

Type 2 Diabetes: An Evidence Based Pharmacotherapy Update

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Faculty Disclosure

- I do not speak for or consult with any pharmaceutical manufacturer.
- I am a consultant for Select Health of South Carolina and a member of the Regional Pharmacy and Therapeutics Committee for AmeriHealth Caritas Family of Companies.
- I am a member of the Pharmacy and Therapeutics Committee for ProCare Rx
- I am a consultant for Crystal Clear Rx

Learning Objectives

- ***Apply the pharmacological treatment of diabetes to case studies.***
- Describe the current 2019 ADA Standards of Medical Care for the Diagnosis and Management of Diabetes Mellitus and the 2018 AACE/ACE Comprehensive Type 2 Diabetes Algorithm.
- Review the data on the newer FDA approved medications for the management of patients with Type 2 diabetes.
- Discuss the appropriate use of evidence-based and cost effective therapies in the management of patients with Type 2 DM.

Diabetes and the Use of Complementary and Alternative Medicine

- In a study published in Diabetes Care June 2018, investigators examined data from the 2012 National Health Interview Survey (NHIS), which included CAM-related information from **1,475 adults age 65 and older with any type of diabetes**. Patients were assessed for type of CAM used, reason for use (treatment only, wellness only, or both treatment and wellness), and prevalence of use over the course of one year. The mean age of patients was 72.4 years and females made up 54.3% of patients.

CAM (Individual)	Prevalence of use %
Herbal therapies	62.8
Chiropractic therapy	23.9
Massage therapy	14.7
Acupuncture	10.2
Yoga	5.2

American Diabetes Association

Research Advancements >> Dramatic Drop in Diabetes-Related Complications



Heart Attack

-67.8%



Stroke

-52.7%



Amputation

-51.4%



Kidney Failure

-28.3%



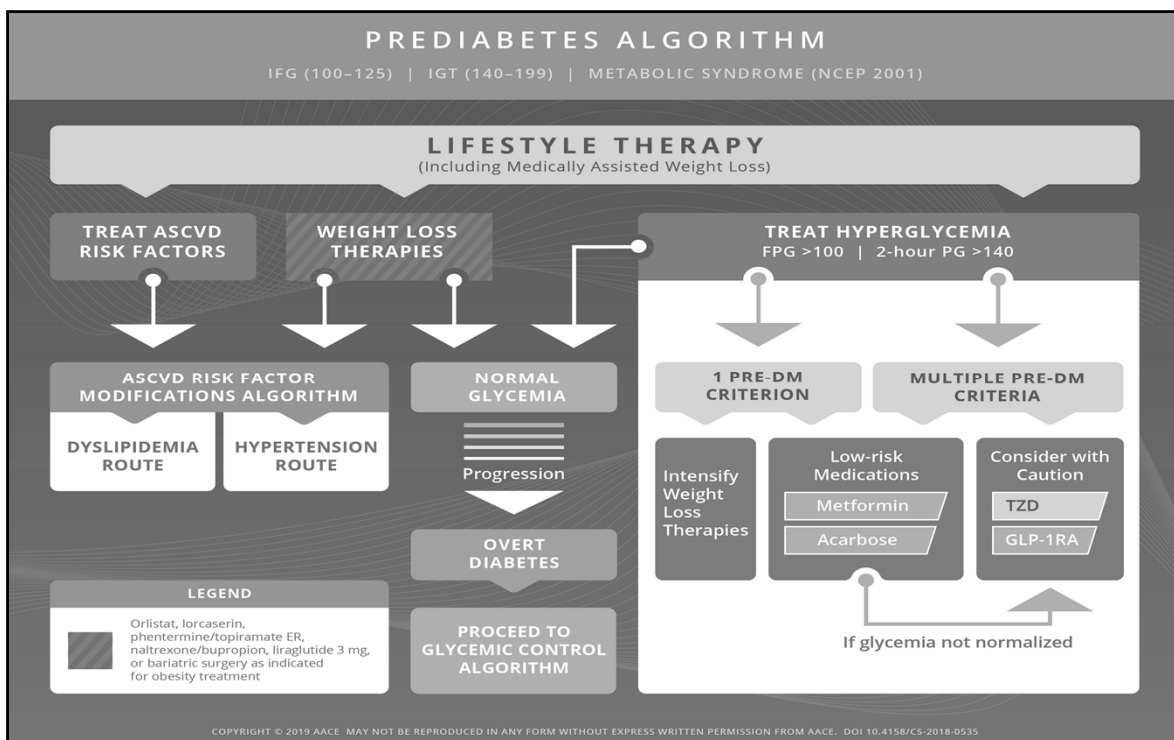
% decline between 1990 and 2010

Economic Costs of Diabetes in the U.S. in 2017

- The total estimated cost of diagnosed diabetes in 2017 is **\$327 billion**, including **\$237 billion** in direct medical costs and **\$90 billion** in reduced productivity.
- For the cost categories analyzed, care for people with diagnosed **diabetes accounts for 1 in 4 health care dollars in the U.S.**, and more than half of that expenditure is directly attributable to diabetes.
- **People with diagnosed diabetes incur average medical expenditures of ~\$16,750 per year, of which ~\$9,600 is attributed to diabetes.** People with diagnosed diabetes, on average, have medical expenditures **~2.3 times higher than what expenditures would be in the absence of diabetes.**
 - Diabetes Care 2018 Mar; dci180007

Prevention or Delay of Type 2 Diabetes 2019

- Patients with prediabetes should be referred to an intensive behavioral lifestyle intervention program modeled on the Diabetes Prevention Program to achieve and maintain 7% loss of initial body weight and increase moderate intensity physical activity (such as brisk walking) to at least 150 min/week. **A**
- Pharmacologic Intervention: **Metformin therapy for prevention of type 2 diabetes should be considered in those with prediabetes, especially for those with BMI ≥ 35 kg/m², those aged < 60 years, and women with prior gestational diabetes mellitus. **A****
- Long-term use of metformin may be associated with biochemical vitamin B12 deficiency, and periodic measurement of vitamin B12 levels should be considered in metformin-treated patients, especially in those with anemia or peripheral neuropathy. **B**
- Diabetes Care 2019 Jan; 42(Supplement 1): S29-S33.



New ADA/EASD Guidance on Diabetes

- **The treatment approach to type 2 diabetes should begin with an assessment of cardiovascular disease (CVD) status, other comorbidities, and patient preferences, according to the 2018 joint consensus statement from the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD).**
 - October 5, 2018 at the EASD annual meeting in Berlin and published in Diabetes Care and Diabetologia.

New ADA/EASD Guidance on Diabetes

- **Lifestyle modification and metformin are still considered the cornerstones of treatment**, although the panel did debate the ongoing role of metformin as the first-line pharmacologic therapy. Ultimately they opted to stick with the recommendation for now because of low cost and proven safety and efficacy.
- **Then, for patients in whom ASCVD predominates, a GLP-1 receptor agonist with proven CVD benefit or SGLT2 inhibitor with proven CVD benefit (provided the patient has adequate kidney function) are recommended, in that order.**
- **The order is reversed in patients for whom heart failure predominates: listed first is an SGLT2 inhibitor with evidence of reducing heart failure in a cardiovascular outcomes trial (if the patient has adequate kidney function), with a GLP-1 receptor agonist with proven CVD benefit as an alternative option.**

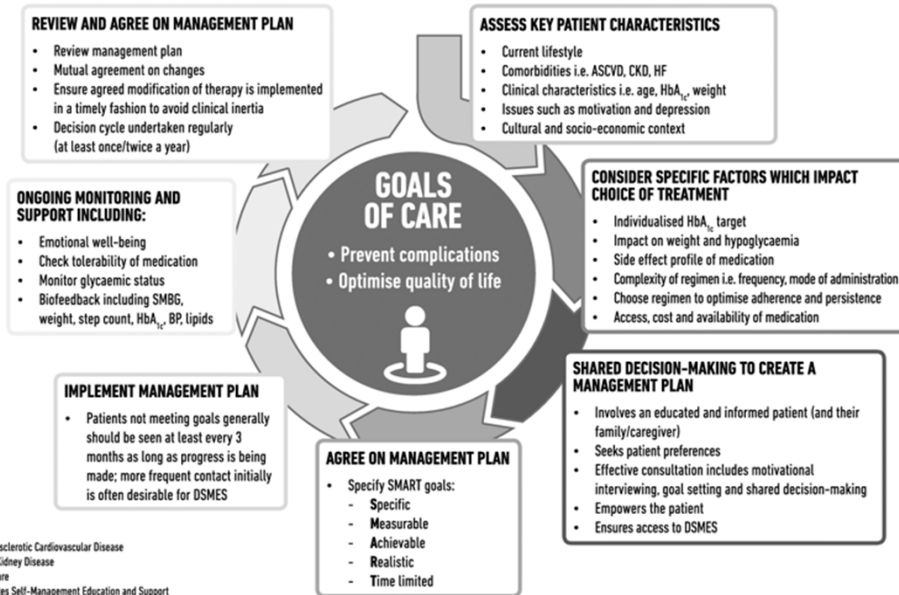
New ADA/EASD Guidance on Diabetes

- **Within the classes, preference is given to liraglutide among GLP-1 receptor agonists based on the LEADER trial, and empagliflozin among SGLT2 inhibitors based on EMPA-REG OUTCOME.**
- **For patients without ASCVD or heart failure, the next priority is to focus on the individual patient's needs and preferences for avoiding weight gain and hypoglycemia.** The document provides guidance for specific agents.

New ADA/EASD Guidance on Diabetes

- **They were careful to discuss the limitations of the evidence. Including the caveat that "beyond dual therapy is an evidence-free zone," and the emphasis that the cardiovascular benefits of SGLT2 inhibitors and GLP-1 receptor agonists have only been proven in patients with established CVD.**
- They also included a "stop light" graphics indicating which medications should be stopped or reduced once other drugs are added, noting, "This is a common question we get from primary care providers about therapy intensification."

DECISION CYCLE FOR PATIENT-CENTRED GLYCAEMIC MANAGEMENT IN TYPE 2 DIABETES



CHOOSING GLUCOSE-LOWERING MEDICATION IN THOSE WITH ESTABLISHED ATHEROSCLEROTIC CARDIOVASCULAR DISEASE (ASCVD) OR CHRONIC KIDNEY DISEASE (CKD)



Use principles in Figure 1

TO AVOID CLINICAL INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3-6 MONTHS)

Use metformin unless contraindicated or not tolerated

If not at HbA_{1c} target:

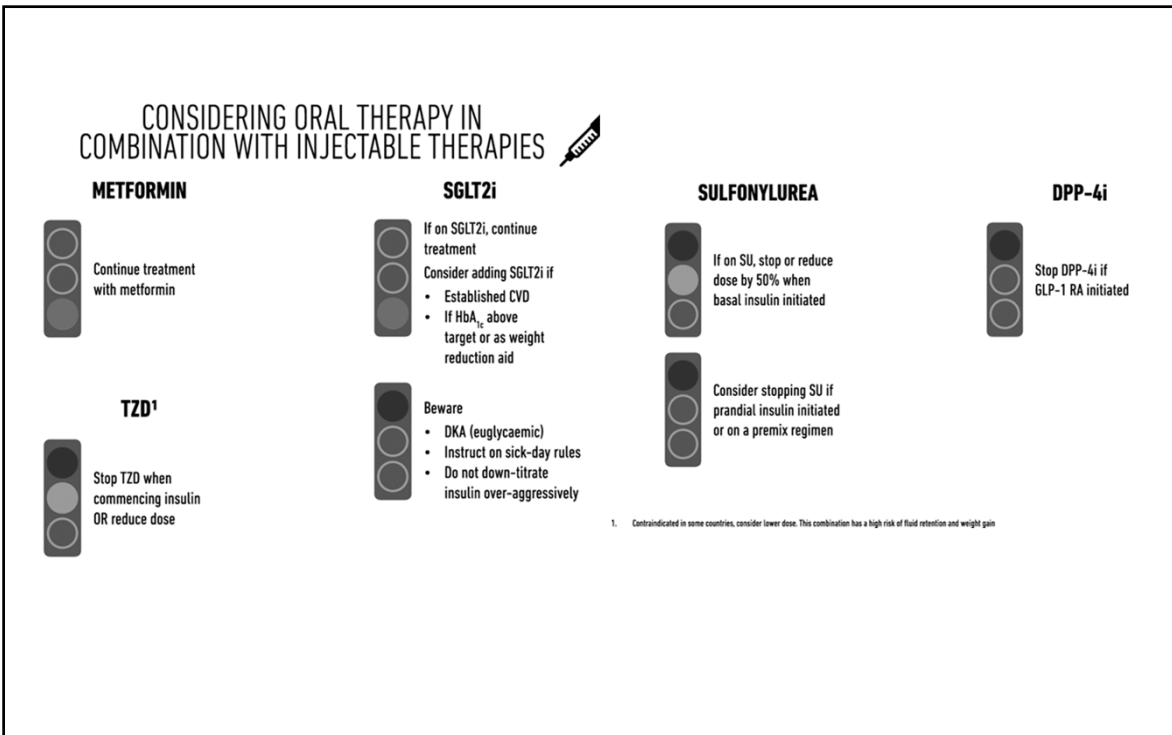
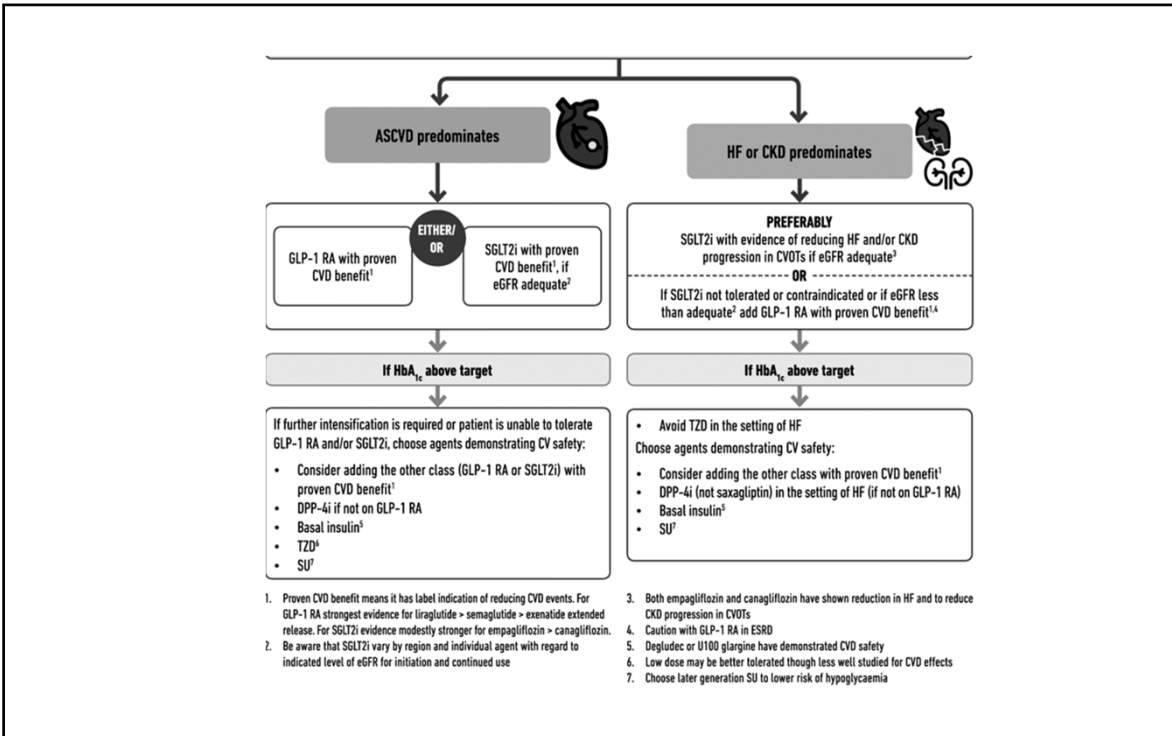
- Continue metformin unless contraindicated (remember to adjust dose/stop metformin with declining eGFR)
- Add SGLT2i or GLP-1 RA with proven cardiovascular benefit! (See below)

If at HbA_{1c} target:

- If already on dual therapy, or multiple glucose-lowering therapies and not on an SGLT2i or GLP-1 RA, consider switching to one of these agents with proven cardiovascular benefit! (See below)

OR reconsider/lower individualised target and introduce SGLT2i or GLP-1 RA

OR reassess HbA_{1c} at 3 month intervals and add SGLT2i or GLP-1 RA if HbA_{1c} goes above target



2019 ADA Standards of Medical Care in Diabetes

Pharmacologic Therapy Recommendations

- **Metformin is the preferred initial pharmacologic agent for the treatment of type 2 diabetes. A**
- **Once initiated, metformin should be continued as long as it is tolerated and not contraindicated; other agents, including insulin, should be added to metformin. A**

- Diabetes Care 2019 Jan; 42(Supplement 1): S90-S102

2019 ADA Standards of Medical Care in Diabetes

- **A patient-centered approach should be used to guide the choice of pharmacologic agents.** Considerations include comorbidities (atherosclerotic cardiovascular disease, heart failure, chronic kidney disease), hypoglycemia risk, impact on weight, cost, risk for side effects, and patient preferences. E
- **Among patients with type 2 diabetes who have established atherosclerotic cardiovascular disease, sodium–glucose cotransporter 2 inhibitors, or glucagon-like peptide 1 receptor agonists with demonstrated cardiovascular disease benefit are recommended** as part of the antihyperglycemic regimen. A

- Diabetes Care 2019 Jan; 42(Supplement 1): S90-S102

2019 ADA Standards of Medical Care in Diabetes

- **The early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when A1C levels (>10%) or blood glucose levels (≥ 300 mg/dL) are very high. E**
- **Consider initiating dual therapy in patients with newly diagnosed type 2 diabetes who have A1C $\geq 1.5\%$ above their glycemic target. E**
 - Diabetes Care 2019 Jan; 42(Supplement 1): S90-S102

2019 ADA Standards of Medical Care in Diabetes

- **Among patients with atherosclerotic cardiovascular disease at high risk of heart failure or in whom heart failure coexists, sodium–glucose cotransporter 2 inhibitors are preferred. C**
- **For patients with type 2 diabetes and chronic kidney disease, consider use of a sodium–glucose cotransporter 2 inhibitor or glucagon-like peptide 1 receptor agonist shown to reduce risk of chronic kidney disease progression, cardiovascular events, or both. C**
 - Diabetes Care 2019 Jan; 42(Supplement 1): S90-S102

2019 ADA Standards of Medical Care in Diabetes

- **In most patients who need the greater glucose-lowering effect of an injectable medication, glucagon-like peptide 1 receptor agonists are preferred to insulin. B**
- Intensification of treatment for patients with type 2 diabetes not meeting treatment goals should not be delayed. B
- The medication regimen should be reevaluated at regular intervals (every 3–6 months) and adjusted as needed to incorporate new patient factors. E
 - Diabetes Care 2019 Jan; 42(Supplement 1): S90-S102

2019 ADA Standards of Medical Care in Diabetes

A1C Recommendations

- **A reasonable A1C goal for many nonpregnant adults is <7%. A**
- Providers might reasonably **suggest more stringent A1C goals (such as <6.5%) for selected individual patients if this can be achieved without significant hypoglycemia or other adverse effects of treatment** (i.e., polypharmacy). Appropriate patients might include those with short duration of diabetes, type 2 diabetes treated with lifestyle or metformin only, long life expectancy, or no significant cardiovascular disease. C
- **Less stringent A1C goals (such as <8% may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, or long-standing diabetes** in whom the goal is difficult to achieve despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin. B
 - Diabetes Care 2019 Jan; 42(Supplement 1): S61-S70

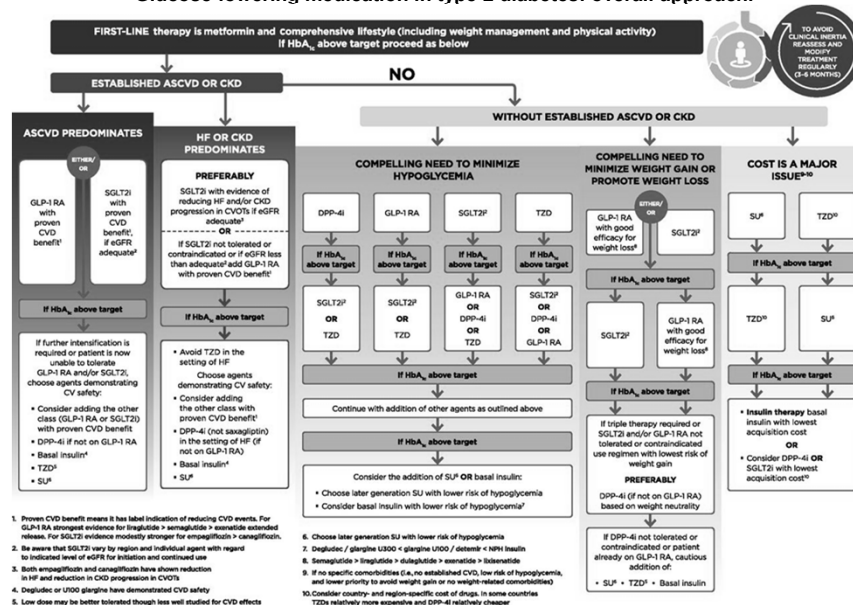
ADA and ACE Glycemic Goals

Biochemical Index	Normal	ADA 2019	AACE/ACE
		Goal*	Target
Fasting/preprandial plasma glucose (mg/dL)	<100	80–130	≤110
Postprandial plasma glucose (mg/dL)	<140	<180	≤140
Hemoglobin A _{1c} (%)	<6	<7	≤6.5

*Goals should be individualized based on: duration of diabetes; age/life expectancy; comorbid conditions; known CVD or advanced microvascular complications; hypoglycemia unawareness; and individual patient considerations. Providers might reasonably suggest more stringent A1C goals (such as <6.5%) if it can be achieved without significant hypoglycemia including patients with short duration of diabetes, type 2 diabetes treated with lifestyle or metformin only, long life expectancy, or no significant cardiovascular disease. C Less stringent A1C goals (such as <8%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions. B

American Diabetes Association. *Diabetes Care*. 2019 42 Suppl 1
AACE Comprehensive Diabetes Management Algorithm, *Endocr Pract*. 2018

Glucose-lowering medication in type 2 diabetes: overall approach.



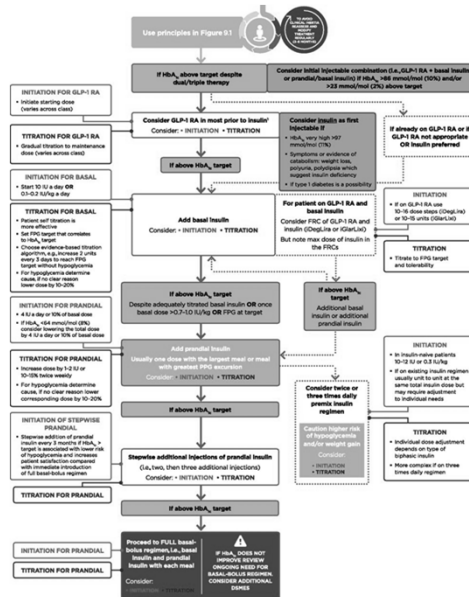
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American Diabetes Association Dia Care 2019;42:S90-S102



CW1

Intensifying to injectable therapies.



American Diabetes Association Dia Care 2019;42:S90-S102



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GLYCEMIC CONTROL ALGORITHM

INDIVIDUALIZE GOALS

A1C ≤6.5% For patients without concurrent serious illness and at low hypoglycemic risk

A1C >6.5% For patients with concurrent serious illness and at risk for hypoglycemia

LIFESTYLE THERAPY (Including Medically Assisted Weight Loss)

Entry A1C <7.5%

Entry A1C ≥7.5%

Entry A1C >9.0%

MONOTHERAPY¹

- ✓ Metformin
- ✓ GLP1-RA^{2,3}
- ✓ SGLT2i^{2,3}
- ✓ DPP4i
- ▲ TZD
- ▲ AGI
- ▲ SU/GLN

If not at goal in 3 months proceed to Dual Therapy

DUAL THERAPY¹

- ✓ GLP1-RA^{2,3}
- ✓ SGLT2i^{2,3}
- ✓ DPP4i
- ▲ TZD
- ✓ Basal Insulin
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGI
- ▲ SU/GLN

If not at goal in 3 months proceed to Triple Therapy

TRIPLE THERAPY¹

- ✓ GLP1-RA^{2,3}
- ✓ SGLT2i^{2,3}
- ▲ TZD
- ▲ Basal Insulin
- ✓ DPP4i
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGI
- ▲ SU/GLN

If not at goal in 3 months proceed to or intensify insulin therapy

SYMPTOMS

NO YES

- DUAL Therapy
- OR
- TRIPLE Therapy
- INSULIN ± Other Agents

ADD OR INTENSIFY INSULIN
Refer to Insulin Algorithm

LEGEND

- ✓ Few adverse events and/or possible benefits
- ▲ Use with caution

1 Order of medications represents a suggested hierarchy of usage; length of line reflects strength of recommendation
2 Certain GLP1-RAs and SGLT2is have shown CVD and CKD benefits—preferred in patients with those complications
3 Include one of these medications if CHD present

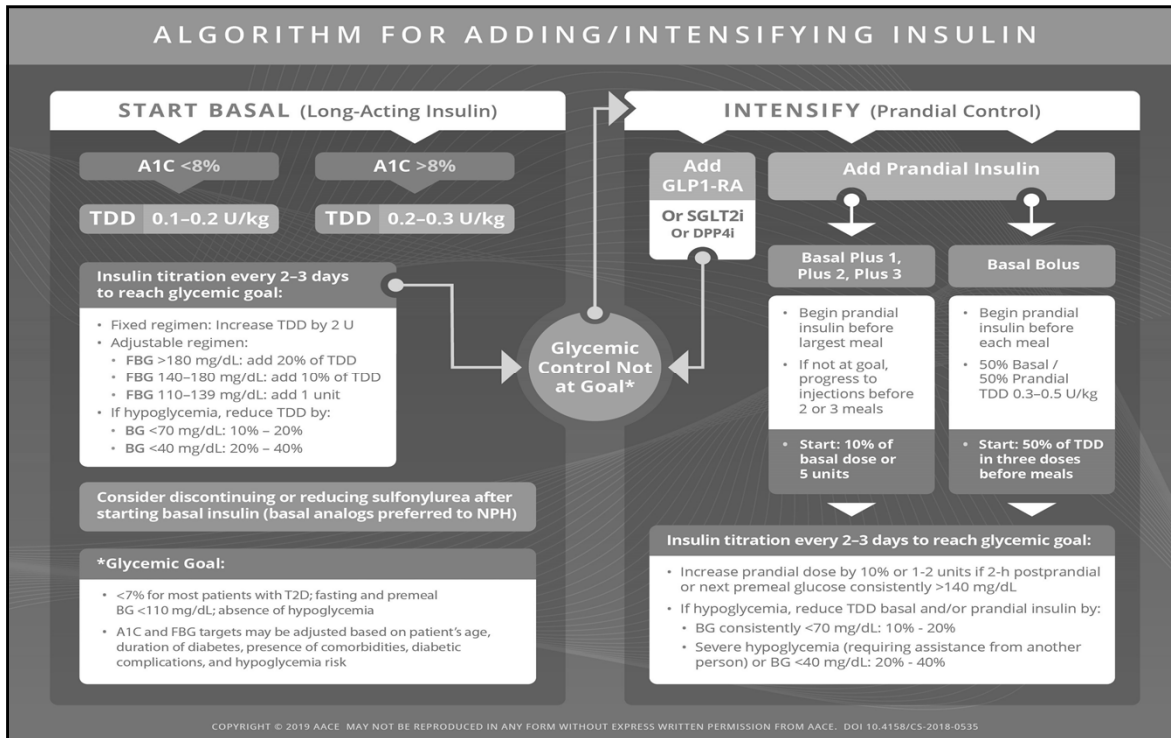
PROGRESSION OF DISEASE

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Slide 25

CW1

Charles Weart, 01/21/2019



PROFILES OF ANTIDIABETIC MEDICATIONS

	MET	GLP1-RA	SGLT2i	DPP4i	AGi	TZD (moderate dose)	SU	GLN	COLSVL	BCR-QR	INSULIN	PRAML
HYPO	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate/Severe	Mild	Neutral	Neutral	Moderate to Severe	Neutral
WEIGHT	Slight Loss	Loss	Loss	Neutral	Neutral	Gain	Gain	Gain	Neutral	Neutral	Gain	Loss
RENAL / GU	Contra-indicated if eGFR <30 mL/min/1.73 m ²	Exenatide Not Indicated CrCl <30 Possible Benefit of Liraglutide	Not Indicated for eGFR <45 mL/min/1.73 m ² Genital Mycotic Infections Possible Benefit of Empagliflozin	Dose Adjustment Necessary (Except Linagliptin) Effective in Reducing Albuminuria	Neutral	Neutral	More Hypo Risk	Neutral	Neutral	Neutral	More Hypo Risk	Neutral
GI Sx	Moderate	Moderate	Neutral	Neutral	Moderate	Neutral	Neutral	Mild	Moderate	Neutral	Moderate	
CHF	Neutral	See #1	See #2	See #3	Neutral	Moderate	Neutral	Neutral	Neutral	CHF Risk	Neutral	
CARDIAC ASCVD						May Reduce Stroke Risk	Possible ASCVD Risk	Benefit	Safe	Neutral		
BONE	Neutral	Neutral	Mild Fracture Risk	Neutral	Neutral	Moderate Fracture Risk	Neutral	Neutral	Neutral	Neutral	Neutral	
KETOACIDOSIS	Neutral	Neutral	DKA Can Occur in Various Stress Settings	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	

- Few adverse events or possible benefits
- Use with caution
- Likelihood of adverse effects

1. Liraglutide—FDA approved for prevention of MACE events.
2. Empagliflozin—FDA approved to reduce CV mortality. Canagliflozin—FDA approved to reduce MACE events.
3. Possible increased hospitalizations for heart failure with alogliptin and saxagliptin.
4. Only empagliflozin and canagliflozin show CVD and CKD benefits.
5. Liraglutide only shows CVD and CKD benefits.

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Why is Metformin First-Line Therapy?

- Do you agree?
 - Yes
 - No
 - Undecided

UK Prospective Diabetes Study Glucose Interventional Trial

Outcome at 10 years	Diet/Met	Diet/Sulf/ Insulin	Diet	RRR/ARR/NNT (Diet/Met vs. Diet)
Any DM related endpoint	28.7%	36.8%	38.9%	26.2%/10.2%/10
Diabetes related death	8.2%	10.8%	13.4%	38.8%/5.2%/19
All cause mortality	14.6%	20%	21.7%	32.7%/7.1%/14
MI	11.4%	14.6%	17.8%	36%/6.4%/16
Stroke	3.5%	6.3%	5.6%	44.4%/2.8\$/36
Micro-vascular events	7.0%	7.8%	9.2%	N/S

U

Lancet, 1998;352:854-865



**Long-term Effects of Metformin on Metabolism
and Microvascular and Macrovascular Disease
in Patients With Type 2 Diabetes Mellitus Treated with Insulin**
Arch Intern Med. 2009;169(6):616-625

- **390 patients treated with insulin in the outpatient clinics of 3 hospitals in a randomized, placebo-controlled trial with a follow-up period of 4.3 years. Either metformin hydrochloride, 850 mg, or placebo (1-3 times daily) was added to insulin therapy.**
- **The primary end point was an aggregate of microvascular and macrovascular morbidity and mortality. The secondary end points were microvascular and macrovascular morbidity and mortality independently.**
 - **“Hyperinsulinemia the Outcome of its Metabolic Effects (HOME)”**

**Long-term Effects of Metformin on Metabolism
and Microvascular and Macrovascular Disease
in Patients With Type 2 Diabetes Mellitus Treated with Insulin**
Arch Intern Med. 2009;169(6):616-625

Results:

- **Metformin treatment prevented weight gain (mean weight gain, -3.07 kg [range, -3.85 to -2.28 kg]; *P*.001),**
- **Improved glycemic control (mean reduction in HbA1c level, 0.4% percentage point [95% CI, 0.55-0.25]; *P*.001), despite the aim of similar glycemic control in both groups,**
- **Reduced insulin requirements (mean reduction, 19.63 IU/d [95% CI, 24.91-14.36 IU/d]; *P*.001).**
- **Metformin was not associated with an improvement in the primary end point.**
- **It was, however, associated with an improvement in the secondary, macrovascular end point (hazard ratio, 0.61 (95% CI, 0.40-0.94; *P*=.02), which was partly explained by the difference in weight.**
- **The number needed to treat to prevent 1 macrovascular end point was 16.1 (95% CI, 9.2-66.6).**
- **These sustained beneficial effects support the policy to continue metformin treatment after the introduction of insulin in any patient with DM2, unless contraindicated.**

FDA Updates Metformin Dosing Information 4-8-2016

- 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, renal function should be assessed more frequently.
- 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/downloads/Drugs/DrugSafety/UCM494140.pdf>

Metformin Pricing?

- Glucophage AB 500 mg/60: \$68.00; 850 mg \$115.00; 1000 mg \$136.00
- **Generic Glucophage AB 500 mg/60 \$0.00-12.00; 850 mg and 1000 mg \$0.00-12.00**
- Glucophage XR AB1 500 mg/60 \$70.00; 750 mg \$100.00
- **Generic Glucophage XR AB1 500 mg/60 \$4-12.00; 750 mg \$10-20.00**
- **Glumetza AB3 500 mg/60 \$3,250.00; 1000 mg/60 \$6,800-7,200.00 (Santarus)**
- **Generic Glumetza AB3 500 mg/60 \$750 - 1500.00; 1000 mg/60 \$1,500.00-5,512.00 (Lupin, Sun and Activis)**
- **Fortamet AB2 500 and 1000 mg/60 \$2,100.00 (Andrx)**
- **Generic Fortamet AB2 1000 mg/60 \$400.00-\$775.00 (Lupin and Mylan)**
 - GoodRx.com 1-4-2018

Sulfonylureas as second line drugs in type 2 diabetes and the risk of cardiovascular and hypoglycaemic events: population based cohort study

- Among 77,138 metformin initiators, 25,699 added or switched to sulfonylureas during the study period. **During a mean follow-up of 1.1 years, sulfonylureas were associated with an increased risk of myocardial infarction (incidence rate 7.8 v 6.2 per 1000 person years, hazard ratio 1.26, 95% confidence interval 1.01 to 1.56), all cause mortality (27.3 v 21.5, 1.28, 1.15 to 1.44), and severe hypoglycaemia (5.5 v 0.7, 7.60, 4.64 to 12.44) compared with continuing metformin monotherapy.**

– BMJ 2018;362:k2693

Sulfonylureas as second line drugs in type 2 diabetes and the risk of cardiovascular and hypoglycaemic events: population based cohort study

- **At 1 year, sulfonylurea use, compared with metformin monotherapy, was associated with significant excess risks for myocardial infarction (2 additional MIs per 1000 person-years), all-cause death (6 additional deaths per 1000 person-years), and severe hypoglycemia (5 additional cases per 1000 person-years).**

– BMJ 2018;362:k2693

Sulfonylureas as second line drugs in type 2 diabetes and the risk of cardiovascular and hypoglycaemic events: population based cohort study

- There was a trend towards increased risks of ischaemic stroke (6.7 v 5.5, 1.24, 0.99 to 1.56) and cardiovascular death (9.4 v 8.1, 1.18, 0.98 to 1.43). Compared with adding sulfonylureas, **switching to sulfonylureas was associated with an increased risk of myocardial infarction (hazard ratio 1.51, 95% confidence interval, 1.03 to 2.24) and all cause mortality (1.23, 1.00 to 1.50)**. No differences were observed for ischaemic stroke, cardiovascular death, or severe hypoglycaemia.
 - BMJ 2018;362:k2693

GLP-1 Agonist Comparison

GLP-1 Agonist Medications Chart

Drug	Generic	Dosing Schedule	Mixing Required	Pre-injection waiting time	Dosing	Smallest Needle Size	Needles included	Use with basal insulin Yes all have data	Auto Injector
Byetta	Exenatide	BID	No	None	5mcg, 10mcg	32 gauge, 4mm needle	No	Yes	No
Bydureon Kit	Exenatide extended release	QW	Yes	None	2mg	23-gauge, 8mm needle	Yes	No Currently studies are evaluating	No
Bydureon Pen	Exenatide extended release	QW	Yes	None	2mg	23-gauge, 8mm needle	Yes	No Currently studies are evaluating	No
Tanzeum Discontinued	Albiglutide	QW	Yes	Yes 15-30 minutes	30mg, 50mg	5mm 29-gauge thin-walled needle	Yes	Yes	No
Trulicity	Dulaglutide	QW	No	None	0.75mg, 1.5mg	Built in to device 29g	Yes part of device	No Currently studies are evaluating	Yes
Victoza	Liraglutide	QD	No	None	.6, 1.2, 1.6mg	32 gauge, 4mm needle	No	Yes	No
Adylxin	Lixisenatide	QD	No	None	10 mcg, 20 mcg	32 gauge, 4-8 mm	No	Yes	No
Ozempic	Semaglutide	QW	No	None	0.25, 0.5, 1.0 mg	32 gauge, 4mm needle	Yes	Yes	No

GLP-1 Analogues

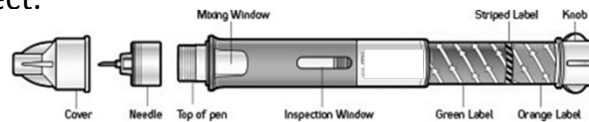
- **FDA Box Warning: (Same as for all members of the GLP-1 class of medications)**
 - **“Thyroid C-cell tumors have been observed in rodent studies with glucagon-like peptide-1 (GLP-1) receptor agonists at clinically relevant exposures. It is unknown whether Trulicity causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans.”**
 - **Patients should tell their healthcare provider if they get a lump or swelling in their neck, have hoarseness, trouble swallowing, or shortness of breath while taking a GLP-1 agonist. These may be symptoms of thyroid cancer.**
- **Additional Warnings and Precautions;**
 - **In clinical trials, acute pancreatitis has been reported in association with GLP-1 agonists. If a patient has pain in their stomach area (abdomen) that is severe and will not go away, they should stop taking the GLP-1 agonist and call their healthcare provider right away.** The pain may happen with or without vomiting. It may be felt going from the abdomen through to the back.
 - Consider other antidiabetic therapies in patients with a history of pancreatitis.

Which GLP-1 would you prescribe?

1. Exenatide – Byetta
 2. Exenatide extended release – Bydureon
 3. Liraglutide – Victoza
 4. Dulaglutide – Trulicity
 5. Lixisenatide – Adylin
 6. Semaglutide – Ozempic
- (Note: assume that all of them are covered by the patients plan)

Extended Release Exenatide (Bydureon Pen)

- **2 mg pens: remove from refrigerator 15 min prior to reconstituting.**
- Attach needle to the pen
- **Hold the pen straight up and turn the knob until the green part of the pen disappears and it clicks, then tap the pen in the palm of your hand to mix the medication, turning the pen every 10 taps (up to 80 times or more) and check for even mixing**
- Still holding the pen upright, you must now **expel any air in the pen by pushing the knob until the orange part of the pen disappears and the injection button is released.**
- Pull off the needle cover and inject.
 - Cost \$742.00 for 4 pens



New Exenatide ER Bydureon BCise Autoinjector

Exenatide extended-release BYDUREON BCise **injectable suspension**, a new formulation in an improved once-weekly, single-dose autoinjector device for adults with type-2 diabetes.

- **Store flat** in the refrigerator at 36°F to 46°F (2°C to 8°C), or Store flat at room temperature (up to 86°F) for up to 4 weeks, Do Not FREEZE,
- **Remove from refrigerator for 15 minutes prior to mixing.**
- **Mix the injection by shaking hard for at least 15 seconds, do not unlock prior to mixing** and may need to continue to shake if not in suspension. Once mixed,
- **Hold the autoinjector up straight with the orange cap toward the ceiling. Turn the knob from the Lock to the Unlock position until you hear a click.**
- **While still holding the autoinjector straight up, firmly unscrew the orange cap.**
- A green shield will pop up after the cap is removed. The green shield hides the needle. It is normal to see a few drops of liquid inside the cap.
- **Push the autoinjector against your skin. You will hear a “click” when the injection begins. • Keep holding the autoinjector against the skin for 15 seconds.** This is to make sure you get the full dose.
- After you receive your injection, you will see an orange rod in the window, and then dispose of the device in a sharps container.
- **Cost ~\$872.00/ 4 pens**



EXSCEL Trial: Exenatide ER CV Safety Trial

- **EXSCEL is a Phase IIIb/IV, double-blind, placebo-controlled, global CV outcomes trial conducted in 35 countries and enrolled more than 14,000 patients with type-2 diabetes with or without additional CV risk factors or prior CV events.** Participants were randomized to receive exenatide once-weekly 2mg or matching placebo by subcutaneous injections. **Primary composite CV endpoint** risk of MACE, a composite endpoint of **CV death, non-fatal myocardial infarction or non-fatal stroke.**
 - EXSCEL was run jointly by two academic research organizations - the Duke Clinical Research Institute (Durham, NC, US) and the University of Oxford Diabetes Trials Unit (Oxford, UK)
 - Astra/Zeneca Press Release May 23, 2017

EXSCEL Trial: Exenatide ER CV Safety Trial

- **The EXSCEL trial met its primary safety objective of non-inferiority for MACE.** These results address the US Food and Drug Administration (FDA) requirement that medicines to treat T2D are not associated with an increase in CV risk. **Fewer CV events were observed in the Bydureon arm of the trial, however, the efficacy objective of a superior reduction in MACE did not reach statistical significance.**
 - A full evaluation of the EXSCEL data is ongoing. The results will be presented at the European Association for the Study of Diabetes (EASD) annual meeting on Thursday, 14 September 2017 in Lisbon, Portugal.

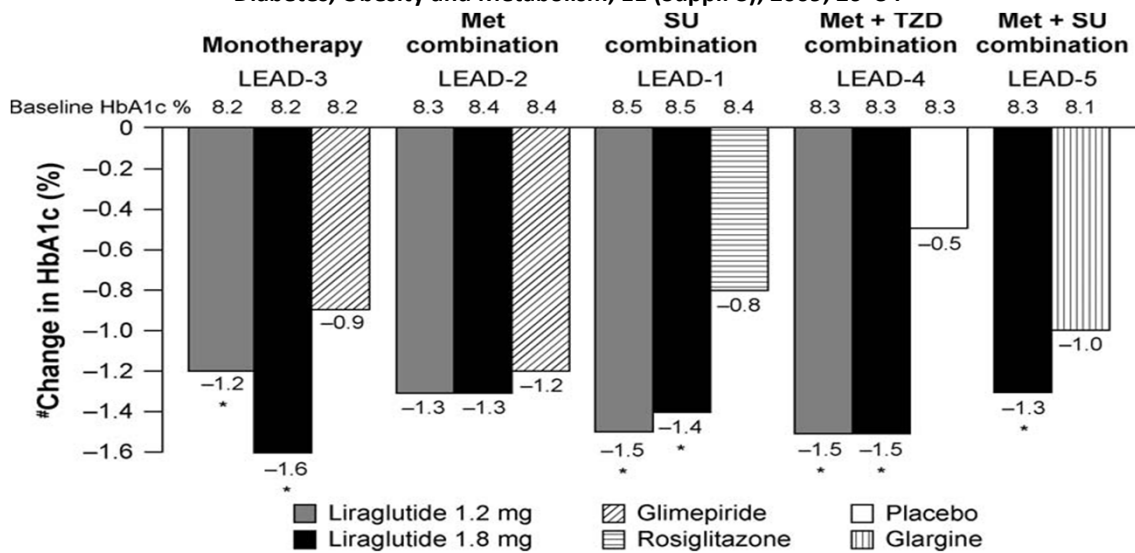
Liraglutide (Victoza)

- A human analog of the glucagon-like peptide-1 (GLP-1) with 97% amino acid sequence homology to endogenous human GLP-1.
 - T1/2 ~11-15 hrs
 - 1.2 mg dose (2 pens/mo)*
 - \$636.00 GoodRx.com
 - 1.8 mg dose (3 pens/mo)
 - \$950.00 GoodRx.com
 - Adjunct to diet and exercise for Type 2 DM but not first line and no data in combo with prandial insulin
 - *preferred dose based upon the A1c reductions?



Liraglutide with or without oral antidiabetic drug therapy in type 2 diabetes: an overview of the LEAD 1–5 studies

Diabetes, Obesity and Metabolism, 11 (Suppl. 3), 2009, 26–34



LEADER CV Safety Trial with Liraglutide

- **9340 patients with type 2 diabetes and high cardiovascular risk** to receive liraglutide or placebo. **The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.**
 - The median follow-up was 3.8 years.
- **The primary outcome** occurred in significantly fewer patients in the **liraglutide** group (608 of 4668 patients [**13.0%**]) than in the **placebo** group (694 of 4672 [**14.9%**]) (**HR 0.87**; 95% CI, 0.78 to 0.97; **P<0.001 for noninferiority**; **P = 0.01 for superiority**) **ARR 1.9%, NNT=53**
 - N Engl J Med 2016; 375:311-322

LEADER CV Safety Trial with Liraglutide

- **Death from cardio-vascular causes** in the **liraglutide** group (219 patients [**4.7%**]) than in the **placebo** group (278 [**6.0%**]) (hazard ratio, 0.78; 95% CI, 0.66 to 0.93; P = 0.007). **ARR 1.3%, NNT 77**
- The rate of **death from any cause** was lower in the **liraglutide** group (381 patients [**8.2%**]) than in the **placebo** group (447 [**9.6%**]) (HR 0.85; 95% CI, 0.74 to 0.97; P = 0.02). **ARR 1.4%, NNT=72**
 - N Engl J Med 2016; 375:311-322

LEADER CV Safety Trial with Liraglutide

- The rates of **nonfatal myocardial infarction (HR 0.88), nonfatal stroke (HR 0.89), and hospitalization for heart failure (HR 0.87)** were all **nonsignificantly lower in the liraglutide group than in the placebo group.**

– N Engl J Med 2016; 375:311-322

Liraglutide (Victoza) New Indication

- **August 25, 2017-** The US Food and Drug Administration (FDA) has approved a new indication for liraglutide (Victoza), for **reducing the risk for myocardial infarction, stroke, and cardiovascular death in adults with type 2 diabetes who have established cardiovascular disease** based upon the data from the Leader Trial.

LEADER CV Safety Trial with Liraglutide

- **Microvascular Outcomes: The incidence of a composite outcome of renal or retinal microvascular events was lower in the liraglutide group than in the placebo group (HR 0.84; 95% CI, 0.73 to 0.97; P= 0.02)**
 - The difference that was **driven by a lower rate of nephropathy events in the liraglutide group (1.5 vs. 1.9 events per 100 patient-years of observation; HR 0.78; 95% CI, 0.67 to 0.92; P = 0.003)**
 - The incidence of **retinopathy events was nonsignificantly higher in the liraglutide group than in the placebo group (0.6 vs. 0.5 events per 100 patient-years; HR 1.15; 95% CI, 0.87 to 1.52; P = 0.33).**
 - N Engl J Med 2016; 375:311-322

LEADER CV Safety Trial with Liraglutide

- **The most common adverse events leading to the discontinuation of liraglutide were gastrointestinal events. The incidence of pancreatitis was nonsignificantly lower in the liraglutide group (18 vs. 23) than in the placebo group.**
 - **Pancreatic carcinoma 13 (0.3) with liraglutide vs. 5 (0.1) with placebo p=0.06**
 - **Medullary thyroid carcinoma 0 with liraglutide vs. 1 (<0.1) with placebo p=0.32**
 - N Engl J Med 2016; 375:311-322

Dulaglutide (Trulicity)



- Available in 0.75-mg and 1.5-mg single-dose pens which do not require mixing, measuring or needle attachment and can be administered any time of day.
 - Insert states that for added comfort patients may want to take the pen out of the refrigerator for ~30 min prior to administration (DO NOT microwave or run under hot water)
- Box of 4 pens (either dose) ~\$750.00 retail (GoodRx.com)

Dulaglutide (Trulicity)

- The AWARD-6 study, once-weekly dulaglutide 1.5 mg achieved the primary endpoint of non-inferiority to once-daily liraglutide 1.8 mg, as measured by the reduction of hemoglobin A1c (HbA1c) from baseline at 26 weeks in 599 patients. (to date the only GLP-1 agonist to demonstrate non-inferiority to liraglutide to date)
 - The Lancet, Early Online Publication, 11 July 2014
doi:10.1016/S0140-6736(14)60976-4

Dulaglutide (Trulicity)

- At the primary endpoint of 26 weeks, **once-weekly dulaglutide 1.5 mg and once-daily liraglutide 1.8 mg significantly reduced HbA1c levels from baseline (-1.42 percent and -1.36 percent, respectively)**, with dulaglutide demonstrating non-inferiority compared to liraglutide. **A similar majority of patients in both treatment groups (68 percent) reached the American Diabetes Association's recommended HbA1c target of less than 7 percent.** Patients treated with once-weekly dulaglutide and once-daily liraglutide showed significant **weight reductions from baseline (-2.9 kg, -3.6 kg, respectively)**. This weight reduction was **statistically greater in the liraglutide treatment arm.**

– The Lancet, Early Online Publication, 11 July 2014 doi:10.1016/S0140-6736(14)60976-4

Dulaglutide (Trulicity)

- FDA required **Rewind (Researching cardiovascular Events with a Weekly INcretin in Diabetes) CV safety trial ~9600 patients 50 and older with Type 2 diabetes with CV disease (only 31% of patients) or older patients with 2 or more CV risk factors treated for up to 6.5 years.**
- **Primary outcome was a 3 point MACE (CV death, non-fatal MI and non-fatal stroke)**
- **The Rewind Trial was completed July 2018 and Lilly announced the top-line results on Nov 5, 2018. The results will presented at the June 2019 ADA Meeting.**

Top-Line Results of Rewind Trial with Dulaglutide

- **“Trulicity® (dulaglutide) 1.5 mg weekly significantly reduced major adverse cardiovascular events (MACE), a composite endpoint of cardiovascular (CV) death, non-fatal myocardial infarction (heart attack) or non-fatal stroke, meeting the primary efficacy objective in the precedent-setting REWIND trial. Eli Lilly and Company's (NYSE: LLY) once-weekly Trulicity is the first type 2 diabetes medicine to demonstrate superiority in the reduction of MACE events in a clinical trial that included a majority of participants who did not have established CV disease.”**
- **“REWIND had a median follow-up period of more than 5 years, the longest for a CV outcome trial in the GLP-1 receptor agonist class. In comparison, other CV outcome trials had more people with a higher baseline A1C and a greater percentage of patients who had established CV disease. Of the 9,901 REWIND participants, the mean baseline A1C was relatively lower at 7.3 percent, and only 31 percent had established CV disease.”**
 - <https://www.prnewswire.com/news-releases/trulicity-dulaglutide-demonstrates-superiority-in-reduction-of-cardiovascular-events-for-broad-range-of-people-with-type-2-diabetes-300743485.html>

Lixisenatide (Adlyxin)

- **FDA approved 7-27-2016 a once a day GLP-1 receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus**
 - **Injection: 50 mcg/mL in 3 mL in green prefilled pen (for 14 pre-set doses; 10 mcg per dose)**
 - **Injection: 100 mcg/mL in 3 mL in burgundy prefilled pen (for 14 pre-set doses; 20 mcg per dose)**
 - **Cost: ~\$660.00/ 2 pens (28 day supply)**
 - **Initiate at 10 mcg once daily for 14 days. On Day 15, increase dosage to 20 mcg once daily**
 - **Administer once daily within one hour before the first meal of the day**

Lixisenatide (Adlyxin)

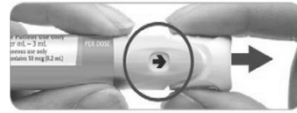
Replace the cap to protect from light



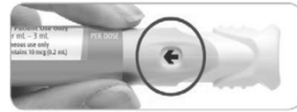
Number of doses remaining



You must activate the pen one time before the first use and not again or you will lose doses, the orange window should only appear prior to the first dose which is discarded and thereafter remain white



Pull the injection button out firmly until it stops and the arrow will now be pointing towards the needle



An insulin needle must be attached to deliver any dose including the discarded initial dose

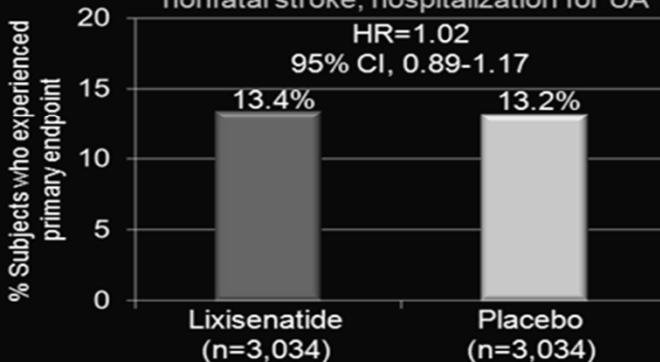


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AphoDio Healthcare
Communications

ADA 2015 Scientific Sessions

ELIXA: No Cardiovascular Risks or Benefits With Lixisenatide Vs Placebo

Primary composite endpoint:
CV death, nonfatal MI,
nonfatal stroke, hospitalization for UA



About ELIXA

First events-driven CV outcomes study to provide data for a GLP-1 receptor agonist

Randomized, double-blind, placebo-controlled trial

N=6,068 subjects with type 2 diabetes and recent ACS event

Randomization:

- Lixisenatide 10 mcg/d*
- Placebo

*Up- or down-titrated to maximum 20 mcg/d
ELIXA=Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With Lixisenatide
HR=hazard ratio; UA=unstable angina
Lixisenatide is an investigational agent, not yet FDA approved in the United States

Pfeffer MA, et al. Presented at the American Diabetes Association 75th Scientific Sessions, June 5-9, 2015, Boston, Massachusetts.

ELIXA: Cardiovascular Outcomes for Lixisenatide Vs Placebo

No increased risk for lixisenatide vs placebo for:

	Lixisenatide	Placebo
Primary composite outcome: CV death, nonfatal MI, nonfatal stroke, hospitalization for UA	13.4%	13.2%
	HR=1.02 (95% CI: 0.89-1.17)	
Primary outcome plus hospitalization for heart failure	HR=0.97 (95% CI: 0.85-1.10)	
Hospitalization for heart failure	HR=0.96 (95% CI: 0.75-1.23)	
All-cause mortality	HR=0.94 (95% CI: 0.78-1.13)	

ELIXA=Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With Lixisenatide
HR=hazard ratio

Pfeffer MA, et al. Presented at the American Diabetes Association 75th Scientific Sessions, June 5-9, 2015, Boston, Massachusetts.

Semaglutide (Ozempic) A once a week GLP-1 analog

- Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
- Available as a carton of 1 Pen (NDC 0169-4132-12) Pen delivers doses of 0.25 mg or 0.5 mg per injection 6 NovoFine® Plus needles Intended for treatment initiation at the 0.25 mg dose and maintenance treatment at the 0.5 mg dose Cost ~\$800.00 for 1 pen
- Carton of 2 Pens (NDC 0169-4136-02) Pen delivers doses of 1 mg per injection 4 NovoFine® Plus needles Intended for maintenance treatment at the 1 mg dose only
- SC solution single-patient-use pen 1.34mg/mL; delivers doses of 0.25mg, 0.5mg, or 1mg. The company has announced that the drug will cost ~\$800.00 per box of 2 pens, which it described as “at parity” with drugs in the same class.



Semaglutide (Ozempic)

Starting and maintenance dose

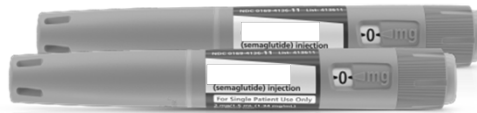
Pen delivers doses of 0.25 mg and 0.5 mg



CONTAINS
x6
NovoFine® Plus needles

Maximum maintenance dose

Pen delivers dose of 1 mg



CONTAINS
x4
NovoFine® Plus needles

Cost for 2 pens
(1 mg dose/week)
is about ~\$800.00
for 28 days or 4
doses

Semaglutide (Ozempic)

- **Dosage:** Start with a 0.25 mg subcutaneous injection once weekly for 4 weeks. The 0.25 mg dose is intended for treatment initiation and is not effective for glycemic control. After 4 weeks on the 0.25 mg dose, increase the dosage to 0.5 mg once weekly. If additional glycemic control is needed after at least 4 weeks on the 0.5 mg dose, the dosage may be increased to 1 mg once weekly. The maximum recommended dosage is 1 mg once weekly.
 - **Administer** semaglutide once weekly, on the same day each week, at any time of the day, with or without meals.
 - **Prior to first use**, semaglutide should be stored in a refrigerator between 36°F to 46°F (2°C to 8°C). Do not store in the freezer or directly adjacent to the refrigerator cooling element. Do not freeze semaglutide and do not use if it has been frozen.
 - **After first use of the semaglutide pen**, the pen can be stored for 56 days at controlled room temperature (59°F to 86°F; 15°C to 30°C) or in a refrigerator (36°F to 46°F; 2°C to 8°C).

Semaglutide CV Data – SUSTAIN 6 Trial

- Sustain 6 randomly assigned **3297 patients with type 2 diabetes who were on a standard-care regimen to receive once-weekly (GLP-1 agonist) semaglutide (0.5 mg or 1.0 mg) or placebo for 104 weeks.**
- The **primary composite outcome was the first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.**
 - At baseline, 2735 of the patients (**83.0%**) had established cardiovascular disease, chronic kidney disease, or both.
 - Mean duration of diabetes was **13.9 years** and mean HbA1c was **8.7%**. **93.5%** were taking antihypertensive medication, **76.5%** were receiving lipid-lowering drugs, and **76.3%** were receiving antithrombotic medications.
 - Drug is **investigational** and was recommended for FDA approval by the FDA Advisory Committee **10/18/2017**
 - NEJM on-line 9-16-2016

Semaglutide CV Data – SUSTAIN 6 Trial

- The **primary outcome occurred in 108 of 1648 patients (6.6%) in the semaglutide group and in 146 of 1649 patients (8.9%) in the placebo group (hazard ratio, 0.74; 95% confidence interval [CI], 0.58 to 0.95; P<0.001 for noninferiority). NNT 45**
- **Nonfatal myocardial infarction occurred in 2.9% of the patients receiving semaglutide and in 3.9% of those receiving placebo (hazard ratio, 0.74; 95% CI, 0.51 to 1.08; P=0.12); nonfatal stroke occurred in 1.6% and 2.7%, respectively (hazard ratio, 0.61; 95% CI, 0.38 to 0.99; P=0.04).**
- **Rates of death from cardiovascular causes were similar in the two groups.**
 - NEJM on-line 9-16-2016

Semaglutide CV Data – SUSTAIN 6 Trial

- From an overall baseline of 8.7%, **semaglutide significantly reduced HbA1c by 1.4% and 1.1% (for the two doses) vs 0.4% for placebo.**
 - Body weight "decreased by almost 5 kg with the 1.0-mg dose of semaglutide, from a mean of 92.1 kg," compared with weight loss of 3.6 kg, on average, in the 0.5-mg group and 0.5 to 0.7 kg in the placebo recipients.
 - Rates of **new or worsening nephropathy were lower in the semaglutide group**, but rates of **retinopathy complications (vitreous hemorrhage, blindness, or conditions requiring treatment with an intravitreal agent or photocoagulation) were significantly higher 3.2% vs. 1.7% (hazard ratio, 1.76; 95% CI, 1.11 to 2.78; P=0.02).** NEJM on-line 9-16-2016
 - This trend was **also seen in the LEADER Trial with liraglutide and in the DCCT with rapid lowering of BG with insulin)**

Semaglutide (Ozempic)

- **Given that the Sustain-6 outcomes trial was relatively brief (~2 years), with fewer patients (~3300) than a trial designed to prove CV benefits, Novo did not ask the FDA for a CV risk-reduction claim for semaglutide and the FDA did not approve a CV label claim.**
- The company does plan a more extensive follow-up study beginning next year to assess those benefits, just as it did with Victoza, which now has an FDA approval as a CV risk-reduction tool.

Semaglutide - SUSTAIN 7 Trial

- **August 16, 2017 - SUSTAIN 7 a phase 3b, 40-week, efficacy and safety trial of 0.5 mg semaglutide vs 0.75 mg dulaglutide and 1.0 mg semaglutide vs 1.5 mg dulaglutide, both once-weekly, as add-on to metformin in 1,201 people with type 2 diabetes.** The primary outcome measure was change in HbA1c from baseline after 40 weeks of treatment with semaglutide compared to dulaglutide.
- From a **mean baseline HbA1c of 8.2%**, 0.5 mg semaglutide achieved a **statistically significant and superior reduction of 1.5%** compared with a **reduction of 1.1%** with 0.75 mg dulaglutide. People treated with **1.0 mg semaglutide** experienced a **statistically significant and superior reduction of 1.8%** compared with a **reduction of 1.4%** with 1.5 mg dulaglutide.

Semaglutide - SUSTAIN 7 Trial

- 68% of people treated with 0.5 mg semaglutide compared with 52% of people treated with 0.75 mg dulaglutide reached the ADA treatment goal A1c of <7.0%, and 79% of people treated with 1.0 mg semaglutide compared to 67% with 1.5 mg dulaglutide reached the treatment goal.
- From a **mean baseline body weight of 95 kg and a BMI of 33.5 kg/m²**, people treated with 0.5 mg semaglutide experienced a **statistically significant and superior weight loss of 4.6 kg** compared to **2.3 kg** with 0.75 mg dulaglutide. People treated with 1.0 mg semaglutide experienced a **statistically significant and superior weight loss of 6.5 kg** compared to **3.0 kg** with 1.5 mg dulaglutide.
- Adverse effects mainly GI (nausea) were similar.

Investigational Oral Semaglutide

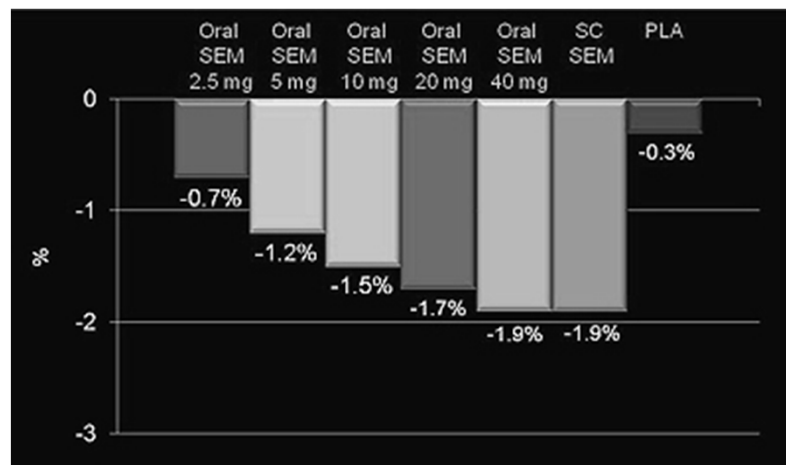
- **Once-daily tablet formulated with SNAC**
- SNAC (Sodium-N-[8-(2-hydroxybenzoyl) amino] caprylate)
 - **Carrier molecule that enhances absorption**
 - Forms weak noncovalent bonds with oral semaglutide
 - Local buffering effect: Prevents breakdown by gastric enzymes and stomach acid
 - Locally absorbed in the stomach near the site of tablet erosion
 - Once absorbed, the weak bonds break and SNAC is rapidly eliminated by the kidneys
- **Once in the blood stream oral semaglutide binds to albumin in the bloodstream resulting in a long half-life (168 hours)**
- Considered safe in patients with eGFR: 30-59 ml/min per CKD-EPI

Davies M. *JAMA*, 2017.
 Malkov D. *Current Drug Delivery*, 2005.
 Arajuo F. *Journal of Diabetes Science and Technology*, 2012.

Investigational Oral Semaglutide

An oral formulation of the investigational GLP-1 receptor agonist, semaglutide, dose dependently lowered A1C and body weight in patients with early type 2 diabetes in a phase 2 study.

The study randomized **632 adults with type 2 diabetes (mean duration, 6 years) to oral semaglutide (2.5, 5, 10, 20, or 40 mg once daily) or placebo, or injectable semaglutide (1.0 mg once weekly)**. Oral semaglutide was initiated at 2.5 mg or 5 mg and up-titrated at 4-week intervals. Mean baseline A1C was 7.9%. The primary endpoint was A1C change at Week 26.



Presented at ENDO 2015. April 1-4, 2016; Boston, Massachusetts. Abstract OR15-3.

Investigational Oral Semaglutide

- **2-22-2018 PIONEER 1** was a 26-week, randomized, double-blinded, placebo-controlled, four-armed, parallel-group, multicenter, multinational trial comparing the efficacy and safety of three dose levels of once-daily oral semaglutide vs placebo in people with type 2 diabetes treated with diet and exercise only. **703 people** were enrolled in PIONEER 1 and randomized 1:1:1:1 to receive either a **dose of oral semaglutide (3, 7 or 14 mg) or placebo once daily**. The primary endpoint was change in HbA1c from baseline at week 26.
- Patients treated with 3, 7 and 14 mg oral semaglutide achieved **reductions in HbA1c of 0.8%, 1.3% and 1.5%, respectively, compared to a reduction of 0.1% in people treated with placebo from a mean baseline of 8.0%.**
- Patients treated with 3, 7 and 14 mg oral semaglutide experienced a **weight loss of 1.7 kg, 2.5 kg and 4.1 kg, respectively, compared to a weight loss of 1.5 kg in people treated with placebo.** (mean baseline body weight of 88 kg and a BMI of 31.8 kg/m²)
 - The most common adverse event for all three oral semaglutide doses was **mild to moderate nausea(5-16% vs. 6% placebo), which diminished over time.**

Albiglutide (Tanzeum) The HARMONY Outcomes Trial (Lancet on-line 10-2-2018)

- **Oct 2, 2018 GSK and Duke CRI** presented the results during the EASD Meeting in Berlin and publication in Lancet.
- **9463 patients aged 40 years and older with type 2 diabetes and cardiovascular disease** (at a 1:1 ratio) to groups that either received a subcutaneous injection of albiglutide (30–50 mg, based on glycemic response and tolerability) or of a matched volume of placebo once a week
- **3 point MACE (CV death, MI or CVA) over 1.6 years** occurred in 9% of the placebo treated patients vs. 7% of the albiglutide treated patients - hazard ratio 0.78, 95% CI 0.68–0.90), which indicated that albiglutide was superior to placebo (p<0.0001 for noninferiority. p=0.0006 for superiority).
- **Results driven by a reduction in fatal and non-fatal MI no reduction in CV death, all cause mortality or stroke.**

The HARMONY Outcomes Trial





	Albiglutide (n=4731)		Placebo (n=4732)		Hazard ratio (95% CI)	p value*
	Number of patients (%)	Incidence rate (number of events per 100 person-years)	Number of patients (%)	Incidence rate (number of events per 100 person-years)		
Primary composite outcome†	338 (7%)	4.57	428 (9%)	5.87	0.78 (0.68–0.90)	<0.0001, 0.0006
Secondary outcomes						
Expanded composite outcome‡	373 (8%)	5.06	468 (10%)	6.45	0.78 (0.69–0.90)	0.0005
Death from cardiovascular causes	122 (3%)	1.61	130 (3%)	1.72	0.93 (0.73–1.19)	0.578
Fatal or non-fatal myocardial infarction	181 (4%)	2.43	240 (5%)	3.26	0.75 (0.61–0.90)	0.003
Fatal or non-fatal stroke	94 (2%)	1.25	108 (2%)	1.45	0.86 (0.66–1.14)	0.300
Composite of death from cardiovascular causes or hospital admission for heart failure	188 (4%)	2.49	218 (5%)	2.92	0.85 (0.70–1.04)	0.113
Death from any cause	196 (4%)	2.44	205 (4%)	2.56	0.95 (0.79–1.16)	0.644

Hazard ratios and p values were estimated with a Cox proportional hazards model with treatment as the sole explanatory variable. *Data for the primary outcome are the p value for non-inferiority, p value for superiority; all other p values are nominal p values for superiority. †Included death from cardiovascular causes (102 patients in the albiglutide group vs 109 patients in the placebo group), non-fatal myocardial infarction (160 patients vs 228 patients), or non-fatal stroke (76 patients vs 91 patients). ‡Included death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke, or urgent coronary revascularisation for unstable angina.

Table 2: Primary and secondary cardiovascular outcomes

Lancet on-line 10-2-2018

Actions of Incretin-Based Therapies for T2D: GLP-1 Receptor Agonists and DPP-4 Inhibitors

Action		GLP-1 Receptor Agonists ^{1,2}	DPP-4 Inhibitors ^{1,2}
	↑ Insulin production	+++	++
	↑ First-phase insulin response	+++	++
	↓ Glucagon; ↓ glucose output	+++	+
	Gastric emptying	Delayed	No effect
	Food intake	Decreased	No effect

1. DeFronzo RA, et al. *Curr Med Res Opin* 2008; 24:2943-2952
2. Drucker DJ and Nauck MA. *Lancet*. 2006;368:1696-1705



DPP-4 Inhibitors

- Sitagliptin – Januvia 25, 50 and 100 mg tabs \$429.00/30 tabs
- Sitagliptin + metformin IR – Janumet 50/500 & 50/1000 mg tabs \$429.00/60 tabs
- Sitagliptin + metformin XR – Janumet XR 100/1000 mg tabs \$429.00/30
- Saxagliptin – Onglyza 2.5 and 5 mg tabs \$416.00/30 tabs
- Saxagliptin + metformin – Kombiglyze XR 2.5/1000, 5/500 & 5/1000 mg tabs ~ \$416.00/month supply at 5 mg dose
- Linagliptin – Trajenta 5 mg tabs \$412.00/30 tabs
- Linagliptin + metformin IR – Jentaduento (BID) 2.5/500, 2.5/850 & 2.5/1000 mg tabs \$412.00/60 tabs
- Linagliptin + metformin XR – Jentaduento XR 2.5/1000 \$206.00/30 tabs & 5/1000 mg tabs \$412.00/30 tabs

DPP-4 Inhibitors

- Sitagliptin – Januvia 25, 50 and 100 mg tabs, Sitagliptin + metformin IR – Janumet 50/500 & 50/1000 mg tabs and Sitagliptin + metformin XR – Janumet XR 100/1000 mg tabs ~ \$429.00/month
- Saxagliptin – Onglyza 2.5 and 5 mg tabs and Saxagliptin + metformin – Kombiglyze XR 2.5/1000, 5/500 & 5/1000 mg tabs ~ \$416.00/month
- Linagliptin – Trajenta 5 mg tabs, Linagliptin + metformin IR – Jentaduento (BID) 2.5/500, 2.5/850 & 2.5/1000 mg tabs and Linagliptin + metformin XR – Jentaduento XR 2.5/1000 \$206.00/30 tabs & 5/1000 mg tabs ~\$412.00/month
- Alogliptin – Nesina 6.25, 12.5 and 25 mg tabs (Generic available), Alogliptin + metformin IR – Kanzeo 12.5/500 & 12.5/1000 mg tabs (Generic available) and Alogliptin + pioglitazone – Oseni 12.5 and 25 mg alogliptin with 15, 30 and 45 mg pioglitazone/tab (Generic available) ~\$404.00/month brand and ~\$182.00/month generic

DPP-4 Inhibitors

- Alogliptin – Nesina 6.25, 12.5 and 25 mg tabs \$404.00/30 tabs (Generic available \$204.00/30 tabs)
- Alogliptin + metformin IR – Kanzeo 12.5/500 & 12.5/1000 mg tabs \$404.00/60 tabs (Generic available \$204.00/60 tabs)
- Alogliptin + pioglitazone – Oseni 12.5 and 25 mg alogliptin with 15, 30 and 45 mg pioglitazone/tab \$404.00/30 tabs (Generic available \$182.00/30 tabs)

SAVOR-TIMI 53 Summary

- 16,492 patients with T2D with CVD or high CVD risk
- Randomized to saxagliptin vs placebo
- 1^o outcome: CV Death/MI/CVA
 - Median follow-up = 2.1 years
- Met the 1^o safety objective of noninferiority (HR, 1.0; 95% CI, 0.89-1.12)
 - Superiority *P* value = .99
- Hospitalization for heart failure: saxagliptin group (3.5%); placebo group (2.8%); HR: 1.27; 95% CI: 1.07, 1.51; p-value = 0.007 **NNH 142**

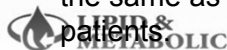
SAVOR – TIMI 53 CV Trial with Saxagliptin

- **April 14, 2015: 14 of 15 panelists from the FDA Endocrinologic and Metabolic Drugs Advisory Committee voted to update the label for saxagliptin, primarily on the increased risk for heart failure. They also wanted to see information on the trend toward higher all-cause mortality.**
 - **Death from any cause 420 (4.9%) Saxagliptin vs 378 (4.2%) Placebo HR: 1.11 (0.96–1.27) P = 0.15**
 - **Warnings and Precautions: Heart Failure: In the SAVOR cardiovascular outcomes trial, more patients treated with ONGLYZA were hospitalized for heart failure compared to placebo. Patients with a prior history of heart failure or renal impairment had a higher risk for hospitalization for heart failure. Consider the risks and benefits of ONGLYZA in patients who have known risk factors for heart failure. Monitor for signs and symptoms. If heart failure develops, consider discontinuation of ONGLYZA.**

EXAMINE

- 5380 patients with T2D post-ACS event
- Randomized to alogliptin vs placebo
- Primary outcome: CV Death/MI/CVA
 - Median follow-up 18 months
- Met the primary safety objective of noninferiority (HR, 0.96; 95% UCL, 1.16)
 - Superiority *P* value = .32

In the alogliptin trial, 3.9% of alogliptin-treated patients were hospitalized for heart failure versus 3.3% in the placebo group. This is the same as 39 out of every 1,000 patients compared to 33 out of every 1,000



White WB, et al. *N Engl J Med*. 2013; Sep 2.

[Epub ahead of print]^[2]



FDA Drug Safety Communication - Risk of Heart Failure (4/5/2016)

- An FDA safety review has found that type 2 diabetes medicines containing saxagliptin and alogliptin may increase the risk of heart failure, particularly in patients who already have heart or kidney disease. As a result, FDA is adding new warnings to the drug labels about this safety issue.
- **RECOMMENDATION: Health care professionals should consider discontinuing medications containing saxagliptin and alogliptin in patients who develop heart failure and monitor their diabetes control.** If a patient's blood sugar level is not well-controlled with their current treatment, other diabetes medicines may be required.
- **Patients taking these medicines should contact their health care professionals right away if they develop signs and symptoms of heart failure such as:**
 - Unusual shortness of breath during daily activities
 - Trouble breathing when lying down
 - Tiredness, weakness, or fatigue
 - Weight gain with swelling in the ankles, feet, legs, or stomach

TECOS Results

Outcome	Sitagliptin (n=7382)	Placebo (n=7339)	HR (95%CI)
Primary Outcome	11.4%	11.6%	0.98 (0.89-1.08)
CV Death, non-fatal MI, non-fatal CVA	10.2%	10.2%	0.99 (0.89-1.10)
CV Death	5.2%	5.0%	1.03 (0.89-1.19)
Hospitalization unstable angina	1.6%	1.8%	0.90 (0.70-1.16)
Fatal or non-fatal MI	4.1%	4.3%	0.95 (0.81-1.11)
Fatal or non-fatal CVA	2.4%	2.5%	0.97 (0.79-1.19)
Hospitalization for HF	3.1%	3.1%	1.00 (0.83-1.20)
Hospitalization for HF or CV Death	7.3%	7.2%	1.02 (0.90-1.15)

NEJM: on-line June 8, 2015

CARMELINA Linagliptin CV Outcome Trial

- **Randomized, placebo-controlled, multicenter noninferiority trial** conducted from August 2013 to August 2016 at 605 clinic sites in 27 countries among **6979 adults with type 2 diabetes, hemoglobin A1c of 6.5% to 10.0%, high CV risk (history of vascular disease and urine-albumin creatinine ratio [UACR] >200 mg/g), and high renal risk (reduced eGFR and micro- or macroalbuminuria)**. Participants with end-stage renal disease (ESRD) were excluded. **Followed up for a median 2.2 years.**
- **Interventions** Patients were randomized to receive **linagliptin, 5 mg once daily (n = 3494), or placebo once daily (n = 3485)** added to usual care.
- **Primary outcome was time to first occurrence of the composite of CV death, nonfatal myocardial infarction, or nonfatal stroke. Secondary outcome was time to first occurrence of adjudicated death due to renal failure, ESRD, or sustained 40% or higher decrease in eGFR from baseline.**
 - JAMA. 2019;321(1):69-79



From: **Effect of Linagliptin vs Placebo on Major Cardiovascular Events in Adults With Type 2 Diabetes and High Cardiovascular and Renal Risk: The CARMELINA Randomized Clinical Trial**
 JAMA. 2019;321(1):69-79. doi:10.1001/jama.2018.18269

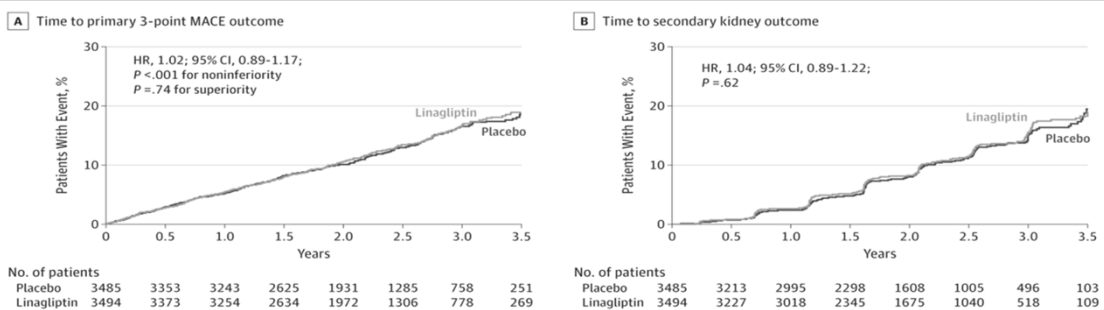


Figure Legend:

Time to Primary and Secondary Outcomes Hazard ratio (HR) based on Cox regression analyses in patients treated with at least 1 dose of study drug. A, Time to 3-point major adverse cardiovascular event (MACE) primary outcome (first cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke). Median observation time was 2.1 (interquartile range [IQR], 1.5-2.9) years for linagliptin and 2.1 (IQR, 1.5-2.8) years for placebo. B, Time to secondary kidney outcome (first sustained end-stage renal disease, death due to renal failure, or sustained decrease of $\geq 40\%$ in estimated glomerular filtration rate from baseline). Median observation time was 1.9 (IQR, 1.2-2.6) years for linagliptin and 1.7 (IQR, 1.2-2.5) years for placebo.

Date of download: 1/21/2019

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FDA Safety Alert: DPP-4 Inhibitors and Potential for Severe Joint Pain

- **8-28-15 FDA is warning that the type 2 diabetes medicines sitagliptin, saxagliptin, linagliptin, and alogliptin may cause joint pain that can be severe and disabling.**
- **The FDA found 33 patients and all experienced arthralgia that resulted in a substantial reduction in their prior level of activity, including 10 patients who were hospitalized due to disabling joint pain.**

FDA Safety Alert: DPP-4 Inhibitors and Potential for Severe Joint Pain

- **In 22 cases, symptoms appeared within 1 month of initiation of treatment with a DPP-4 inhibitor. In 20 of the 33 cases, the DPP-4 inhibitor was suspected as a possible cause of arthralgia and was discontinued within a month following the onset of symptoms. However, 8 of the remaining 13 cases reported a period of 44 days to 1 year between the onset of symptoms and discontinuation of the DPP-4 inhibitor. In 23 of the 33 cases, symptoms resolved less than 1 month after discontinuation of the drug.**
 - **eight of the 33 cases documented a positive rechallenge with the same or other drug in the class**

Dipeptidyl peptidase-4 inhibitors and incidence of inflammatory bowel disease among patients with type 2 diabetes

- A UK cohort of 141,170 patients, at least 18 years of age, starting antidiabetic drugs between 1 January 2007 and 31 December 2016, with follow-up until 30 June 2017.
- During 552,413 person years of follow-up, 208 incident inflammatory bowel disease events occurred (crude incidence rate of 37.7 (95% confidence interval 32.7 to 43.1) per 100 000 person years). **Overall, use of dipeptidyl peptidase-4 inhibitors was associated with an increased risk of inflammatory bowel disease (53.4 v 34.5 per 100 000 person years; hazard ratio 1.75, 95% confidence interval 1.22 to 2.49).** Hazard ratios gradually increased with longer durations of use, reaching a peak after three to four years of use (hazard ratio 2.90, 1.31 to 6.41) and decreasing after more than four years of use (1.45, 0.44 to 4.76).
- These findings need to be replicated, but physicians should be made aware of this possible association.

– BMJ 2018; 360:k872

SGLT-2 Inhibitors

Characteristics of Approved SGLT2Is

	Canagliflozin Invokana	Dapagliflozin Farxiga	Empagliflozin Jardiance
SGLT-2 selectivity (vs SGLT-1) ⁴	1:414	1:1200	>1:2500
Dosages (tablets)	100 mg, 300 mg	5 mg, 10 mg	10 mg, 25 mg
Half-life ⁴ (#h)	12-15 h	17 h	10-19 h
Peak Levels ⁴ (#h after dosing)	2.8-4.0 h	1.5 h	1.5 h
24-hr UGE	300 mg: 51.4 g ^{3a}	10 mg: 40.8 g ^{3a}	25 mg: 56.5 g ^{3a}

⁴In healthy participants
Renal Dosing AVOID with eGFR
<45

<60

<45

ENDOCRINOLOGY
NETWORK

Cost:

All cost ~ \$475-525.00/mo supply except ertugliflozin ~\$300.00

Ertugliflozin - Steglatro

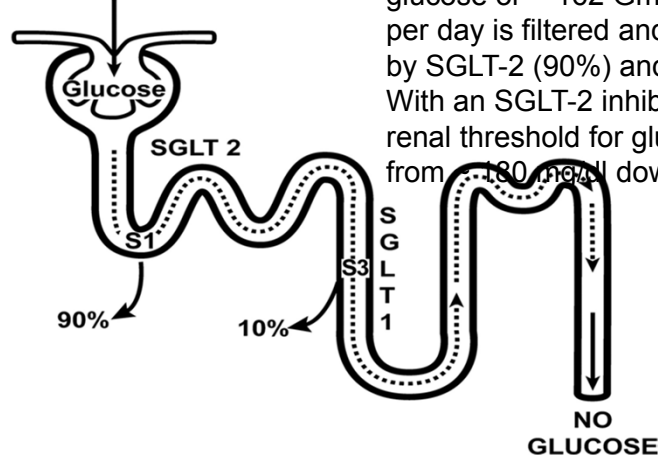
SGLT-2 selectivity vs. SGLT-1 ~ 2,000

5 mg, 15 mg

16.5 h

<30 (avoid when eGFR 30-60)

Plasma Glucose
(180 L/day) (900 mg/L) = 162 g/day



Normally we filter ~ 180 L of plasma per day with ~90 mg/dl of plasma glucose or ~ 162 Gms of glucose per day is filtered and reabsorbed by SGLT-2 (90%) and SGLT-1 (10%). With an SGLT-2 inhibitor we reset the renal threshold for glucose reabsorption from ~180 mg/dl down to 70-90 mg/dl

From: Role of Sodium-Glucose Cotransporter 2 (SGLT 2) Inhibitors in the Treatment of Type 2 Diabetes
Endocr Rev. 2011;32(4):515-531. doi:10.1210/er.2010-0029
Endocr Rev | Copyright © 2011 by The Endocrine Society

Which SGLT-2 Inhibitor would you prescribe?

1. Canagliflozin – Invokana
 2. Dapagliflozin – Farxiga
 3. Empagliflozin – Jardiance
 4. Ertugliflozin – Steglatro
- Note: assume all are available on the patients drug plan at a similar co-pay

Empagliflozin – Jardiance New Indication

December 2, 2016

- The U.S. Food and Drug Administration today approved a **new indication for empagliflozin (Jardiance) to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and cardiovascular disease.**
- Based on a post market **Empa Reg Outcome trial of more than 7,000 patients with type 2 diabetes and cardiovascular disease.** In the trial, Jardiance was **shown to reduce the risk of cardiovascular death compared to a placebo when added to standard of care therapies for diabetes and atherosclerotic cardiovascular disease.**

EMPA-REG OUTCOME Trial

- The **primary outcome (CV mortality, non-fatal MI and non-fatal stroke)** occurred in 490 of 4687 patients (**10.5%**) in the **pooled empagliflozin group** and in 282 of 2333 patients (**12.1%**) in the **placebo group** (hazard ratio in the empagliflozin group, **0.86**; 95.02% confidence interval, 0.74 to 0.99; **P=0.04 for superiority**).
 - ARR = 1.6%, NNT 63
 - No significant differences in rates of MI or CVA
 - No significant difference with 10 vs. 25 mg doses.
 - Death from cardiovascular causes (3.7%, vs. 5.9% in the placebo group; 38% relative risk reduction; ARR = 2.2%, NNT 46
 - NEJM on-line 9-17-2015

EMPA-REG OUTCOME Trial

- **Hospitalization for heart failure (2.7% and 4.1%, respectively; 35% relative risk reduction) NNT = 72**
- **Death from any cause (5.7% and 8.3%, respectively; 32% relative risk reduction) NNT = 39**
- **Among patients receiving empagliflozin, there was an increased rate of genital infection (1 in 20 or 5%) but no increase in other adverse events.**
 - NEJM on-line 9-17-2015

EMPA-REG OUTCOME Trial: Renal Data

Microvascular Outcome

- **The prespecified composite microvascular outcome in the overall trial population occurred in 577 of 4132 patients (14.0%) in the empagliflozin group and in 424 of 2068 patients (20.5%) in the placebo group, a significant RRR 38% ARR 6.5%, NNT=16**
 - **the overall result for this composite microvascular outcome was driven entirely by the renal component** NEJM on-line June 14, 2016

EMPA-REG OUTCOME Trial

Potential mechanism(s) for CV benefit?

- Dr Inzucchi and colleagues found that about half of the mortality benefit of empagliflozin, a sodium glucose cotransporter-2 (SGLT-2) inhibitor, **could be explained by changes in hematocrit and hemoglobin (51.8% and 48.9%, respectively), with smaller contributions from changes in uric acid, plasma glucose, and HbA1c (maximum 29.3%).** In contrast, changes in some traditional cardiovascular risk factors, including obesity, blood pressure, lipids, and renal function, played only minor roles. Notably, **the change in hematocrit was about +3% in the empagliflozin arm, likely a reflection of a decrease in plasma volume.**

– Diabetes Care (2018;41:356-363)

SGLT-2 Inhibitors in HF?

- More definitive conclusions in that population await results from **ongoing studies in patients with heart failure, both with and without type 2 diabetes. These include EMPEROR-Reduced (6/2020), EMPEROR-Preserved (6/2020), and Dapa-HF (Reduced 9/2019 and Preserved 12/2019)**

Canagliflozin: CANVAS and CANVAS R Trials

- Integrated data from two trials involving a total of **10,142 participants with type 2 diabetes and high cardiovascular risk (65.6% had a history of ASCVD)**. Participants in each trial were randomly assigned to receive **canagliflozin or placebo and were followed for a mean of 188.2 weeks (3.62 years)**.
- **The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.**
 - Initially tested for non-inferiority ($p < 0.001$) and then if appropriate for superiority ($p = 0.02$)
 - N Engl J Med 2017; 377:644-657

Canagliflozin: CANVAS and CANVAS R Trials

- **Primary end-point (CV death, non-fatal MI and non-fatal stroke) 26.9 events/1000 pt years canagliflozin vs. 31.5 placebo; HR = 0.86 (95% CI 0.75-0.97); NNT = ~200**
- **Secondary end-points (events/1000 patient years)**
 - CV death 11.6 vs 12.8; HR = 0.87 (95% CI 0.72-1.06) NS
 - Non-fatal MI 9.7 vs. 11.6; HR = 0.85 (95% CI 0.69-1.05) NS
 - Non-fatal stroke 7.3 vs. 8.4; HR = 0.90 (95% CI 0.71-1.15) NS
 - **Hospitalization for heart failure 0.5 vs. 0.9; HR = 0.67 (95% CI 0.52-0.87); NNT = ~250**
 - Death any cause 17.3 vs. 19.5; HR = 0.87 (95% CI 0.74- 1.01) NS
 - N Engl J Med 2017; 377:644-657

CANVAS and CANVAS R Trials

- **Oct 2018 label indication to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease.**
- **Renal events - the composite outcome of a sustained 40% reduction in the estimated glomerular filtration rate, the need for renal-replacement therapy, or death from renal causes (hazard ratio, 0.60; 95% CI, 0.47 to 0.77): 5.5/1000 pt. yrs. Vs. 9.0; NNT = ~250**
 - N Engl J Med 2017; 377:644-657

Canagliflozin: CANVAS and CANVAS R Trials

- **Diabetic ketoacidosis: 0.6/1000 pt. yrs. vs. 0.3 (p=0.14 NS)**
- **Amputations: 6.3/1000 pt. yrs. vs. 3.4 (p<0.001) NNH = ~300**
- **Fractures (all): 15.4/1000 pt. yrs. vs. 11.9 (p=0.02) NNH = ~286**
- **Volume depletion: 26/1000 pt. yrs. vs. 18.5 (p=0.009) NNH = ~140**
- **Infection of male genitalia : 34.9/1000 pt. yrs. vs. 10.8 (p<0.001) NNH = ~42**
- **Female mycotic genital infection: 68.8/1000 pt. yrs. vs. 17.5 (p<0.001) NNH = ~19**
 - N Engl J Med 2017; 377:644-657

CANVAS Trial Amputations

	Placebo N=1,441	Canagliflozin 100 mg N=1,445	Canagliflozin 300 mg N=1,441	Canagliflozin (pooled) N=2,886
Patients with an amputation, n (%)	22 (1.5)	50 (3.5)	45 (3.1)	95 (3.3)
Total amputations*	33	83	79	162
Amputation incidence rate (per 1,000 patient-years)	2.8	6.2	5.5	5.9
Hazard ratio (95% CI)	—	2.24 (1.36, 3.69)	2.01 (1.20, 3.34)	2.12 (1.34, 3.38)

* Some patients had more than one amputation

Amputations of the toe and middle of the foot were the most common; however, amputations involving the leg, below and above the knee, also occurred. Some patients had more than one amputation, some involving both limbs.

Canagliflozin combined data 3.3% vs 1.5% placebo; HR 2.12, ARI 1.8%, NNH 56
<https://www.fda.gov/downloads/Drugs/DrugSafety/UCM558427.pdf>

CANVAS R Trial Amputations

	Placebo N=2,903	Canagliflozin 100 mg - to 300 mg) N=2,904
Patients with an amputation, n (%)	25 (0.9)	45 (1.5)
Total amputations*	36	59
Amputation incidence rate (per 1,000 patient-years)	4.2	7.5
Hazard ratio (95% CI)	—	1.80 (1.10, 2.93)

* Some patients had more than one amputation.

Canagliflozin combined data 1.5% vs. 0.9% with placebo; HR 1.80; ARI 0.6%, NNH 167

(This renal safety study was only a mean duration of 2.1 years)

<https://www.fda.gov/downloads/Drugs/DrugSafety/UCM558427.pdf>

FDA Drug Safety Alert 5-18-2016

- **Canagliflozin (Invokana, Invokamet): Drug Safety Communication - Clinical Trial Results Find Increased Risk of Leg and Foot Amputations**
 - FDA is alerting the public about interim safety results from an ongoing clinical trial that found an increase in leg and foot amputations, mostly affecting the toes.
 - **Patients taking canagliflozin should notify their health care professionals right away if they notice any new pain or tenderness, sores or ulcers, or infections in their legs or feet.**

New FDA Safety Alert

- **[5-16-2017]: “Based on new data from two large clinical trials, the FDA has concluded that the type 2 diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR) causes an increased risk of leg and foot amputations. We are requiring new warnings, including our most prominent **Boxed Warning**, to be added to the canagliflozin drug labels to describe this risk.”**
- **Before initiating canagliflozin, consider factors in the patient’s history that may predispose them to the need for amputations, such as a history of prior amputation, peripheral vascular disease, neuropathy, and diabetic foot ulcers.**
 - <https://www.fda.gov/downloads/Drugs/DrugSafety/UCM558427.pdf>

On-Going CV/Outcome Trials with Dapagliflozin

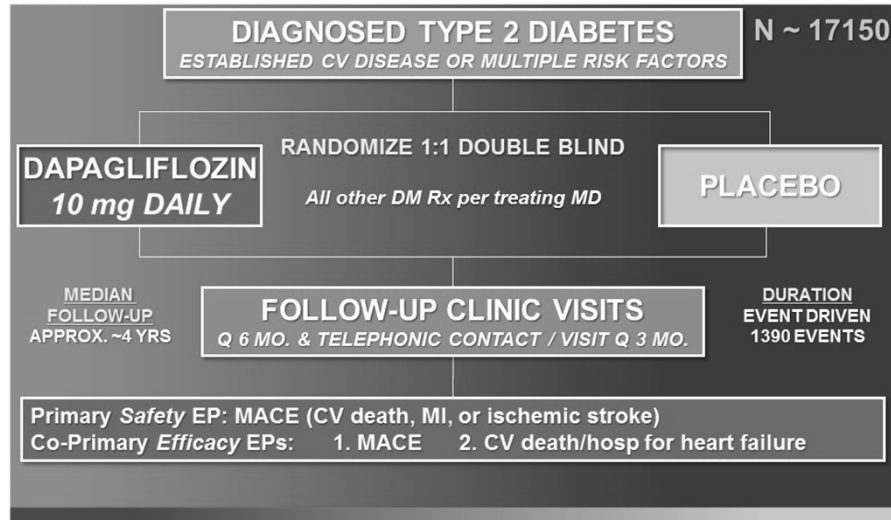
- **DECLARE is a robust randomized, double-blind, multicenter, placebo-controlled cardiovascular outcomes trial enrolling more than 17,000 patients around the world, designed to evaluate the cardiovascular outcomes of dapagliflozin compared with placebo in addition to standard of care, in adults with T2D and high risk of cardiovascular disease (either established cardiovascular disease or multiple cardiovascular risk factors). Expected completion July 2018**
- **DAPA-HF and DAPA-CKD trials, to help to define the potential role of dapagliflozin in the management of chronic heart failure and chronic kidney disease respectively, in people with and without type-2 diabetes**

DECLARE-TIMI-58 Trial

- Dapagliflozin Effect on Cardiovascular Events A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Effect of Dapagliflozin 10 mg Once Daily on the Incidence of Cardiovascular Death, Myocardial Infarction or Ischemic Stroke in Patients With Type 2 Diabetes
- A Phase III cardiovascular (CV) outcomes trial (CVOT) for Farxiga (dapagliflozin), the broadest SGLT2 inhibitor CVOT conducted to date. The trial evaluated the **CV outcomes of dapagliflozin vs. placebo over a period of up to five years, across 33 countries and in more than 17,000 adults with type-2 diabetes (T2D) who have multiple CV risk factors (59.4% had at least one RF of dyslipidemia, HBP or smoking) or established CV disease (40.6% had ASCVD upon entry).**
- Mean A1c 8.3% +/- 1.2%, mean age 63.8 yrs +/- 6.8 yrs; duration of diabetes 11.8 +/- 7.8 yrs, 62.6% male and body mass index 32.1 ± 6.0 kg/m²
 - Diabetes Obes Metab. 2018 May;20(5):1102-1110



Trial Schema



DECLARE-TIMI-58 Trial

- 17,160 patients, including 10,186 without atherosclerotic cardiovascular disease, who were followed for a median of 4.2 years.
- In the primary safety outcome analysis, **dapagliflozin met the prespecified criterion for noninferiority to placebo with respect to 3 point MACE**. In the two primary efficacy analyses, **dapagliflozin did not result in a lower rate of MACE (8.8% in the dapagliflozin group and 9.4% in the placebo group; hazard ratio, 0.93; 95% CI, 0.84 to 1.03; P=0.17) but did result in a lower rate of cardiovascular death or hospitalization for heart failure (4.9% vs. 5.8%; hazard ratio, 0.83; 95% CI, 0.73 to 0.95; P=0.005), which reflected a lower rate of hospitalization for heart failure (hazard ratio, 0.73; 95% CI, 0.61 to 0.88); there was no between-group difference in cardiovascular death (hazard ratio, 0.98; 95% CI, 0.82 to 1.17).**
 - NEJM November 10, 2018 DOI: 10.1056/NEJMoa1812389

DECLARE-TIMI-58 Trial

- **Secondary efficacy outcomes were a renal composite ($\geq 40\%$ decrease in estimated glomerular filtration rate to < 60 ml per minute per 1.73 m² of body-surface area, new end-stage renal disease, or death from renal or cardiovascular causes) and death from any cause.**
- **A renal event occurred in 4.3% in the dapagliflozin group and in 5.6% in the placebo group (hazard ratio, 0.76; 95% CI, 0.67 to 0.87), and death from any cause occurred in 6.2% and 6.6%, respectively (hazard ratio, 0.93; 95% CI, 0.82 to 1.04).**
- **Diabetic ketoacidosis was more common with dapagliflozin than with placebo (0.3% vs. 0.1%, $P=0.02$)**
 - NEJM November 10, 2018 DOI: 10.1056/NEJMoa1812389

Ertugliflozin (Steglatro)

- Dec. 20, 2017 the FDA approved ertugliflozin – Steglatro a sodium glucose co-transporter 2 (SGLT2) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
- **Dosage: Recommended starting dose is 5 mg once daily, taken in the morning, with or without food. Increase dose to 15 mg once daily in those tolerating ertugliflozin and needing additional glycemic control.**
 - Elimination T_{1/2} is ~ 16.5 hours
 - Initiation or continued use is not recommended in patients with an eGFR of 30 to less than 60 mL/minute/1.73 m².

Ertugliflozin (Steglatro)

- **Lower Limb Amputation: Across seven Phase 3 clinical trials in which ertugliflozin was studied as monotherapy and in combination with other antihyperglycemic agents, non-traumatic lower limb amputations occurred in 1 of 1,450 (0.1%) in the non-ertugliflozin group, 3 of 1,716 (0.2%) in the ertugliflozin 5 mg group, and 8 of 1,693 (0.5%) in the ertugliflozin 15 mg group.**
 - consider factors in the patient history that may predispose them to the need for amputations, such as a history of prior amputation, peripheral vascular disease, neuropathy and diabetic foot ulcers.

Ertugliflozin (Steglatro)

- **Cost: Merck has established a list price (Wholesale Acquisition Cost) of \$10.00 per day for STEGLATRO (about 40% less than other SGLT-2's)**
- **Place in therapy? Probably not first line SGLT-2 inhibitor, does not appear to be any more effective or safer.**
- **The CVOT Trial VERTIS CV Study (MK-8835-004) has enrolled 8,000 patients with evidence or a history of atherosclerosis involving the coronary, cerebral or peripheral vascular systems. Randomized to 5 mg or 15 mg of ertugliflozin or placebo and followed for up to 6 plus years, anticipated completion fall of 2019.**
- **Primary Outcome: Time to First Occurrence of MACE (Composite Endpoint of Major Adverse Cardiovascular Events [Cardiovascular Death, Non-fatal Myocardial Infarction or Non-fatal Stroke])**

Ertugliflozin Combinations

- **Ertugliflozin plus metformin (Segluromet) BID WAC ~\$10.00/day**
 - 2.5 mg plus 500 mg
 - 2.5 mg plus 1000 mg
 - 7.5 mg plus 500 mg
 - 7.5 mg plus 1000 mg
- **Ertugliflozin plus sitagliptin (Steglujan) QD WAC ~\$19.45/day**
 - 5 mg plus 100 mg
 - 15 mg plus 100 mg

Concerns with SGLT-2 Inhibitors?

- I would not routinely recommend an SGLT-2 inhibitor in the following patients:
 - **Patients with impaired renal function (eGFR of < 45 ml/min maybe less than 60?).**
 - **Patients with diabetic neuropathy, previous foot ulcers, previous amputations and/or peripheral vascular disease.**
 - **Patients at risk for falls or with orthostatic hypotension.**
 - **Patients with a history of osteoporosis, osteopenia, decreased BMD or history of fractures.**

FDA Safety Announcement

- [5-15-2015] The FDA is warning that the **SGLT-2 inhibitors: canagliflozin, dapagliflozin, and empagliflozin may lead to ketoacidosis**, a serious condition where the body produces high levels of blood acids called ketones that may require hospitalization.
- Patients should pay close attention for any **signs of ketoacidosis** and seek medical attention immediately if they experience **symptoms such as difficulty breathing, nausea, vomiting, abdominal pain, confusion, and unusual fatigue or sleepiness.**

SGLT-2 Inhibitors and DKA

- A new analysis from Wake Forest, UNC and Duke found **39 cases of DKA among 11,197 people with prescriptions for SGLT2 inhibitors (74% in patients with Type 2 DM/ 82% C; 15% D and 3% E). Of these, 26 patients had glucose \leq 300 mg/dL, with a mean glucose of 266 mg/dL.** Symptoms reported included **nausea and vomiting (49%),** although researchers said “it is unclear if that was a cause, contributor, or consequence of the DKA.” Also, **67% of the patients had some other obvious event such as surgery, an insulin dose reduction, or weight loss.**
- The authors recommend “**a high index of suspicion for DKA in patients taking SGLT2 inhibitors with unexplained malaise or gastrointestinal symptoms and recommend measuring urine or plasma ketones in that setting,**”

– Diabetes Care 2017 Mar 28 dc162591.

SGLT-2 Inhibitors and Necrotizing Fasciitis of the Perineum MedWatch 8-29-2018

- FDA is warning that cases of a rare but serious infection of the genitals and area around the genitals have been reported with the class of type 2 diabetes medicines called sodium-glucose cotransporter-2 (SGLT2) inhibitors. This **serious rare infection, called necrotizing fasciitis of the perineum, is also referred to as Fournier's gangrene. We are requiring a new warning about this risk to be added to the prescribing information of all SGLT2 inhibitors and to the patient Medication Guide.**
- **In the five years from March 2013 to May 2018, the FDA identified 12 cases (7 men and 5 women) of Fournier's gangrene in patients taking an SGLT2 inhibitor.** This number includes only reports submitted to FDA and found in the medical literature.

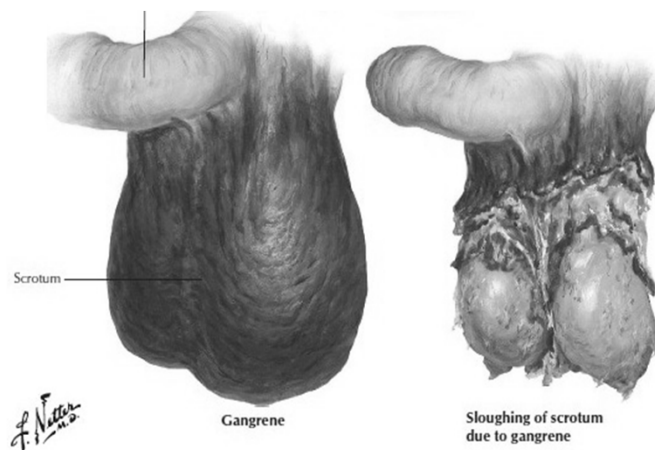
SGLT-2 Inhibitors and Necrotizing Fasciitis of the Perineum MedWatch 8-29-2018

- All 12 patients were hospitalized and required surgery and one patient died.
- Looking at all drugs for diabetes over 34 years the FDA was only able to identify a total of 6 previous cases, all in men.
- **Patient Information: Seek medical attention immediately if you experience any symptoms of tenderness, redness, or swelling of the genitals or the area from the genitals back to the rectum, and have a fever above 100.4 F or a general feeling of being unwell. These symptoms can worsen quickly.**

Fournier's Gangrene Clinical Presentation

- **Begins with insidious onset of pruritus and discomfort of external genitalia**
- **Prodromal symptoms of fever and lethargy, which may be present for 2-7 days before gangrene**
- **The hallmark of Fournier gangrene is out of proportion pain and tenderness in the genitalia.**
- **Increasing genital pain and tenderness with progressive erythema of the overlying skin**
- **Dusky appearance of the overlying skin; subcutaneous crepitation; feculent odor**
- **Obvious gangrene of a portion of the genitalia; purulent discharge from wounds**
- **As gangrene develops, pain subsides (Nerve necrosis)**

Fournier's Gangrene



Insulin Glargine (Basaglar)

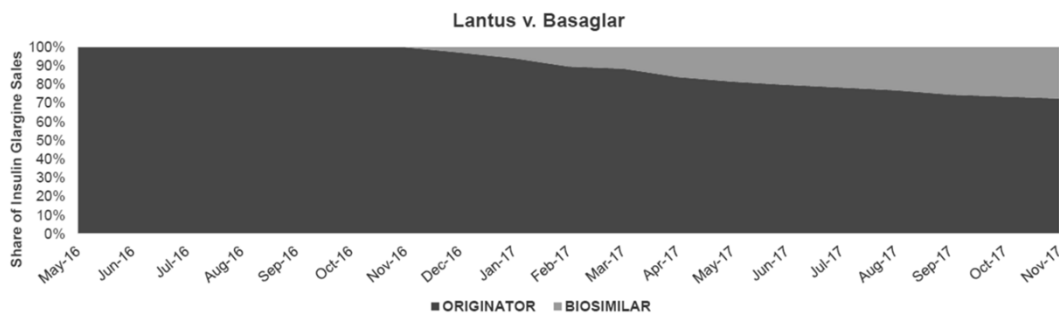
- Dec 16, 2015 FDA approved Basaglar (insulin glargine) but not launched until after Dec 2016 based upon court action. The first insulin product approved through an abbreviated approval pathway under the FDA 505(b) (2) application which did rely partly on the safety and effectiveness of Lantus (insulin glargine by Sanofi).
- Cost: ~\$ 343.00 / 5 pens
- Lantus SoloStar ~\$403.00 / 5 pens ~15% lower than Lantus



The FDA determined that Basaglar was sufficiently similar to Lantus and in addition Basaglar was studied in two large trials (543 Type 1 and 744 Type 2 patients with diabetes). Like Lantus FDA approved for patients age 6 and up.

Basaglar is considered a “follow-on” NOT FDA approved as a “Biosimilar” product. (There is no reference listed drug for Lantus under the Public Health Services Act) CVS/Caremark is now excluding Lantus as of 2017

Basaglar is taking Market Share from Lantus



Molecule	Class	2015	2016	YTD NOV 2017
Insulin Glargine	Originator (Lantus)	\$3,761,997,359	\$3,242,925,104	\$2,389,475,051
		100.0%	99.7%	81.1%
	Biosimilar (Basaglar)	\$0	\$8,925,988	\$558,113,256
		0.0%	0.3%	18.9%

Source: IQVIA, National Sales Perspectives, January 2018



American Diabetes Association Issues Resolution and Launches Petition Calling for Access to Affordable Insulin

- **November 17, 2016** the American Diabetes Association issued a resolution and the launch of a petition calling on all entities in the insulin supply chain to increase transparency and to ensure that no person with diabetes is denied affordable access to insulin. The Association is also calling on Congress to hold hearings with all entities in the insulin supply chain to identify the reasons for the dramatic increases in insulin prices (3 fold in 10 years) and to take action to ensure affordable access to insulin for all who need it.
- See more at: <http://www.diabetes.org/newsroom/press-releases/2016/american-diabetes-insulin-affordability-petition.html#sthash.fVCD16aM.dpuf>

Lowest Priced Insulins

- **WalMart contracts with Novo Nordisk for Reli-On Regular, NPH and 70/30 NPH/Reg Insulins in 10 cc vials only for ~\$25.00/vial**
- **CVS/Caremark is partnering with Novo Nordisk on a new program called Reduced Rx to provide Regular, NPH and 70/30 NPH/Reg insulins available for \$25.00 a 10cc vial**
- **BD Insulin Syringes Ultra-Fine 6mm Needle with Half-Unit Scale - 31G 3/10cc 15/64" - BX 100 ~\$36.00**
- **BD Ultra-Fine II Short Needle Insulin Syringe - 31G 1cc 5/16" - BX 90 ~\$25.00**
- **BD Ultra Fine Pen Needles Mini 5mm X 31G (100 Needles) ~\$40.00**

Human Insulin for Type 2 Diabetes An Effective, Less-Expensive Option

JAMA July 4, 2017 Volume 318, Number 1

How Treatment With Human Insulins Differs - Some differing properties of human N insulin and human R insulin, compared with those of insulin analogues, require modest but important differences in therapeutic approaches.

- **Duration of Action.** The action of human N insulin does not reliably cover 24 hours so more than 1 daily injection is often required.
- **Hypoglycemia Risk.** Among patients with type 2 diabetes, long-acting insulin analogues modestly reduce the rate of nocturnal hypoglycemia compared with human N insulin. (A1c goal, education and bedtime snacks).
- **Timing With Meals.** Human R insulin begins to act no sooner than 30 minutes after injection, while rapid acting insulin analogues (lispro, aspart, and glulisine) have a shorter onset of action of 5 to 15 minutes.

Human Insulin for Type 2 Diabetes An Effective, Less-Expensive Option

JAMA July 4, 2017 Volume 318, Number 1

- **Vial vs Pen.** NPH, Regular and 70/30 are only available in a vial
- **Injection Techniques.** Human N insulin is a cloudy particulate suspension. To avoid inconsistent effects, it must be gently agitated before drawing into a syringe for injection. Absorption of human R insulin is fastest when injected in abdominal sites, followed by the upper arm and thigh; whereas absorption kinetics of rapid-acting insulin analogues seem less site dependent.
- **Premixed 70/30 human insulin (70% N insulin with 30% R insulin)** can be used as a 2-injection regimen, taken before breakfast and dinner. Although this regimen is simple, it is limited by higher risk of hypoglycemia in midday and near midnight, the times of its peaks of action.

Human Insulin for Type 2 Diabetes An Effective, Less-Expensive Option

JAMA July 4, 2017 Volume 318, Number 1

Switching to Human Insulin

- **Patients can safely switch from insulin analogues to human insulins. Total daily insulin dose can be initially reduced by 20%**, because of the different profiles of action and because some patients may have been taking less analogue insulin than had been prescribed.
- **For patients already treated with multiple insulin analogue injections, the number of injections and distribution of dosage can remain the same but with a 20% reduction of dosage for safety.** Early contact between the physician and the patient by phone or in person is desirable to ensure that an unexpectedly large reduction of glucose has not occurred due to improved adherence.
- In summary, many patients with type 2 diabetes can be treated with human insulin. Due to high costs of analogue insulins, use of human insulin may be the only practical option for some patients, and clinicians should be familiar with its use.

New Ultra-Rapid Insulin Aspart – Fiasp by Novo-Nordisk

- Sept. 29, 2017 the U.S. Food and Drug Administration (FDA) approved **Fiasp® (insulin aspart injection) 100 Units/mL, a fast-acting mealtime insulin indicated to improve glycemic control in adults with type 1 and type 2 diabetes.**
- **Fiasp® can be dosed at the beginning of a meal or within 20 minutes after starting a meal. Fiasp® is a new formulation of NovoLog®, in which the addition of niacinamide (vitamin B3) helps to increase the speed of the initial insulin absorption, resulting in an onset of appearance in the blood in approximately 2.5 minutes.**
- Fiasp® will be available in a pre-filled delivery device **FlexTouch® pen and a 10 mL vial at the same price as Novolog**



New Ultra-Rapid Insulin Aspart – Fiasp

- The approval of Fiasp® is based on results from the onset phase 3a clinical development program. The clinical trials enrolled more than 2,000 adults with type 1 and type 2 diabetes to evaluate the efficacy and safety of **Fiasp® administered both at mealtime and after starting a meal. Data from the trials showed that Fiasp® demonstrated a reduction in A1C in adults with type 1 and type 2 diabetes.** Common adverse reactions, excluding hypoglycemia, occurring in ≥5% of subjects included nasopharyngitis, upper respiratory tract infection, nausea, diarrhea and back pain.

New Ultra-Rapid Insulin Aspart – Fiasp

- Pharmacokinetic results from a euglycemic clamp study in adult patients with type 1 diabetes (N=51) showed that **insulin aspart appeared in the circulation ~ 2.5 minutes and maximum insulin concentrations was achieved ~63 minutes after administration of FIASP. T_{1/2} elimination is ~1.1 hrs.**
- **If converting from another mealtime insulin to FIASP, the change can be done on a unit-to-unit basis.**
- **DO NOT dilute or mix FIASP with any other insulin products or solutions, except infusion fluids.**
- **May be stored at room temperature for up to 28 days.**

Insulin Lispro follow on – Admelog by Sanofi

- Dec. 11, 2017: The FDA approved Sanofi's Admelog[®], the first follow-on insulin lispro.
- 100 Units/mL will be available in U.S. in vial and SoloStar pen. It was approved in Europe as a Biosimilar earlier this summer under the proprietary name, Insulin lispro Sanofi[®].
- Indicated in adults and pediatric patients 3 years and older with type 1 diabetes mellitus and adults with type 2 diabetes mellitus.
- Approved for use as an injection, via pump, or intravenously.



STENO 2 Trial

- The original intervention (mean treatment duration 7.8 years) involved **160 patients with type 2 diabetes and microalbuminuria who were randomly assigned (using sealed envelopes) to receive either conventional therapy or intensified, multifactorial treatment** including both behavioral and pharmacological approaches.
- **After 7.8 years the study continued as an observational follow-up with all patients receiving treatment as for the original intensive-therapy group.**
 - Diabetologia 2016 DOI 10.1007/s00125-016-4065-6

STENO Type 2 DM Trial

(Lancet 1999;353:617-22/NEJM 2003;348:383-93)

Outcomes	Intensive	Standard	RRR	NNT
Nephropathy	11%	25%	56%	7
Retinopathy progression	26%	43%	49%	6
Blindness in 1 eye	1%	9%	85%	13
Progression of autonomic neuropathy	11%	29%	62%	6
Combined death and macrovascular events	34%	54%	37%	5

STENO 2 Trial after 21 Years

- The **primary endpoint** of this follow-up 21.2 years after intervention start was **difference in median survival time between the original treatment groups with and without incident cardiovascular disease.**
- The **patients in the intensive therapy group survived for a median of 7.9 years longer than the conventional-therapy group patients. Median time before first cardiovascular event after randomization was 8.1 years longer in the intensive-therapy group (p= 0.001).**
- The **hazard for all microvascular complications was decreased in the intensive-therapy group in the range 0.52 to 0.67, except for peripheral neuropathy (HR 1.12).**

– Diabetologia 2016 DOI 10.1007/s00125-016-4065-6

How would you treat this patient?

- 50 y/o overweight, non-smoker female with newly diagnosed Type 2 DM (A1c 8.1%) with controlled BP on lisinopril 40 mg HS, controlled lipids on atorvastatin 40 mg AM, and labs WNL?
- About 3 years later after good control (A1c <7%) she has increasing A1c (8.2%) despite good adherence to her regimen and she has now had 2 stents placed for CAD which caused her provider to increase her atorvastatin to 80 mg QAM and she is now on dual antiplatelet therapy with clopidogrel plus low dose aspirin. What would you add to her glucose control regimen?

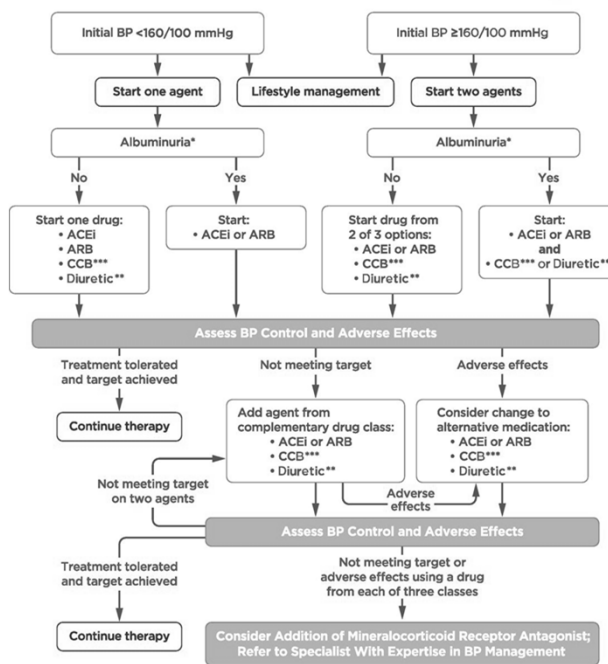
Recommendations for the treatment of confirmed hypertension in people with diabetes. *An ACE inhibitor (ACEi) or angiotensin receptor blocker (ARB) is suggested to treat hypertension for patients with urine albumin-to-creatinine ratio 30–299 mg/g creatinine and strongly recommended for patients with urine albumin-to-creatinine ratio ≥ 300 mg/g creatinine. **Thiazide-like diuretic; long-acting agents shown to reduce cardiovascular events, such as chlorthalidone and indapamide, are preferred. *Dihydropyridine calcium channel blocker (CCB).**

Dia Care 2019;42:S103-S123



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Recommendations for the Treatment of Confirmed Hypertension in People With Diabetes



2019 ADA Standards of Medical Care in Diabetes

BP Treatment Goals Recommendations

- For patients with diabetes and hypertension, blood pressure targets should be individualized through a shared decision-making process that addresses cardiovascular risk, potential adverse effects of antihypertensive medications, and patient preferences. C
- **For individuals with diabetes and hypertension at higher cardiovascular risk (existing atherosclerotic cardiovascular disease or 10-year atherosclerotic cardiovascular disease risk >15%), a blood pressure target of <130/80 mmHg may be appropriate, if it can be safely attained. C**
- **For individuals with diabetes and hypertension at lower risk for cardiovascular disease (10-year atherosclerotic cardiovascular disease risk <15%), treat to a blood pressure target of <140/90 mmHg. A**
 - Diabetes Care 2019 Jan; 42(Supplement 1): S103-S123

2019 ADA Standards of Medical Care in Diabetes

- Patients with confirmed office-based blood pressure $\geq 140/90$ mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of pharmacologic therapy to achieve blood pressure goals. A
- **Patients with confirmed office-based blood pressure $\geq 160/100$ mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of two drugs or a single-pill combination of drugs demonstrated to reduce cardiovascular events in patients with diabetes. A**
- **Treatment for hypertension should include drug classes demonstrated to reduce cardiovascular events in patients with diabetes (ACE inhibitors, angiotensin receptor blockers, thiazide-like diuretics, or dihydropyridine calcium channel blockers). A**
 - Diabetes Care 2019 Jan; 42(Supplement 1): S103-S123

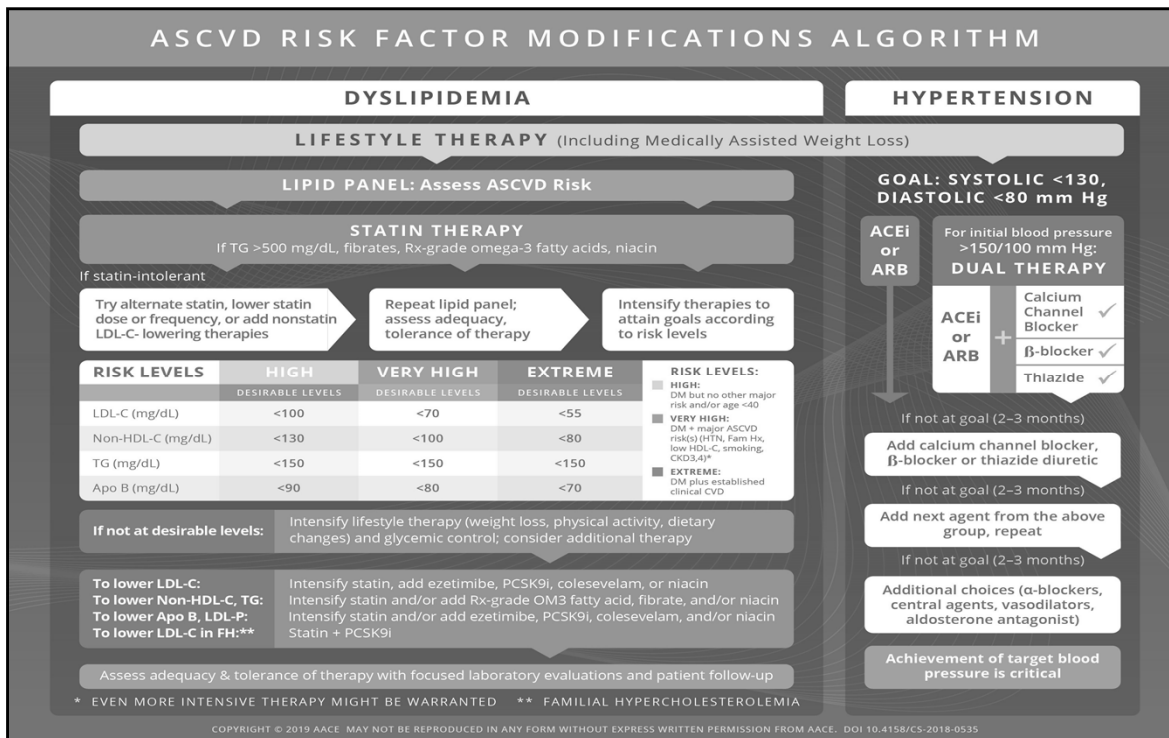
2019 ADA Standards of Medical Care in Diabetes

Statin Treatment Recommendations

- **For patients of all ages with diabetes and atherosclerotic cardiovascular disease or 10-year atherosclerotic cardiovascular disease risk >20%, high-intensity statin therapy should be added to lifestyle therapy. A**
- **For patients with diabetes aged <40 years with additional atherosclerotic cardiovascular disease risk factors, the patient and provider should consider using moderate-intensity statin in addition to lifestyle therapy. C**
- **For patients with diabetes aged 40–75 years A and >75 years B without atherosclerotic cardiovascular disease, use moderate-intensity statin in addition to lifestyle therapy.**
 - Diabetes Care 2019 Jan; 42(Supplement 1): S103-S123.

2019 ADA Standards of Medical Care in Diabetes

- In patients with diabetes who have multiple atherosclerotic cardiovascular disease risk factors, it is reasonable to consider high-intensity statin therapy. C
- For patients who do not tolerate the intended intensity, the maximally tolerated statin dose should be used. E
- **For patients with diabetes and atherosclerotic cardiovascular disease, if LDL cholesterol is ≥ 70 mg/dL on maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor). A Ezetimibe may be preferred due to lower cost.**
- Statin therapy is contraindicated in pregnancy. B
 - Diabetes Care 2019 Jan; 42(Supplement 1): S103-S123.



2019 ADA Standards of Medical Care in Diabetes

ANTIPLATELET AGENTS Recommendations

- Use aspirin therapy (75–162 mg/day) as a secondary prevention strategy in those with diabetes and a history of atherosclerotic cardiovascular disease. **A**
- For patients with atherosclerotic cardiovascular disease and documented aspirin allergy, clopidogrel (75 mg/day) should be used. **B**
- Dual antiplatelet therapy (with low-dose aspirin and a P2Y12 inhibitor) is reasonable for a year after an acute coronary syndrome **A** and may have benefits beyond this period. **B**
- Aspirin therapy (75–162 mg/day) may be considered as a primary prevention strategy in those with diabetes who are at increased cardiovascular risk, after a discussion with the patient on the benefits versus increased risk of bleeding. **C**
 - Diabetes Care 2019 Jan; 42(Supplement 1): S103-S123.

ASCEND (A Study of Cardiovascular Events iN Diabetes)

- A randomized 2x2 factorial design study of aspirin 100 mg EC versus placebo, and of omega-3 fatty acid supplementation 1 gram versus placebo, for the primary prevention of cardiovascular events in people with diabetes
- Randomly assigned **15,480 adults** (mean age 63 +/- 9.2 yrs, 63% male, 96.5% white, 94% Type 2 DM) **who had diabetes but no evident cardiovascular disease to receive aspirin at a dose of 100 mg daily or matching placebo and omega 3 FA 1 Gm daily or olive oil placebo.** The **primary efficacy outcome was the first serious vascular event (i.e., myocardial infarction, stroke or transient ischemic attack, or death from any vascular cause, excluding any confirmed intracranial hemorrhage).** The **primary safety outcome was the first major bleeding event (i.e., intracranial hemorrhage, sight-threatening bleeding event in the eye, gastrointestinal bleeding, or other serious bleeding).** **Secondary outcomes included gastrointestinal tract cancer.**
 - published on August 26, 2018, at NEJM.org.

ASCEND Trial

Factorial design of trial

	Aspirin Tablets	Placebo Tablets	
Omega-3 FA capsules	2500 Aspirin + Omega-3 FA	2500 Omega-3 FA	Subtotal 1: 5000 Omega-3 FA
Placebo capsules	2500 Aspirin	2500 Neither	Subtotal 2: 5000 Placebo
Protocol amended to enroll 15,000 patients and extend f/u to 7 years in 2011	Subtotal A: 5000 Aspirin	Subtotal B: 5000 Placebo	

ASCEND Trial - Aspirin

- During a mean follow-up of 7.4 years, serious vascular events occurred in a significantly lower percentage of participants in the aspirin group than in the placebo group (658 participants [8.5%] vs. 743 [9.6%]; rate ratio, 0.88; 95% confidence interval [CI], 0.79 to 0.97; P=0.01). In contrast, major bleeding events occurred in 314 participants (4.1%) in the aspirin group, as compared with 245 (3.2%) in the placebo group (rate ratio, 1.29; 95% CI, 1.09 to 1.52; P=0.003), with most of the excess being gastrointestinal bleeding and other extracranial bleeding. There was **no significant difference between the aspirin group and the placebo group in the incidence of gastrointestinal tract cancer (157 participants [2.0%] and 158 [2.0%], respectively) or all cancers (897 [11.6%] and 887 [11.5%])**; long-term follow-up for these outcomes is planned.
 - published on August 26, 2018, at NEJM.org.

ASCEND Trial – Omega 3 FA

- Patients were given 840 mg of marine n–3 fatty acids (460 mg of eicosapentaenoic acid [EPA] and 380 mg of docosahexaenoic acid [DHA]) (fatty acid group) or a matching placebo capsule (olive oil) to be taken once daily.
- During a mean follow-up of 7.4 years (adherence rate, 76%), a serious vascular event occurred in 689 patients (8.9%) in the fatty acid group and in 712 (9.2%) in the placebo group (rate ratio, 0.97; 95% confidence interval [CI], 0.87 to 1.08; P=0.55). The composite outcome of a serious vascular event or revascularization occurred in 882 patients (11.4%) and 887 patients (11.5%), respectively (rate ratio, 1.00; 95% CI, 0.91 to 1.09). Death from any cause occurred in 752 patients (9.7%) in the fatty acid group and in 788 (10.2%) in the placebo group (rate ratio, 0.95; 95% CI, 0.86 to 1.05). There were **no significant between-group differences in the rates of nonfatal serious adverse events.**
 - published on August 26, 2018, at NEJM.org.

Learning Assessment Question #1

Within the GLP-1 receptor agonist class, which agent is given preference in the ADA/EASD guidance in patients in whom ASCVD predominates?

- a) Dulaglutide
- b) Exenatide
- c) Liraglutide**
- d) Semaglutide

Learning Assessment Question #2

Within the SGLT2 inhibitor class, which agent is given preference in the ADA/EASD guidance in patients in whom ASCVD predominates?

- a) Canagliflozin
- b) Dapagliflozin
- c) Empagliflozin**
- d) Ertugliflozin

Learning Assessment Question #3

Pair the following GLP-1 receptor agonists with their cardiovascular outcomes study:

- | | | |
|-----------------|---|------------|
| a) Dulaglutide | → | 1) ELIXA |
| b) Exenatide | → | 2) EXSCEL |
| c) Liraglutide | → | 3) LEADER |
| d) Lixisenatide | → | 4) REWIND |
| e) Semaglutide | → | 5) SUSTAIN |
-

Learning Assessment Question #4

Pair the following SGLT2 inhibitors with their cardiovascular outcomes study:

- | | | |
|------------------|---|-----------------|
| a) Canagliflozin | → | 1) EMPA-REG |
| b) Dapagliflozin | → | 2) CANVAS |
| c) Empagliflozin | → | 3) DECLARE-TIMI |
| d) Ertugliflozin | → | 4) VERTIS CV |
-

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