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Focus on Diabetes – Part 2: Risks and Benefits of Diabetes Treatment in Older Adults

- by Allen Lefkovitz

Within the American Diabetes Association's (ADA) "Standards of Medical Care in Diabetes – 2018" (hereafter referred to as simply the Standards), the risks and benefits of more common treatment options for diabetes are highlighted.

This focus article will overview the relative risks and when appropriate, the potential benefits of commonly used medications to treat type 2 diabetes (DM2) in regard to:

- hypoglycemia
- weight changes
- cardiovascular disease
- kidney disease

Hypoglycemia

The need to avoid hypoglycemia in older adults is repeatedly emphasized in the 2018 Standards. The Standards include a recommendation that "in older adults at increased risk of hypoglycemia, medication classes with low risk of hypoglycemia are preferred." As such, an understanding of which medications carry the greatest risk of hypoglycemia is essential.

Higher Risk of Hypoglycemia	Lower Risk of Hypoglycemia
Insulins (e.g., Regular, glargine)	AG Inhibitors (e.g., acarbose)
Meglitinides (e.g., repaglinide)	DPP-4 Inhibitors (e.g., sitagliptin)
Pramlintide (Symlin)	GLP1-agonists [e.g., Trulicity (dulaglutide)]
Sulfonylureas (e.g., glipizide, glyburide)	Metformin
	SGLT2 Inhibitors [e.g., Farxiga (dapagliflozin)]
	Thiazolidinediones (e.g., pioglitazone)

AG = alpha-glucosidase; DPP-4 = dipeptidyl peptidase; GLP-1 = glucagon-like peptide 1; SGLT2 = sodium-glucose co-transporter 2

When used in combination, any of the above agents can increase the risk of developing hypoglycemia.

Weight Change

Achieving and maintaining a healthy body weight is commonly a cornerstone of managing DM2, thus it is important to consider how different antidiabetic medications impact weight. Agents that are weight neutral or associated with a modest decrease in weight may provide additional benefit.

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Weight Loss	Weight Neutral	Weight Gain
GLP-1 agonists	AG Inhibitors	Insulins
Pramlintide (Symlin)	DPP-4 Inhibitors	Meglitinides
SGLT2 Inhibitors	Metformin*	Sulfonylureas
		Thiazolidinediones

AG = alpha-glucosidase; DPP-4 = dipeptidyl peptidase; GLP-1 = glucagon-like peptide 1; SGLT2 = sodium-glucose co-transporter 2
* Potential for modest weight loss is possible with metformin

Cardiovascular Disease

According to the ADA, cardiovascular disease, "defined as coronary heart disease, cerebrovascular disease, or peripheral arterial disease presumed to be of atherosclerotic origin – is the leading cause of morbidity and mortality for individuals with diabetes and is the largest contributor to the direct and indirect costs of diabetes." An estimated 68% of older adults with DM2 die from heart disease. Since 2008, the FDA has required manufacturers to conduct trials to determine whether or not new treatments for DM2 "result in an unacceptable increase in cardiovascular risk."

Beyond conventional treatments of heart disease (e.g., controlling blood pressure and cholesterol), the Standards suggest that for those with DM2 and established cardiovascular disease, metformin should be used in addition to lifestyle management (e.g., diet and exercise). After metformin, the Standards state consideration should be given to initiating antidiabetic medications that have been "proven to reduce major adverse cardiovascular events and cardiovascular mortality." Currently, only three drugs have such established labeling:

- empagliflozin-containing products (i.e., Jardiance, Glyxambi, Synjardy, Synjardy XR)
- canagliflozin-containing products (i.e., Invokana, Invokamet, Invokamet XR)
- liraglutide-containing products (i.e., Victoza, Xultophy)

In contrast to benefits of select agents, it is also important to recognize that some antidiabetic medications may pose potential risks to those with DM2 and heart failure (HF). Thiazolidinediones (i.e., pioglitazone and rosiglitazone) have been associated with increased risk of HF and therefore have a boxed warning stating they should be avoided in individuals with symptomatic HF.

In 2016 the FDA added a warning to address the risk of HF, particularly in individuals with history of HF or kidney disease, to the following products:

- saxagliptin-containing (i.e., Onglyza and Kombiglyze XR)
- alogliptin-containing medications (i.e., Nesina, Kazano, Oseni)

This warning addresses the increased risk of HF, particularly in individuals with history of HF or kidney disease.

Prescribers should take an individual's risk of cardiovascular disease and heart failure into account when treating DM2 and those responsible for their care should closely monitor each individual for signs of cardiovascular disease (e.g., chest pain, edema, shortness of breath).

Kidney Disease

According to the ADA, diabetic kidney disease (aka chronic kidney disease attributed to diabetes) occurs in 40% of patients with diabetes (type 1 or 2), and is the leading cause of end stage kidney disease requiring dialysis or kidney transplantation. While other treatments are considered as neutral, the Standards again list three medications as having benefit in slowing the progression of diabetic kidney disease:

- empagliflozin-containing products (i.e., Jardiance, Glyxambi, Synjardy, Synjardy XR)
- canagliflozin-containing products (i.e., Invokana, Invokamet, Invokamet XR)
- liraglutide-containing products (i.e., Victoza, Xultophy)

While considered neutral overall, it should be noted that metformin, a first-line treatment for most individuals with DM2, should be used with caution in those with kidney disease as those with renal impairment are at increased risk of the life-threatening complication of lactic acidosis. Routine monitoring of kidney function is necessary for those receiving metformin-containing products and use is contraindicated in those with severe kidney disease (e.g., eGFR < 30 mL/min/1.73 m^2).

Boxed Warning Removed from Inhaled Corticosteroids/Long-acting Beta Agonist Combinations

- By Costadina Costianis and Allen Lefkovitz

The use of long-acting beta agonists (LABA) is associated with an increased risk of asthma-related death. However, the BOXED WARNING regarding asthma-related death while receiving inhaled corticosteroid (ICS) and LABA combination products was recently removed by the Food and Drug Administration (FDA). Four trials were conducted to evaluate serious asthma outcomes (e.g., asthma-related death, intubation, hospitalization) with ICS/LABA use. Results showed that the combined use of a LABA with an ICS over 6 months does not significantly increase the risk of serious asthma outcomes compared to an ICS alone. Additionally, ICS/LABA combination products were more effective in decreasing asthma attacks than ICS alone.

The use of a LABA alone to treat asthma is associated with an increased risk of asthma-related death, and this is reflected in a BOXED WARNING on relevant products. Similarly, the BOXED WARNING also remains on long-acting muscarinic agonist (LAMA) and LABA combination products. Individual and combination products containing a LABA and whether or not the product continues to have a boxed warning are outlined in the table below.

Brand Name	Asthma-related death BOXED WARNING	ICS	LABA	LAMA
Brovana	Yes		arformoterol	
Foradil, Perforomist	Yes		formoterol	
Arcapta	Yes		indacaterol	
Striverdi	Yes		olodaterol	
Serevent	Yes		salmeterol	
Advair	No	fluticasone	salmeterol	
Breo	No	fluticasone	vilanterol	
Dulera	No	mometasone	formoterol	
Symbicort	No	budesonide	formoterol	
Anoro	Yes		vilanterol	umeclidinium
Utibron	Yes		indacaterol	glycopyrrolate
Bevespi	Yes		formoterol	glycopyrrolate
Stiolto	Yes		olodaterol	tiotropium
Trelegy	Yes*	fluticasone	vilanterol	umeclidinium

* The manufacturer is working with the FDA to remove the boxed warning, but at the time of this article, the FDA-approved labeling for this product continues to carry the boxed warning about asthma-related death.

Additional information is available at: https://www.fda.gov/Drugs/DrugSafety/ucm589587.htm

NEW Generic Medications

- by Allen Lefkovitz

Generic Name	Brand Name	Date Generic Available
Trientine 250 mg Capsule	Syprine® Capsule	2/12/18
Efavirenz 600 mg Tablet	Sustiva® Tablet	2/2/18
Tobramycin 300 mg/5 mL Inhalation Solution	Kitabis™ Inhalation Solution	1/19/18

NEW Drug

Firvanq™ (vancomycin hydrochloride) Oral Solution

- by Dave Pregizer

Brand Name (Generic Name)	**Firvanq [FIR vank] (vancomycin) [van koe MYE sin]**
How Supplied	Powder for oral solution and grape-flavored diluent to produce 25 mg/mL or 50 mg/mL vancomycin concentrations
Therapeutic Class	Glycopeptide antibacterial
Approved Indication	Adults and pediatric patients less than 18 years of age for the treatment of: *Clostridium difficile*-associated diarrhea, Enterocolitis caused by *Staphylococcus aureus* (including methicillin-resistant strains).
Usual Dosing	*Clostridium difficile*-associated diarrhea: Adults (18 years of age and older): 125 mg orally 4 times daily for 10 days. *Staphylococcal* enterocolitis: Adults (18 years of age and older): 500 mg to 2 g orally in 3 or 4 divided daily doses for 7 to 10 days.
Select Drug Interactions	No drug interaction studies have been conducted using orally administered vancomycin hydrochloride products
Most Common Side Effects	Nausea, abdominal pain, and hypokalemia
Miscellaneous	Orally administered vancomycin hydrochloride is not effective for treatment of other types of infections. Nephrotoxicity has occurred following oral vancomycin therapy and can occur either during or after completion of therapy. The risk is increased in geriatric patients.
Website	http://cutispharma.com/firvanq/

New Drug continued on next page

Admelog® (insulin lispro) Injection

Brand Name (Generic Name)	**Admelog [ad mah log] (insulin lispro) [IN soo lin LYE sproe]**
How Supplied	100 units/mL (U-100) insulin lispro available as: 10 mL multiple-dose vials and 3 mL single patient use prefilled pens
Therapeutic Class	Rapid-acting human insulin analog
Approved Indication	To improve glycemic control in adults and pediatric patients 3 years and older with type 1 diabetes mellitus and adults with type 2 diabetes mellitus.
Usual Dosing	Subcutaneous injection: Administer subcutaneous injection within 15 minutes before a meal or immediately after a meal. Intravenous Infusion: Administer intravenous infusion ONLY after dilution and under medical supervision. The dosage must be individualized.
Select Drug Interactions	Adjustment of insulin dosage may be needed with drugs affecting glucose metabolism. Signs and symptoms of hypoglycemia may be reduced or absent with antiadrenergic drugs (e.g., beta-blockers, clonidine, guanethidine, reserpine).
Most Common Side Effects	Hypoglycemia, allergic reactions, injection site reactions, lipodystrophy, pruritus, and rash
Miscellaneous	Do not use during episodes of hypoglycemia.
Website	https://www.admelogpro.com/

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