The Diabetes Download: Diabetes Update 2017

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Objectives

Pharmacist Objectives:
- Explain the 2016 FDA safety alerts and labeling changes for diabetes medications
- Counsel patients on diabetic medications incorporating the information from the FDA safety alerts
- Discuss the 2017 updates to the American Diabetes Association standards of care in diabetes

Technician Objectives:
- Identify medications affected by recent FDA safety alerts
- Describe the 2016 safety alerts and labeling changes for diabetes medications
- Discuss the 2017 updates to the American Diabetes Association standards of care in diabetes

Safety Studies for Diabetes Medications

- FDA change in 2008 regarding expectation of drug studies for new diabetic medications to ensure there is no unacceptable cardiovascular risk
- Prompted by recommendations of the 2008 Endocrinologic and Metabolic Drugs Advisory Committee
- High cardiovascular risk in patients with diabetes
- Safety issues with rosiglitazone, muraglitazar
  - Intense glucose lowering in the ACCORD trial

DPP4 Inhibitors

- FDA 1st safety communication about saxagliptin and heart failure

Sitagliptin 2006
Saxagliptin 2009
Linagliptin 2011
Alogliptin 2013

And then this year...
DPP4 Inhibitors and Heart failure

4.5.2016

*FDA Drug Safety communication: FDA adds warnings about heart failure risk to labels of type 2 diabetes medicines containing saxagliptin and alogliptin*1

A tale of three studies...

<table>
<thead>
<tr>
<th>Study Name</th>
<th>n of patients</th>
<th>Study drug</th>
<th>A1C Range (%)</th>
<th>Primary Outcome (DPP4 vs placebo)</th>
<th>Hospitalization due to heart failure (DPP4 vs placebo)</th>
<th>P value</th>
<th>Comments/other results</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAVOR-TIMI 53</td>
<td>16,492</td>
<td>Saxagliptin</td>
<td>6.5 - 12</td>
<td>Non-inferior</td>
<td>288 (1.5%) vs 223 (2.8%)</td>
<td>0.007</td>
<td>Higher risk HF in history of HF, renal impairment</td>
</tr>
<tr>
<td>EXAMINE-5</td>
<td>5,380</td>
<td>Alogliptin</td>
<td>6.5 - 11</td>
<td>Non-inferior</td>
<td>106 (5.9%) vs 89 (3.3%)</td>
<td>0.22</td>
<td>Significant higher risk of hospitalization due to heart failure in patients without previous history of HF, P = 0.026</td>
</tr>
<tr>
<td>TECOS</td>
<td>14,671</td>
<td>Sitagliptin</td>
<td>6.5 - 8</td>
<td>Non-inferior</td>
<td>228 (2.1%) vs 229 (2.1%)</td>
<td>0.98</td>
<td>Excluded patients with eGFR &lt;30 ml/min per 1.73m²</td>
</tr>
</tbody>
</table>

DPP4 Inhibitors and Heart failure: Retrospective Study8

- Evaluated new users of:
  - Saxagliptin
  - Sitagliptin
  - Second generation sulfonylureas
  - Pioglitazone
  - Long acting insulin
- Follow up time <1 year
- No overall increase in incidence of hospitalization due to HF in new users of saxagliptin and sitagliptin compared to pioglitazone, sulfonylureas, or long acting insulin

DPP4 Inhibitors and Heart failure: Retrospective Study8

- Recommend cautious interpretation
- Retrospective study design
- Short follow up time
- Reinforces lack of association of sitagliptin with heart failure

But, 23 cohort studies found a positive association of sitagliptin with heart failure.12 And...

Results from the FDA Adverse Event Reporting System (FAERS)12
Results from the FDA Adverse Event Reporting System (FAERS)

- Two large trials ongoing, results not out yet
- CARMELINA—cardiovascular
- CAROLINA—cardiovascular and renal outcomes
- Pooled study of 19 study results and ADEs
  - Increased heart failure incidence but not clear if significant
  - Must interpret with caution since pooled data

DPP4 Inhibitors and Heart Failure: Clinical Considerations

- Conflicting evidence regarding HF risk
- Avoid DPP4 if HF and other treatment options available
- If to use DPP4, sitagliptin likely safest option
  - Careful in renal impairment
  - Still may have some HF risk
- May consider alternate option even if any risk factors for HF
- Do not recommend with very poor blood sugar control
  - Low level of A1C lowering
- Possibility that poorer control may be more associated with higher HF risk

Counseling on DPP4 Inhibitors

- Possibility of heart failure
- Patients need to contact their provider right away if:
  - Difficulty breathing when laying down
  - Edema/swelling in ankles, feet, legs, stomach
  - Unusual SOB
  - Dyspnea on exertion
- If on a renally adjusted dose, HF education may be more important
- Other possible ADEs to educate on:
  - Arthralgias
  - Pancreatitis
  - Hypoglycemia

Empagliflozin and CV Protection

- 12/2/2016
- Jardiance® (Empagliflozin) gains new FDA approval
  - To reduce cardiac death in patients with type 2 DM
- Approval based on EMPA-REG study
  - Significant improvement in various cardiovascular endpoints
    - Composite cardiovascular outcomes
    - Death from cardiovascular causes
    - Non-fatal stroke
    - Non-fatal MI
    - Hospitalization for heart failure

The New Kids on the Block

**Empa-REG Study Results**

CV benefit thought to be due to mechanisms other than just A1C lowering:
- Changes in arterial stiffness, cardiac function, and cardiac oxygen demand
- Cardiorenal effects
- Reduction in:
  - Albuminuria
  - uric acid
  - Weight
  - Visceral adiposity
  - Blood pressure
  - Improved blood sugar

**Empagliflozin and CV Protection**

- Significant safety outcomes:
  - UTI in women than placebo
  - Acute renal failure
  - Acute kidney injury
  - ADEs leading to study discontinuation
  - More than placebo
  - Genital infections in both men and women
  - Non-significant but more urosepsis

**Empagliflozin For Everyone?**

- CV benefit impressive:
  - Prevents death in 1 in 45 patients over 3 years
  - Prevents overall mortality in 1 in 39 patients

- Points to keep in mind:
  - Benefit was shown in patients:
    - with cardiovascular disease
    - in addition to optimal treatment
  - Patients without cardiovascular disease were not a part of the study
  - No significant reduction in stroke or heart attack
  - Empagliflozin isn’t cheap

- Although less than other SGLT2s, empagliflozin has side effects

**Moving Forward with Empagliflozin**
Canagliflozin and Amputations

- FDA warns of increase risk of leg and foot amputations, mostly affecting the toes, with the diabetes medicine canagliflozin.
- Investigating cardiovascular safety
- 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 was permitted to continue

European Medicine's Agency (EMA) has also started to review canagliflozin after this interim result from CANVAS.

Application to Clinical Practice

- Noteworthy possible risk but shouldn’t significantly affect prescribing
- Avoid and/or discontinue in patient with lower limb complications
- Closely monitor patients with risk factors for amputation
- Peripheral vascular disease
- Neuropathy
- Previous amputations
- Education on preventative foot care and good hydration important

Canagliflozin and Amputations

- European Medicine’s Agency (EMA) has also started to review canagliflozin after this interim result from CANVAS.
- CANVAS R trial (A study of the effects of canagliflozin on renal endpoints in adult participants with type 2 diabetes mellitus)
- Hasn’t shown same results
- Non-statistically significant difference between canagliflozin and placebo for amputations
- 16 amputations in canagliflozin group, 12 in placebo
- Estimated incidence 7/1000 compared to 5/1000
- Inagaki et al

SGLT2 and Renal Impairment

- FDA strengthens kidney warnings for diabetes medicines canagliflozin (Invokana®, Invokamet®) and dapagliflozin (Farxiga®, Xigduo XR®)

Prompted by case reports after drug approval

- Oct 2014 - Sept 2015, ~1.5 million got prescription for dapagliflozin or canagliflozin
- In 2.5 years (March 2013-Oct 2015), 101 confirmed cases of acute kidney injury (AKI) with dapagliflozin or canagliflozin use
  - 16 required hospitalization
  - 22 admitted to intensive care units
  - 4 deaths (2 cardiac-related)
  - 13 patients received dialysis
  - 3 had underlying CAD
  - 6 were also on ACEI and diuretic
  - ~50% happened within 1 month of drug start
Canagliflozin/Dapagliflozin and Renal Impairment

- Patient characteristics
  - 28-79 yo, median age 57
  - Over 50% <60 yo
  - 51 on ACEI
  - 26 diabetic
  - 6 NSAID
  - 10 previous CKD

- Change in renal function
  - Median reported increase of SCr = 1.5mg/dL
  - Median decrease in eGFR 46 ml/min/1.73m²
  - Most cases reversible but not all (76 reported discontinuation)
  - 56 reported improvement
  - 11 didn't improve (including 4 deaths)
  - 3 recovered with long-term follow-up

Canagliflozin and Renal Effects

- Generally a drop in GFR in the first 3-6 weeks of canagliflozin initiation ~2-6mL/min/1.73m² across studies
  - Trends of eGFR similar across most subsets
  - Degree of eGFR slightly higher in elderly and worsened renal function but clinical significance questionable
  - Most eGFR drops stabilize or are attenuated by 26-104 weeks
  - >30% reductions in eGFR more common in CKD patients with canagliflozin vs placebo
    - Canagliflozin 100mg - 0/332 (0.1%)
    - Canagliflozin 300mg - 0/352 (0.9%)
    - Placebo - 0/367 (0.2%)
  - >50% reduction not significantly different across groups with normal renal function and moderate renal impairment (all less than 1%)
    - Normal renal function
      - Canagliflozin 100mg - none
      - Canagliflozin 300mg - 1/332 (0.3%)
      - Placebo - 1/367 (0.2%)
    - Stage 3 CKD pts: canagliflozin 1.5% w/50% drop in SCr, 0.9% of 300, none for placebo
      - Canagliflozin 100mg - 5/332 (1.5%)
      - Canagliflozin 300mg - 3/352 (0.9%)
    - No deaths noted
  - In all cases, fewer patients had significant reductions at last post-baseline assessment

Canagliflozin and eGFR

Dapagliflozin and eGFR
Decrease in eGFR Generally Reversible\textsuperscript{22}

Intern tells you he learned in class SGLT2s may be renal protective...

SGLT2 effect on the Kidney\textsuperscript{22}

Empagliflozin and Renal Protection

- EMPAREG OUTCOME study\textsuperscript{24}
  - Empagliflozin showed renal protection
  - Less incident nephropathy (12.7% vs 18.8%, \( P < 0.001 \))
  - Most independent components significantly less in empagliflozin group as well (shown as empagliflozin vs placebo)
  - Progression to macroalbuminuria (11.2% vs 16.2%), RRR 38%
  - Doubling of serum creatinine (1.5 vs 2.6%), RRR 44%
  - Progression to renal replacement therapy (0.3% vs 0.6%), RRR 55%
  - Benefits seen across pre-specified subgroups and both doses
  - Less acute renal failure in empagliflozin than placebo

EMPAREG and Renal Outcomes\textsuperscript{24}
**EMPAREG and Renal Outcomes**

- **Good or Bad?**

Some studies have shown reductions in albumin to creatinine ratios with canagliflozin.

- Most favored improvement in albuminuria but not statistically significant

- Kahn et al showed dapagliflozin more likely to regress to a lower albumin excretion category

**Other SGLT2s and Albuminuria**

- Some studies have shown reductions in albumin to creatinine ratios with canagliflozin.

- Most favored improvement in albuminuria but not statistically significant

- Kahn et al showed dapagliflozin more likely to regress to a lower albumin excretion category

**SGLT2 and Renal Impairment**

- Concern for risk of acute renal impairment

- Canagliflozin

- Dapagliflozin

- Empagliflozin

- Important time for monitoring is in the first 4-6 weeks

- Use caution in:
  - HF
  - Poor hydration status
  - Fluid loss
  - Acute GI illness
  - Other meds which can potentially cause renal impairment
  - Normotensive patients

**SGLT2 Counseling**

- Preventative foot care

- Monitoring for cuts/soreness

- Seek attention if any open wounds, discoloration, or new onset pain or tenderness

- Importance of good hydration

- Seek attention to loss of water or salt loss

- Use caution with diuretics, HF

- Signs of renal impairment

- Decreased urine production

- Swelling in legs or feet

- Importance of lab follow up
SGLT2 Counseling

- Risk of genital infection/UTI, corresponding symptoms
- Risk of hypotension
  - Seek attention if develops dizziness
  - Recommend blood pressure monitoring while on tx
- DKA
  - Counsel symptoms and risk
  - Highly importance of seeking IMMEDIATE attention if has symptoms
- Highlight for empagliflozin only
  - CV benefit in patients with CV disease
  - Renal protection

Metformin and Renal Dosing

- Previous labeling:
  - Contraindicated
    - Men with SCr > 1.5 mg/dL
    - Women with SCr > 1.4 mg/dL
  - Intended to prevent use in patients with any type of renal impairment for safety
  - Main concern was lactic acidosis risk

- Intended to prevent use in patients with any type of renal impairment for safety

- CV benefit in patients with CV disease
- Renal protection

Metformin and Renal Dosing

- 4/8/2016
- FDA determined after evaluating the current evidence
- eGFR should be used for determination of renal function
- Safe use of metformin in mild renal impairment
- Labeling modified
- New guidance has been used prior to FDA label change

<table>
<thead>
<tr>
<th>eGFR Level</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>&gt;90 ml/min per 1.73m²</td>
<td>Continue metformin</td>
</tr>
<tr>
<td>60 - 90 ml/min per 1.73m²</td>
<td>Assess the benefits and risks of continuing treatment</td>
</tr>
<tr>
<td>45 - 59 ml/min per 1.73m²</td>
<td>Discontinue if currently taking</td>
</tr>
<tr>
<td>≤45 ml/min per 1.73m²</td>
<td>New guidance has been used prior to FDA label change</td>
</tr>
</tbody>
</table>

FDA Changes to Metformin Labeling

- Before starting, check creatinine/determine eGFR
- Check eGFR
  - At least annually
  - More often in high risk populations
- Iodinated contrast imaging
  - Stop prior in below patients
    - eGFR ≤ 30 ml/min per 1.73m²
    - Liver disease
    - Alcoholism
  - Recheck eGFR 48 hours after
    - Resume when renal function stable

Metformin and Renal Dosing: Clinical Application

- Possible implications
  - Decrease in medical costs
  - Delayed need for insulin
  - May decrease weight in some patients from net decrease in insulin requirements
- Other factors beyond renal impairment must be considered prior to metformin initiation/continuation
TZDs and Bladder Cancer

- 12/12/2016
- "Updated FDA review concludes that use of type 2 diabetes medicine pioglitazone may be linked to an increased risk of bladder cancer."
- Risk already included in current labeling
- FDA approved label updates to include new data that has been reviewed
- Animal models have shown bladder tumors with pioglitazone exposure
- Higher reporting of bladder cancer to FDA Adverse Event Reporting System for pioglitazone than other diabetes treatment
- Human studies produced conflicting evidence

Is Pioglitazone Associated with a Higher Risk of Bladder cancer?

**Studies with significant risk**
- Levels at 5 year interim analysis
  - Only in patients on pio >2 years
    - Hazard ratio 1.4 (CI 1.03-2.0)
- Tuccori et al
  - Higher risk overall (HR1.63, 1.22-2.19)
  - Higher risk >2 years use (HR1.78, 1.21-2.64)
  - Dose response relation (p <0.01 for trend)
- Fereciano meta-analysis:
  - Overall risk (HR 1.23, CI 1.09-1.39)

**Studies with no significant risk**
- Lewis et al 10 Year follow up study
  - No significant difference overall, based on duration OR dose
  - PROactive trial
    - 14/2605 in pio vs 6/2633 in placebo
    - P = 0.069
    - P = 0.309 when cases in first year were excluded
  - PROactive 10 year follow up
    - 21 (1.2%) in pio vs 14 (0.8%) in placebo, (RR 0.65, CI 0.33-1.28)

What Do We Make of All This?

- Incidence of bladder cancer in pio and placebo is low
- Causality cannot be confirmed
- RCT study suggests no significant risk
- Risk in observational studies may be in part related to unequal distribution of risk factors in pioglitazone vs placebo
- Bladder cancer risk cannot be excluded
- Until more definitive conclusions, must use caution and take heed of this possible risk
- Not recommended in patients with bladder cancer or a history of bladder cancer
- Recommend caution in family history of bladder cancer or other risk factors for bladder cancer
- Risk/benefit must be weighed on a patient specific basis

Counseling

- Advise patients to seek attention if:
  - Blood in urine
  - New or worsening urge to urinate
  - Pain when urinating
- Other counseling points
  - Edema
  - SOB
  - Weight gain

Reminders from 2016 FDA Alerts

- With new medication benefits come new risks
- Diabetes treatment selection is highly patient specific
- Education is very important for patient safety

American Diabetes Association 2017 Updates

- Recommend periodic B12 monitoring in patients on metformin
- Figure 8.1 updated to acknowledge high insulin costs
American Diabetes Association 2017 Updates

Update to Figure 8.2

New Table 8.2

New Table 8.3

American Diabetes Association 2017 Updates

- Specific recommendations added for treatment of neuropathic pain
  - Pregabalin
  - Duloxetine
- Inpatient diabetes management
  - Basal + correctional scale ok in non-critically ill patients but not correctional scale alone

Recommendation to consider empagliflozin or liraglutide in patients with history of cardiovascular disease to reduce risk of mortality

Section on new biosimilar insulins

Any of following recommended for hypertension treatment if no albuminuria
  - ACEIs
  - ARBs
  - Thiazide diuretics
  - Dihydropyridine calcium channel blockers

Specific recommendations added for treatment of neuropathic pain

Inpatient diabetes management

Basal + correctional scale ok in non-critically ill patients but not correctional scale alone
American Diabetes Association 2017 Updates

- Non pharmacologic updates (included but not limited to)
  - Advise interruption of sitting every 30 minutes
  - Possibly discuss unifying DM classification scheme based on beta cell function
  - Blood pressure targets for pregnant women changed:
    - 120-160/80-105
    - Optimize maternal health without inducing tremors
  - Recommendations added surrounding incorporating social considerations into treatment decisions

Pharmacists’ Roles in Diabetes

Potential Areas of Pharmacist Impact in Diabetes

**Medication-related**
- Proper
- Timing
- Administration
- Storage
- Hypoglycemia
- Sign and symptoms
- Treatment
- Optimizing drug treatment
- Safety
- Efficacy
- Cost

**Lifestyle/Other**
- Risks of poor DM control
- Eating behaviors
- Exercise
- Lab monitoring
- Blood sugar testing
- Glucose/A1c targets
- Lancets
- Social support

“**It’s the little details that are vital. Little things make big things happen.**”

~ John Wooden

Questions?

References


Yoda photo - DARTSHARD - http://www.mims.co.uk/sglt2


References