Joyce M. Vergili, EdD, RD, CDN, CDE, FAND jmn76@columbia.edu

Antihyperglycemic Therapy in Type 2 Diabetes
American Diabetes Association Standards of Medical Care in Diabetes – 2016

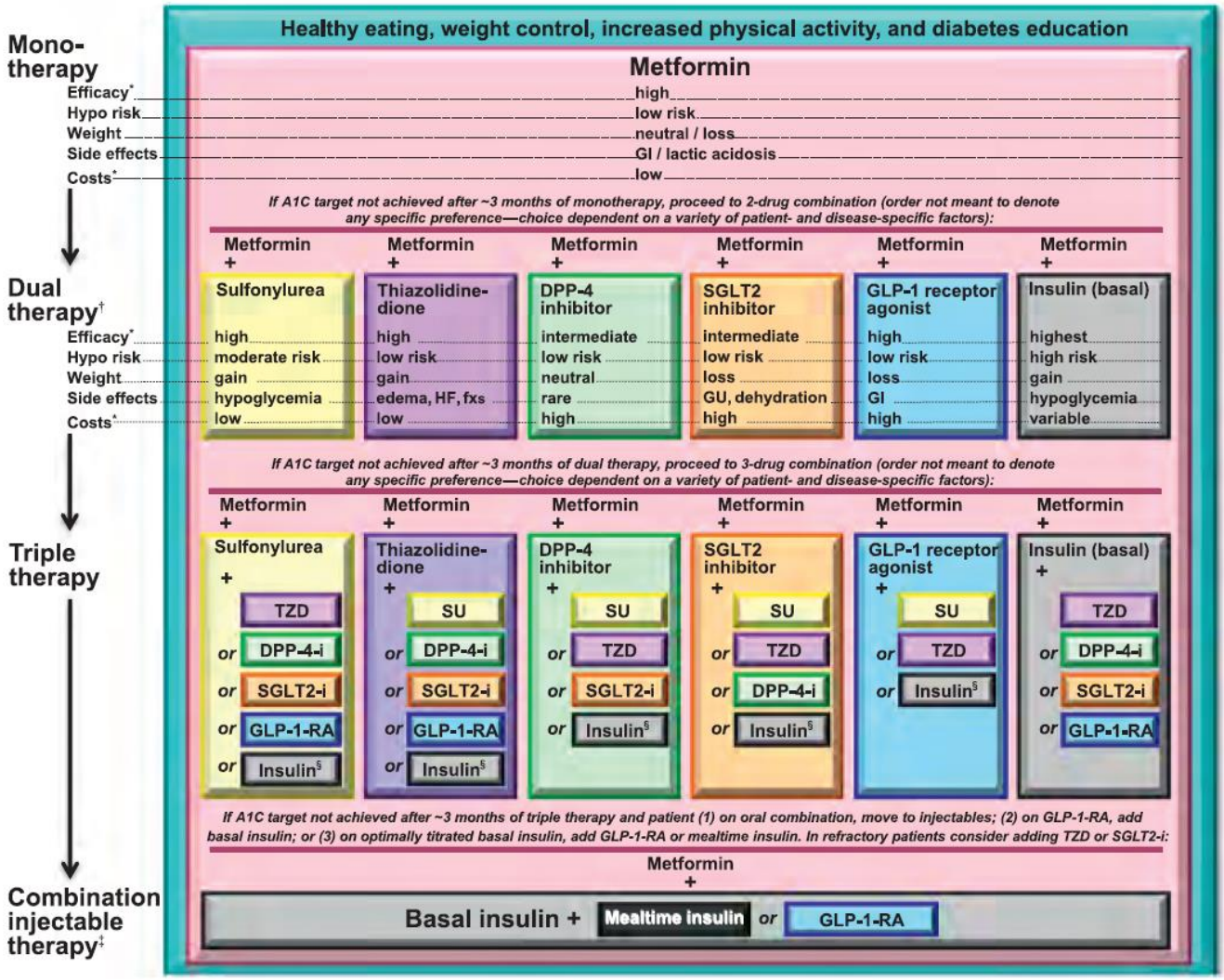
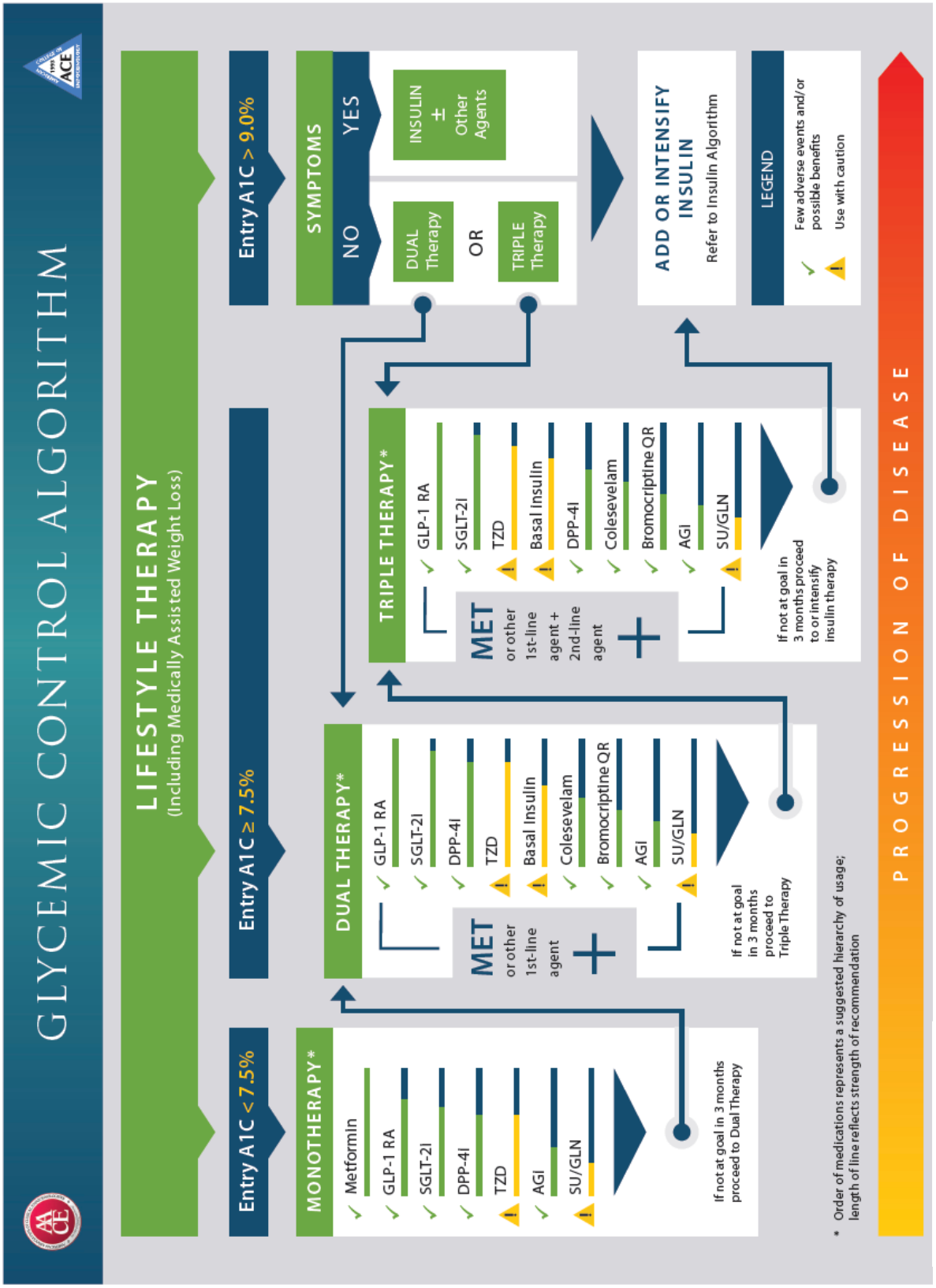


Figure 7.1—Antihyperglycemic therapy in type 2 diabetes: general recommendations (17). The order in the chart was determined by historical availability and the route of administration, with injectables to the right; it is not meant to denote any specific preference. Potential sequences of antihyperglycemic therapy for patients with type 2 diabetes are displayed, with the usual transition moving vertically from top to bottom (although horizontal movement within therapy stages is also possible, depending on the circumstances). DPP-4-i, DPP-4 inhibitor; fxs, fractures; GI, gastrointestinal; GLP-1-RA, GLP-1 receptor agonist; GU, genitourinary; HF, heart failure; Hypo, hypoglycemia; SGLT2-i, SGLT2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione. *See ref. 17 for description of efficacy categorization. †Consider starting at this stage when A1C is ≥9% (75 mmol/mol). ‡Consider starting at this stage when blood glucose is ≥300–350 mg/dL (16.7–19.4 mmol/L) and/or A1C is ≥10–12% (86–108 mmol/mol), especially if symptomatic or catabolic features are present, in which case basal insulin + mealtime insulin is the preferred initial regimen. §Usually a basal insulin (NPH, glargine, detemir, degludec). Adapted with permission from Inzucchi et al. (17).



Garber *et al*, 2016

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DPP-4 Inhibitors Summary Chart

	In general	Sitagliptin (Januvia)	Saxagliptin (Onglyza)	Linagliptin (Tradjenta)	Alogliptin (Nesina)
Efficacy	↓ A1C by ~0.75 percentage points	↓ A1C by ~0.7 to 0.8 percentage points	↓ A1C by ~0.5 to 0.9 percentage points	↓ A1C by ~0.4 to 0.7 percentage points	↓ A1C by ~0.4 to 0.6 percentage points
Advantages	• Low risk of hypoglycemia • Weight neutral			No dose change needed for ↓ renal function	Only DPP-4 avail in combination with a TZD (Oseni); no ↑ CV risk
Dosing	Once daily, without regard to time of day, without regard to food (take same time every day)	• 100 mg in normal renal • 50 mg in moderate / 25 mg in severe renal impair-ment	• 5 mg in normal renal function • 2.5 in renal impairment	5 mg/day for all – no dose adjustment needed in renal disease	• 25 mg in normal renal • 12.5 mg in moderate / 6.25 mg in severe renal impairment
Common side effects	"Cold" symptoms	URI, naso-pharyngitis, headache	URI, UTI, headache	Naso-pharyngitis	URI, naso-pharyngitis, headache
Most serious potential side effects	Acute pancreatitis, hypersensitivity reactions, joint pain, heart failure [?]	Acute pancreatitis, acute renal failure, allergic & hyper-sensitivity reactions (e.g., anaphylaxis), joint pain	Acute pancreatitis, serious hypersensitivity reactions, joint pain, heart failure hospitalizations [?]	Pancreatitis	Acute pancreatitis; hypersensitivity reactions; joint pain; hepatic failure, sometimes fatal
Patient Ed	**Sx pancreatitis; Sx of hypersensitivity / allergic reactions**				

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GLP-1 Receptor Agonists Summary Chart

	In general . . .	**Exenatide (Byetta)**	**Liraglutide (Victoza)**	**Exenatide ER (Bydureon) (kit & pen)**	**Albiglutide (Tanzeum) (April 2014; GSK)**	**Dulaglutide (Trulicity) (Sept 2014; Lilly)**
Efficacy:	↓ A1C by ~1 percentage point	↓ A1C by 0.7 to 1.0 percentage point	↓ A1C by 1.0 to 1.5 percentage points	↓ A1C by 1.0 (3-year data) & by 1.0 to 1.9 %age pts in clinical trials	↓ A1C by 0.6 to 1.0 percentage point	↓ A1C by 0.7 to 1.6 percentage points
Advantages	• low risk of hypoglycemia • wgt loss • ? CV protection • May preserve / improve β-cell fxn	No "black box" warnings	↓ risk of major CV events in Type 2.	• Once a week dosing • 3-year data indicate good efficacy over time	• Once a week dosing. • May be best tolerated of all QW GLP-1RAs [?]	• Once a week dosing • May be easiest of all QW GLP-1 RAs for pt to administer
Contra-indicated in pts with… **Cautions/ Warnings**	• h/o pancreatitis • Gastroparesis, IBD <u>Renal</u>: • Exenatide/ER (cleared by kidneys); contra-indicated if CrCl <30 • Use caution when initiating or ↑ dose in pts w/ renal impairment • Monitor renal function in pts w/ renal impairment reporting severe GI rxns	• GFR <30	WARNING: Risk of thyroid C-cell tumors; ∴ contra- indicated in pts w/ personal / family h/o MTC or MEN2.	• GFR <30 • WARNING: Risk of thyroid C-cell tumors ∴ contraindicated in pts w/ personal / family h/o MTC or MEN2.	WARNING: Carcinogenicity could not be assessed but carries same warning (risk of thyroid C-cell tumors) ∴ contra-indicated in pts w/ personal / family h/o MTC or MEN2.	WARNING: Risk of thyroid C-cell tumors ∴ contraindicated in pts w/ personal / family h/o MTC or MEN2.
Dosing	Variable (all but Byetta can be given without regard to meals)	2x/day dosing (1 hr ac b'fast & 1 hr ac dinner); ↑ from 5 to 10 mcg if needed after 1 mo	1x/day dosing; ↑ from 0.6 to 1.2 mcg after 1 wk; max dose is 1.8.	1x/week 2 mg	1x/week Start with 30 mg, ↑ to 50 mg if needed	1x/week Start with 0.75 mg, ↑ to 1.5 mg if needed.
Common S/E	Nausea, vomiting, diarrhea	Nausea: 8-44% Vomiting:3-18%	Nausea: 8-35% Vomiting: 6-12%	Nausea: 11-27% Vomiting:11%	Diarrhea: 13% Nausea: 11%	Nausea: 12-21% Diarrhea: 9-13% Vomiting: 6-13% Abd pain: 7-9%
Patient Education	SMBG; correct injection technique; how to reconstitute Bydureon & Tanzeum; Sx pancreatitis	How to use Byetta pen	How to use Victoza pen	How to assemble single dose tray ("kit"); how to use pen (reconstitution required for both)	How to reconstitute lyophilized powder in pen	Available as a pen (no reconstitution necessary but some training still needed)

Joyce M. Vergili, EdD, RD, CDN, CDE, FAND jmn76@columbia.edu

SGLT-2 Summary Chart

	Canagliflozin (Invokana)	Dapagliflozin (Farxiga)	Empagliflozin (Jardiance)
Efficacy	↓ A1C by ~ 0.7 to 1 percentage point	↓ A1C by ~ 0.5 to 0.7 percentage points	↓ A1C by ~ 0.4 to 0.9 percentage points
eGFR must be	≥ 45 mL/min	≥ 60 mL/min	≥ 45 mL/min
Dose	100 mg/day, before 1st meal of day; ↑ to 300 mg if needed *and* if eGFR ≥ 60	5 mg/day, taken in morning, with or w/out food; ↑ to 10 mg if needed	10 mg/day, taken in morning, with or w/out food; ↑ to 25 mg if needed
Advantages	• Low risk of hypoglycemia • ↓ wgt by 2.2-3.3% (~ 5 lb) • ↓ systolic BP by ~3 to 5 mm Hg • ↑ HDL by ~8%	• Low risk of hypoglycemia • ↓ wgt by ~ 5 lb • ↓ systolic BP by ~3 to 5 mm Hg	• Low risk of hypoglycemia • ↓ wgt by ~ 3 lb • ↓ systolic BP by ~3 to 5 mm Hg
Disadvantages	↑ LDL by ~4 to 8%	↑ LDL by 2.9%	↑ LDL by ~5-7%
Common side effects	• Genital yeast infections (women: 10-11%; men: 4%) • UTI: 4 to 6% • Increased urination • Dehydration • Hyperkalemia	• Genital yeast infections (women: 7-8%; men: 3%) • UTI: 4 to 6% • Increased urination • Dehydration • Nasopharyngitis	• Genital yeast infections (women: 5-6%; men: 2-3%) • UTI: 8 to 9% • Increased urination • Dehydration
Use with Caution in Patients	• ≥ 65 years old (more prone to volume depletion; lower efficacy) • At risk for hyperkalemia (pts taking ACEi or ARB) • Prone to DKA	• ≥ 65 years old (more prone to volume depletion) • With h/o bladder cancer, bladder cancer risk factors, hematuria • Prone to DKA	• ≥ 75 years old (more prone to volume depletion & UTIs) • Prone to DKA
Patient Education	(1) Drink plenty of fluids; (2) Talk to HCP if ↓ in kcal intake; (3) Sx of ketoacidosis; (4) Sx of UTI		

Factors predisposing to DKA:

- insulin deficiency (e.g., T1DM, h/o pancreatitis or pancreatic surgery)
- insulin dose reduction
- acute febrile illness
- reduced calorie intake d/t illness or surgery
- calorie restriction disorders
- alcohol abuse

Symptoms of ***ketoacidosis*** include **nausea, vomiting, abdominal pain, tiredness, and trouble breathing.**
Symptoms of ***UTI*** include **a feeling of burning when urinating or the need to urinate often or right away; pain in the lower part of the stomach area or pelvis; fever; or blood in the urine.**

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Summary of the 11 Classes of Non-Insulin Therapies for Diabetes

	Oral Medications								Injectable Medications	
	Metformin	**Insulin secret-agogues** Sulfonyl-ureas / Megli-tindes	**Thiazolidine-diones (TZDs)**	**α-glucosidase inhibitors**	**DPP-4 inhibitors**	**Bromo-criptine (Cycolset)**	**Colesevalam (Welchol)**	**SGLT2 inhibitors**	**GLP-1 receptor agonists**	**Amylin analog (Symlin)**
Mechanism of Action	↓ hepatic glucose production; ↑ insulin sensitivity	↑ insulin secretion from β-cells in pancreas	↑ insulin sensitivity in peripheral tissue (muscle, fat, liver)	↓ rate of carbohydrate digestion	Prolong survival of GLP-1, thereby ↑ insulin & ↓ glucagon secretion in a glucose dependent manner	Unknown; may ↓ the hypothalamic drive that stimulates early morning hepatic glucose output	Unknown; may ↓ glucose absorption	Glucuretics – ↑ urinary glucose excretion	Mimics GLP-1: ↑ insulin & ↓ glucagon secretion in a glucose de-pendent manner; ↓ rate of gastric emptying; stimulates satiety center in brain	Amylin-like effect (inhibits glucagon secretion; slows gastric emptying)
A1C reduction	1.0 – 1.2	1.25 Nat 0.75; Rep ~1	1.25 rosi 1.0 pio	1.0 (at dose of ≥ 150 mg/d)	~0.75	0.1 – 0.6	0.5	0.5 – 1.0	~1.0	0.5 – 0.7
Adverse Events / Risks / Cautions	GI disturb-ances, lactic acidosis (rare but serious), HOLD before & after contrast dye studies	Hypo-glycemia, weight gain, low durability	Heart failure, edema, wgt gain, bone fractures	GI disturb-ances; **only *glucose tabs or gel*** will be effective in treating hypoglycemia	Acute pancreatitis, URI, cold sx, hypersensitivity / allergic rxns, joint pain, heart failure [?]	Hypotension if taking ergot meds (eg, Cafergot); syncope	May ↑ TG - not recom-mended if TG > 500; constipation, nausea, dyspepsia	Genital yeast infections, UTI, polyuria, dehydration → hypotension, DKA	Pancreatitis, N/V, injection site rxns, gastroparesis; monitor renal function	Nausea, hypo-glycemia

Diabetes Medication Update for Healthcare Professionals 2016

Joyce M. Vergili, EdD, RD, CDN, CDE, FAND jmn76@columbia.edu

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