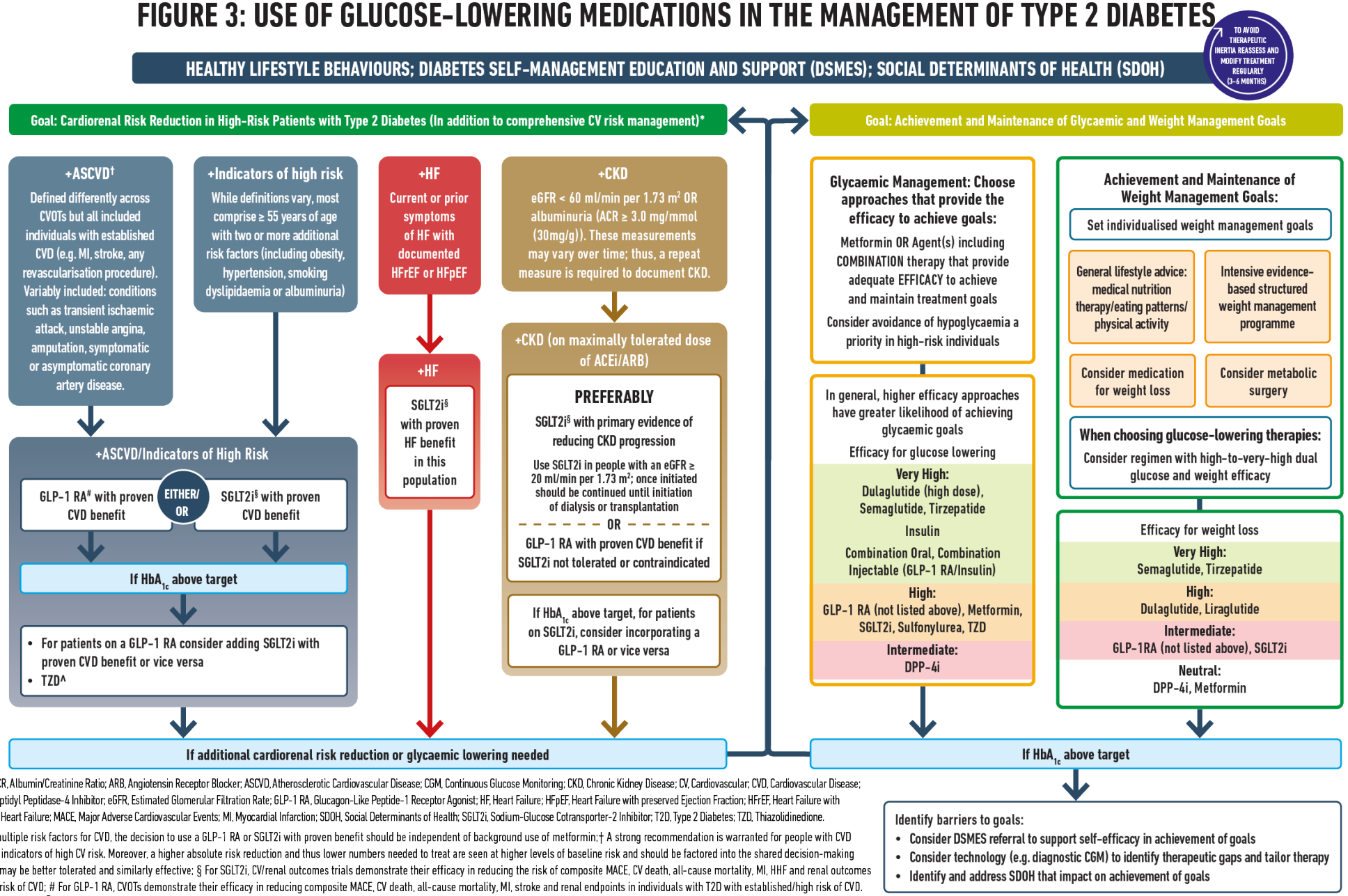
FIGURE 3: USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES



ACEi, Angiotensin-Converting Enzyme Inhibitor; ACR, Albumin/Creatinine Ratio; ARB, Angiotensin Receptor Blocker; ASCVD, Atherosclerotic Cardiovascular Disease; CGM, Continuous Glucose Monitoring; CKD, Chronic Kidney Disease; CV, Cardiovascular; CVD, Cardiovascular Disease; CVOT, Cardiovascular Outcomes Trial; DPP-4i, Dipeptidyl Peptidase-4 Inhibitor; eGFR, Estimated Glomerular Filtration Rate; GLP-1 RA, Glucagon-Like Peptide-1 Receptor Agonist; HF, Heart Failure; HFpEF, Heart Failure with preserved Ejection Fraction; HFrEF, Heart Failure with reduced Ejection Fraction; HHF, Hospitalisation for Heart Failure; MACE, Major Adverse Cardiovascular Events; MI, Myocardial Infarction; SDOH, Social Determinants of Health; SGLT2i, Sodium-Glucose Cotransporter-2 Inhibitor; T2D, Type 2 Diabetes; TZD, Thiazolidinedione.

* In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin; † A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke and renal endpoints in individuals with T2D with established/high risk of CVD.

American Diabetes Association.

Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, Rosas SE, Del Prato S, Mathieu C, Mingrone G, Rossing P, Tankova T, Tsapas A, Buse JB

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EASD European Association for the Study of Diabetes

Noninsulin Therapies for Type 2 Diabetes (Short Form)

Class Brand Name	Generic Name	Typical Dosing Directions	Effect on A1C	Hypo. Risk	Cost	Weight Change ↑↓↔	Use in Renal Disease	Monitoring Labs	Other
Oral Medication									
Biguanides			**Decrease hepatic glucose output, sensitizer**						**Targets fasting BG**
Glucophage®	metformin	1000 mg BID with morning and evening meals	Up to 2%	No	$	↔ to ↓	↓ dose per eGFR; stop if eGFR<30	eGFR, ALT	First-line therapy; black box warning for lactic acidosis (rare); no binge alcohol; use caution with contrast; GI side effects, less with XR; titrate slowly; may lower vit. B12
Glucophage XR®	metformin ER	2000 mg at evening meal							
Sulfonylureas			**Increase release of insulin**						**Targets fasting & postmeal BG**
Amaryl®	glimepiride	1–8 mg with AM meal	Up to 1.5%	↑	$	↑	Use caution and ↓ dose; avoid glyburide if GFR <60	eGFR, ALT	Works quickly, may be less effective late in disease; avoid glyburide due to high risk of hypoglycemia; ensure consistent carbohydrate at meals to avoid hypoglycemia; glipizide and glimepiride preferred with renal impairment.
Glucotrol®	glipizide	5–20 mg BID 30 min before meals		↑↑					
Glucotrol XL ®	glipizide XL	2.5–20 mg with AM meal		↑					
Micronase®	glyburide	2.5–10 mg QD		↑↑					
Glynase	glyburide	1.5–12 mg QD with meal							
Meglitinides (short-acting)			**Increase release of insulin**						**Targets postmeal BG**
Prandin®	repaglinide	0.5–4 mg TID with meals	1–2%	↑	$$	↑	Yes, if eGFR <30 ↓ dose	eGFR, ALT	Inconvenient mealtime dosing; good for variable meal schedule; consider lower dose if hepatic impairment.
Starlix®	nateglinide	60–120 mg TID with meals							
Thiazolidinedione			**Increase insulin sensitivity**						**Targets fasting BG**
Actos®	pioglitazone	15–45 mg QD	1–2%	No	$$	↑↑	Yes	ALT	Black box warning for CHF; weight gain, edema and long-term use associated with bone fracture; increased risk of bladder cancer; generic available; limit dose to 30 mg.
DPP-4 Inhibitors			**Increase insulin, decrease glucagon**						**Targets postmeal BG**
Januvia®	sitagliptin	100 mg QD	Up to 1%	No	$$$	↔	Yes, ↓ dose	eGFR	Don't use with history of pancreatitis; overall well tolerated; possible hypersensitivity reaction and severe joint pain (rare); consider lower dose of SU/insulin; CV neutral (safe); increased risk for HF with saxagliptin.
Onglyza™	saxagliptin	2.5–5 mg QD					Yes, ↓ dose		
Tradjenta™	linagliptin	5 mg QD					Yes		
Nesina®	Alogliptin	25 mg QD					Yes, ↓ dose		
Alpha-glucosidase Inhibitors			**Slow breakdown of carbohydrate**						**Targets postmeal BG**
Precose®	acarbose	25–100 mg TID with meals	0.5–1%	No	$$	↔	Yes, avoid if eGFR <30	eGFR ALT	GI side effects: flatulence (titrate slowly), avoid if bowel disorder; treat low glucose with glucose tabs or milk.
Glyset®	miglitol	25–100 mg TID with meals							

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Noninsulin Therapies for Type 2 Diabetes (Short Form)

Class Brand Name	Generic Name	Typical Dosing Directions	Effect on A1C	Hypo Risk	Cost	Weight Change ↑↓↔	Use in Renal Disease	Monitoring Labs	Other
SGLT2 Inhibitors			**Lowers renal threshold for glucose**						**Targets fasting & postmeal BG**
Invokana®	canagliflozin	100–300 mg before first meal of day	~1%	No	$$$	↓	Yes, do not initiate if eGFR <30	eGFR, ALT, LDL	Risk of hypotension and dehydration, genital fungal infections, modest increase in LDL, DKA (rare); hypo with SU or insulin; risk of necrotizing fasciitis of perineum; reduces CV events and hospitalization for HF; slows progression of CKD; use until dialysis, then contraindicated; do not use for glucose lowering if eGFR <45 Canagliflozin: Hyperkalemia possible in high-risk patients (renal impaired, on ACE-I or ARB); may increase risk of amputation. Ertugliflozin: May increase risk of amputation; does not have ASCVD and CKD benefit like other SGLT2 inhibitors.
Farxiga™	dapagliflozin	5–10 mg in the morning with or without food					Yes, do not initiate if eGFR <25	eGFR, LDL	
Jardiance®	empagliflozin	10–25 mg in the morning with or without food					Yes, do not initiate if eGFR <20	eGFR, LDL	
Steglatro™	ertugliflozin	5–15 mg in the morning; correct volume depletion before initiation					Yes, do not initiate if eGFR <45	eGFR, LDL	
Injectable Medications									
GLP-1 Receptor Agonists		**Increase insulin, decrease glucagon, increase satiety, slow gastric emptying**							**Targets fasting & postmeal BG**
Byetta®	exenatide	5–10 mcg BID, up to 1 hour before meals	Up to 2.0%	No	$$$	↓↓	Do not use if eGFR <30	eGFR	Black box warning for thyroid C-cell tumors in rodents: don't use with history of medullary thyroid carcinoma or MEN syndrome type 2; GI side effects common (but transient), titrate slowly; avoid use if other GI disease; pancreatitis (rare), discontinue if pancreatitis occurs; may need ↓dose SU/meal insulin (up to 50%); CV benefit in patients with established CVD; increased risk of diabetic retinopathy with semaglutide; take oral semaglutide upon waking with <4 oz water 30 minutes before any food, liquids or medications.
Bydureon®	exenatide ER	2 mg/week							
Victoza®	liraglutide	Start 0.6 mg QD, titrate to 1.2–1.8 mg QD					Yes, use caution	eGFR	
Ozempic™	semaglutide	Start 0.25 mg/week, titrate to 0.5–2.0 mg/week					Yes, use caution when starting and adjusting dose with renal impairment		
Rybelsus®	oral semaglutide	Start 3 mg/day for 30 days, then 7 mg/day for 30 days; may increase to 14 mg/day							
Trulicity™	dulaglutide	0.75–4.5 mg/week							
GIP/GLP-1 Receptor Agonist		**Increase insulin, decrease glucagon, increase satiety, slow gastric emptying**							**Targets fasting & postmeal BG**
Mounjaro®	tirzepatide	2.5 mg weekly for 4 wks then increase to 5.0 mg weekly; if needed, increase in 2.5 mg increments every 4 weeks to max dose 15 mg weekly	Up to 2.5%	No	$$$	↓↓↓	Yes, use caution	eGFR	Black box warning for thyroid C-cell tumors in rodents: don't use with history of medullary thyroid carcinoma or MEN syndrome type 2; GI side effects common, titrate slowly; discontinue promptly if pancreatitis is suspected; increased risk of diabetic retinopathy; CVOT underway

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Metformin Start and Adjust Guideline

Medication	Dosing	Labs/Effect on Glycemic Parameters	Clinical Uses	Cautions and Comments
Metformin (Glucophage®) Immediate Release	**Starting Dose:** 500 mg q. pm **Adjust dose:** add 500 mg every week until 1000 mg bid **Max dose**: 2,250 mg/day (850 mg tid)	**Labs needed to start:** eGFR and LFTs within 3 months **Ongoing monitoring:** eGFR every 12 months if normal, every 3 months if <45 ml/min **Effect of Glycemic Parameters** **SMBG** ↓ FPG 40-70 mg/dL ↓ PPG 40-50 mg/dL **CGM** ↓ Mean glucose 40-50 mg/dL **A1C** (or CGM derived equivalent GMI): 1.5-2.0 percentage point reduction **Comment:**	⌖ Consider as first line therapy for all patients if tolerated and no contraindications ⌖ Lower cost ⌖ Effective in obese and lean patients ⌖ Weight neutral to modest weight loss ⌖ No hypoglycemia as monotherapy ⌖ Can be used in combination with: SU, TZD, insulin, DPP-4 inhibitor, GLP-1 agonist, and SGLT2 inhibitor ⌖ May reduce CVD risk (modest lowering of TG and LDL) ⌖ Used off-label for PCOS, GDM and diabetes prevention ⌖ For extended release must swallow pill	⌖ GI side effects common, slow dose titration recommended ⌖ Baseline ALT and SrCr (eGFR) required **Black box warning for lactic acidosis (rare); metformin should be avoided if:** ⌖ Impaired kidney function (see below) ⌖ Conditions predisposing patient to hypoxia (e.g. acute congestive heart failure, acute myocardial infarction) ⌖ Clinical or laboratory evidence of advanced liver disease or end stage liver disease (e.g. cirrhosis, hepatitis). Consider continuing metformin if patient has nonalcoholic fatty liver disease (NAFLD) or what is commonly called "fatty liver". ⌖ Use with caution if ALT >2.5 times upper limit of normal and history of NAFLD or nonalcoholic steatohepatitis (NASH) ⌖ IDC dosing recommendation based on eGFR: ⌖ ≥60; up to 2000 mg/day; eGFR annually ⌖ 59-45; up to 2000 mg/day; eGFR at least annually, more if declining eGFR, elderly ⌖ 44-30; reduce dose 50%, do not start metformin, more frequent eGFR (q 4 mo.) ⌖ <30 contraindicated ⌖ Stop at time of iodinated contrast procedure if:
Metformin extended release (GlucophageXR®)	**Starting Dose:** 500 mg with evening meal **Adjust dose:** add 500 mg weekly until 2000 mg/day Consider 1000 mg bid **Max dose**: 2,000 mg/day			
Metformin extended release (Glumetza™)	**Starting Dose:** 500 mg with evening meal **Adjust dose:** add 500 mg every 1-2 weeks until 2000 mg/day **Max dose**: 2,000 mg/day			

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Medication	Dosing	Labs/Effect on Glycemic Parameters	Clinical Uses	Cautions and Comments
Metformin oral solution (Riomet®)	**Starting Dose:** 500 mg/5 ml; 5 ml bid with meal **Adjust dose**: titrate weekly until 10 ml bid (2000 mg total/day) **Max dose**: 2,250 mg/day	• Most appropriate for elevated FPG • Significant glucose reduction without hypoglycemia (unless treated with SU or insulin)	whole and patient may see insoluble shell in feces	⌖ eGFR 30-60 ml/min ⌖ History of liver disease, alcoholism, or heart failure ⌖ Intra-arterial iodinated contrast will be administered ⌖ Re-evaluate eGFR in 48 hrs and restart if stable ⌖ Not recommended for patients who consume large amounts of alcohol or binge drink ⌖ May lower vitamin B_{12} levels, consider checking B12 level if peripheral neuropathy or anemia and after 3 years on therapy and every three years thereafter ⌖ Pregnancy: Fetal risk cannot be ruled out

Sulfonylurea (SU) Start and Adjust Guideline

Medication	Dosing	Labs/Effect on Glycemic Parameters	Clinical Uses	Cautions and Comments
Glipizide (Glucotrol®) **Glipizide-GITS** (Glucotrol XL®)	**Glipizide:** **Starting Dose:** 5 mg before breakfast **Adjust dose**: titrate in 5 mg increments every 1-2 weeks based on BG; doses >15 mg should be divided **Max dose**: 20 mg bid (before breakfast and evening meals) **Glipizide-GITS:** **Starting Dose:** 5 mg before breakfast **Adjust dose**: titrate in 5 mg increments every 1-2 weeks based on BG **Max dose**: 20 mg daily before breakfast	**Labs needed to start:** eGFR and LFTs within 3 months **Ongoing monitoring:** eGFR and LFTs every 12 months if normal, every 3 months if abnormal **Effect of Glycemic Parameters** **SMBG** ↓ FPG 30-60 mg/dL ↓ PPG 40-70 mg/dL **CGM** ↓ Mean glucose 40-60 mg/dL	⌖ Works quickly especially lean patient, and significant hyperglycemia BG 200-350 mg/dL ⌖ Can be used in combination with metformin, TZD, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 agonist and insulin ⌖ Glipizide preferred with renal disease- no dose adjustment ⌖ eGFR <60 stop glyburide ⌖ Switch glyburide to glipizide if age >65	⌖ Hypoglycemia ⌖ Weight gain ⌖ Less effective “late” in disease ⌖ Use caution in renal/hepatic disease ⌖ Food plan needed to minimize risk of hypoglycemia ⌖ Lower cost ⌖ Consider decreasing insulin dose or stopping insulin if total daily units of insulin <20 units when starting SU ⌖ Strongly consider stopping SU when initiating background insulin and stopping SU for premixed or background + mealtime (basal-bolus) insulin ⌖ Glyburide is off-label with GDM ⌖ Micronase and Glynase Pres Tab pregnancy category B, others pregnancy category C ⌖ Avoid glyburide due to higher risk of hypoglycemia compared to other SUs.

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Medication	Dosing	Labs/Effect on Glycemic Parameters	Clinical Uses	Cautions and Comments
Glyburide (Micronase,® Diabeta®)	**Starting Dose:** 2.5 mg in AM **Adjust dose**: titrate every 1-2 weeks based on BG **Max dose**: 20 mg daily (10 mg bid or 20 mg qd)	**A1C** (or CGM derived equivalent GMI): up to 2.0 percentage point reduction **Comment:** • Effective at lowering both fasting and postmeal BG • Significant glucose reduction with risk of hypoglycemia	and any renal insufficiency ⌖ eGFR <30 stop glimepiride ⌖ IDC recommends stopping all SUs when eGFR <15 ml/min	⌖ CAROLINA trial showed glimepiride CV neutral (safe) compared to linagliptin. ⌖ GRADE Study demonstrated glimepiride CV neutral (safe) and had longer durability in A1C lowering than sitagliptin, but less than liraglutide and background insulin
Glyburide-micronized (Glynase PresTab®)	**Starting Dose:** 1.5 mg in AM **Adjust dose**: titrate dose to 3, 6, 9 or 12 mg every 1-2 weeks based on BG **Max dose**: 12 mg qd in AM			
Glimepiride (Amaryl®)	**Starting Dose:** 1 mg in AM with meal **Adjust dose**: titrate every 1-2 weeks based on BG **Max dose**: 8 mg qd			

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Thiazolidinedione (TZD) Start and Adjust Guideline

Medication	Dosing	Labs/Effect on Glycemic Parameters	Clinical Uses	Cautions and Comments
Pioglitazone (Actos®)	**Starting Dose:** 15 mg daily **Adjust dose**: titrate in 15 mg increments every 8-12 weeks based on BG and tolerability **Max dose**: 45 mg daily **ADA recommends using lower dose of 15-30 mg/day to minimize side effects**	**Labs needed to start:** electrolytes and LFTs within 3 months **Ongoing monitoring:** electrolytes and LFTs every 12 months if normal, every 3 months if abnormal **Effect of Glycemic Parameters** **SMBG** ↓ FPG 30-80 mg/dL **CGM** ↓ Mean glucose 40-60 mg/dL **A1C** (or CGM derived equivalent GMI): up to 2.0 percentage point reduction **Comment:** • Effective at lowering fasting BG • Usually takes several weeks to see optimal response • Significant glucose reduction without hypoglycemia (unless treated with SU or insulin)	⌖ For very insulin resistant patients (severe obesity, metabolic syndrome, acanthosis nigricans) ⌖ Insulin sensitizer in peripheral tissue (muscle, liver, and fat) ⌖ Use as monotherapy or in combination with other diabetes medications ⌖ Improves dyslipidemia: ↓ TG, ↑ HDL ⌖ Consider if intolerant to or inappropriate for metformin ⌖ Can use in renal insufficiency ⌖ Avoid high-dose use, especially in postmenopausal women	⌖ **Black Box Warning for CHF** ⌖ Pioglitazone is preferred, generic available ⌖ TZDs may cause or exacerbate CHF, follow-up for signs of CHF including rapid weight gain, dyspnea and/or edema after initiation and dose increases ⌖ Contraindicated in NYHA Class 3 or 4 cardiac status; use with caution in patients with NYHA Class 1 or 2 cardiac status ⌖ Peripheral edema, weight gain; consider final dose of 30 mg pioglitazone to minimize side effects ⌖ Use caution in patients with hepatic impairment ⌖ If ALT greater than 3 times the upper limit of normal, treatment should be stopped and etiology investigated ⌖ Pioglitazone should not be restarted in patients who have serum ALT greater than 3 times upper limit of normal and with serum total bilirubin greater than 2 times the reference range without alternative etiologies ⌖ Low risk of hypoglycemia ⌖ Long-term use of TZDs shown to increase risk of bone fractures in men and women ⌖ Trend for CV event risk reduction with pioglitazone shown in PROACTIVE study ⌖ Long-term use associated with increased risk of bladder cancer with pioglitazone compared to rosiglitazone ⌖ Avoid if active or history of macular edema ⌖ Pregnancy: fetal risk cannot be ruled out
Rosiglitazone (Avandia®) (not recommended)	As of 11-25-2013, the US Food and Drug Administration is removing the prescribing and dispensing restrictions for rosiglitazone products. Therefore, healthcare professionals, pharmacies, and patients are no longer required to enroll in the restricted distribution program.			

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Dipeptidyl peptidase-4 (DPP-4) Inhibitor Start and Adjust Guideline

Medication	Dosing	Labs/Effect on Glycemic Parameters	Clinical Uses	Cautions and Comments
Information that applies to all DPP-4 inhibitors	(see below for drug specific dosing information)	**Labs needed to start:** eGFR within 3 months **Ongoing monitoring:** eGFR every 12 months if normal, every 3 months if abnormal **Effect of Glycemic Parameters** **SMBG** ↓ FPG 15-20 mg/dL ↓ PPG 30-50 mg/dL **CGM** ↓ Mean glucose 20-30 mg/dL **A1C** (or CGM derived equivalent GMI): up to 1 percentage point reduction **Comment:** • Effective at lowering post meal BG • Modest efficacy	⌖ Inhibits DPP-4 enzyme resulting in 2-3 fold increase in glucagon-like peptide-1 (GLP-1) ⌖ Targets elevated post-meal glucose by improving beta-cell function and lowering post-meal glucagon levels ⌖ Use as monotherapy and in combination with metformin, pioglitazone, SU, insulin, SGLT2 Inhibitor ⌖ Do not use with GLP-1 or GLP-1/GIP receptor agonists	⌖ Take with or without food ⌖ Very well tolerated ⌖ Low risk of hypoglycemia ⌖ Not for use with type 1 diabetes or ketoacidosis ⌖ Weight neutral ⌖ Higher cost ⌖ CV safety trials show class to be CV neutral (or CV safe) ⌖ Hypersensitivity reactions (angioedema, anaphylaxis and exfoliative skin reactions) have been reported within 3 months on starting therapy ⌖ Severe and persistent joint pain has been reported ⌖ Associated with increased risk of inflammatory bowel disease ⌖ There is an increased risk of hypoglycemia when DPP-4 inhibitor is added to an insulin secretagogue (e.g., SU) or insulin therapy. Consider lowering the dose of the SU or insulin to reduce the risk of hypoglycemia ⌖ Use with caution if history of pancreatitis; discontinue if signs or symptoms develop (e.g. abdominal pain radiating to back, nausea, vomiting, fever) ⌖ Do not use in combination with GLP-1 or GLP-1/GIP receptor agonists ⌖ Pregnancy: fetal risk cannot be ruled out
Sitagliptin (Januvia®) See also above "Information that applies to all DPP-4 inhibitors"	**Starting Dose:** 100 mg daily with or without food **Max dose**: 100 mg daily **Dose for renal disease:** 50 mg qd if eGFR 30-49 25 mg qd if eGFR <30	See above	See above	⌖ In addition to class effect (above): ⌖ Reduced dose for impaired renal function (see dose recommendation to left) ⌖ Patients to call provider if they experience signs/symptoms of pancreatitis (severe abdominal pain with or without vomiting)

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Medication	Dosing	Labs/Effect on Glycemic Parameters	Clinical Uses	Cautions and Comments
Saxagliptin (Onglyza™) See also above "Information that applies to all DPP-4 inhibitors"	**Starting Dose:** 2.5 or 5 mg daily with or without food **Max dose**: 5 mg daily **Dose for renal disease (eGFR <50):** 2.5 mg daily	See above	See above	⌖ In addition to class effect (above): ⌖ Reduced dose for impaired renal function ⌖ Co-administration with strong CYP3A4/5 inhibitors (eg. Ketoconazole) significantly increases saxagliptin concentrations; recommend limiting dose to 2.5 mg qd ⌖ SAVOR Trial showed 27% relative higher risk of hospitalization for heart failure (HHF) with saxagliptin compared to placebo; other DPP-4 inhibitors do not increase risk of HHF
Linagliptin (Tradjenta™) See also above "Information that applies to all DPP-4 inhibitors"	**Starting Dose:** 5 mg daily with or without food **Max dose**: 5 mg daily	See above	See above	⌖ In addition to class effect (above): ⌖ No dose adjustment needed for renal or hepatic impairment ⌖ P-glycoprotein/CYP 3A4 inducer: efficacy may be reduced when administered in combination (e.g., with rifampin). Use of alternative treatments is strongly recommended
Alogliptin (Nesina™) See also above "Information that applies to all DPP-4 inhibitors"	**Starting Dose:** 25 mg daily with or without food **Max dose**: 25 mg daily **Dose for renal disease:** 12.5 mg qd if eGFR 30-59 6.25 mg qd if eGFR <30	See above	See above	⌖ In addition to class effect (above): ⌖ Reduced dose for impaired renal function ⌖ Promptly discontinue if pancreatitis is suspected. ⌖ Post-marketing reports of liver failure. If liver failure occurs, stop alogliptin and determine etiology of liver failure. Do not restart alogliptin if no other etiology of liver failure is identified.

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Sodium Glucose Cotransporter-2 (SGLT2) Inhibitor Start and Adjust Guideline

Medication	Dosing	Labs/Effect on Glycemic Parameters	Clinical Uses	Cautions and Comments
Information that applies to all SGLT2 inhibitors	(see below for drug specific dosing information)	**Labs needed to start:** eGFR and electrolytes within 3 months **Ongoing monitoring:** eGFR and electrolytes after 3 months and every 12 months thereafter if normal, every 3 months if abnormal **Effect of Glycemic Parameters** **SMBG** ↓ FPG 20-40 mg/dL ↓ PPG 30-50 mg/dL **CGM** ↓ Mean glucose 30- 45 mg/dL **A1C** (or CGM derived equivalent GMI): 1 to 1.5 percentage point reduction **Comment:** • Effective at lowering both fasting and post meal BG	⌖ **Not indicated for type 1 diabetes (Endocrinology may prescribe off-label even with increased risk of DKA)** ⌖ For patients desiring effective glucose lowering and modest weight loss in a pill ⌖ Consider other options if patient has a significant history of genital fungal infections ⌖ Can be used as monotherapy and in combination with metformin, pioglitazone, SU, DPP-4 inhibitor, GLP-1 RA, GLP-1/GIP RA and insulin ⌖ **The 2022 ADA/EASD Type 2 Diabetes Consensus Statement recommends** 1. Starting SGLT2i for patients with CKD if the eGFR is ≥20 ml/min and maintain until initiation of dialysis or transplantation 2. Starting SGLT2i for patients with HF and any level of ejection fraction (HFrEF and HFpEF)	⌖ Check renal function initially and periodically thereafter; acute renal injury may occur in settings of reduced oral intake or fluid loss ⌖ Adverse reactions include genital mycotic (yeast) infection (especially in patients with history of genital mycotic infection and uncircumcised males) ⌖ No increased risk of hypoglycemia above placebo unless if used with SU/ or insulin; a reduction in dose of SU or insulin may be required to minimize risk of hypoglycemia. ⌖ May cause: • volume depletion (correct hypovolemia prior to initiating) • hypotension (especially in elderly) • modest increase in LDL-cholesterol • short-term increased serum creatinine and decreased eGFR ⌖ Not recommended in severe hepatic impairment ⌖ Do not use with patients on dialysis ⌖ DKA (rare in T2 DM), higher risk when used in patients treated with insulin ⌖ Modest weight loss (-2.5%) ⌖ Reduce systolic BP ~4 mmHg ⌖ Post marketing reports of rare cases of Fournier gangrene of the perineum ⌖ SGLT2 inhibitors as a class reduce risk of hospitalization for heart failure and slow progression of kidney disease ⌖ SGLT2 inhibitor with demonstrated CVD benefit recommended for patients with established ASCVD (see below)

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Medication	Dosing	Labs/Effect on Glycemic Parameters	Clinical Uses	Cautions and Comments
Canagliflozin (Invokana™)	**Starting Dose:** 100 mg once daily before first meal of the day **Adjust Dose**: dose may be increased to 300 mg once daily based on response, tolerability and if eGFR ≥60 **Max dose**: 300 mg once daily and 100 mg once daily if eGFR 30-59	See above	In addition to above: ⌖ Indicated to reduce the risk of major adverse CV events (cardiovascular death, nonfatal M.I. and nonfatal stroke) in adults with type 2 diabetes and established CVD ⌖ Indicated to reduce the risk of ESKD, doubling of serum creatinine, cardiovascular (CV) death, and hospitalization for heart failure in adults with type 2 diabetes and diabetic nephropathy with albuminuria greater than 300 mg/day (eGFR threshold lowered to 30 ml/min for 100 mg dose)	⌖ In addition to class effect (above): ⌖ Do not initiate if eGFR is below 30, but if albuminuria is greater than 300 mg/day may continue with 100 mg orally once daily until dialysis ⌖ May cause hyperkalemia, monitor serum potassium if moderate renal impairment and those taking medications that can increase serum potassium (potassium-sparing diuretics ACE-I and ARB) ⌖ Package insert updated in 2016 with warning of increased bone fractures ⌖ May increase risk of amputation, use caution in patients with PVD, history of ulcers ⌖ CANVAS trial showed cardiovascular protection (benefit) with reduced cardiovascular events in patients with established CVD or at very high risk ⌖ CREDENCE trial showed renal protection in patients with albuminuria and no increased risk of amputation or fracture ⌖ Pregnancy: Fetal risk cannot be ruled out
Dapagliflozin (Farxiga™)	**Starting Dose:** 5 mg once daily, taken in the morning **Adjust Dose**: dose may be increased to 10 mg once daily based on response and tolerability **Max dose**: 10 mg once daily	See above	In addition to above: ⌖ Indicated to reduce the risk of hospitalization for heart failure in adults with type 2 diabetes and established cardiovascular disease or multiple cardiovascular risk factors ⌖ Indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure with reduced ejection fraction (NYHA class II-IV). ⌖ Indicated to reduce the risk of sustained estimated GFR decline, end-stage kidney disease,	⌖ In addition to class effect (above): ⌖ Do not use for glycemic management if eGFR <45 ⌖ If eGFR 25 ml/min or greater use 10 mg to prevent progression of CKD, to lower risk for HHF and CV death ⌖ If eGFR <25 don't initiate but may continue therapy until dialysis ⌖ Contraindicated for patients on dialysis ⌖ DECLARE-TIMI 58 trial showed a lower rate of cardiovascular death or hospitalization for heart failure vs placebo ⌖ DAPA-HF showed reduced worsening of HF and CV death in patients with reduced ejection fraction ⌖ DAPA-CKD showed renal protection in patients with eGFR 25-75 and albuminuria ⌖ DELIVER trial showed dapagliflozin reduced the combined risk of worsening HF or CV

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Medication	Dosing	Labs/Effect on Glycemic Parameters	Clinical Uses	Cautions and Comments
			cardiovascular death, and hospitalization for heart failure in adults with chronic kidney disease at risk of progression	death among patients with HF and a mildly reduced or preserved ejection fraction (HFpEF) ⌖ Pregnancy: Fetal risk cannot be ruled out
Empagliflozin (Jardiance®)	**Starting Dose:** 10 mg once daily, taken in the morning **Adjust Dose**: dose may be increased to 25 mg once daily based on response and tolerability **Max dose**: 25 mg once daily	See above	In addition to above: ⌖ Indicated to reduce the risk of CV death in adults with type 2 diabetes and established CVD ⌖ Indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure	⌖ In addition to class effect (above): ⌖ Not recommended with eGFR <30 for glucose management; insufficient data to support dosing recommendation if eGFR <20 ⌖ Contraindicated in patients on dialysis ⌖ EMPA-REG trial demonstrated significant reduction in CV mortality and hospitalization for heart failure in pts with established CVD ⌖ EMPEROR-Reduced Trial and EMPEROR-Preserved Trial showed 10 mg/day empagliflozin reduced risk of hospitalization for HF and CV death in patients with HFrEF and HFpEF, respectively ⌖ Pregnancy: Fetal risk cannot be ruled out
Ertugliflozin (Steglatro™)	**Starting Dose:** 5 mg once daily, taken in the morning; correct any volume depletion prior to initiation **Adjust Dose**: dose may be increased to 15 mg once daily based on response and tolerability **Max dose**: 15 mg once daily	See above	**Note, clinical trials of ertugliflozin have not shown the clinical benefit for patients with ASCVD or CKD compared to other SGLT2i. It does reduce hospitalization for HF similar to other SGLT2i in the class**.	⌖ In addition to class effect (above): ⌖ Do not initiate if eGFR is <45 ml/min ⌖ Continued use not recommended if eGFR persistently <45 ml/min ⌖ Contraindicated with dialysis ⌖ No dose adjustment for mild to moderate hepatic impairment; do not use is severe hepatic impairment ⌖ Increased risk of amputation, consider factors that may increase the risk (e.g. history of previous amputation, PVD, neuropathy, and diabetic foot ulcers) ⌖ Pregnancy: Fetal risk cannot be ruled out

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Miscellaneous Therapies

Medication	Dosing	Effect on FPG	Effect on A1C	Clinical Uses	Cautions and Comments
Bromocriptine (Cycloset®) (dopamine receptor agonist)	0.8 mg daily (1.6 to 4.8 mg daily) Increased weekly until maximal tolerated daily dose Take within two hours after waking with food	↓18-20 mg/dL	0.5%	⌖ Use for type 2 diabetes ⌖ Not considered 1st or 2nd line therapy ⌖ Can be used with SU ⌖ Limited efficacy data in combination with TZD ⌖ Efficacy has not been confirmed in combination with insulin	⌖ Hypotension: Use caution if taking anti-hypertensive medications ⌖ May exacerbate psychotic disorders or reduce the effectiveness of drugs to treat psychosis. Not recommended if severe psychotic disorder ⌖ Side effects: somnolence, nausea, fatigue, dizziness, vomiting, and headache ⌖ Do not use with dopamine antagonists (neuroleptic agents) or other dopamine receptor agonists ⌖ Pregnancy: Fetal risk cannot be ruled out
Colesevelam (Welchol®) (bile acid sequestrant)	Tablets: 625 mg Oral suspension: 3.75 and 1.875 gram packet	↓15-30 mg/dL	0.5%	⌖ Use for type 2 diabetes ⌖ Not considered 1st or 2nd line therapy ⌖ Can be used in combination with metformin, SU, pioglitazone and insulin ⌖ Has not been studied with DPP-4 Inhibitors	⌖ Do not use if history of bowel obstruction, triglyceride (TG) >500 mg/dL, history of hypertriglyceridemia-induced pancreatitis ⌖ Side effects constipation, dyspepsia, nausea ⌖ Can decrease drug levels of: glimepiride, glipizide, glyburide, levothyroxine, some oral contraceptives, phenytoin and warfarin ⌖ Can increase levels of metformin if co-administered with metformin XR ⌖ Pregnancy; Fetal risk is minimal

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Medication	Dosing	Effect on FPG	Effect on A1C	Clinical Uses	Cautions and Comments
Meglitinide Repaglinide (Prandin®) ***D Phenylalanine derivative*** Nateglinide (Starlix®)	0.5-4 mg within 30 min prior to each meal 60-120 mg 1 to 30 min. before meals (up to tid)	↓ 30-70	1-1.5%	⌖ Targets post-meal hyperglycemia ⌖ Use if variable meal schedule ⌖ Alternative to SU (if significant hypoglycemia) ⌖ May limit weight gain if prior hypoglycemia	⌖ Higher cost ⌖ Use early in disease course ⌖ Lower Starlix dose if hepatic disease ⌖ Hypoglycemia, weight gain ⌖ Compliance issues with multiple doses qd ⌖ Effective for patients requiring flexible meal schedule or those that skip meals ⌖ If eGFR < 30, dose conservatively (Prandin) ⌖ Pregnancy; Fetal risk cannot be ruled out
Alpha Glucosidase Inhibitor Acarbose (Precose®) Miglitol (Glyset®)	50-100 mg tid with meals (start 25 mg at one meal for 1-2 weeks, titrate gradually, q 2-4 weeks)	15-30	~0.5%	⌖ Targets post-meal glucose ⌖ No hypoglycemia ⌖ Limits weight gain ⌖ Can be used in combination with noninsulin therapies and insulin	⌖ Significant GI side effects (flatulence very common) ⌖ Slowly titrate dose to minimize GI side effects ⌖ Limited glucose lowering effect, thus use only if within 0.5 percentage points of A1C target and postmeal BG elevation are concern ⌖ Avoid if other significant bowel diseases ⌖ Avoid if eGFR <30 ⌖ Pregnancy: Fetal risk cannot be ruled out

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Combination Therapy Formulations

			Dosing → Individualized based on current regimen, effectiveness, tolerability	
Brand Name	**Generic Name**	**Generic Name**	**Initial dose:**	**Max daily dose:**
ACTO*plus*met™	pioglitazone	metformin	Tablet forms: 15 mg pioglitazone / 500 mg metformin and 15 mg pioglitazone / 850 mg metformin	pioglitazone 45 mg / metformin 2550 mg
Duetact™	pioglitazone	glimepiride	pioglitazone 30 mg / glimepiride 2 mg or pioglitazone 30 mg / glimepiride 4 mg	pioglitazone 30 mg / glimepiride 4 mg
Glucovance™	glyburide	metformin	glyburide 1.25 mg / metformin 250 mg with meals; titration increments glyburide 1.25 mg, metformin 250 mg per day q2weeks	glyburide 20 mg / metformin 2000 mg
Glyxambi®	empagliflozin	linagliptin	empagliflozin 10 mg / linagliptin 5 mg	empagliflozin 25 mg / linagliptin 5 mg
Invokamet®	canagliflozin	metformin	Twice daily: canagliflozin 50 mg / metformin 500 mg	Canagliflozin 150 mg / metformin 1000 mg twice daily
Invokamet®XR	canagliflozin	metformin XR	2 tablets canagliflozin 50 mg / metformin XR 500 mg once daily	2 tablets canagliflozin 150 mg / metformin XR 1000 mg once daily
Janumet ™	sitagliptin	metformin	No current metformin treatment or taking metformin 500 mg twice daily: sitagliptin 50 mg / metformin 500 mg twice daily	sitagliptin 100 mg / metformin 2000 mg
Janumet XR™	sitagliptin	metformin XR	Maintain same daily dose if switching from regular to XR	sitagliptin 100 mg / metformin XR 2000 mg
Jentadueto™	linagliptin	metformin	No current metformin: linagliptin 2.5 mg / metformin 500 mg twice daily Current metformin: linagliptin 2.5 mg + one-half of current metformin dose twice daily	linagliptin 5 mg / metformin 2000 mg
JentaduetoXR™	linagliptin	metformin XR	No current metformin: linagliptin 5 mg / metformin 1000 mg once daily with a meal Current metformin: linagliptin 5 mg total + similar total daily dose of metformin once daily with a meal.	linagliptin 5 mg / metformin XR 2000 mg
Kazano™	alogliptin	metformin	Tablets available: alogliptin 12.5 mg / metformin 500 or 1000 mg, taken twice daily with food	alogliptin 25 mg / metformin 2000 mg

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KombiglyzeXR™	saxagliptin	metformin XR	saxagliptin 2.5 mg / metformin 500 mg	saxagliptin 5 mg / metformin 2000 mg
Metaglip™	glipizide	metformin	glipizide 2.5 mg / metformin 250 mg daily with food	Titrate to (in divided doses) glyburide 10 mg / metformin 2000 mg every 2 weeks
Oseni®	alogliptin	pioglitazone	alogliptin 12.5 mg / pioglitazone 15 mg	alogliptin 25 mg / pioglitazone 45 mg
Qtern®	dapagliflozin	saxagliptin	dapagliflozin 10 mg/saxagliptin 5 mg orally once daily in the morning	dapagliflozin 10 mg/saxagliptin 5 mg orally once daily in the morning
Qternmet® XR	dapagliflozin	saxagliptin and metformin	dapagliflozin 5 mg/saxagliptin 5 mg/metformin XR 1000 mg or 2000 mg once daily in the morning with food	dapagliflozin 10 mg/saxagliptin 5 mg/metformin XR 2000 mg once daily in the morning with food
Segluomet™	ertugliflozin	metformin	ertugliflozin 2.5 mg / metformin 500 mg or ertugliflozin 2.5 mg / metformin 1000 mg twice daily depending on current therapy with gradual dose escalation	ertugliflozin 7.5 mg / metformin 1000 mg twice daily (note ertugliflozin 7.5 mg / metformin 500 mg tablets also available)
Steglujan™	ertugliflozin	sitagliptin	ertugliflozin 5 mg / sitagliptin 100 mg in morning with or without food	ertugliflozin 15 mg / sitagliptin 100 mg in morning with or without food
Synjardy®	empagliflozin	metformin	Use current regimen to determine starting dose; empagliflozin/metformin tablets available 5 mg/500 mg, 5 mg/1000 mg, 12.5 mg/500 mg, and 12.5 mg/1000 mg	empagliflozin 25 mg/ 2000 mg metformin per day
Synjardy® XR	empagliflozin	metformin XR	Use current regimen to determine starting dose; empagliflozin /metformin XR tablets available 5 mg/1000 mg, 10 mg/1000 mg, 12.5 mg/1000 mg, and 25 mg/1000 mg	empagliflozin 25 mg/ 2000 mg metformin XR per day
Trijardy XR	empagliflozin	Linagliptin and metformin XR	Use current regimen to determine starting dose of Empagliflozin/Linagliptin/ MetforminXR tablets available 5 mg/2.5 mg/1000 mg, 10 mg/5 mg/1000 mg, 12.5 mg/2.5 mg/1000 mg and 25 mg/5 mg/1000 mg	empagliflozin 25 mg/linagliptin 5 mg/metformin 2000 mg daily
Xigduo XR™	dapagliflozin	metformin	dapagliflozin 5 mg / metformin 500 mg	dapagliflozin 10 mg / metformin 2000 mg

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Glucagon Like Peptide-1 (GLP-1) Receptor Agonist Start and Adjust Guideline

Note: As a class of medications the GLP-1 receptor agonists can be used very effectively with insulin. Each of the medications in the class may or may not be approved for use with insulin or approved with only a specific type of insulin regimen (e.g. background versus mealtime insulin). However, numerous clinical trials and post-marketing experience has demonstrated that each of the medications in the class have a similar efficacy when used in combination with insulin. Hypoglycemia can occur when combining GLP-1 agonists with insulin. Reduce the total daily dose of insulin by 20% if A1C ≤ 8% and maintain current dose if A1C is >8%. The American Diabetes Association (ADA) recommends starting a GLP-1 receptor agonist before starting insulin due to efficacy, weight loss and lower risk of hypoglycemia compared to Insulin. The ADA also recommends starting a GLP-1 receptor agonist with demonstrated CV benefit (dulaglutide, liraglutide, and semaglutide) for patients with type 2 diabetes and established CVD, or those at high CV risk, regardless of level of glycemic management.

Medication	Dosing	Labs/Effect on Glycemic Parameters	Clinical Uses	Cautions and Comments
Exenatide (Byetta®)	Comes in prefilled pen **Starting Dose**: 5 mcg subcutaneous dose BID ⌖ Dose up to 60 minutes before breakfast and evening meal, don't administer after meals ⌖ Make sure at least 6 hours between injections **Adjust Dose**: Increase to 10 mcg BID after 1 month based on level of glycemic management and tolerability **Max Dose:** 10 mcg BID	**Labs needed to start:** eGFR within 12 months if normal and within 3 months if abnormal **Ongoing monitoring:** eGFR every 12 months thereafter if normal, every 3 months if abnormal **Effect of Glycemic Parameters** **SMBG** ↓ FPG 10-15 mg/dL ↓ PPG 50-60 mg/dL **CGM** ↓ Mean glucose 30- 45 mg/dL **A1C** (or CGM derived equivalent GMI): 1 to 1.5 percentage point reduction **Comment:** Very effective at lowering postmeal BG	⌖ Can be used in combination with metformin, SU, SGLT2 inhibitor, TZD and insulin ⌖ Targets post-meal glucose ⌖ Weight loss common (6-10 lbs at 1 year) ⌖ No hypoglycemia unless used with other hypoglycemic meds (SU, insulin)	⌖ Not indicated for use in type 1 diabetes ⌖ Contraindicated if eGFR <30ml/min ⌖ If eGFR 30-50 ml/min use caution when increasing dose from 5-10 mcg ⌖ ↑ nausea for eGFR 30-80 ml/min when titrating dose from 5 to 10 mcg ⌖ Part of REMS program for medullary thyroid carcinoma and pancreatitis ⌖ Nausea may decrease over time ⌖ Not recommended with severe gastrointestinal disease (gastroparesis) ⌖ Take medications requiring rapid absorption 1 hr prior to dose due to delayed gastric emptying ⌖ Associated with pancreatitis (rare) ⌖ Dose of SU or mealtime insulin may need to be reduced (up to 50%) to avoid hypoglycemia ⌖ Pregnancy: Fetal risk cannot be ruled out

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Medication	Dosing	Labs/Effect on Glycemic Parameters	Clinical Uses	Cautions and Comments
Exenatide Extended Release (Bydureon®)	⌖ Administer 2 mg subcutaneous dose once every 7 days ⌖ Administer immediately after powder is suspended ⌖ Can be given any time of day regardless of mealtime ⌖ Bydureon BCise single use pen with hidden 23 gauge needle	**Labs needed to start:** eGFR within 12 months if normal and within 3 months if abnormal **Ongoing monitoring:** eGFR every 12 months thereafter if normal, every 3 months if abnormal **Effect of Glycemic Parameters** **SMBG** ↓ FPG 40-50 mg/dL ↓ PPG 30-40 mg/dL **CGM** ↓ Mean glucose 40- 50 mg/dL **A1C** (or CGM derived equivalent GMI): 1 to 1.5 percentage point reduction **Comment:** ⌖ Effective at lowering fasting and postmeal BG	⌖ Indicated as adjunct to diet and exercise to improve glucose control in type 2 diabetes ⌖ Can be used in combination with metformin, SU, TZD, SGLT2 inhibitor and insulin ⌖ Do not use in combination with DPP-4 inhibitor ⌖ Does increase risk of hypoglycemia unless used with insulin or insulin secretagogues ⌖ Modest weight loss ⌖ Injection site reactions have been reported, especially subcutaneous nodules to resolve with time	⌖ Not indicated for use in type 1 diabetes ⌖ Black box warning for risk of thyroid C-cell tumors; causes thyroid C-cell tumors in rodents; unsure of relevance in humans ⌖ Contraindicated if patient or family has history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN 2) ⌖ Part of REMS program for medullary thyroid carcinoma and pancreatitis ⌖ Not recommended with severe gastrointestinal disease (gastroparesis) ⌖ Contraindicated if eGFR <30 ml/min or ESRD ⌖ Dose of SU or mealtime insulin may need to be reduced (up to 50%) to avoid hypoglycemia ⌖ EXSCEL trial showed CV neutral (safe) with non-statistically significant trend for CV protection compared to placebo in patients with CVD or at high risk ⌖ Pregnancy: Fetal risk cannot be ruled out

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Medication	Dosing	Labs/Effect on Glycemic Parameters	Clinical Uses	Cautions and Comments
Liraglutide (Victoza®)	⌖ 0.6 mg daily for 1 week, then titrate to clinically effective dose 1.2 mg daily ⌖ Max dose is 1.8 mg daily ⌖ Administered subcutaneously once daily, any time of day (before or after meals) **Note,** liraglutide (Saxenda®) has been approved as a weight loss medication with a max dose of 3.0 mg daily.	**Labs needed to start:** eGFR within 12 months if normal and within 3 months if abnormal **Ongoing monitoring:** eGFR every 12 months thereafter if normal, every 3 months if abnormal **Effect of Glycemic Parameters** **SMBG** ↓ FPG 50-60 mg/dL ↓ PPG 30-40 mg/dL **CGM** ↓ Mean glucose 40- 50 mg/dL **A1C** (or CGM derived equivalent GMI): ~1.5 percentage point reduction **Comment:** ⌖ Effective at lowering fasting and postmeal BG	⌖ Indicated as an adjunct to diet and exercise to improve glycemic management in type 2 diabetes ⌖ Approved for patients 10 years of age and older ⌖ Indicated to reduce the risk of CV events including CV death, non-fatal M.I., and non-fatal stroke in adults with type 2 diabetes and established CVD ⌖ Can be used in combination with metformin, SU, TZD, SGLT2 inhibitor and insulin ⌖ Do not use in combination with DPP-4 inhibitor ⌖ Does not increase risk of hypoglycemia unless used with insulin or insulin secretagogues ⌖ Modest weight loss ⌖ G.I. side effects common and transient usually diminishing after several weeks	⌖ Not indicated for use in type 1 diabetes ⌖ Black box warning for risk of thyroid C-cell tumors; causes thyroid C-cell tumors in rodents; unsure of relevance in humans ⌖ Contraindicated if patient or family has history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2 (MEN 2) ⌖ Part of REMS program for medullary thyroid carcinoma and pancreatitis ⌖ Most common side effects are headache, nausea, diarrhea ⌖ Use with caution if patient with renal or hepatic disease, however no dose adjustment is recommended ⌖ Associated with pancreatitis (rare); use with caution in patients with history of pancreatitis ⌖ Dose of SU or mealtime insulin may need to be reduced (up to 50%) to avoid hypoglycemia ⌖ LEADER trial demonstrated significant reduction in CV events in high-risk CV patients ⌖ GRADE Study demonstrated liraglutide was CV protective and had longer durability in A1C lowering than glimepiride and sitagliptin ⌖ Pregnancy: Contraindicated

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Medication	Dosing	Labs/Effect on Glycemic Parameters	Clinical Uses	Cautions and Comments
Dulaglutide (Trulicity®)	⌖ Initiate at 0.75 mg subcutaneously once weekly. ⌖ Dose can be increased to 1.5 mg once weekly for additional glycemic control. ⌖ If needed, dose may be increased to 3.0 mg once weekly after 4 weeks at 1.5 mg/week dose ⌖ If needed, dose may be increased to 4.5 mg once weekly (max dose) after 4 weeks at 3.0 mg/week dose ⌖ Single pre-filled pen device with thin hidden needle ⌖ **Skipped dose:** ⌖ If at least 72 hrs until next scheduled dose, administer missed dose as soon as possible, and then give next dose on regularly scheduled day ⌖ If less than 72 hours until next scheduled dose, skip missed dose and administer next dose on regularly scheduled day	**Labs needed to start:** eGFR within 12 months if normal and within 3 months if abnormal **Ongoing monitoring:** Monitoring eGFR when escalating doses of dulaglutide in patients with renal impairment or those reporting severe adverse gastrointestinal reactions. **Effect of Glycemic Parameters** **SMBG** ↓ FPG 40-50 mg/dL ↓ PPG 40-50 mg/dL **CGM** ↓ Mean glucose 40- 50 mg/dL **A1C** (or CGM derived equivalent GMI): ~1.5-2.0 percentage point reduction **Comment:** ⌖ Effective at lowering fasting and postmeal BG	⌖ Indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes ⌖ Indicated to reduce the risk of major adverse CV events (cardiovascular death, non-fatal M.I. or non-fatal stroke) in adults with type 2 diabetes who have established CVD or multiple CV risk factors. ⌖ Can be used in combination with metformin, SU, TZD, SGLT2 inhibitor and insulin ⌖ Do not use in combination with DPP-4 inhibitor ⌖ No hypoglycemia above placebo level unless used with other hypoglycemic meds (SU, insulin) ⌖ Modest weight loss at lower dose; more significant weight loss at higher dose.	⌖ Not indicated for use in type 1 diabetes ⌖ Black box warning for risk of thyroid C-cell tumors; causes thyroid C-cell tumors in rodents; unsure of relevance in humans. ⌖ Contraindicated if patient or family has history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2 (MEN 2) ⌖ Part of REMS program for medullary thyroid carcinoma and pancreatitis ⌖ Most common side effects reported have been nausea, vomiting, diarrhea, abdominal pain and decreased appetite. ⌖ Use caution in patients with hepatic impairment ⌖ Not recommended with severe gastrointestinal disease (gastroparesis) ⌖ Discontinue promptly if pancreatitis is suspected; do not restart if confirmed. ⌖ Use caution when starting and adjusting dose with renal impairment and monitor renal function if severe GI reaction ⌖ REWIND trial showed CV benefit in both patients with established CVD and those with risk factors for CVD ⌖ Pregnancy: Fetal risk cannot be ruled out

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Medication	Dosing	Labs/Effect on Glycemic Parameters	Clinical Uses	Cautions and Comments
Semaglutide (Ozempic®)	⌖ Subcutaneous injection, fine needle using pen device ⌖ 0.25 mg once weekly dose for 4 weeks then increase to 0.5 mg weekly ⌖ After four weeks may increase to 1 mg once weekly dose if additional glucose lowering needed and patient tolerating 0.5 mg dose ⌖ After four weeks may increase to max dose of 2 mg once weekly dose if additional glucose lowering needed ⌖ Take missed dose if within 5 days of scheduled dose, otherwise wait for regular scheduled time. **Note,** semaglutide (Wegovy™) has been approved as a weight loss medication with a max dose of 2.4 mg daily.	**Labs needed to start:** eGFR within 12 months if normal and within 3 months if abnormal **Ongoing monitoring:** Monitoring eGFR when escalating doses of semaglutide in patients reporting severe adverse gastrointestinal reactions. **Effect of Glycemic Parameters** **SMBG** ↓ FPG 40-50 mg/dL ↓ PPG 40-50 mg/dL **CGM** ↓ Mean glucose 40- 50 mg/dL **A1C** (or CGM derived equivalent GMI): ~1.5-2.0 percentage point reduction for injectable ~1.0-1.5 percentage point reduction for oral semaglutide **Comment:** ⌖ Effective at lowering fasting and postmeal BG	⌖ Indicated as an adjunct to diet and exercise to improve glycemic management in type 2 diabetes ⌖ Indicated to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease ⌖ Can be used in combination with metformin, SU, TZD, SGLT2 inhibitor and insulin ⌖ Do not use in combination with DPP-4 inhibitor ⌖ No hypoglycemia above placebo level unless used with other hypoglycemic meds (SU, insulin) ⌖ Improves both first and second phase insulin secretion ⌖ Significant weight loss ⌖ Semaglutide has been shown to be the most effective GLP-1 receptor agonist at lowering A1C and causing weight loss	⌖ Not indicated for use in type 1 diabetes ⌖ Black box warning for risk of thyroid C-cell tumors; causes thyroid C-cell tumors in rodents; unsure of relevance in humans ⌖ Contraindicated if patient or family has history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2 (MEN 2) ⌖ Gastrointestinal side effects most common (diarrhea, vomiting, nausea) ⌖ Serious hypersensitivity reactions, including anaphylaxis and angioedema, have been reported with GLP-1 receptor agonists ⌖ Discontinue promptly if pancreatitis is suspected; do not restart if confirmed ⌖ No dose adjustment for renal or hepatic impairment but use caution when starting and adjusting dose with renal impairment ⌖ Diabetic retinopathy complications have been reported especially in patients with a history of diabetic retinopathy, monitoring is recommended. ⌖ SUSTAIN 6 Trial showed semaglutide resulted in significantly fewer CV events (MI, stroke CV death) than placebo ⌖ PIONEER 6 trail showed oral semaglutide CV neutral (safe) ⌖ Pregnancy: Fetal risk cannot be ruled out
Oral Semaglutide (Rybelsus®)	⌖ Start 3 mg/day for 30 days ⌖ Take oral semaglutide upon waking with <4 oz water 30 minutes before any food, liquids or other oral medications ⌖ Increase dose to 7 mg/day for 30 days ⌖ May increase to 14 mg/day based on tolerability and need for additional glucose lowering			

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Glucagon Like Peptide-1 (GLP-1) and Glucose-Dependent Insulinotropic Polypeptide (GIP) Receptor Agonist Start and Adjust Guideline

Medication	Dosing	Labs/Effect on Glycemic Parameters	Clinical Uses	Cautions and Comments
Tirzepatide (Mounjaro®)	⌖ Single 39 amino acid modified peptide that selectively binds to and activates both the GIP and GLP-1 receptors ⌖ Subcutaneous injection weekly using single use pen into the thigh, abdomen, or upper arm; rotate injection sites ⌖ 2.5 mg once weekly dose for 4 weeks then increase to 5.0 mg weekly ⌖ If additional glycemic control is needed, increase dosage in 2.5-mg increments after at least 4 weeks on the current dose ⌖ Max dose is 15 mg once weekly ⌖ Take missed dose if within 4 days of scheduled dose; if after 4 days skip the missed dose and resume regular scheduled time.	**Labs needed to start:** Monitor renal function (eGFR) when initiating therapy **Ongoing monitoring:** Monitor renal function (eGFR) when escalating doses and in patients reporting severe adverse gastrointestinal reactions, especially in patients with history of renal impairment; if serum calcitonin levels are elevated, patient should be further evaluated; routine monitoring of serum calcitonin is of uncertain value **Effect of Glycemic Parameters** **CGM** TIR of ~90% **A1C** (or CGM derived equivalent GMI): 2.0-2.5 percentage point **Comment:** ⌖ Effective at lowering fasting and postmeal BG ⌖ The most effective noninsulin therapy developed to date	⌖ Indicated as an adjunct to diet and exercise to improve glycemic management in adults with type 2 diabetes ⌖ Enhances 1st and 2nd phase insulin secretion and reduces glucagon levels in a glucose-dependent manner ⌖ Has been studied as monotherapy and in combination with metformin, sulfonylurea, SGLT-2i and insulin ⌖ Do not use in combination with DPP-4 inhibitor or GLP-1 receptor agonist ⌖ No hypoglycemia above placebo level unless used with SU or insulin; consider reducing dose of SU or insulin to reduce the risk of hypoglycemia ⌖ Significant dose dependent weight loss of 10-15% ⌖ Compared to other GLP-1 receptor agonists tirzepatide has been shown to be more effective at lowering A1C and reducing weight	⌖ Not indicated for use in type 1 diabetes ⌖ Black box warning for risk of thyroid C-cell tumors; causes thyroid C-cell tumors in rodents; unsure of relevance in humans ⌖ Contraindicated if patient or family has history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2 (MEN 2) ⌖ Gastrointestinal side effects most common (diarrhea, vomiting, nausea); not recommended in patients with severe gastrointestinal disease, including severe gastroparesis ⌖ Serious hypersensitivity reactions, including anaphylaxis and angioedema, have been reported with GLP-1 receptor agonists ⌖ Has not been studied in patients with a history of pancreatitis; discontinue promptly if pancreatitis is suspected (persistent severe abdominal pain, sometimes radiating to the back with or without vomiting); do not restart if confirmed ⌖ No dose adjustment for renal or hepatic impairment ⌖ Rapid glucose lowering may temporarily worsen diabetic retinopathy ⌖ Increased risk of diabetic retinopathy complications in patients with a history of diabetic retinopathy; monitoring recommended ⌖ Acute events of gallbladder disease, such as cholelithiasis and cholecystitis has been reported with GLP-1 receptor agonists ⌖ CV protection has not been established yet, CVOTs underway ⌖ Pregnancy: May cause fetal harm

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