

Part 2: Starting Non-Insulin Medication in the Primary Care Setting for Type 2 Diabetes

Matthew Stryker, Pharm.D.

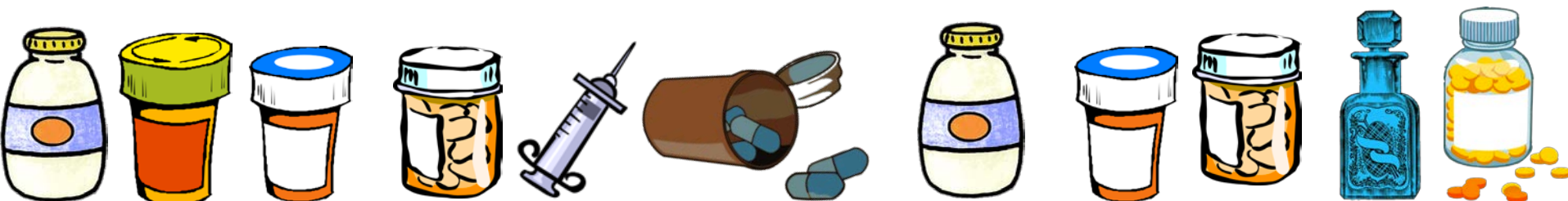
matthew.stryker@acphs.edu

Assistant Professor

Clinical Pharmacy Specialist

Albany College of Pharmacy and Health Sciences

Albany Medical Center – Division of Community Endocrinology



Albany College of Pharmacy and Health Sciences

Disclosures

In compliance with the accrediting board policies, the American Diabetes Association requires the following disclosure to the participants:

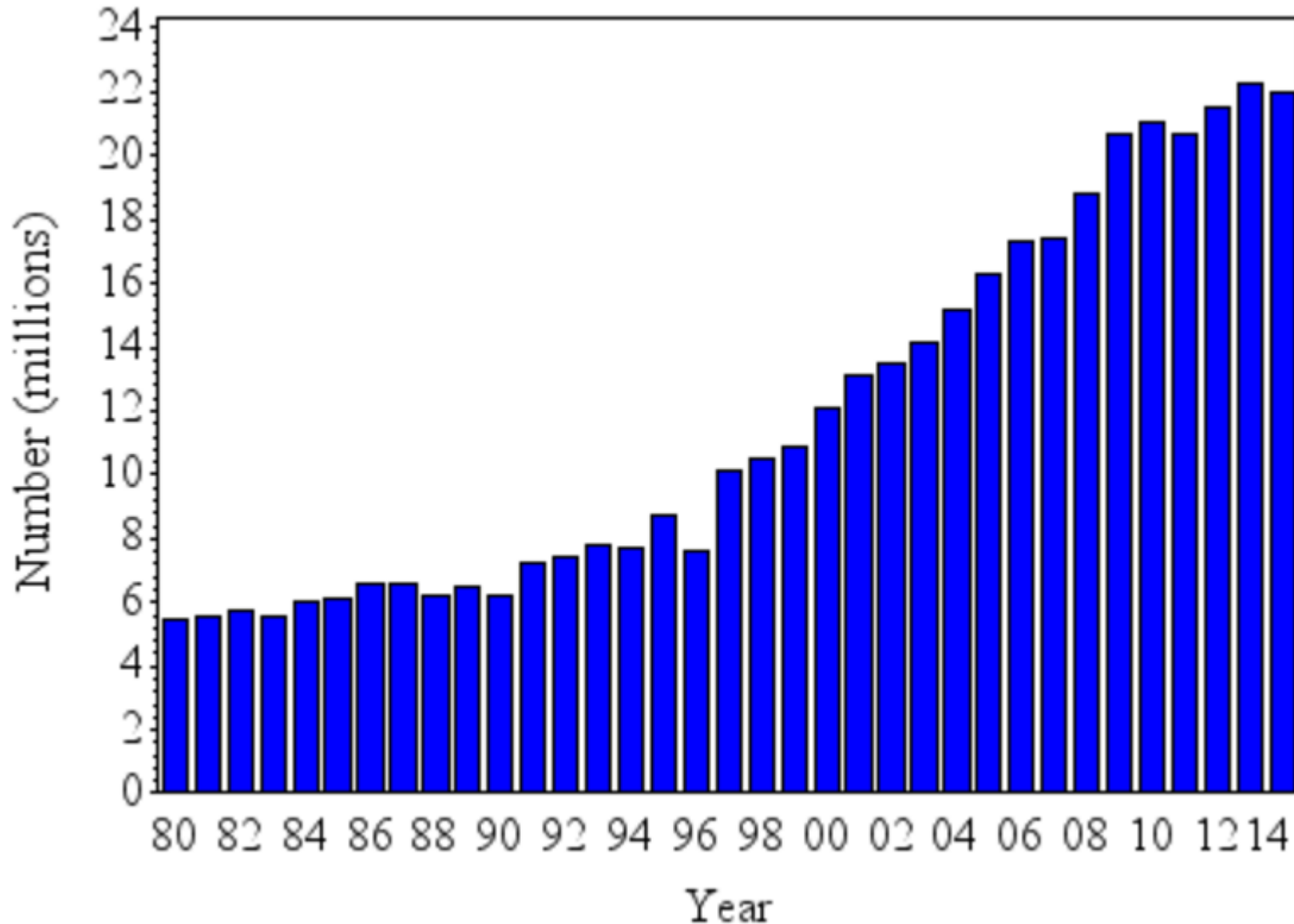
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Disclosed no conflict of interest

Learning Objectives

- Summarize treatment differences between the American Diabetes Association and American Association of Clinical Endocrinologists' guidelines for patients with type 2 diabetes mellitus
- Apply guideline recommendations and primary literature to a patient case scenario
- Compare anti-diabetic medication classes, and agents within a class, to identify nuances among each

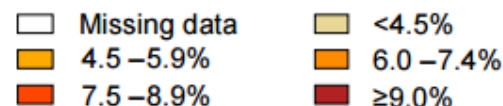
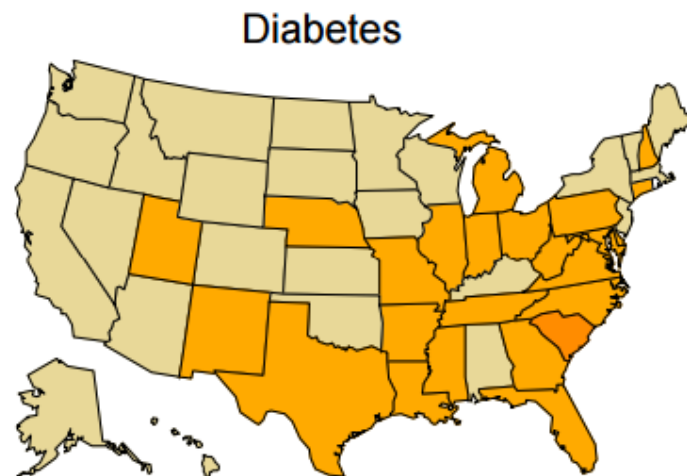
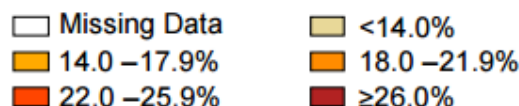
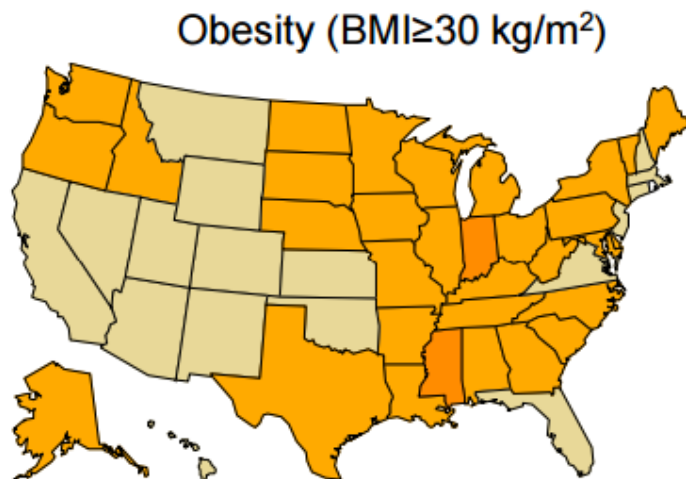
Number of Americans Diagnosed with Diabetes 1980 – 2014



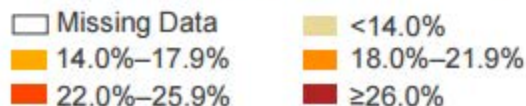
1. Centers for Disease Control and Prevention. Diabetes Public Health Resource. Available at: <http://www.cdc.gov/diabetes/statistics/prev/national/figpersons.htm>. Accessed: 24 October 2016.

Age-Adjusted Prevalence of Obesity and Diagnosed Diabetes Among US Adults²

1994

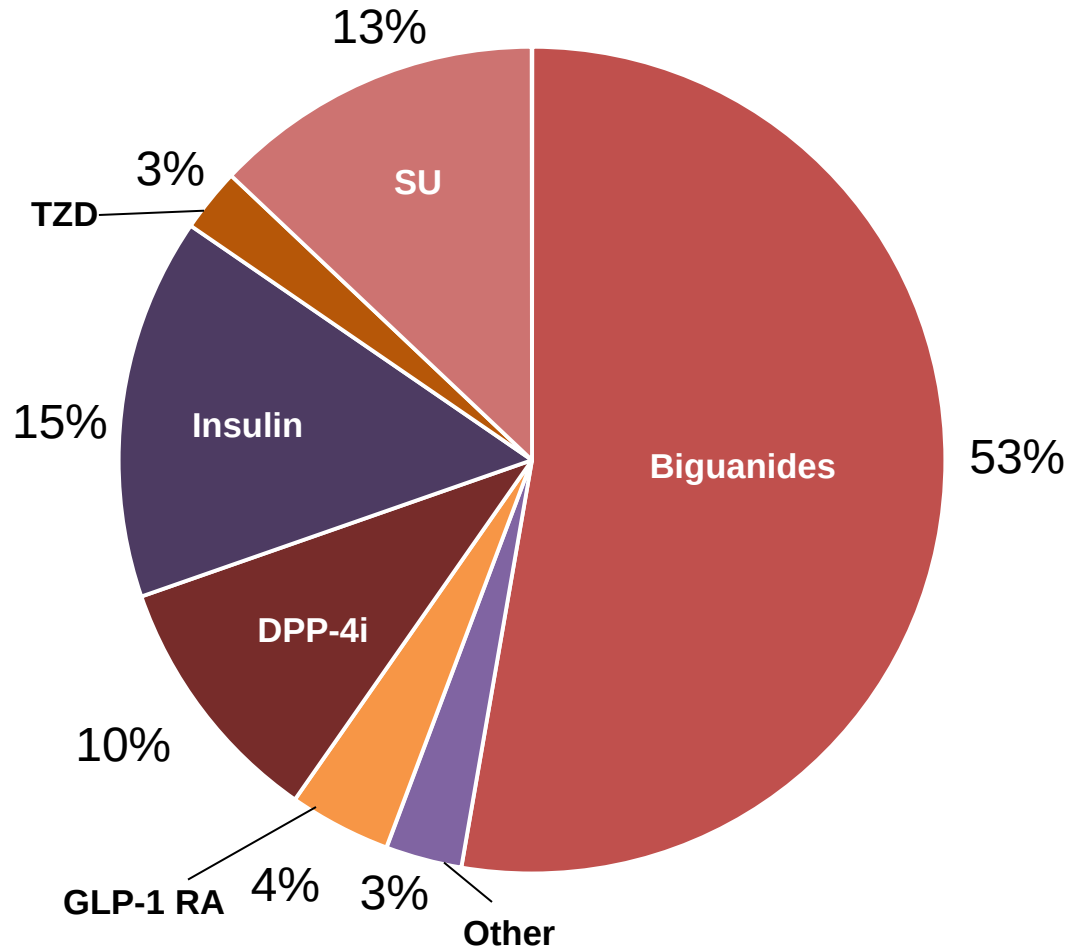


2014



Diabetes Prescribing Trends³

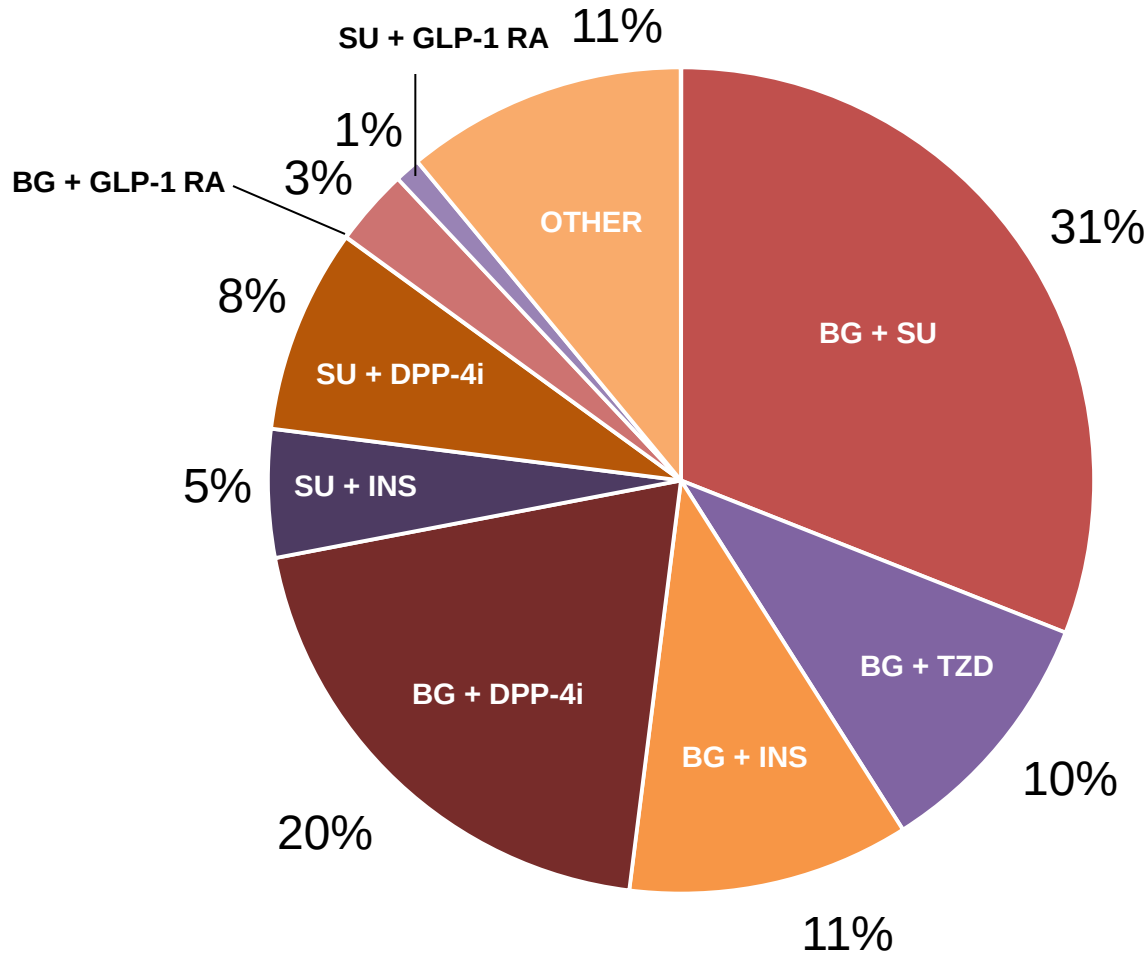
Monotherapy Use, 2012



Abbreviations: DPP-4i – dipeptidyl peptidase-4 inhibitor; GLP-1 RA – glucagon-like peptide-1 receptor agonist; SU – sulfonylureas; TZD - thiazolidinedione

Diabetes Prescribing Trends³

Combination Therapy Use, 2012



Abbreviations: BG – biguanide; DPP-4i – dipeptidyl peptidase-4 inhibitor; GLP-1 RA – glucagon-like peptide-1 receptor agonist; INS – insulin; SU – sulfonylureas; TZD - thiazolidinedione



EC is a 56-year-old male who has been referred to the endocrinologist for the management of his type 2 diabetes mellitus (T2DM). He has had T2DM for almost 4 years. He endorses no complaints during his visit. His past medical history and supporting clinical information are summarized below.

Past medical history: hyperlipidemia; hypertension; hypothyroidism; obesity; sleep apnea

Vitals

- 289.4 lbs. (BMI: 41.5 kg/m²)
- Blood pressure: 120/74 mm Hg
- Pulse: 74 beats per minute

Current medications

- Diltiazem 120 mg ER: 1 PO once daily
- Levothyroxine 200 mcg: 1PO twice daily six days per week
- Losartan 100 mg: 1 PO once daily
- Metformin 1000 mg: 1 PO twice daily

Pertinent lab data

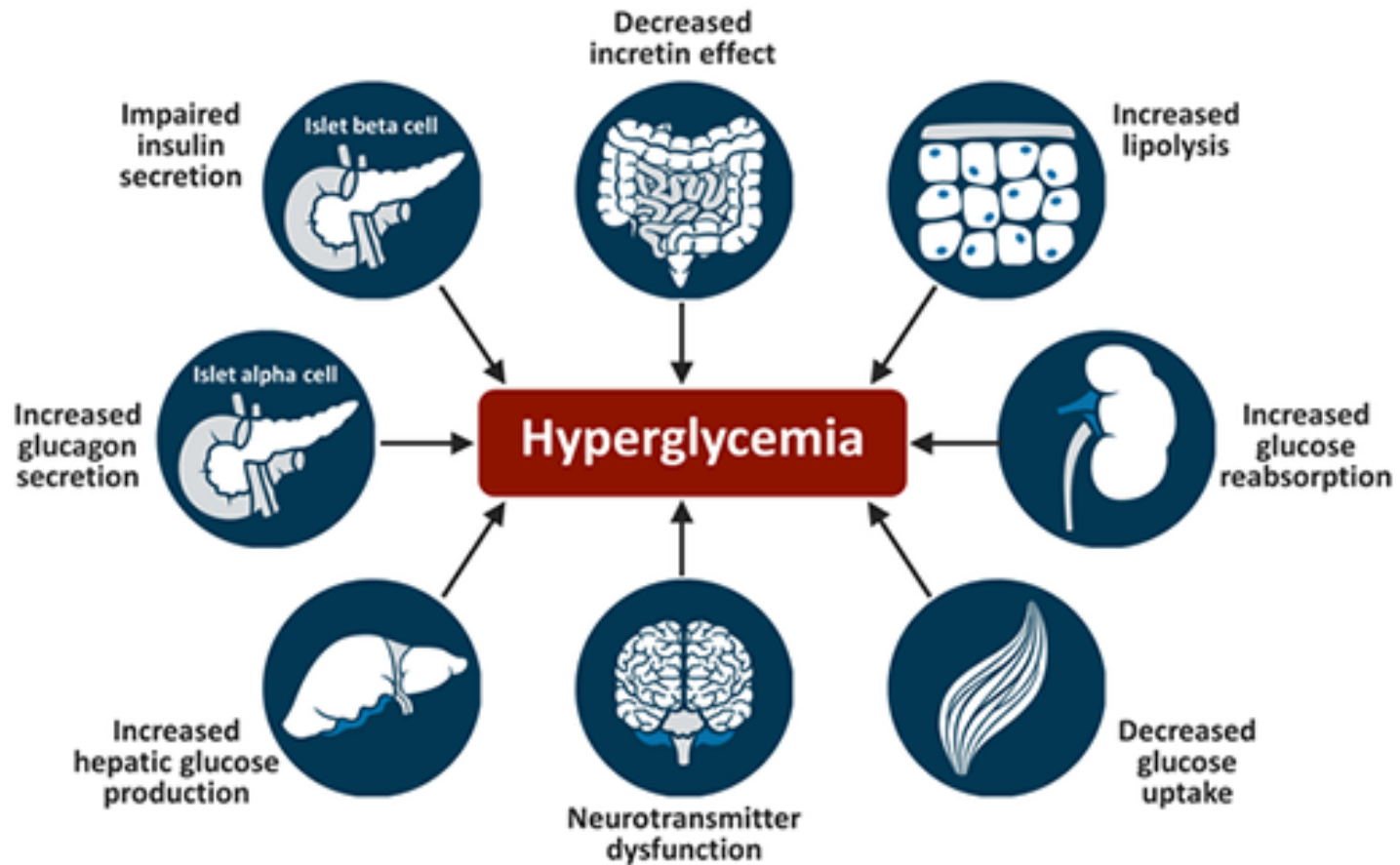
- | | |
|---------------------------------------|--|
| - HbA _{1c} : 9.16% | - Non-HDL-C: 202 mg/dL |
| - LDL-C: 168 mg/dL | - TSH: 2.1 milli-international units/L |
| - eGFR: 55 mL/min/1.73 m ² | |

Abbreviations: BMI – body mass index; eGFR – estimated glomerular filtration rate; ER – extended-release; lbs. – pounds; LDL-C – low-density lipoprotein cholesterol; non-HDL-C – non-high-density lipoprotein cholesterol; PO – by mouth; TSH – thyroid-stimulating hormone

Image: https://www.tradjenta.com/?sc=TRAACQWEBSEMGL0214001&utm_source=google&utm_medium=cpc&utm_term=tradjenta&utm_campaign=decision_-_branded&gclid=CPjQ5-3R7M8CFVDr6Qod6C4MZg&gclid=ds

The Ominous Octet

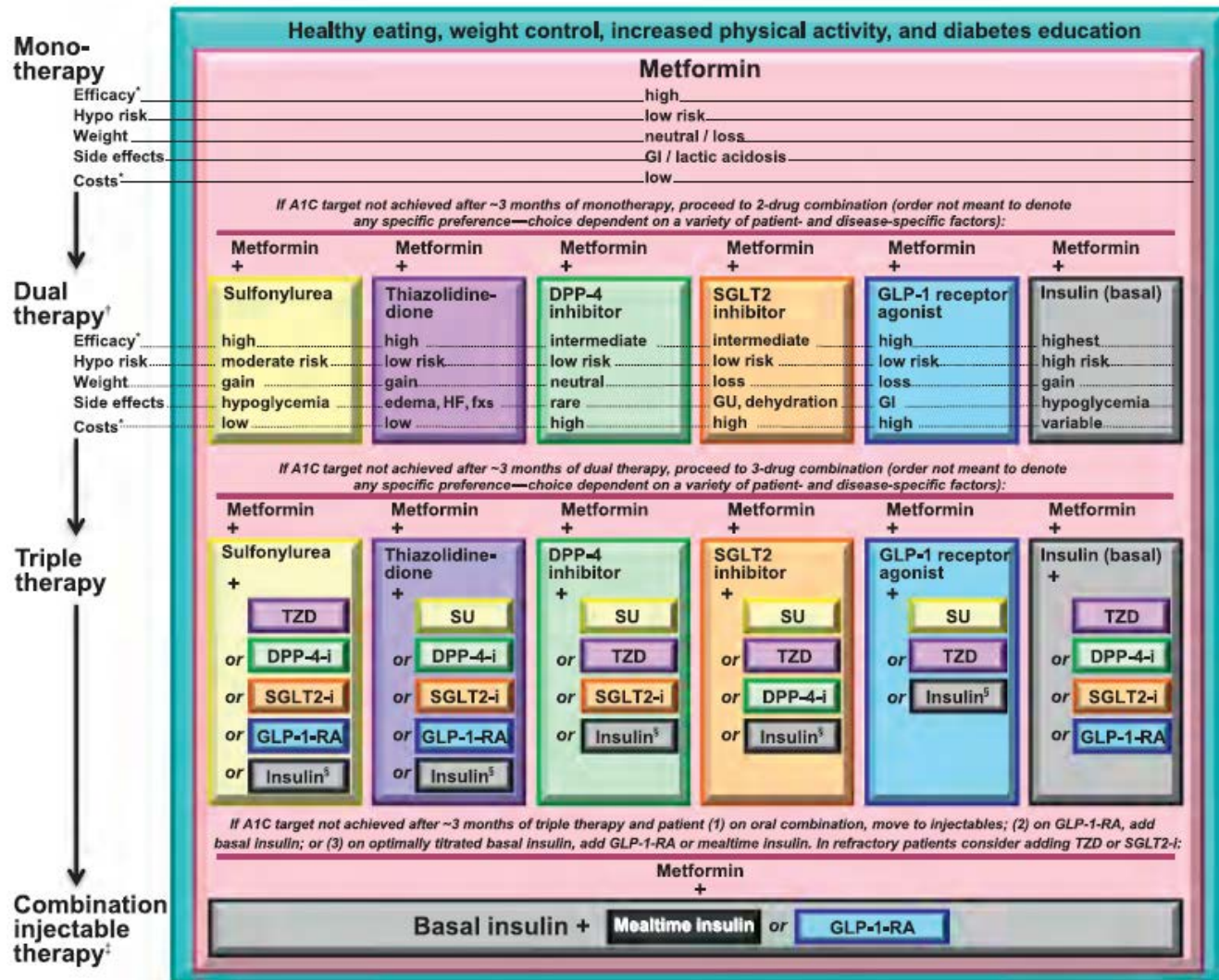
Type 2 Diabetes Mellitus



4. DeFronzo RA. Banting Lecture. From the Triumvirate to the Ominous Octet: A New Paradigm for the Treatment of Type 2 Diabetes Mellitus. Diabetes. 2009 Apr;58(4):773-95. doi: 10.2337/db09-9028.

Current Guideline Recommendations

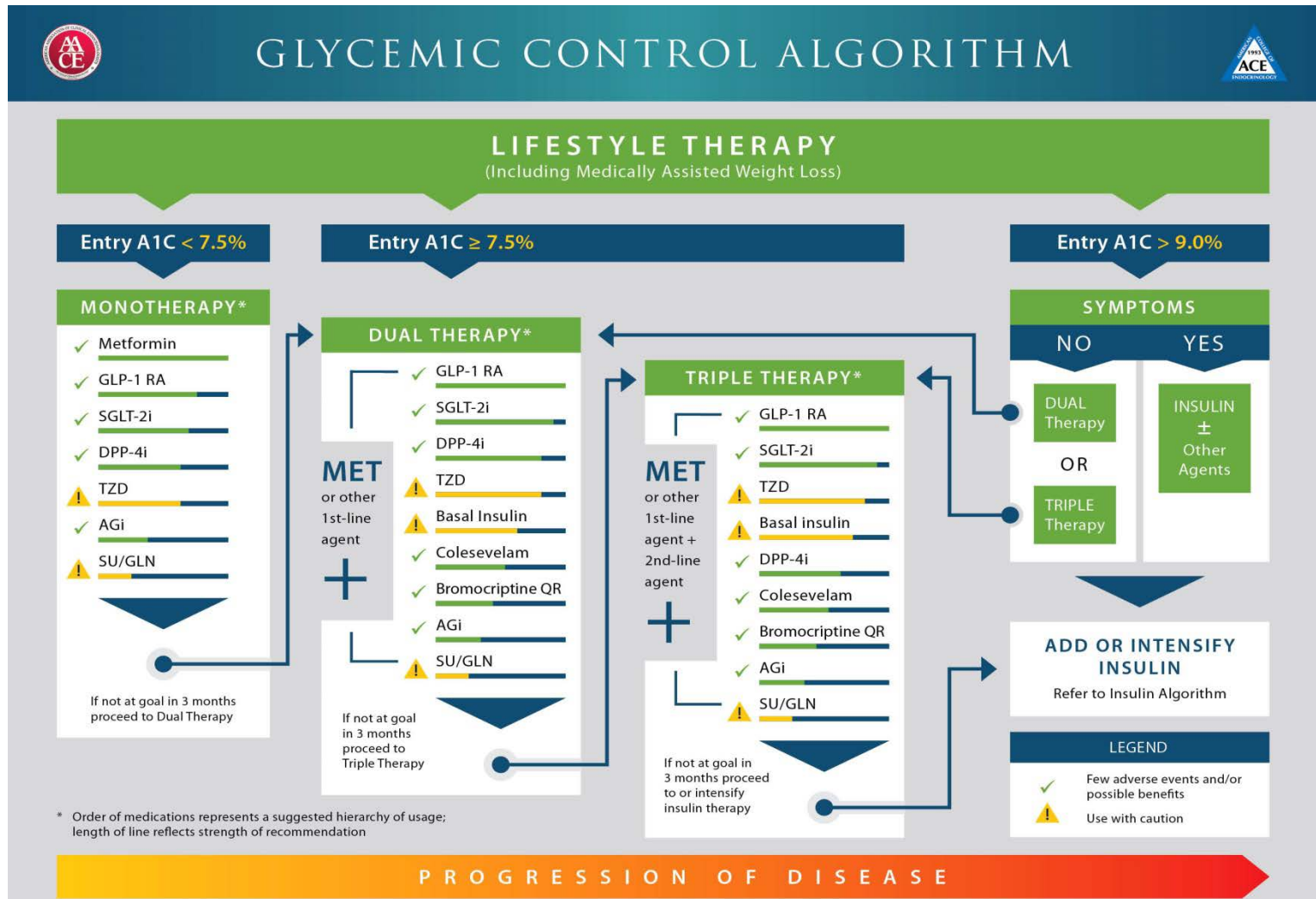
American Diabetes Association



5. Standards of Medical Care in Diabetes-2016 Abridged for Primary Care Providers. Clin Diabetes. 2016;34(1):3-21. Epub 2016/01/26. doi: 10.2337/diaclin.34.1.3. PubMed PMID: 26807004; PubMed Central PMCID: PMC4714725.

Current Guideline Recommendations

American Association of Clinical Endocrinologists



6. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm - 2016 Executive Summary. Endocr pract. 2016;22(1):84-113. Epub 2016/01/06. Doi: 10.4158/ep151126.Cs. Pubmed PMID: 26731084.

Food and Drug Administration-Approved Non-Insulin Anti-Diabetic Monotherapy Medications

Class	Medications	Class	Medications
Amylinomimetic	Pramlintide (SymlinPen)	Meglitinides	Nateglinide (Starlix) Repaglinide (Prandin)
Biguanide	Metformin (Fortamet; Glucophage; Glucophage XR; Glumetza; Riomet)	SGLT2i	Canagliflozin (Invokana) Dapagliflozin (Farxiga) Empagliflozin (Jardiance)
Bile Acid Sequestrant	Colesevelam (Welchol)	Sulfonylureas	Chlorpropamide (Diabinese) Glimepiride (Amaryl) Glipizide (Glucotrol; Glipizide XL; Glucotrol XL) Glyburide (Diabeta; Micronase; Glynase Prestabs) Tolazamide (Tolinase) Tolbutamide (Orinase; Tol-Tab)
Dopamine Agonist	Bromocriptine (Cycloset)	TZD	Pioglitazone (Actos) Rosiglitazone (Avandia)
DPP-4 Inhibitors	Alogliptin (Nesina) Linagliptin (Tradjenta) Saxagliptin (Onglyza) Sitagliptin (Januvia)	α-Glucosidase Inhibitors	Acarbose (Precose) Miglitol (Glyset)
GLP-1 Receptor Agonists	Albiglutide (Tanzeum) Dulaglutide (Trulicity) Exenatide (Byetta; Bydureon) Liraglutide (Victoza) Lixisenatide (Adlyxin)		

Abbreviations: DPP-4i – dipeptidyl peptidase-4 inhibitor; GLP-1 – glucagon-like peptide-1; SGLT2i – sodium-glucose cotransporter-2 inhibitors; TZD - thiazolidinediones

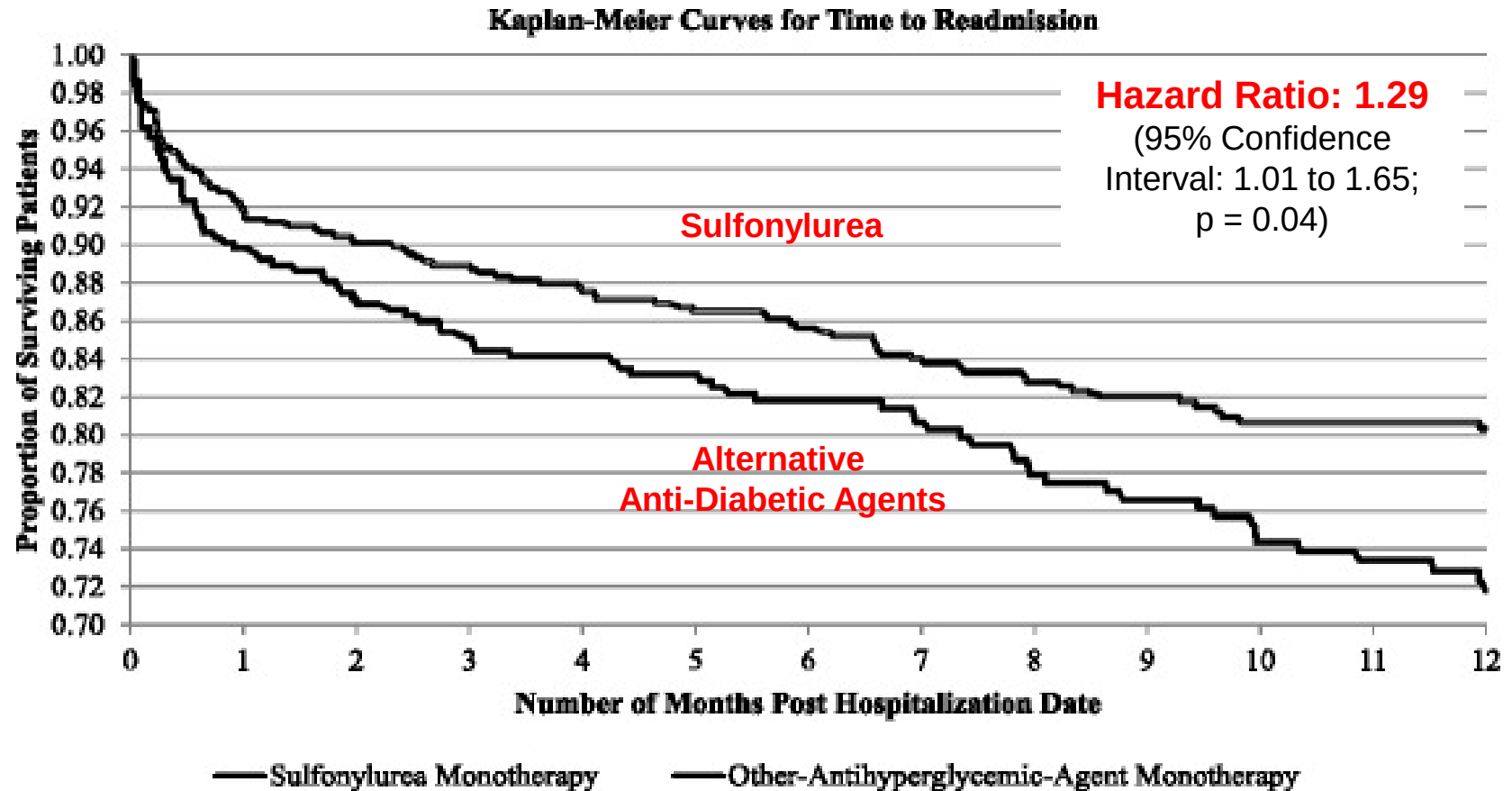
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Time to Readmission

Anti-hyperglycemic Agent Use



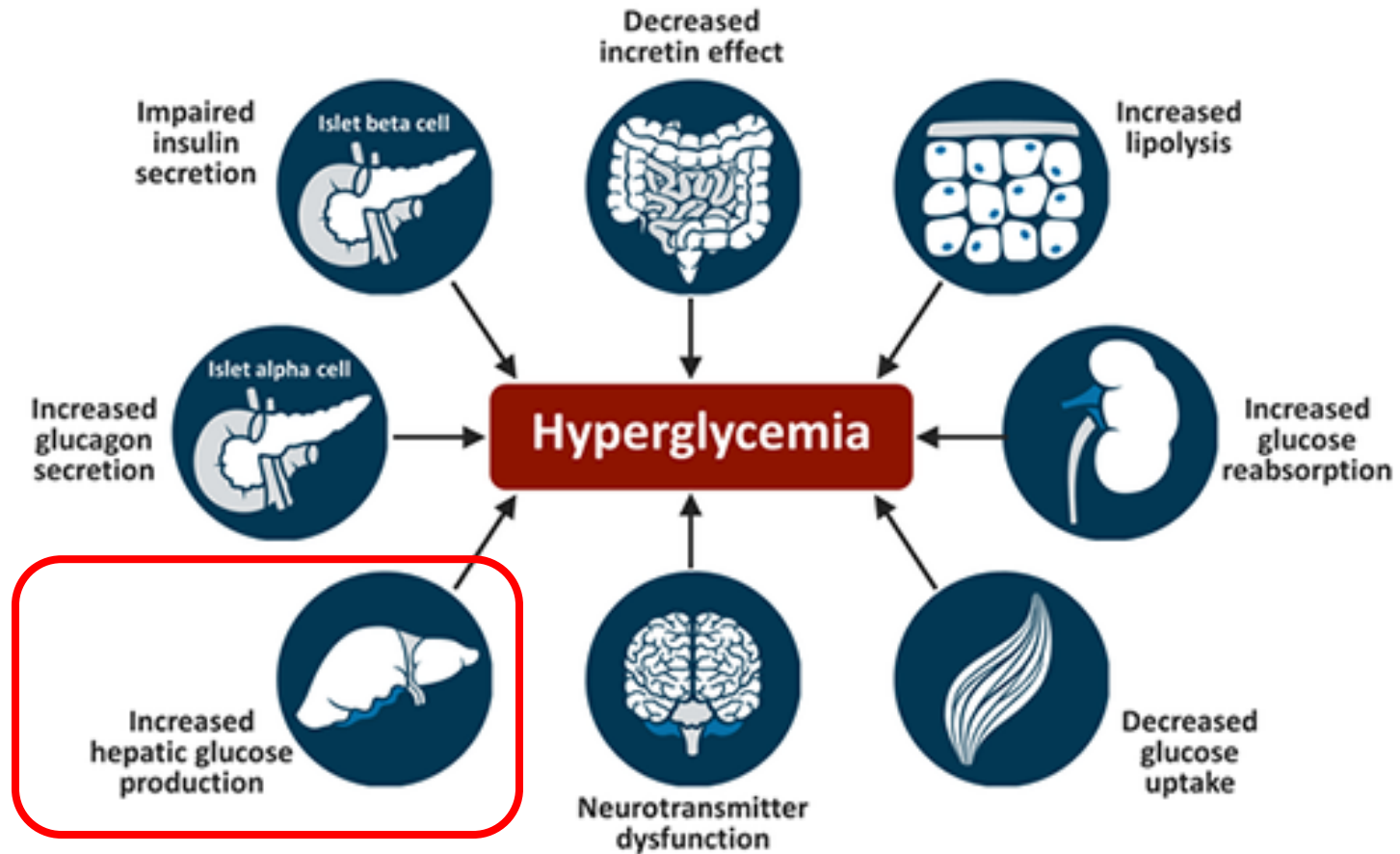
7. Heaton PC, Desai VC, Kelton CM et al. Sulfonylurea Use and the Risk of Hospital Readmission in Patients with Type 2 Diabetes. BMC Endocr Disord. 2016;16:4. Epub 2016/01/21. doi: 10.1186/s12902-016-0084-z. PubMed PMID: 26786291; PubMed Central PMCID: PMC4719386.

Hospital Readmission Rates and Average Readmission Costs⁷

Patient Cohort	Total Number (SE)	Number Readmitted (SE)	Readmission Percentage (%)	Mean Readmission Cost , 2010 Dollars (SE)
All patients	13,537,803 (519,634)	2,578,538 (198,384)	19.1	\$8,814 (\$580)
All SU Patients	7,871,912 (368,351)	1,667,043 (153,735)	21.1	\$9,204 (\$769)
SU Monotherapy	3,217,089 (235,951)	746,579 (106,554)	23.2	\$11,148 (\$1,558)
SU + other AHA	4,654,823 (274,495)	920,464 (113,487)	19.8	\$7,624 (\$412)
All Other Oral AHA	5,665,891 (291,467)	911,495 (108,690)	16.1	\$8,098 (\$737)
Monotherapy, No SFU	5,488,378 (288,154)	881,984 (107,289)	16.1	\$7,673 (\$763)
> 1 Non-SU AHA	177,512 (N/A)	29,511 (N/A)	16.6	\$20,772 (N/A)
Abbreviations: AHA – anti-hyperglycemic agents; N/A – not available; SE – standard error; SFU –sulfonylurea				

The Ominous Octet

Biguanides



4. DeFronzo RA. Banting Lecture. From the Triumvirate to the Ominous Octet: A New Paradigm for the Treatment of Type 2 Diabetes Mellitus. Diabetes. 2009 Apr;58(4):773-95. doi: 10.2337/db09-9028.

Food and Drug Administration-Approved Monotherapy Formulations of Metformin

	Immediate-Release		Extended-Release		Modified-Release
	Glucophage ⁸	Riomet ⁹	Fortamet ¹⁰	Glucophage XR ¹¹	Glumetza ¹²
Dosing	500 mg PO twice daily or 850 mg PO once daily Up-titrate every week or other week, as tolerated MDD: 2550 mg	No fixed dosage regimen Up-titrate every week or other week, as tolerated MDD: 2550 mg	500 to 1000 mg PO once daily May up-titrate by 500 mg weekly, as tolerated MDD: 2500 mg	500 mg PO once daily May up-titrate by 500 mg weekly, as tolerated MDD: 2000 mg	500 mg PO once daily May up-titrate by 500 mg weekly, as tolerated MDD: 2000 mg
Renal Dosing	<u>eGFR > 45 mL/min/1.73 m²: no dose adjustment necessary;¹³ monitor renal function annually or every 3 to 6 months if eGFR > 45 to < 60 mL/min/1.73 m²¹⁴</u> <u>eGFR 30 to 45 mL/min/1.73 m²: initiation not recommended;¹³ consider risks and benefits¹³ and/or a 50% dose reduction and monitor renal function every 3 months¹⁴</u> <u>eGFR < 30 mL/min/1.73 m²: contraindicated¹³</u>				
Administration	With food	With food	Full glass of water with evening meal	With evening meal	With evening meal
How Supplied	Tablets; 500 mg, 850 mg, 1000 mg	Solution; 500 mg/5 mL (cherry or strawberry flavor)	Tablets; 500 mg, 1000 mg	Tablets; 500 mg, 750 mg	Tablets; 500 mg, 1000 mg
Abbreviations: eGFR – estimated glomerular filtration rate; MDD – maximum daily dose; PO – by mouth					

Food and Drug Administration-Approved Monotherapy Formulations of Metformin

	Immediate-Release		Extended-Release		Modified-Release
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Administration	With food	With food	Full glass of water with evening meal	With evening meal	With evening meal
How Supplied	Tablets; 500 mg, 850 mg, 1000 mg	Solution; 500 mg/5 mL (cherry or strawberry flavor)	Tablets; 500 mg, 1000 mg	Tablets; 500 mg, 750 mg	Tablets; 500 mg, 1000 mg
Abbreviations: eGFR – estimated glomerular filtration rate; MDD – maximum daily dose; PO – by mouth					

Clinical Considerations

Biguanides

Advantages	Disadvantages
▪ Durable effects ▪ Extensive clinical experience ▪ Inexpensive ▪ Placebo-like risk for hypoglycemia	▪ Gastrointestinal side effects ▪ Lactic acidosis ▪ Vitamin B₁₂ deficiency

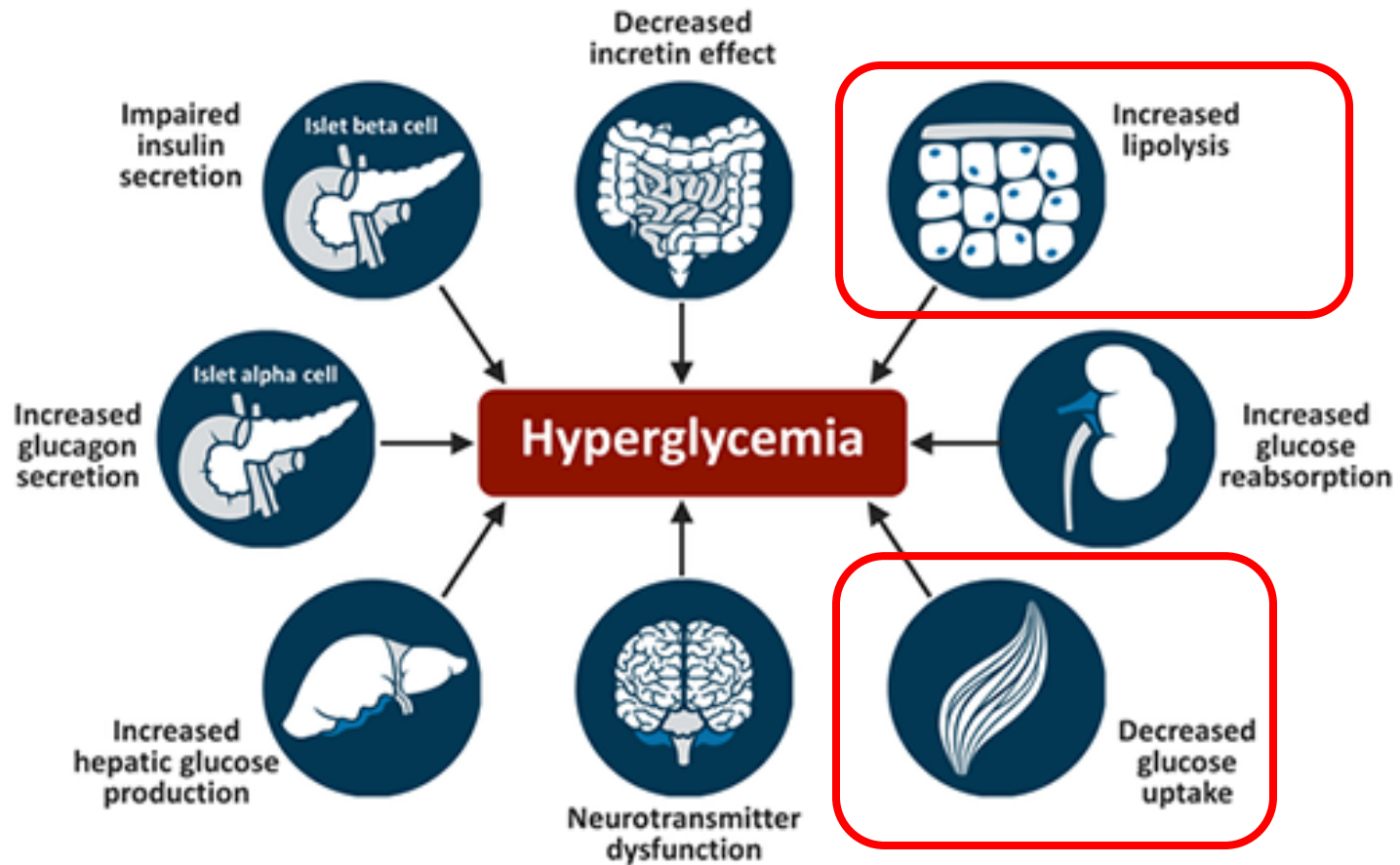
- Patient education
 - Common side effects (i.e., gastrointestinal)
 - Note administration times
 - Use measuring device for liquid solution

5. Standards of Medical Care in Diabetes-2016 Abridged for Primary Care Providers. Clin Diabetes. 2016;34(1):3-21. Epub 2016/01/26. doi: 10.2337/diaclin.34.1.3. PubMed PMID: 26807004; PubMed Central PMCID: PMC4714725.

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The Ominous Octet

Thiazolidinediones



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Food and Drug Administration-Approved Monotherapy Formulations of Thiazolidinediones

	Pioglitazone (Actos) ¹⁵	Rosiglitazone (Avandia) ¹⁶
Dosing	15 – 30 mg PO once daily NYHA class I or II heart failure: 15 mg PO once daily Use with strong CYP2C8 inhibitors (e.g., gemfibrozil): MDD 15 mg MDD: 45 mg	4 mg PO daily in a single or divided dose MDD: 8 mg in a single or divided dose
Warnings and Precautions	<u>Contraindicated:</u> NYHA class III or IV heart failure (<i>boxed warning</i>) <u>Warnings and Precautions:</u> Bladder cancer (pioglitazone) Dose-related edema and weight gain Fractures Heart failure (boxed warning) Macular edema Postmarketing reports of hepatic failure, some fatal	
Administration	Take ± food	
Generic Available	Yes	No
How Supplied	Tablets; 15 mg, 30 mg, 45 mg	Tablets; 2 mg, 4 mg
<u>Abbreviations:</u> MDD – maximum daily dose; NYHA – New York Heart Association; PO – by mouth		

Food and Drug Administration-Approved Thiazolidinedione Combination Products				
	Alogliptin-Pioglitazone (Oseni) ¹⁷	Pioglitazone-Glimepiride (Duetact) ¹⁸	Pioglitazone-Metformin (Actoplus Met; Actoplus Met XR) ^{19,20}	Rosiglitazone-Metformin (Avandamet) ²¹
Dosing	(Dosing based on background medication) 1 PO once daily NYHA class I or II heart failure or use with strong CYP2C8 inhibitors (e.g., gemfibrozil): MDD 25 mg-15 mg MDD: 25 mg-45 mg	(Dosing based on background medication) 1 PO once daily MDD: 30 mg-4 mg	IR: 15 mg-500 mg PO twice daily or 15 mg-850 mg PO once daily NYHA class I or II heart failure: 15 mg-500 mg or 15 mg-850 mg PO once daily MDD: 45 mg-2550 mg ER: 15 mg to 30 mg-1000 mg PO once daily Use with strong CYP2C8 inhibitors (e.g., gemfibrozil): MDD of 15 mg-850 mg once daily (IR) or 15 mg-1000 mg (ER) MDD: 45 mg-2000 mg	(Dosing based on background medication) 1 PO once or twice daily MDD: 8 mg-2000 mg
Renal Dosing	<u>Cl_{Cr} ≥ 30 to < 60 mL/min:</u> maximum dose 12.5 mg-45 mg <u>Cl_{Cr} < 30 mL/min/ESRD:</u> use not recommended	No	Refer to metformin renal dosing slide	Refer to metformin renal dosing slide
Administration	Take ± food Do not split or divide	Take with first main meal of the day	Take with food; ER: Swallow whole; do not crush, split or chew; ghost tablet may be seen in stool	Take with food, generally, in divided doses
Generic Available	Yes	Yes	IR only	No
How Supplied	Tablets; 12.5 mg-15 mg, 12.5 mg-30 mg, 12.5 mg-45 mg, 25 mg-15 mg, 25 mg-30 mg, 25 mg-45 mg	Tablets; 30 mg-2 mg, 30 mg-4 mg	Tablets; IR: 15 mg-500 mg, 15 mg-850 mg ER: 15 mg-1000 mg, 30 mg-1000 mg	Tablets; 2 mg-500 mg, 2 mg-1000 mg
Abbreviations: Cl _{Cr} – creatinine clearance; ER – extended-release; ESRD – end-stage renal disease; IR – immediate-release; MDD – maximum daily dose; NYHA – New York Heart Association; PO – by mouth				

Clinical Considerations

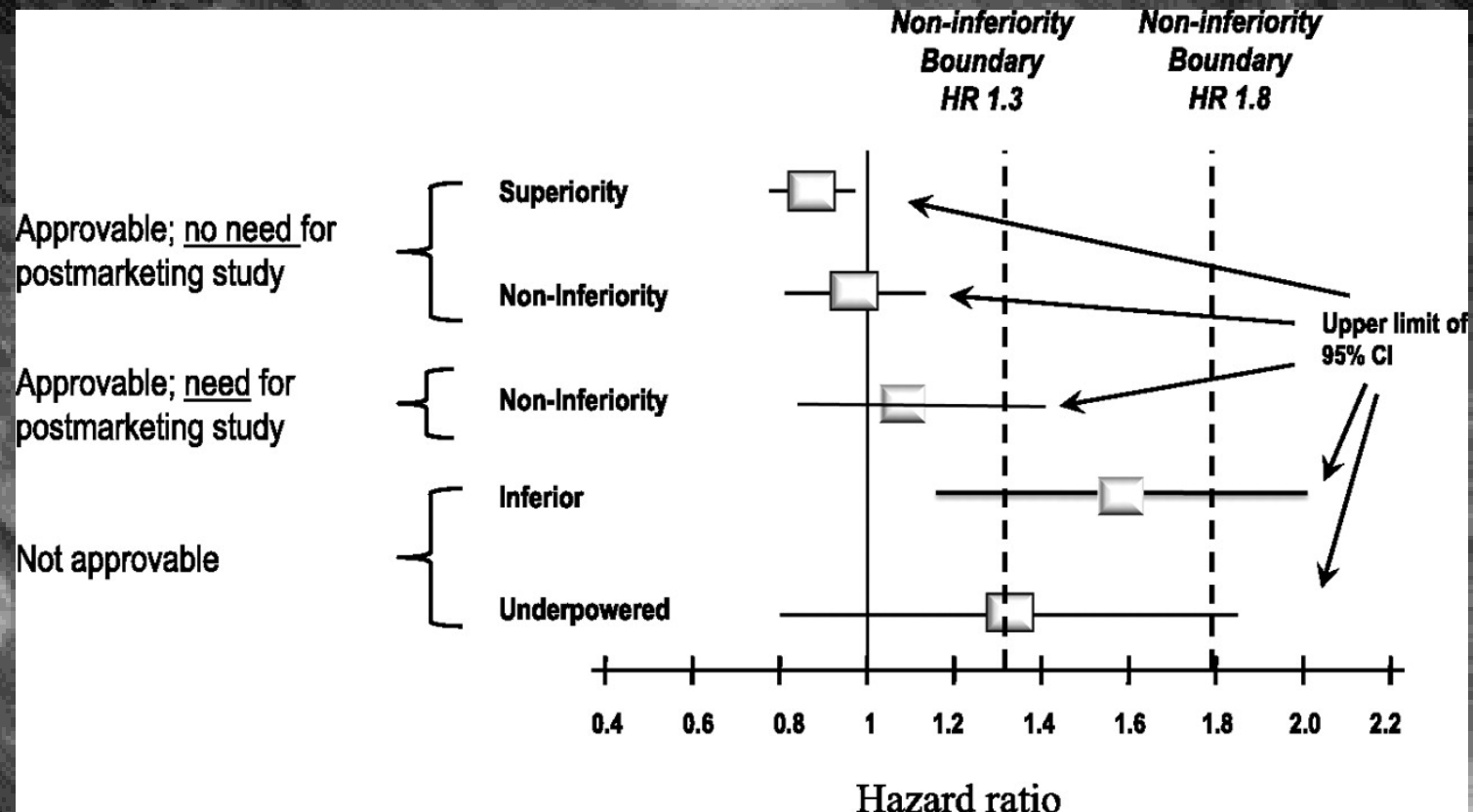
Thiazolidinediones^{5,6}

Advantages	Disadvantages
▪ ↑ HDL-C ▪ ↓ triglycerides by 10% to 20% (pioglitazone) ▪ Durability ▪ Generic (pioglitazone) ▪ Placebo-like risk for hypoglycemia ▪ Potential cardiovascular benefit (pioglitazone)	▪ ↑ LDL-C by 5% to 15% (rosiglitazone) ▪ Bone fractures ▪ Edema ▪ Heart failure ▪ Weight gain
<u>Abbreviations:</u> HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol	

- Patient education
 - Side effects
 - Abdominal pain, changes in vision, fluid retention, poly- or dysuria, weight gain
 - Signs or symptoms of heart failure
 - Dyspnea, edema, rapid weight gain



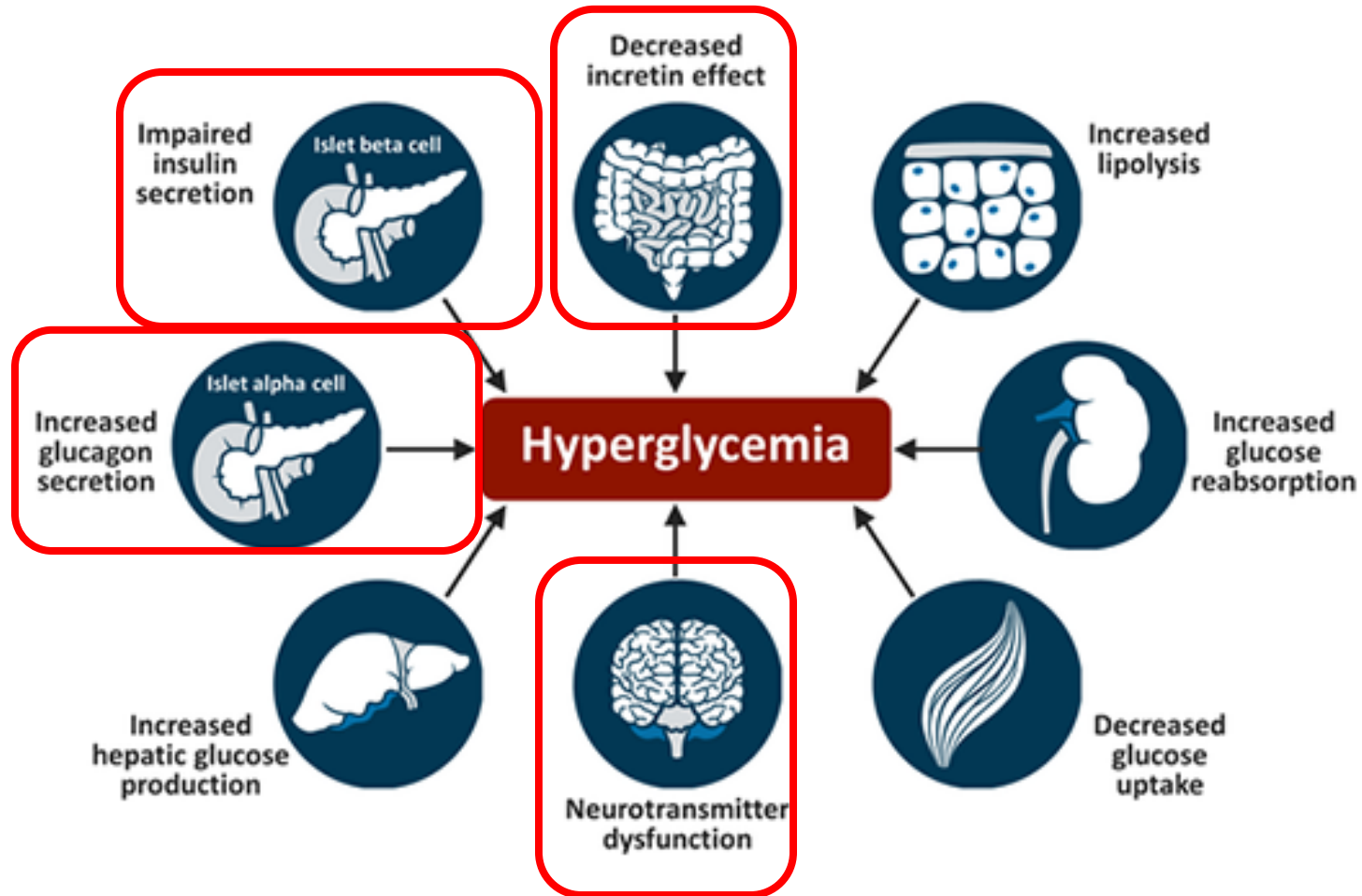
APPROVED



22. Hirshberg B, Raz I. Impact of the U.S. Food and Drug Administration Cardiovascular Assessment Requirements on the Development of Novel Antidiabetes Drugs. Diabetes Care. 2011;34 Suppl 2:S101-6. Epub 2011/05/06. doi: 10.2337/dc11-s202. PubMed PMID: 21525438; PubMed Central PMCID: PMC3632144.

The Ominous Octet

Glucagon-like Peptide-1 Receptor Agonists



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Food and Drug Administration-Approved GLP-1 Receptor Agonists

	Albiglutide (Tanzeum) ²³	Dulaglutide (Trulicity) ²⁴	Exenatide (Byetta) ²⁵	Exenatide ER (Bydureon) ²⁶	Liraglutide (Victoza) ²⁷	Lixisenatide (Adlyxin) ²⁸
Dosing	30 mg SQ once weekly May up-titrate to 50 mg once weekly	0.75 mg SQ once weekly May up-titrate to 1.5 mg once weekly	5 mcg SQ twice daily May up-titrate to 10 mcg twice daily after 1 month	2 mg SQ once weekly	0.6 mg SQ once daily for 1 week then increase to 1.2 mg May up-titrate to 1.8 mg once daily	10 mcg SQ once daily for 2 weeks then increase to 20 mcg
Approved for use with Basal Insulin	Yes	No	Yes	No	Yes	No
Use in Patients with $Cl_{Cr} < 30$ mL/min	Acceptable	Acceptable	Avoid	Avoid	Acceptable	Acceptable
Specific Dosing Instructions	No	No	≤ 1 h before 2 main meals (≥ 6 h apart)	No	No	≤ 1 h before first meal of the day
CV Outcomes Data Available	No	No	No	No	Yes	Yes

Abbreviations: CV – cardiovascular; ER – extended-release; GLP-1 – glucagon-like peptide-1; h – hour; SQ – subcutaneously

Food and Drug Administration-Approved GLP-1 Receptor Agonists

	Albiglutide (Tanzeum) ²³	Dulaglutide (Trulicity) ²⁴	Exenatide (Byetta) ²⁵	Exenatide ER (Bydureon) ²⁶	Liraglutide (Victoza) ²⁷	Lixisenatide (Adlyxin) ²⁸
Dosing	30 mg SQ once weekly May up-titrate to 50 mg once weekly	0.75 mg SQ once weekly May up-titrate to 1.5 mg once weekly	5 mcg SQ twice daily May up- titrate to 10 mcg twice daily after 1 month	2 mg SQ once weekly	0.6 mg SQ once daily for 1 week then increase to 1.2 mg May up-titrate to 1.8 mg once daily	10 mcg SQ once daily for 2 weeks then increase to 20 mcg
Approved for use with Basal Insulin	Yes	No	Yes	No	Yes	No
Use in Patients with Cl_{Cr} < 30 mL/min	Acceptable	Acceptable	Avoid	Avoid	Acceptable	Acceptable
Specific Dosing Instructions	No	No	≤ 1 h before 2 main meals (≥ 6 h apart)	No	No	≤ 1 h before first meal of the day
CV Outcomes Data Available	No	No	No	No	Yes	Yes

Abbreviations: CV – cardiovascular; ER – extended-release; GLP-1 – glucagon-like peptide-1; h – hour; SQ – subcutaneously

Cardiovascular Outcomes Data for Glucagon-like Peptide-1 Receptor Agonists

Agent	Liraglutide (Victoza)	Lixisenatide (Adlyxin)	Semaglutide (N/A)
Clinical Trial	LEADER ²⁹	ELIXA ³⁰	SUSTAIN-6 ³¹
Study Design	DB, MC, NI → S, PC, R trial	DB, MC, NI → S, PC, R trial	DB, MC, NI , PC, R trial
Intervention	Liraglutide 1.8 mg SQ once daily	Lixisenatide 10 – 20 mcg SQ once daily	Semaglutide 0.5 mg to 1 mg SQ once weekly
Patient Population	≥ 50-years-old coexisting with a CV condition* or ≥ 60-years-old with ≥ 1 CV risk factor^; baseline HbA _{1c} : 8.7%; T2DM	≥ 30-years-old; acute coronary event ≤ 180 days before screening; baseline HbA _{1c} : ~7.65%; T2DM	≥ 50-years-old with CV disease or chronic HF or CKD ≥ stage 3; ≥ 60-years-old with ≥ 1 CV risk factor^; baseline HbA _{1c} : ~8.7%; T2DM
Primary Endpoint	Time-to-event for first occurrence of death from CV causes, nonfatal MI or nonfatal stroke	Time-to-event for first occurrence of death from CV causes, nonfatal MI, nonfatal stroke, hospitalization for UA	Time-to-event for first occurrence of death from CV causes, nonfatal MI (including silent) or nonfatal stroke
Primary Endpoint Outcome, P vs. I	14.9% vs. 13% [HR 0.87; 95% CI: 0.78 – 0.97; p < 0.001 for NI; p = 0.01 for S]	13.2% vs. 13.4% [HR 1.02; 95% CI: 0.89 – 1.17; p < 0.001 for NI; p = 0.81 for S]	8.9% vs. 6.6% [HR 0.74; 95 CI 0.58 to 0.95; p < 0.001; p = 0.02 for S {not prespecified}]
Number Needed to Treat	66 patients over 3 years	N/A	N/A

* e.g., cerebrovascular disease; coronary heart disease; peripheral vascular disease

^ e.g., hypertension; microalbuminuria

Abbreviations: CI – confidence interval; CV – cardiovascular; DB – double-blind, HR – hazard ratio; I – intervention; MC – multi-center; MI – myocardial infarction; N/A – not applicable; NI – noninferiority; P – placebo; PC – placebo-controlled; R – randomized; S – superiority; SQ – subcutaneously; T2DM – type 2 diabetes mellitus

Clinical Considerations

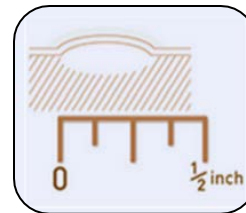
Glucagon-Like Peptide-1 Receptor Agonists

Advantages	Disadvantages
▪ Placebo-like risk for hypoglycemia ▪ Positive cardiovascular outcomes data ▪ Weight loss	▪ Acute pancreatitis ▪ C-cell hyperplasia/medullary thyroid tumors observed in animal models ▪ Cost ▪ Gastrointestinal side effects (i.e., nausea, vomiting, diarrhea) ▪ Increased heart rate ▪ Injectable with training requirements

Clinical Considerations

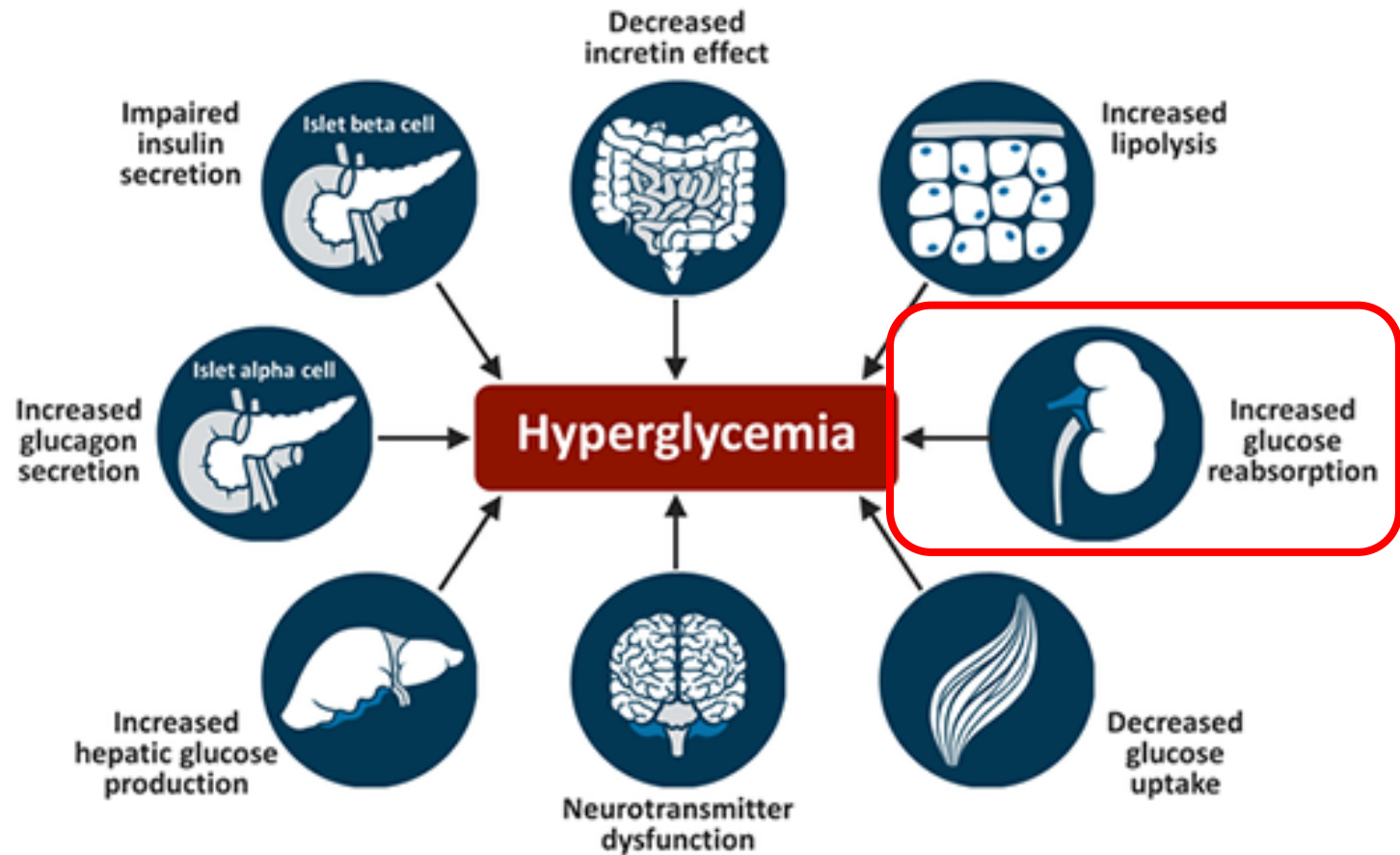
Glucagon-Like Peptide-1 Receptor Agonists

- Patient education
 - Eat slowly
 - Consider halving meals
 - Signs and symptoms of pancreatitis
 - Abdominal pain, nausea $\pm$ vomiting
 - Injection training
 - Anecdotally, dulaglutide (Trulicity) tends to be a user-friendly device
 - Exenatide ER (Bydureon)
 - Consider adjustment of medications that can cause hypoglycemia
 - e.g., insulin, sulfonylureas



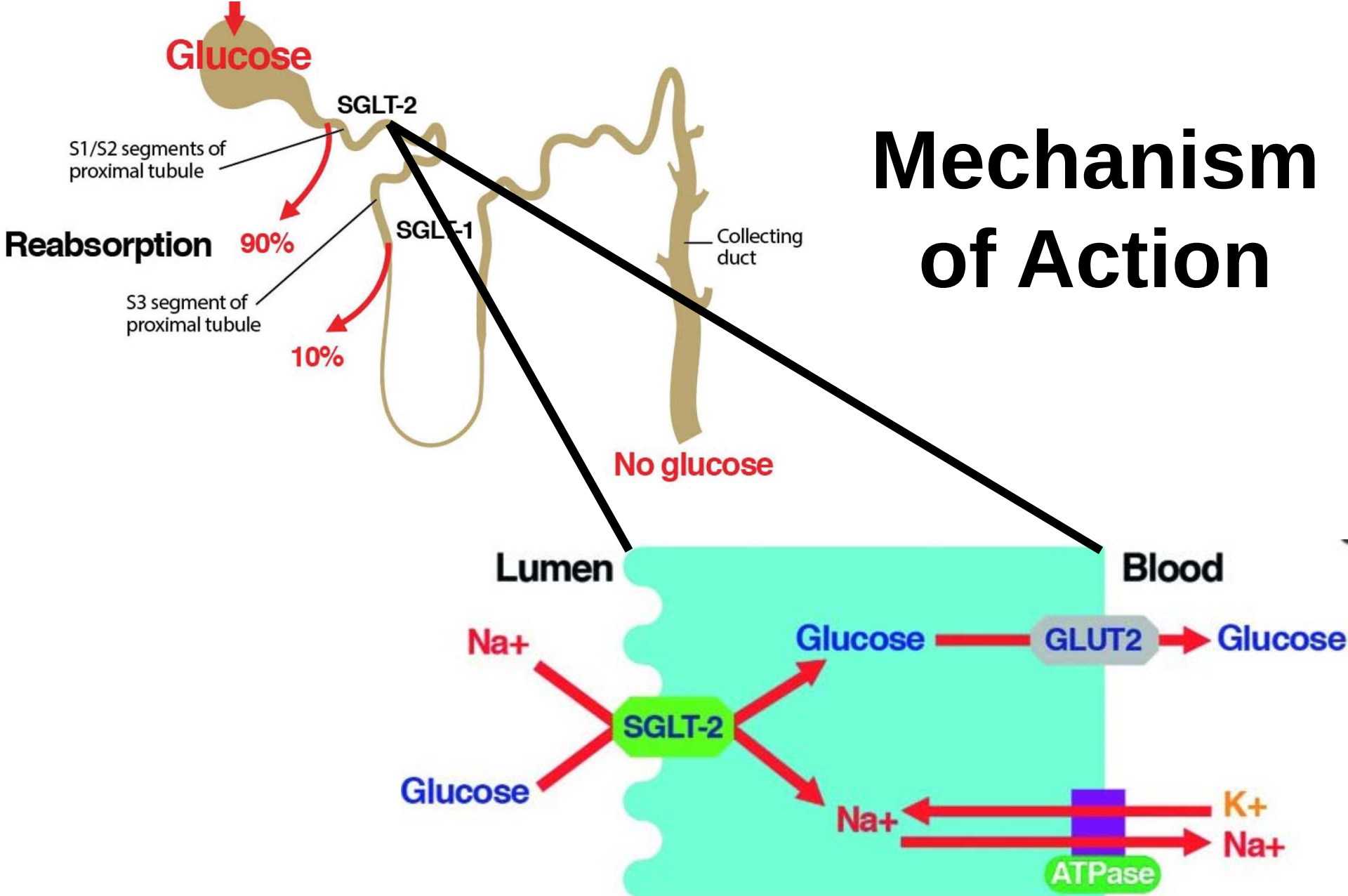
The Ominous Octet

Sodium-Glucose Cotransporter-2 Inhibitors



4. DeFronzo RA. Banting Lecture. From the Triumvirate to the Ominous Octet: A New Paradigm for the Treatment of Type 2 Diabetes Mellitus. Diabetes. 2009 Apr;58(4):773-95. doi: 10.2337/db09-9028.

Mechanism of Action



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Canagliflozin
(Invokana)

Empagliflozin-Linagliptin
(Glyxambi)
Empagliflozin-Metformin
(Synjardy)

2013

2014

2015

2016

Dapagliflozin
(Farxiga)

Empagliflozin
(Jardiance)

Canagliflozin-Metformin
(Invokamet)

Dapagliflozin-Metformin ER
(Xigduo XR)

Canagliflozin-Metformin ER
(Invokamet XR)

SGLT2 INHIBITORS

Food and Drug Administration-Approved Monotherapy Formulations of SGLT2 Inhibitors

	Canagliflozin (Invokana) ³³	Dapagliflozin (Farxiga) ³⁴	Empagliflozin (Jardiance) ³⁵
Dosing	100 mg PO once daily May up-titrate to 300 mg PO once daily if eGFR $\geq$ 60 mL/min/1.73 m ²	5 mg PO once daily May up-titrate to 10 mg PO once daily	10 mg PO once daily May up-titrate to 25 mg PO once daily
Renal Dosing	<u>eGFR 45 to < 60 mL/min/1.73 m²</u> : MDD 100 mg <u>eGFR $\geq$ 30 to < 45 mL/min/1.73 m²</u> : do not initiate therapy; discontinue if persistently in this range <u>eGFR < 30 mL/min/1.73 m² /ESRD/Hemodialysis</u> : use is contraindicated	<u>eGFR < 60 mL/min/1.73 m²</u>: do not initiate therapy; discontinue therapy if persistently in this range <u>eGFR < 30 mL/min/1.73 m² /ESRD/Hemodialysis</u> : use is contraindicated	<u>eGFR < 45 mL/min/1.73 m²</u> : do not initiate therapy; discontinue if persistently in this range <u>eGFR < 30 mL/min/1.73 m² /ESRD/Hemodialysis</u> : use is contraindicated
Administration	Recommended to take before first meal of the day	Take in the morning $\pm$ food	Take in the morning $\pm$ food
CV Outcomes Data Available	No	No	Yes

Abbreviations: CV – cardiovascular; eGFR – estimated glomerular filtration rate; ESRD – end-stage renal disease; MDD – maximum daily dose; PO – by mouth; SGLT2 – sodium-glucose cotransporter-2

Food and Drug Administration-Approved Monotherapy Formulations of SGLT2 Inhibitors

	Canagliflozin (Invokana) ³³	Dapagliflozin (Farxiga) ³⁴	Empagliflozin (Jardiance) ³⁵
Dosing	100 mg PO once daily May up-titrate to 300 mg PO once daily if eGFR $\geq$ 60 mL/min/1.73 m ²	5 mg PO once daily May up-titrate to 10 mg PO once daily	10 mg PO once daily May up-titrate to 25 mg PO once daily
Renal Dosing	<u>eGFR 45 to < 60 mL/min/1.73 m²</u> : MDD 100 mg <u>eGFR $\geq$ 30 to < 45 mL/min/1.73 m²</u> : do not initiate therapy; discontinue if persistently in this range <u>eGFR < 30 mL/min/1.73 m² /ESRD/Hemodialysis</u> : use is contraindicated	<u>eGFR < 60 mL/min/1.73 m²</u>: do not initiate therapy; discontinue therapy if persistently in this range <u>eGFR < 30 mL/min/1.73 m² /ESRD/Hemodialysis</u> : use is contraindicated	<u>eGFR < 45 mL/min/1.73 m²</u> : do not initiate therapy; discontinue if persistently in this range <u>eGFR < 30 mL/min/1.73 m² /ESRD/Hemodialysis</u> : use is contraindicated
Administration	Recommended to take before first meal of the day	Take in the morning $\pm$ food	Take in the morning $\pm$ food
CV Outcomes Data Available	No	No	Yes

Abbreviations: CV – cardiovascular; eGFR – estimated glomerular filtration rate; ESRD – end-stage renal disease; MDD – maximum daily dose; PO – by mouth; SGLT2 – sodium-glucose cotransporter-2

Cardiovascular Outcomes Data for SGLT2 Inhibitors	
Agent	Empagliflozin (Jardiance)
Clinical Trial	EMPA-REG OUTCOME
Study Design	DB, MC, NI → S, PC, R trial
Intervention	Empagliflozin 10 – 25 mg PO once daily
Patient Population	≥ 18-years-old; high CV risk (e.g., PAD, MI, single- or multi-vessel CAD, stroke); baseline HbA _{1c} : ~8.08%; T2DM
Primary Endpoint	Time-to-event for first occurrence of death from CV causes (including fatal MI and fatal stroke), nonfatal MI (excluding silent MI) and nonfatal stroke
Primary Endpoint Outcome, P vs. I	12.1% vs. 10.5% [HR 0.86; 95.02% CI: 0.74 – 0.99; p < 0.001 for NI; p = 0.04 for S]
Number Needed to Treat	39 patients over 3 years
<u>Abbreviations:</u> CAD – coronary artery disease; CI – confidence interval; CV – cardiovascular; DB – double-blind, HR – hazard ratio; I – intervention; MC – multi-center; MI – myocardial infarction; NI – noninferiority; P – placebo; PAD – peripheral artery disease; PC – placebo-controlled; PO – by mouth; R – randomized; S – superiority; SGLT2 – sodium-glucose cotransporter-2; T2DM – type 2 diabetes mellitus	

36. Rosenstein R, Hough A. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2016;374(11):1093-4. Epub 2016/03/18. doi: 10.1056/NEJMc1600827#SA4. PubMed PMID: 26981944.

Food and Drug Administration-Approved SGLT2 Inhibitor Combination Products

	Canagliflozin-Metformin (Invokamet) ³⁷	Canagliflozin-Metformin ER (Invokamet XR) ³⁸	Dapagliflozin-Metformin ER (Xigduo XR) ³⁹	Empagliflozin-Linagliptin (Glyxambi) ⁴⁰	Empagliflozin-Metformin (Synjardy) ⁴¹
Dosing	(Dosing based on background medication) 1 tablets PO twice daily May up-titrate to 300 mg-2000 mg	(Dosing based on background medication) 2 tablets PO once daily May up-titrate to 300 mg-2000 mg	(Dosing based on background medication) 1 to 2 tablets once daily May up-titrate to 10 mg-2000 mg	10 mg-5 mg PO once daily May up-titrate to 25 mg-5 mg	(Dosing based on background medication) 1 PO twice daily May up-titrate to 25 mg-2000 mg
Renal Dosing	<u>eGFR 45 to < 60 mL/min/1.73 m²:</u> MDD 100 mg canagliflozin <u>eGFR < 45 mL/min/1.73 m² /ESRD/ Hemodialysis:</u> use is contraindicated	<u>eGFR 45 to < 60 mL/min/1.73 m²:</u> MDD 100 mg canagliflozin <u>eGFR < 45 mL/min/1.73 m² /ESRD/ Hemodialysis:</u> use is contraindicated	<u>eGFR < 60 mL/min/1.73 m² /Hemodialysis:</u> contraindicated	<u>eGFR < 45 mL/min/1.73 m²:</u> do not initiate therapy; discontinue if persistently in this range <u>eGFR < 30 mL/min/1.73 m² /ESRD/Dialysis:</u> use is contraindicated	<u>eGFR < 45 mL/min/1.73 m² /ESRD/Dialysis:</u> use is contraindicated
Administration	Recommended to take with first meal of the day	Recommended to take with first meal of the day Swallow whole; do not crush cut or chew	Take in the morning with food Swallow whole; do not crush cut or chew	Take in the morning ± food	Take with food

Abbreviations: eGFR – estimated glomerular filtration rate; ESRD – end-stage renal disease; MDD – maximum daily dose; PO – by mouth; SGLT2 – sodium-glucose cotransporter-2

Clinical Considerations

Sodium-Glucose Cotransporter-2 Inhibitors

Advantages	Disadvantages
▪ Decrease in blood pressure and serum uric acid ▪ Placebo-like risk for hypoglycemia ▪ Positive cardiovascular outcomes data ▪ Weight loss	▪ Diabetic ketoacidosis ▪ Genitourinary tract infections ▪ Increased LDL-C ▪ Polyuria ▪ Transient increase in serum creatinine ▪ Urinary tract infections leading to pyelonephritis and urosepsis ▪ Volume depletion/hypotension/dizziness
<u>Abbreviations:</u> LDL-C – low-density lipoprotein cholesterol	

Clinical Considerations

Sodium-Glucose Cotransporter-2 Inhibitors

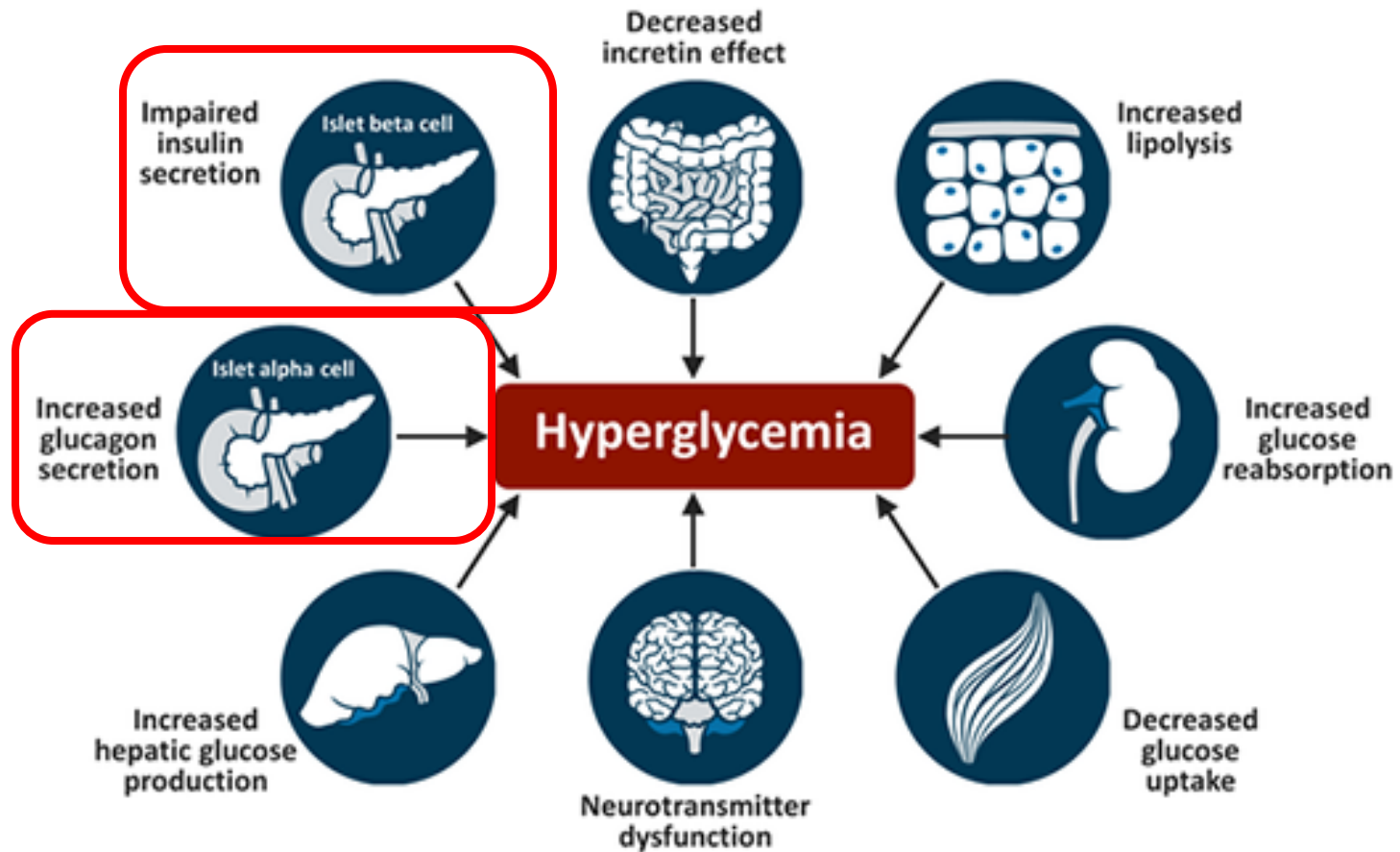
- Patient education
 - Polyuria
 - Hydration
 - Hygiene
 - Signs and symptoms of DKA
 - When to hold therapy
- Glycosuria
 - 2+



42. Peters AL, Buschur EO, Buse JB, et al. Euglycemic Diabetic Ketoacidosis: A Potential Complication of Treatment With Sodium-Glucose Cotransporter 2 Inhibition. *Diabetes Care*. 2015;38(9):1687-93. Epub 2015/06/17. doi: 10.2337/dc15-0843. Pubmed PMID: 26078479; PMCID: 4542270. Image: http://www.nephrologynews.com/wp-content/uploads/2015/06/TS_Diabetes_167164767.jpg

The Ominous Octet

Dipeptidyl Peptidase-4 Inhibitors



4. DeFronzo RA. Banting Lecture. From the Triumvirate to the Ominous Octet: A New Paradigm for the Treatment of Type 2 Diabetes Mellitus. Diabetes. 2009 Apr;58(4):773-95. doi: 10.2337/db09-9028.

Food and Drug Administration-Approved Monotherapy Formulations of DPP-4 Inhibitors

	Alogliptin (Nesina) ⁴³	Linagliptin (Tradjenta) ⁴⁴	Saxagliptin (Onglyza) ⁴⁵	Sitagliptin (Januvia) ⁴⁶
Dosing	25 mg PO once daily	5 mg PO once daily	2.5 to 5 mg PO once daily Use with strong CYP3A4/5 inhibitors: MDD: 2.5 mg	100 mg PO once daily
Renal Dosing	<u>$Cl_{Cr} \geq 30$ to < 60 mL/min:</u> 12.5 mg PO once daily <u>$Cl_{Cr} < 30$ mL/min /Hemodialysis:</u> 6.25 mg PO once daily	No dosage adjustment necessary	<u>$Cl_{Cr} \leq 50$ mL/min:</u> 2.5 mg PO once daily <u>Hemodialysis:</u> 2.5 mg PO once daily <i>postdialysis</i>	<u>$Cl_{Cr} \geq 30$ to < 50 mL/min:</u> 50 mg PO once daily <u>$Cl_{Cr} < 30$ mL/min/Hemodialysis/</u> <u>Peritoneal Dialysis:</u> 25 mg PO once daily
Administration	Take $\pm$ food	Take $\pm$ food	Take $\pm$ food Swallow whole Do not split or cut	Take $\pm$ food
Generic Available	Yes	No	No	No
How Supplied	Tablets; 6.25 mg, 12.5 mg, 25 mg	Tablets; 5 mg	Tablets; 2.5 mg, 5 mg	Tablets; 25 mg, 50 mg 100 mg

Abbreviations: Cl_{Cr} : creatinine clearance; DPP-4 – dipeptidyl peptidase-4; ESRD – end-stage renal disease; MDD – maximum daily dose; PO – by mouth

Food and Drug Administration-Approved DPP-4 Inhibitor Combination Products*

	Alogliptin-Metformin (Kazano) ⁴⁷	Linagliptin-Metformin (Jentadueto; Jentadueto XR) ^{48,49}	Saxagliptin-Metformin (Kombiglyze XR) ⁵⁰	Sitagliptin-Metformin (Janumet; Janumet XR) ^{51,52}
Dosing	(Dosing based on background medication) 1 PO twice daily MDD: 25 mg-2000 mg	(Dosing based on background medication) 1 PO once or twice daily MDD: 5 mg-2000 mg	(Dosing based on background medication) 1 PO once daily Use with strong CYP3A4/5 inhibitors: MDD of 2.5 mg-1000 mg MDD: 5 mg-2000 mg	(Dosing based on background medication) 1 PO once or twice daily MDD: 100 mg-2000 mg
Renal Dosing	<u>eGFR < 60 mL/min/1.73 m²: avoid</u> <u>eGFR < 30 mL/min/1.73 m²: contraindicated</u> OR Refer to metformin and alogliptin renal dosing slides	Refer to metformin renal dosing slide	<u>S_{Cr} ≥ 1.5 mg (males) or ≥ 1.4 mg (females) or abnormal Cl_{Cr}: contraindicated</u> OR Refer to metformin and saxagliptin renal dosing slides	<u>S_{Cr} ≥ 1.5 mg (males) or ≥ 1.4 mg (females) or abnormal Cl_{Cr}: contraindicated</u> OR Refer to metformin and sitagliptin renal dosing slides
Administration	Take with food Swallow whole Do not split or divide	Take with food ER: Swallow whole Do not split or divide	Take with evening meal Swallow whole Do not crush, cut or chew	Take with food (ER: evening meal) Swallow whole (ER) Do not chew (ER), crush (ER) or split
Generic Available	Yes	No	No	No

* Not listed: alogliptin-pioglitazone (Oseni); empagliflozin-linagliptin (Glyxambi) – please refer to other class slides noted earlier

Abbreviations: DPP-4 – dipeptidyl peptidase-4; eGFR – estimated glomerular filtration rate; ER – extended-release; MDD – maximum daily dose; PO – by mouth; S_{Cr} – serum creatinine

Clinical Considerations

Dipeptidyl Peptidase-4 Inhibitors

Advantages	Disadvantages
▪ Placebo-like risk for hypoglycemia ▪ Weight neutral ▪ Well tolerated	▪ ↑ heart failure hospitalization ▪ Acute pancreatitis ▪ Angioedema/urticaria ▪ Cost

- Patient education
 - Signs and symptoms of pancreatitis
 - Abdominal pain, nausea ± vomiting
 - Discontinue if starting a glucagon-like peptide-1 receptor agonist (GLP-1 RA)



EC is a 56-year-old male who has been referred to the endocrinologist for the management of his type 2 diabetes mellitus (T2DM). He has had T2DM for almost 4 years. He endorses no complaints during his visit. His past medical history and supporting clinical information are summarized below.

Past medical history: hyperlipidemia; hypertension; hypothyroidism; obesity; sleep apnea

Vitals

- 289.4 lbs. (BMI: 41.5 kg/m²)
- Blood pressure: 120/74 mm Hg
- Pulse: 74 beats per minute

Current medications

- Diltiazem 120 mg ER: 1 PO once daily
- Levothyroxine 200 mcg: 1PO twice daily six days per week
- Losartan 100 mg: 1 PO once daily
- Metformin 1000 mg: 1 PO twice daily

Pertinent lab data

- | | |
|---------------------------------------|--|
| - HbA1c : 9.16% | - Non-HDL-C: 202 mg/dL |
| - LDL-C: 168 mg/dL | - TSH: 2.1 milli-international units/L |
| - eGFR: 55 mL/min/1.73 m ² | |

Abbreviations: BMI – body mass index; eGFR – estimated glomerular filtration rate; ER – extended-release; lbs. – pounds; LDL-C – low-density lipoprotein cholesterol; non-HDL-C – non-high-density lipoprotein cholesterol; PO – by mouth; TSH – thyroid-stimulating hormone

Image: https://www.tradjenta.com/?sc=TRAACQWEBSEMGL0214001&utm_source=google&utm_medium=cpc&utm_term=tradjenta&utm_campaign=decision_-_branded&gclid=CPjQ5-3R7M8CFVDr6Qod6C4MZg&gclid=ds

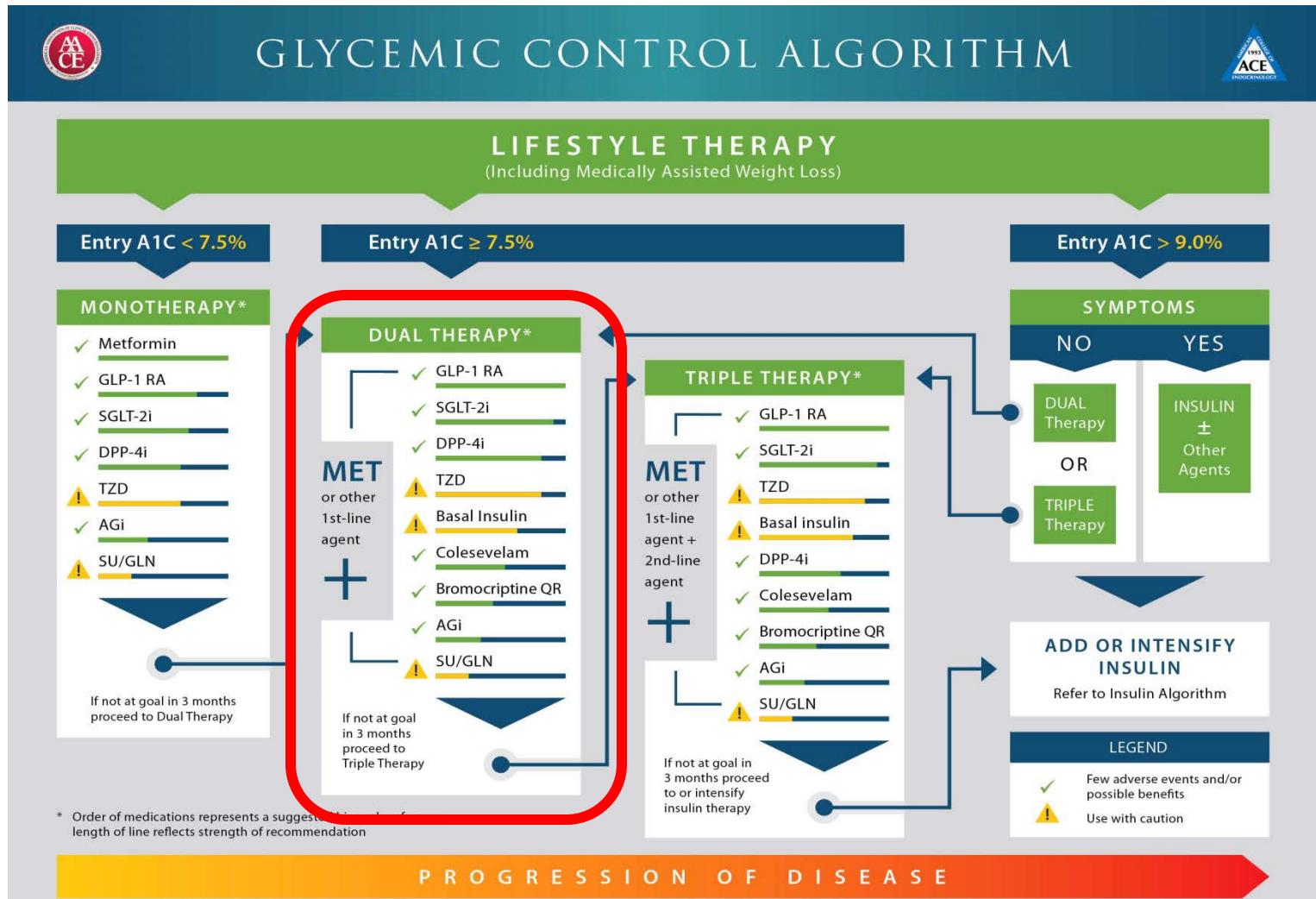


What would be your recommendation for the management of EC's T2DM?

1. Increase metformin to 2,550 mg daily
2. Initiate alogliptin (Nesina) 25 mg by mouth once daily
3. Initiate empagliflozin-metformin (Synjardy) 5 mg-1000 mg by mouth twice daily
4. Initiate dulaglutide (Trulicity) 0.75 mg subcutaneously once weekly

Current Guideline Recommendations

American Association of Clinical Endocrinologists



6. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm - 2016 Executive Summary. Endocr pract. 2016;22(1):84-113. Epub 2016/01/06. Doi: 10.4158/ep151126.Cs. Pubmed PMID: 26731084.



What would be your recommendation for the management of EC's T2DM ?

1. Increase metformin to 2,550 mg daily
2. Initiate alogliptin (Nesina) 25 mg by mouth once daily
3. Initiate empagliflozin-metformin (Synjardy) 5 mg-1000 mg by mouth twice daily
4. **Initiate dulaglutide (Trulicity) 0.75 mg subcutaneously once weekly**



Which of the following is/are appropriate counseling point(s) to inquire/educate EC about for his new dulaglutide (Trulicity) prescription?

1. Common side effects: nausea, vomiting and diarrhea
2. Injection technique
3. Inquire about any known history of heart failure
4. Rare, but serious side effects: diabetic ketoacidosis, urosepsis
5. (1) and (2)
6. (3) and (4)



Which of the following is/are appropriate counseling point(s) to inquire/educate EC about for his new dulaglutide (Trulicity) prescription?

1. Common side effects: nausea, vomiting and diarrhea
2. Injection technique
3. Inquire about any known history of heart failure
4. Rare, but serious side effects: diabetic ketoacidosis, urosepsis
- 5. (1) and (2)**
6. (3) and (4)

Conclusions

- As of 2014, the incidence of diabetes has quadrupled since 1980¹
 - ~1 out of 10 individuals has diabetes
- Anti-diabetic medications have demonstrated the ability to reduce micro- and macrovascular complications
- Efforts should be made to tailor anti-diabetic therapy for each patient while minimizing one's risk for hypoglycemia

Part 2: Starting Non-Insulin Medication in the Primary Care Setting for Type 2 Diabetes

Matthew Stryker, Pharm.D.

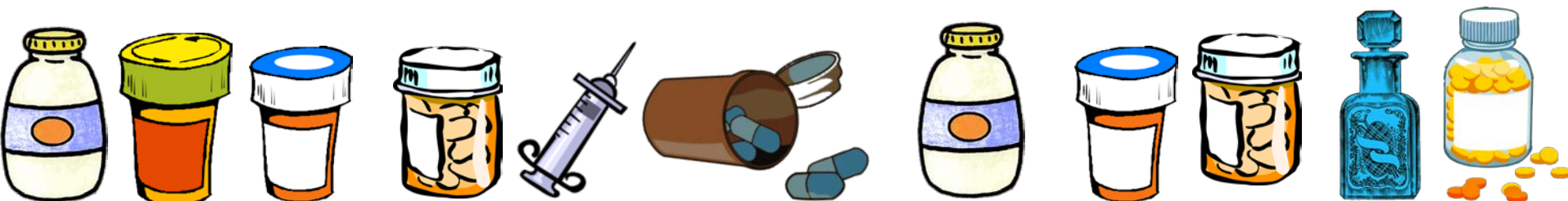
matthew.stryker@acphs.edu

Assistant Professor

Clinical Pharmacy Specialist

Albany College of Pharmacy and Health Sciences

Albany Medical Center – Division of Community Endocrinology



Albany College of Pharmacy and Health Sciences

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