2016 Update on Diabetes Mellitus

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Objectives

- Discuss changes to the American Diabetes Association Standard of Medical Care in Diabetes – 2016
- Compare and contrast ADA and AACE/ACE guidelines for the management of Type 2 Diabetes Mellitus
- List the therapeutic goals for patients with diabetes mellitus
- Discuss updates in treatment options for patients with Type 2 Diabetes Mellitus
Terminology change

In alignment with the American Diabetes Association’s (ADA’s) position that diabetes does not define people,

**The word “diabetic” will no longer be used when referring to individuals with diabetes in the “Standards of Medical Care in Diabetes.”**

The ADA will continue to use the term “diabetic” as an adjective for complications related to diabetes (e.g., diabetic retinopathy).
Strategies for Improving Care: Vulnerable Populations - Food insecurity

- 14% in US (1:7 people)
- Must consider when addressing hypo- and hyperglycemia and medication adherence
- Type 1: prefer long-acting peakless basal. may use rapid-acting analogs immediately after meals, may use strategies similar to sick day management
- Type 2: maybe shorter acting sulfonylurea like glipizide immediately before a meal. Maybe focus on drugs with less risk of hypoglycemia.
- Homelessness
  - Issues with storage and securing medications and supplies
  - Literacy and numeracy issues

Strategies for Improving Care: Vulnerable Populations

- Health Disparities
  - Community health workers, peers, lay leaders
  - Promote strong social support
  - Integration of culture, language, religion, literacy skills
Strategies for Improving Care: Vulnerable Populations – Cognitive Dysfunction and Mental Illness

- Hyperglycemia and severe hypoglycemia are associated with cognitive decline
- Cognitive decline is more rapid with higher A1c and longer duration of diabetes
- “Tight glucose control does not improve cognitive function in individuals with poor cognitive function or severe hypoglycemia, glycemic therapy should be tailored to avoid significant hypoglycemia.”
- There is insufficient evidence for dietary interventions
- Statins should be used in high CVD risk regardless of cognitive function
- 1.7 fold increase in severe mental disorders in DM
- Treatment of depression may improve short-term glycemic control
- “If a second-generation antipsychotic medication is prescribed, changes in weight, glycemic control, and cholesterol levels should be carefully monitored and the treatment regimen should be reassessed.”

Strategies for Improving Care: Vulnerable Populations - HIV

- Screen for diabetes and prediabetes with a fasting glucose level before starting antiretroviral therapy and 3 months after starting or changing
  - Normal initial screen: fasting glucose each year
  - Prediabetes: monitor every 3–6 months
  - Protease inhibitors and nucleoside reverse transcriptase inhibitors can increase DM risk
    - PI: 5% new-onset DM, 15% prediabetes, associated with insulin resistance, possible apoptosis of beta cells
    - NRTIs: affect insulin resistance through affect on fat distribution
    - Can possibly consider drug substitution
Revised screening recommendations for Type 2 Diabetes Mellitus

Screen **all adults regardless of weight** starting at **age 45 years**

All overweight or obese adults with ≥ 1 additional risk factors

- Physical inactivity
- 1st degree relative with DM
- High-risk race/ethnicity
- Women who delivered a baby weighing > 9 lb or were diagnosed with GDM
- Hypertension (≥140/90 mmHg or on therapy for hypertension)
- HDL-C < 35 mg/dl and/or triglycerides > 250 mg/dL
- Women with PCOS
- A1C ≥ 5.7%, IGT, or IFG on previous testing
- Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
- History of CVD

Classification and Diagnosis of Diabetes: Monogenic Diabetes

- Uncommon: < 5% of DM
- Early onset: usually before age 25 yrs
- Dx should be considered in children with:
  - Dx of DM in first 6 mo of life,
  - Strong family hx of atypical DM
  - Mild FBG w/o T2DM features
  - Negative autoantibodies w/o features of T2DM features

- Recommendations:
  - All children diagnosed with DM in the first 6 months of life should have genetic testing
  - Maturity-onset diabetes of the young should be considered in mild stable fasting hyperglycemia and multiple family members with atypical diabetes
  - Consider specialist referral for atypical diabetes presentation
Obesity Management for the Treatment of Type 2 Diabetes

- This new section, which incorporates prior recommendations related to bariatric surgery, has new recommendations related to the comprehensive assessment of weight in diabetes and to the treatment of overweight/obesity with behavior modification and pharmacotherapy.

<table>
<thead>
<tr>
<th>Table 6.1—Treatment for overweight and obesity in type 2 diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI category (kg/m²)</td>
</tr>
<tr>
<td>Diet, physical activity, and behavioral therapy</td>
</tr>
<tr>
<td>Pharmacotherapy</td>
</tr>
<tr>
<td>Bariatric surgery</td>
</tr>
</tbody>
</table>

+Treatment may be indicated for selected motivated patients. *Cutoff points for Asian American individuals.

Cardiovascular Disease and Risk Management

- “Atherosclerotic cardiovascular disease” (ASCVD) has replaced the former term “cardiovascular disease” (CVD), as ASCVD is a more specific term.
- In older adults pharmacologic treatment of BP to < 130/70 is not recommended
- Consider aspirin therapy in men and women aged ≥ 50 years.
- ASA not recommended in low risk individuals < 50 yo and clinical judgement recommended in age intermediate risk (5-10%)?
- Ezetimibe + moderate-intensity statin for patients with ACS and LDL > 50.
- New table of statin intensities
Microvascular Complications and Foot Care

- “Nephropathy” was changed to “diabetic kidney disease”

- Guidance added:
  - Refer for **renal replacement treatment** when GFR < 30 mL/min/1.73 m²
  - Refer to physicians experienced in the care of diabetic kidney disease for uncertainty about the etiology of kidney disease, difficult management issues, and rapidly progressing kidney disease.
  - Intravitreal injections of antivascular endothelial growth factor are indicated for center-involved diabetic macular edema, which occurs beneath the foveal center and may threaten reading vision.

Older Adults

- The scope of this section is more comprehensive, capturing the nuances of diabetes care in the older adult population.
  - Neurocognitive function
  - Hypoglycemia
  - Treatment goals
  - Care in skilled nursing facilities/nursing homes
  - End-of-life considerations
Children and Adolescents

- The scope of this section is more comprehensive, capturing the nuances of diabetes care in the pediatric population. This includes new recommendations addressing diabetes self-management education and support, psychosocial issues, and treatment guidelines for type 2 diabetes in youth.
- The recommendation to obtain a fasting lipid profile in children starting at age 2 years has been changed to age 10 years, based on a scientific statement on type 1 diabetes and cardiovascular disease from the American Heart Association and the ADA.


Management of Diabetes in Pregnancy

- The scope of this section is more comprehensive, providing new recommendations on pregestational diabetes, gestational diabetes mellitus, and general principles for diabetes management in pregnancy.
- A new recommendation was added to highlight the importance of discussing family planning and effective contraception with women with preexisting diabetes.
- A1C recommendations for pregnant women with diabetes were changed, from a recommendation of < 6% (42 mmol/mol) to a target of 6–6.5% (42–48 mmol/mol), although depending on hypoglycemia risk the target may be tightened or relaxed.
- Glyburide in gestational diabetes mellitus was deemphasized based on new data suggesting that it may be inferior to insulin and metformin.

Diabetes Care in the Hospital

- This section was revised to focus solely on diabetes care in the hospital setting. This comprehensive section addresses hospital care delivery standards, more detailed information on glycemic targets and antihyperglycemic agents, standards for special situations, and transitions from the acute care setting.
- This section also includes a new table on basal and bolus dosing recommendations for continuous enteral, bolus enteral, and parenteral feedings.


Other additions

- Foundations of Care and Comprehensive Medical Evaluation
  - Section 3 “Initial Evaluation and Diabetes Management Planning” and Section 4 “Foundations of Care: Education, Nutrition, Physical Activity, Smoking Cessation, Psychosocial Care, and Immunization” from the 2015 Standards were combined into one section for 2016 to reflect the importance of integrating medical evaluation, patient engagement, and ongoing care that highlight the importance of lifestyle and behavioral modification. The nutrition and vaccination recommendations were streamlined to focus on those aspects of care most important and most relevant to people with diabetes.
- Prevention of Delay of Type 2 Diabetes
  - Recommendation added to leverage new technology to help with lifestyle modifications
- Glycemic Targets
  - Recommendation added to continue access to CGM and pumps after 65 yo
- Diabetes Advocacy
  - “Diabetes Care in the School Setting: A Position Statement of the American Diabetes Association” was revised in 2015. This position statement was previously called “Diabetes Care in the School and Day Care Setting.” The ADA intentionally separated these two populations because of the significant differences in diabetes care between the two cohorts.
### Difference in the ADA and AACE Guidelines

#### Pre-Diabetes: Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>AACE</th>
<th>ADA</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG / IFG</td>
<td>100 – 125 mg/dl</td>
<td>100-125 mg/dl</td>
</tr>
<tr>
<td>2-hr OGTT / IGT</td>
<td>140 – 199 mg/dl</td>
<td>140 – 199 mg/dl</td>
</tr>
<tr>
<td>A1c</td>
<td>N/A</td>
<td>5.7% - 6.4%</td>
</tr>
</tbody>
</table>
| Metabolic Syndrome* (≥ 3 criteria) | Abdominal Obesity*  
Waist Circumference 
Men ≥40 inches  
Women ≥ 35 inches  
Triglycerides ≥150 mg/dL  
HDL cholesterol  
Men < 40 mg/dL  
Women < 50 mg/dL  
Blood pressure ≥130/85 mmHg  
Fasting glucose ≥100 mg/dL | N/A |

*Population and country specific definitions

[Link to ADA guidelines](http://care.diabetesjournals.org/site/misc/2016-Standards-of-Care.pdf)
[Link to AACE guidelines](www.aace.com/publications/algorithm)
Pre-Diabetes: Treatment

AACE
- Lifestyle Modifications
- CVD Risk Factors
- Anti-Obesity Therapies
  - Lifestyle, medication, or surgery
- Antihyperglycemic therapy
  - Metformin or acarbose
  - TZD or GLP-1

ADA
- Lifestyle modifications
  - 7% weight loss
  - Moderate physical activity
    - 150 min/week
- Antihyperglycemic therapy
  - Metformin
    - BMI > 35
    - Age < 60 yo
    - Hx GDM
  - More severe hyperglycemia
- Assess CV Risk Factors

www.aace.com/publications/algorithm

Angela is a 44 yo obese WF with T2DM. What is Angela’s fasting BG goal according to the ADA

A. 70 – 130
B. 80 – 130
C. 90 – 130
D. 90 – 150
Angela is a 44 yo obese WF with T2DM. What is Angela’s fasting BG goal according to the ADA

A. 70 – 130
B. **80 – 130**
C. 90 – 130
D. 90 – 150

Comparison of Glycemic Goals

<table>
<thead>
<tr>
<th></th>
<th>AACE</th>
<th>ADA</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1c</td>
<td>≤ 6.5% - general population</td>
<td>&lt; 7% - general population</td>
</tr>
<tr>
<td>Fasting and pre-meal</td>
<td>&lt; 110</td>
<td><strong>80</strong> -130</td>
</tr>
<tr>
<td>Post-Prandial</td>
<td>&lt; 180</td>
<td>&lt; 180</td>
</tr>
</tbody>
</table>

www.aace.com/publications/algorithm
Bronzie is a 75 y.o. male with T2DM, HTN, HLD. He had an MI and CABG five years ago and a stroke last year which left him with mild cognitive impairment.

What should be Bronzie’s fasting BG goal per the ADA?

A. 80 – 130  
B. 90 – 130  
C. 90 – 150  
D. 100 - 180
Medication Recommendations

**AACE**
- Clearly stratified by initial A1c
  - < 7.5% vs ≥ 7.5% vs > 9% w/o sx and > 9% with sx
  - Includes GLP-1, SGLT-2, and DDP-4 as viable monotherapy options
  - Medication recommendations given in order of preference
  - Includes alpha-glucosidase inhibitors, colesevalam, and bromocriptine

**ADA**
- Stratifies by initial A1c in the fine print below the algorithm
  - ≥ 9%
  - BG 300-350 mg/dL or A1c ≥ 10-12%
  - After metformin no other medication class is given preference for use.
  - Lists SU, TZD, DPP-4, SGT-2, GLP-1 and basal insulin as equally valid choices
Medication Recommendation - ADA

A1c ≥ 9%

BG ≥ 300-350 mg/dl and/or
A1c ≥ 10-12%
Insulin Therapy

**AACE**
- Initial dose determined by A1c level
- Titration % every 2-3 days based on fasting BG ranges
- Intensification options
  - GLP-1, SGLT-2, or DPP-4
  - Prandial insulin
- Basal +1 and full basal bolus provided with 50/50 dosing

**ADA**
- Initial dose 10 units or 0.1-0.2 units/kg
- Titration 1-2 times weekly
  - 10-15% or 2-4 units – basal
  - 10-15% or 1-2 units
- Hypoglycemia: decrease 4 units or 10-20%
- Intensification options
  - Prandial insulin or GLP-1
- Basal + 1, Pre-mixed BID, or basal-bolus

Dyslipidemia Management: ADA

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>&lt; 40 years</th>
<th>40-75 years</th>
<th>&gt; 75 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ASCVD risk factors</td>
<td>No statin</td>
<td>Moderate intensity statin</td>
<td>Moderate intensity Statin</td>
</tr>
<tr>
<td>ASCVD risk factors</td>
<td>Moderate or high intensity statin</td>
<td><strong>High intensity statin</strong></td>
<td>Moderate or high intensity statin</td>
</tr>
<tr>
<td>Overt ASCVD</td>
<td>High intensity statin</td>
<td>None</td>
<td>Moderate or high High</td>
</tr>
<tr>
<td>ACS and LDL-C &gt; 50 mg/dL in patients who cannot tolerate high-dose statins</td>
<td>No recommendation given</td>
<td>Moderate intensity statin + ezetimibe</td>
<td>Moderate intensity statin + ezetimibe</td>
</tr>
</tbody>
</table>

*Statins should be used in conjunction with TLC. ASCVD Risk Factors: LDL ≥ 100 mg/dl, high BP, smoking and overweight or obesity
### Dyslipidemia Management: AACE

<table>
<thead>
<tr>
<th>Risk Levels</th>
<th>Moderate</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DM with no additional risk factors and/or age &lt; 40</td>
<td>DM + ASCVD Risk Factors (HTN, family history, low HDL, smoking) or overt CVD</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>&lt; 100</td>
<td>&lt; 70</td>
</tr>
<tr>
<td>Non-HDL (mg/dl)</td>
<td>&lt; 130</td>
<td>&lt; 100</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>&lt; 150</td>
<td>&lt; 150</td>
</tr>
<tr>
<td>TC/HDL</td>
<td>&lt; 3.5</td>
<td>&lt; 3.0</td>
</tr>
</tbody>
</table>

If not able to reach goal on initial statin therapy may consider intensification of statin and/or addition of non-statin medication.

### 2013 ACC/AHA Blood Cholesterol Guidelines

#### High-Intensity Statin Therapy

- Daily dose lowers LDL–C on average, by approximately ≥50%

#### Moderate-Intensity Statin Therapy

- Daily dose lowers LDL–C on average, by approximately 30% to <50%

<table>
<thead>
<tr>
<th>High-Intensity Statin Therapy</th>
<th>Moderate-Intensity Statin Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atorvastatin (40†)–80 mg</strong></td>
<td><strong>A torvastatin 10 (20) mg</strong></td>
</tr>
<tr>
<td><strong>Rosuvastatin 20 (40) mg</strong></td>
<td><strong>Rosuvastatin (5) 10 mg</strong></td>
</tr>
<tr>
<td><strong>Simvastatin 20–40 mg†</strong></td>
<td><strong>Simvastatin 20–40 mg†</strong></td>
</tr>
<tr>
<td><strong>Pravastatin 40 (80) mg</strong></td>
<td><strong>Pravastatin 40 (80) mg</strong></td>
</tr>
<tr>
<td><strong>Lovastatin 40 mg</strong></td>
<td><strong>Lovastatin 40 mg</strong></td>
</tr>
<tr>
<td><strong>Fluvastatin XL 80 mg</strong></td>
<td><strong>Fluvastatin XL 80 mg</strong></td>
</tr>
<tr>
<td><strong>Fluvastatin 40 mg bid</strong></td>
<td><strong>Fluvastatin 40 mg bid</strong></td>
</tr>
<tr>
<td><strong>Pitavastatin 2–4 mg</strong></td>
<td><strong>Pitavastatin 2–4 mg</strong></td>
</tr>
</tbody>
</table>

### Hypertension

<table>
<thead>
<tr>
<th>AACE1</th>
<th>ADA2</th>
<th>JNC83</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Goal BP</strong></td>
<td><strong>Goal BP</strong></td>
<td><strong>Goal BP</strong></td>
</tr>
<tr>
<td>&lt;130/80</td>
<td>&lt; 140/90</td>
<td>&lt; 140/90</td>
</tr>
<tr>
<td><strong>Initial Treatment</strong></td>
<td><strong>&lt; 130/80</strong></td>
<td>≥18 years start tx at</td>
</tr>
<tr>
<td>&gt; 130/80: ACEI or ARB monotherapy</td>
<td>&lt; 140/90</td>
<td>SBP ≥ 140mmHg or DBP ≥ 90mmHg</td>
</tr>
<tr>
<td>&gt; 150/90: ACEI or ARB + (thiazide, CCB, or BB)</td>
<td>appropriate in some patients</td>
<td>Target &lt; 140/90mmHg,</td>
</tr>
<tr>
<td><strong>Add-on therapy:</strong></td>
<td><strong>Initial therapy</strong></td>
<td><strong>Initial therapy</strong></td>
</tr>
<tr>
<td>Add from above categories</td>
<td>ACEI or ARB monotherapy</td>
<td>Nonblack population:</td>
</tr>
<tr>
<td>5th line: alpha blockers, central agents, vasodilators, spironolactone</td>
<td>Add-on Therapy</td>
<td>thiazide, CCB,</td>
</tr>
<tr>
<td>Reassess q2-3 months until at goal</td>
<td>amlodipine, HCTZ or chlorthalidone</td>
<td>ACEI, or ARB</td>
</tr>
</tbody>
</table>

Add-on therapy: Add from above categories 5th line: alpha blockers, central agents, vasodilators, spironolactone

Reassess q2-3 months until at goal

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1. www.aace.com/publications/algorithm

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### New Medications for the Treatment of Type 2 DM
Millie is 60 yo female with T2DM who recently had labs drawn. Her SCr was 1.6 and his eGFR was 42. Her T2DM has been well controlled on metformin 1000mg BID for several years. Which of the following is consistent with FDA recommendations?

A. Stop metformin for SCr > 1.4
B. Stop metformin for SCr > 1.5
C. Stop metformin for eGFR < 45
D. Continue metformin for eGFR > 30
Metformin – FDA labeling changes

- FDA is requiring manufacturers to revise the labeling of metformin-containing drugs.
- Safe for use in patients with mild to moderate renal impairment.
- The measure of kidney function has changed from Scr to eGFR.
- Before starting metformin, obtain the patient’s eGFR.
- Metformin is contraindicated in patients with an eGFR below 30 mL/minute/1.73 m².
- Starting metformin in patients with an eGFR between 30-45 mL/minute/1.73 m² is not recommended.
- Obtain an eGFR at least annually in all patients taking metformin. In patients at increased risk for the development of renal impairment such as the elderly, assess more frequently.

http://www.fda.gov/Drugs/DrugSafety/ucm493244.htm

Metformin – FDA labeling changes

- In patients taking metformin whose eGFR later falls below 45 mL/minute/1.73 m², assess the benefits and risks of continuing treatment.
- Discontinue metformin if the patient’s eGFR later falls below 30 mL/minute/1.73 m².

- Discontinue metformin at the time of or before an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/minute/1.73 m²; in patients with a history of liver disease, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast.
- Re-evaluate eGFR 48 hours after the imaging procedure; restart metformin if renal function is stable.

http://www.fda.gov/Drugs/DrugSafety/ucm493244.htm
**Afrezza**

- Initial US Approval in 2014
- Manufactured by MannKind
- Marketed in partnership with Sanofi until January 2015
- Future Plans?
  - Lower price
  - Break into foreign markets
  - Improve third party coverage


**Tresiba (insulin degludec)**

- Manufactured by NovoNordisk
  - US Approval in 2015
  - Available as U-100 and U-200 FlexTouch pens
    - Stable at room temperature for 56 days
- “Ultra-Long” Acting
  - Onset 0.5-1.5 hours
  - Peak 10-12 hours
  - Duration 42 hours
- Given once daily with rapid-acting insulin given at other meals if needed

**Coming Soon?**

**Dual I**
- insulin degludec/liraglutide vs insulin degludec vs liraglutide
- Adults with T2DM, insulin-naïve on metformin +/- pioglitazone
- Non-inferior to insulin degludec alone and superior to liraglutide alone for change in HbA1c from baseline

**DUAL II**
- insulin degludec/liraglutide vs insulin degludec alone (max 50 units)
- Adults with type 2 diabetes previously on basal insulin + metformin
- Insulin degludec/liraglutide was superior to insulin degludec alone for change in HbA1c from baseline

[Source: www.nice.org.uk](https://www.nice.org.uk/advice/ermm40/chapter/key-points-from-the-evidence)

**Also Coming Soon?**

- **Lixisenatide (Lyxumia)**
  - Approved in Europe in 2013
  - FDA decision expected July 2016
  - ELIXA: lixisenatide vs standard care in T2DM w/ recent ACS
    - Non-inferior to placebo, no sig difference in HF hospitalizations

- **Insulin glargine/lixisenatide**
  - FDA decision expected August 2016
  - Endocrinologic and Metabolic Drugs Advisory Committee voted 12 to 2 (one non-vote) to recommend approval


[Source: www.nies-senpa.us](http://www.nies-senpa.us/2015-09-29-Sanofi-New-Drug-Application-for-Lixisenatide-Accepted-for-Review-by-FDA)
All premixed insulins are cloudy

- True
- False
Ryzodeg 70/30
(Premixed insulin degludec / insulin aspart)

- Manufactured by NovoNordisk
- US Approval in 2015
- Available as U-100 FlexTouch pens
  - Stable at room temperature for **28 days**
- CLEAR APPEARANCE
- “Ultra-Long” Acting
  - Onset 14 minutes
  - Peak 72 minutes
  - Duration 42 hours (degludec component)

HumaLOG (U-200)

- Manufactured by Eli Lilly
- Available only in KwikPen
- Bioequivalent to U-100 Humalog preparation
  - Provides 600 units per pen vs 300 units in the U-100 pen
HumuLIN U-500 Kwikpen

- FDA approval in 2015
- Launched in 2016
- Stable at room temperature up to 28 days
- Dials in 5 units increment
- Unique aqua colored pen body

http://www.humulin.com/hcp-home.aspx

Which of the following statements about DPP-4 inhibitors is TRUE?

A. They decrease the risk for heart failure
B. They are associated with ketoacidosis
C. They are associated with joint pain
D. They improve cardiovascular outcomes
Which of the following statements about DPP-4 inhibitors is TRUE?

A. They decrease the risk for heart failure
B. They are associated with ketoacidosis
C. They are associated with joint pain
D. They improve cardiovascular outcomes

DPP-4 inhibitors - Update

- Joint pain - 08-28-2015
  - FDA warns that DPP-4 inhibitors may cause severe joint pain that can be severe or disabling
  - Symptoms can begin anywhere from 1 day to years after start of therapy
- Heart Failure Risk – 04-05-2016
  - Warning added to labels of Onglyza (saxagliptin) and Nesina (alogliptin)
  - May increase the risk of heart failure, particularly in patients who already have heart or kidney disease

http://www.fda.gov/Drugs/DrugSafety/ucm459579.htm
DPP-4 inhibitors – Januvia (sitagliptin) Update

- Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes (TECOS)
  - Randomized, double-blind RCT
  - Sitagliptin vs placebo both added to existing therapy
  - Primary endpoint: Composite of death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina
  - Median follow-up of 3 years
- Results
  - Sitagliptin was non-inferior to placebo for the primary endpoint
  - Rates of hospitalization for heart failure were not different between the groups


DPP-4 inhibitors - Tradjenta (linagliptin) Update

- Cardiovascular Outcome Study of linagliptin Versus Glimepiride in Patients with Type 2 Diabetes (CAROLINA)
  - Ongoing
- Cardiovascular safety of linagliptin in type 2 diabetes: a comprehensive patient-level pooled analysis of prospectively adjudicated cardiovascular events
  - Published 2015
  - Not associated with increase in CV risk
  - Not able to draw conclusions about risk of heart failure

Which of the following statements is true regarding SGLT-2 inhibitors?
(Select all that apply)

A. Empagliflozin is associated with a decrease in CV events
B. Canagliflozin may be associated with an increase in lower extremity amputations
C. Dapagliflozin is associated with bladder tumors
D. They are all associated with a possible risk of ketoacidosis

Which of the following statements is true regarding SGLT-2 inhibitors?
(Select all that apply)

A. Empagliflozin is associated with a decrease in CV events
B. Canagliflozin may be associated with an increase in lower extremity amputations
C. Dapagliflozin is associated with an increased risk of bladder tumors
D. All are associated with a possible risk of ketoacidosis
SGLT-2 Inhibitors - Update

05-15-2015
- FDA warns of increased risk for ketoacidosis

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG)
- Published in New England Journal of Medicine in November 2015
- Randomized, double-blind, placebo-controlled
- Empagliflozin 10mg vs 25mg vs placebo
- Primary outcome: composite of death from cardiovascular causes, nonfatal myocardial infarction (excluding silent myocardial infarction), or nonfatal stroke
- Mean duration for treatment 2.6 years, median observation time 3.1 years
- Results: Primary outcome occurred 10.5% empagliflozin vs 12.1% placebo
  - HR 0.86 CI 0.74-0.99; p < 0.001


SGLT-2 Inhibitors - Update

FDA Drug Safety Communication
- In the ongoing Canagliflozin Cardiovascular Assessment Study (CANVAS) clinical trial, the trial’s independent data monitoring committee (IDMC) identified an increased risk of leg and foot amputations. The amputations occurred about twice as often in patients treated with canagliflozin compared to patients treated with placebo, which is an inactive treatment. An interim analysis showed that over one year’s time, the risks of amputation for patients in the trial were equivalent to:
  - 7 out of every 1,000 patients treated with 100 mg daily of canagliflozin
  - 5 out of every 1,000 patients treated with 300 mg daily of canagliflozin
  - 3 out of every 1,000 patients treated with placebo
- Patients in the CANVAS trial have been followed for an average of 4.5 years to date. The IDMC has recommended, based on an overall assessment, that the CANVAS trial continue.

http://www.fda.gov/Drugs/DrugSafety/ucm500965.htm
Additional References


Questions?

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