Disclosure to Participants

- **Notice of Requirements For Successful Completion**
  - Please refer to learning goals and objectives.
  - Learners must attend the full activity and complete the evaluation in order to claim continuing education credits/hours.

- **Conflicts of Interest (COI) and Financial Relationship Disclosures:**
  - Presenter: Emily Weidman-Evans, PharmD, BC-ADM – No disclosures.

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Learning Objectives

1. Discuss the implications of relevant clinical trials as they relate to blood glucose control and cardiovascular outcomes.
2. Compare the effects on cardiovascular outcomes and risk factors of currently available diabetes drugs, and the possible mechanisms behind those effects.
3. Develop a treatment plan for a person with diabetes considering both glucose-lowering ability and cardiovascular risks/benefits of available drugs.

We have...

- 12 drug classes
- Blood glucose

How Sweet is Your Heart?
Diabetes drugs and cardiovascular risks
We know…

Blood glucose

DCCT, UKPDS, ACCORD, ADVANCE, VADT

So, does…

Blood glucose

What do the (big) studies say?

<table>
<thead>
<tr>
<th></th>
<th>DCCT</th>
<th>UKPDS</th>
<th>ADVANCE</th>
<th>VADT</th>
<th>ACCORD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yep</td>
<td>Uh-huh…</td>
<td>No</td>
<td>(or maybe?)</td>
<td>Nuh-uh</td>
<td>Definitely not</td>
</tr>
</tbody>
</table>

Overall—Small, but statistically significant decrease in major CVD outcomes (non-fatal MI), but no change in mortality.

Risk vs. benefit…

Conclusions…

- CVD is the #1 killer of people with diabetes
- And lowering blood glucose may or may not impact CVD…

So let’s come up with more drugs that do the same things as the old ones!!!
FDA Guidance...
- In response to rosiglitazone “situation”, required that all new drugs provide proof that no harm will ensue.
- Ideally, provide proof that improvements in CV outcomes may occur.
  - Long term studies?
  - Surrogate markers?

SO WHAT SHOULD OUR PATIENTS BE TAKING?
WHAT EFFECTS DO THESE DRUGS HAVE ON MARKERS OF CV RISK?
**AND WHICH ONES ACTUALLY EFFECT CV OUTCOMES??**

Meet J.G.
- J.G. is an overweight 55-year-old white male who is newly diagnosed with Type 2 DM. His A1c upon diagnosis was 9.1%, so he was started on metformin and referred for DSMT and MNT.
- His comorbid conditions are HTN, dyslipidemia, and NYHA II HF. His 10-yr calculated ASCVD risk is 16.3%.
- Unfortunately, even with medication compliance and lifestyle changes, his A1c is still 8.3%....
- He really hates the idea of needles and states that he’s not ready to give himself a “shot” every day...

American College of Clinical Endocrinologists says...
- Metformin
  - 0 markers of inflammation (hs-CRP, TNF-α)
  - 0 markers of impaired endothelial function (VWF, sCAMs, fPA, PAI-1)
  - 0 LDL-C, 0 HDL-C

Outcomes
- When compared to placebo:
  - Decreases MI’s (slightly...) 
  - Also DM-related events and all-cause mortality
- When compared to other active drugs — No difference???
Metformin—What’s going on?

- Decreased chronic/vascular inflammation?
- Glucose lowering effects?
- Preserved/improved cardiac function?

GLP-1 receptor agonists (GLP-1 RA)

Markers
- ↓ weight, BP, and lipids
- ↑ LVEF and exercise tolerance in those with cardiac insufficiency
- ↓ PAI-1, hs-CRP, BNP

Outcomes
- Decrease CVD and CVD-related hospitalizations (???)

GLP-1 RAs—What’s going on?

- Improved metabolic parameters?
- Decreased chronic/vascular inflammation?

SGLT-2 inhibitors (SGLT-2i)

Markers
- Decrease weight
- Decrease BP
- Increase HDL

Outcomes
- No change in CV events
- “Signal” for increased stroke risk in the first 30 days of therapy (??)

SGLT-2i’s—What’s going on?

- Effects on metabolic parameters a function of diuresis?
  - Not enough to change CV outcomes...

DPP-4 inhibitors (DPP-4i)

Markers
- ↓ total cholesterol (small) and post-prandial lipids
- ↓ markers of chronic inflammation (CRP, IL-6, IL-18)
- ↑ vascular function (FMD, platelet aggregation)

Outcomes
- No difference in CV events or mortality
- ↑ new-onset and hospitalizations for heart failure
DPP-4i’s—What’s going on?
- Improvements in CV risk markers didn’t come to fruition…
- Only theories on relationship with HF…
  - BNP? VIP? Other substances?

AGi’s—What’s going on?
- No effect on markers of chronic inflammation or vascular function (other than cIMT)
- CV benefits may be a function of degree of POST-PRANDIAL glucose lowering…

Alpha-glucosidase inhibitors (AGi)
- Reduced HTN
- Reduced cIMT(?)
- Decreased MI and total CV events

Thiazolidinediones (TZD)
- Both drugs cause fluid retention to uncover or worsen heart failure!

So what the <bleep> is going on with TZDs?
- Peroxisome proliferative activator-receptor (PPAR) effects?
- Differences in lipid profiles?
- Differences in potency of anti-inflammatory effects?

Sulfonylureas (SU)
- No change in markers of inflammation or endothelial function
- Increase CVD events and mortality
  - Tolbutamide, glyburide
  - Glipizide, glimepiride
- Esp. pronounced after AMI or angioplasty
SU’s—What’s going on?

- Blocked ischemic preconditioning…
- Independent risk factors for CVD…

Meglitinides

**Markers**
- ↓ inflammatory markers (IL-6, CRP, adiponectin)
- ↓ markers of impaired endothelial function (PAI-1, sCAMs, vWF)
- ↓ LDL, trigs
- ↓ cIMT

**Outcomes**
- No evidence of any effect on clinical outcomes…

Meglitinides—What’s going on?

- ???

Let’s talk about INSULIN…

- Initially, linked to POOR outcomes
  - Why???
- Now, either NEUTRAL or POSITIVE outcomes.

So what about J.G.? What can be added to his therapy? Why?

- GLP-1 agonist?
- SGLT-2 inhibitor?
- DPP-4 inhibitor?
- Alpha-glucosidase inhibitor?
- Thiazolidinedione?
- Sulfonylurea?
- Meglitinide?
- Insulin?

TAKE-HOME POINTS—If you have a patient with DM and high CVD risk…

- Consider a higher A1c goal (7.5-8%)
  - Correlates to an AVERAGE glucose of 170mg/dL
- Stick with metformin as 1st-line therapy.
- Avoid OLDER sulfonylureas & rosiglitazone.
- Dose insulin appropriately, but avoid hypoglycemia.
**References**


17. GLP-1 agonists


23. US FDA Endocrinologic and Metabolic Drugs Advisory Committee. Fda briefing document. NDA202293:
documents/AdvisoryCommittee/UCM378076.pdf

QUESTIONS? COMMENTS?

THANK YOU!!!!

**QUESTIONS? COMMENTS?**

THANK YOU!!!!
References

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