (Liraglutide)
- SUSTAIN 6 (Semaglutide)
- CANVAS-R (Canagliflozin)
- OMNEON 018 (DPP-4 Inhibitor QW)
- CARMELINA (Linagliptin)
- EXSCEL (Exenatide QW)
- CANVAS-R (Canagliflozin)
- FREEDOM CVO (ITCA Q 6 months)
- CAROLINA (Linagliptin)
- DEVOTE (Degludec)
- REWIND (Dulaglutide QW)
- DECLARE-TIMI 58 (Dapagliflozin)
- CREDENCE (Canagliflozin)
- Ertugliflozin CVOT (Ertugliflozin)

Class of drug of interest being evaluated:

- DPP-4 Inhibitor
- GLP-1 receptor agonist
- SGLT2 inhibitor
- Basal insulin
# Large CV Outcome Trials in Type 2 Diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>SAVOR</th>
<th>EXAMINE</th>
<th>TECOS</th>
<th>CAROLINA</th>
<th>CARMELINA</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP4-I</td>
<td>saxagliptin</td>
<td>alogliptin</td>
<td>sitagliptin</td>
<td>linagliptin</td>
<td>linagliptin</td>
</tr>
<tr>
<td>Comparator</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>glimeperide</td>
<td>placebo</td>
</tr>
<tr>
<td>Results Reported</td>
<td>2013</td>
<td>2013</td>
<td>2015</td>
<td>2018?</td>
<td>2018?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>ELIXA</th>
<th>LEADER</th>
<th>SUSTAIN 6</th>
<th>EXSCEL</th>
<th>REWIND</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP1-RA</td>
<td>lixisenatide</td>
<td>liraglutide</td>
<td>semaglutide</td>
<td>exenatide LR</td>
<td>dulaglutide</td>
</tr>
<tr>
<td>Comparator</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
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<table>
<thead>
<tr>
<th>Study</th>
<th>EMPA-REG</th>
<th>CANVAS</th>
<th>DECLARE</th>
<th>VERTIS-CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGLT2-I</td>
<td>empagliflozin</td>
<td>canagliflozin</td>
<td>dapagliflozin</td>
<td>ertugliflozin</td>
</tr>
<tr>
<td>Comparator</td>
<td>placebo</td>
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<td>2015</td>
<td>2017</td>
<td>2019?</td>
<td>2020?</td>
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</table>
Critical (but BRIEF!) Analysis of 4 Recent Studies!

- TECOS – Sitagliptin (DPP-4 inhibitor)
- LEADER – Liraglutide (GLP-1 agonist)
- EMPA-REG OUTCOME – Empagliflozin (SGLT-2 inhibitor)
- CANVAS – Canagliflozin (SGLT-2 inhibitor)
Study 1 – TECOS Study


Study Design: Randomized, double blind, parallel, non-inferiority

<table>
<thead>
<tr>
<th>Key Element</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>Patients with DM type 2 with established CV disease (n=14,671)</td>
</tr>
<tr>
<td>Intervention</td>
<td>Sitagliptin + other antihyperglycemics to reach A1c goal</td>
</tr>
<tr>
<td>Comparator</td>
<td>Placebo + other antihyperglycemics to reach goal A1c</td>
</tr>
</tbody>
</table>
| Outcomes    | Glycemic control – slightly better with sitagliptin (-0.29%)  
Composite outcome – no difference (11.4% vs. 11.6%; HR = 0.98)  
Hospitalization for HF – no difference (HR=1.00) |
Study 2 – LEADER Study


Study Design: Randomized, double blind, parallel, non-interiority

<table>
<thead>
<tr>
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<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>Patients with type DM with ASCVD or multiple risk factors (n=9340)</td>
</tr>
<tr>
<td>Intervention</td>
<td>Liraglutide + other antihyperglycemics</td>
</tr>
<tr>
<td>Comparator</td>
<td>Placebo + other antihyperglycemics</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Time-to-event first CV event – <strong>superior</strong> (13.0% vs 14.9%; HR = 0.87)</td>
</tr>
<tr>
<td></td>
<td>Death from CV causes – <strong>superior</strong> (4.7% vs 6.0%; HR = 0.78)</td>
</tr>
<tr>
<td></td>
<td>All cause mortality – <strong>superior</strong> (8.2% vs 9.6%; HR = 0.85)</td>
</tr>
<tr>
<td></td>
<td>GI side effects more common but not pancreatitis</td>
</tr>
</tbody>
</table>
Study 3 – EMPA-REG OUTCOME


Study Design: Randomized, parallel

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Patients</td>
<td>Patient with DM type 2 with ASCVD or multiple risk factors (n=7020)</td>
</tr>
<tr>
<td>Intervention</td>
<td>Empagliflozin 10 or 25mg daily + other antihyperglycemics</td>
</tr>
<tr>
<td>Comparator</td>
<td>Placebo + other antihyperglycemics</td>
</tr>
</tbody>
</table>
| Outcomes      | Pooled analysis (both treatment doses of empagliflozin)  
Composite endpoint – superior (10.5% vs 12.1%; HR = 0.86)  
CV death (3.7% vs. 5.9%); HF (2.7% vs 4.1%);  
all cause mortality (5.7% vs. 8.3%) all superior.  
GU infections more frequent. |
**Study 4 – CANVAS**


**Study Design:** Randomized, double blind, parallel

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>Patients with DM type 2 with ASCVD or multiple risk factors (n=10,142)</td>
</tr>
<tr>
<td>Intervention</td>
<td>Canagliflozin 100 or 300mg daily + other antihyperglycemics</td>
</tr>
<tr>
<td>Comparator</td>
<td>Placebo + other antihyperglycemics</td>
</tr>
</tbody>
</table>
| Outcomes    | Fatal/Non-fatal stroke or MI – **superior** (26.9 vs 31.5*; HR = 0.86)  
All cause mortality – **no difference** (17.3 vs 19.5*; HR = 0.87)  
Hospitalization for HF - **superior** (5.5 vs. 8.7*; HR = 0.67)  
Amputation (6.3 vs 3.4*), fractures (15.4 vs 11.9*), GU infections in men |

* Event rate per 1000 patient-years
Applying Evidence
Patient Case

PG is a 69 year old woman who is recovering from an ischemic stroke.
Key Clinical Questions

1) What factors place this patient at risk for a recurrent cardiovascular event?
2) What is the “optimal” (effective and safe) medication regimen for this patient?
Critical Analysis

PG’s risk for recurrent stroke or other CV event:

HPI: Recent ischemic stroke

PMHx: Hypertension, Diabetes, Dyslipidemia, Obesity

Family History: Diabetes, HTN, and stroke

Social History: None

Medications: Glyburide, NSAID use

Objective: Age, BP (well controlled), lipids (on high potency statin and LDL < 70mg/dL), A1c > 8%
Critical Analysis

- **Oxfordshire Community Stroke Project (1994)**\(^1\) – recurrence of ischemic stroke after first stroke
  - 6 months – 9% (95% CI 6-11%)
  - 1 year – 13% (95% CI 10-16%)
  - 5 years – 29.7% (95% CI 19-40%)

- **Meta-analysis (2011)**\(^2\) shows variable risk but generally 2-5% in first 30 days, 10-15% at 1 year, 25-35% at 5 years.

Key Clinical Questions

1) What factors place this patient at risk for a recurrent cardiovascular event?
2) What is the “optimal” (effective and safe) medication regimen for this patient?
Critical Analysis – Application

Findings from which of the following study (or studies) can be applied to PG?

A) TECOS study
B) LEADER study
C) EMPA-REG study
D) CANVAS study

Key concepts:
Study inclusion criteria; feasibility of implementing the intervention
Critical Analysis – Application

Results from which of the following study suggest that PG would derive the most compelling benefit(s)?

A) TECOS study
B) LEADER study
C) EMPA-REG study
D) CANVAS study

Key concepts:
Composite vs. single outcomes; RRR vs. ARR; NNT
Critical Analysis – Application

Results from which of the following study suggest that PG would potentially suffer the most harm?

A) TECOS study
B) LEADER study
C) EMPA-REG study
D) CANVAS study

Key concepts: Severity of harms; NNH
What’s Your Plan?

What treatment changes do you recommend for PG?
A) Nothing, no changes to her current regimen
B) D/C glyburide and add a DPP-4 inhibitor
C) D/C glyburide and add a GLP-1 agonist
D) D/C glyburide and add an SGLT2 inhibitor
E) Something else

Why? What is your rationale?
Conclusions

- Patients with DM are at higher risk for CV events
- Estimating CV risk and addressing modifiable risk factors is critical to long-term outcomes
- Antidiabetes medications may have a detrimental, neutral, or positive impact on CV event rates
- Recent data suggest:
  - Some SGTL2 inhibitors and GLP-1 receptor agonists have a positive impact on CV outcomes and mortality
  - DDP-4 inhibitors appear to have a neutral impact on CV outcomes
QUESTIONS

- who?
- what?
- how?
- why?
- when?
- knowing
- investigation
- discovering
- asking questions
- challenge
- who?
- clues
Assessment Question #1

BB is a 61 year old man with type 2 diabetes, HTN, dyslipidemia, and is morbidly obese. He had an MI 8 months ago and had two coronary stents placed. In addition to guideline recommended treatments for the prevention of recurrent atherosclerotic cardiovascular (ASCVD) events, BB is taking metformin and glyburide. His A1c today is 7.3%, BP = 124/62, and LDL-C = 52 mg/dL. What is BB’s risk for an ASCVD event in the next 10 years?

A. Less than 5% (Low)
B. 5-10% (Moderate)
C. More than 10% (High)
D. Unclear; need smoking and family ASCVD history
Assessment Question #2

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A. Glyburide
B. Metformin
C. Both glyburide and metformin
D. Neither glyburide or metformin
Assessment Question #3

BB is a 61 year old man with type 2 diabetes, HTN, dyslipidemia, and is morbidly obese. He had an MI 8 months ago and had two coronary stents placed. In addition to guideline recommended treatments for the prevention of recurrent atherosclerotic cardiovascular (ASCVD) events, BB is taking metformin and glyburide. Which of the following antidiabetic agents, if added, would reduce BB’s ASVCD risk and lower his risk of death over the next few years?

A. Alogliptin  
B. Canagliflozin  
C. Exenatide LR  
D. Liraglutide