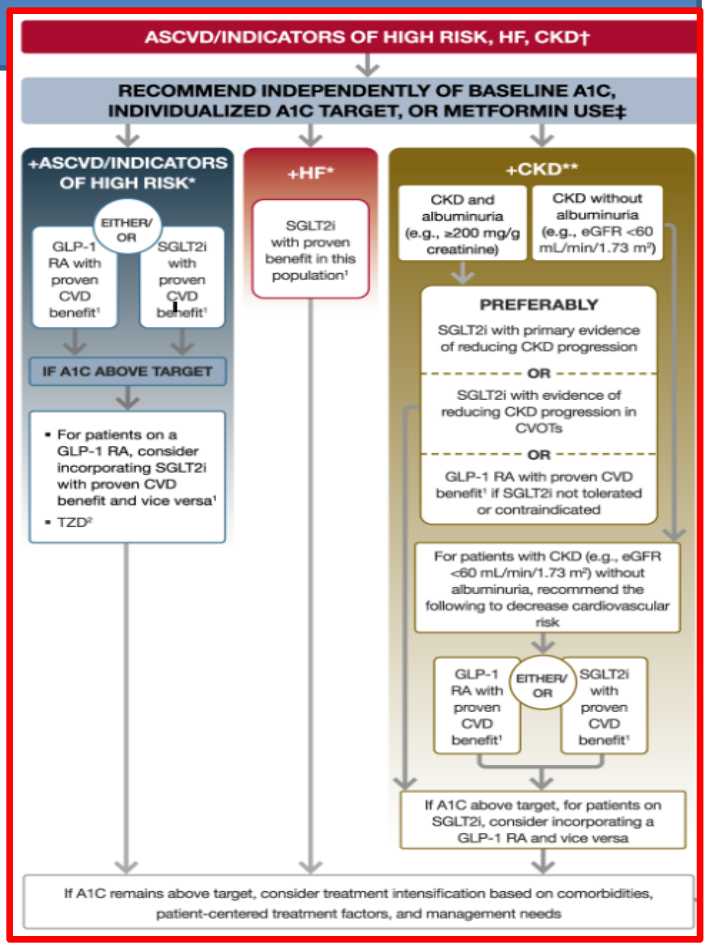
Beth Israel Lahey Health Focused Diabetes Prescribing Quick Guide
Sodium–Glucose Cotransporter-2 Inhibitors (SGLT-2is) and Glucagon-like Peptide-1 Receptor Agonists (GLP-1RAs)

Updated 10/2022 - Refer to ADA guideline section on Pharmacologic Therapies for overall approach to pharmacotherapy

Abbreviations and definitions at the end of this document

Introduction: This guide provides an approach to including SGLT-2is and/or GLP-1RAs in the treatment of patients with Type 2 Diabetes, with guidance for patients with specific cardiorenal risk factors. These therapeutic classes are recommended independently of baseline HbA1c, individualized HbA1c targets, or metformin use. However, metformin is recommended as initial therapy when possible.

Metformin Prescribing Pearls	
Maximize dosing	• Normal renal function: 2000 mg/day in divided doses • eGFR 30-45 mL/min/1.73m^2: 1000 mg/day • eGFR < 30 mL/min/1.73m^2: Contraindicated
Manage GI side effects	Consider retrial and use slower titration schedule and/or extended release formulation
Additional therapies	Continue upon initiation of insulin and combination injectable therapy for ongoing glycemic and metabolic effects (unless contraindicated or not tolerated)



Step 1: Determine preferred therapeutic class based on presence of ASCVD* (or indicators of high risk), HF, CKD**

Selection of the agent should be based on the evidence in their role in reducing cardiorenal complications of diabetes.

- Differences among agents in CVOT primary endpoints/outcomes vary slightly and should not preclude use.

SGLT2 inhibitors with proven CARDIORENAL benefit		
Benefits include reduction in MACE^, HHF, and CKD progression		
Empagliflozin (Jardiance)	**Dapagliflozin (Farxiga)**	**Canagliflozin (Invokana)**
Moderate A1c lowering, moderate weight loss potential, low hypoglycemic risk		
GLP-1 receptor agonists with proven CARDIAC benefits		
Benefits include reduction in MACE and possibly CKD progression		
Semaglutide (SQ only) (Ozempic)	**Liraglutide (Victoza)**	**Dulaglutide (Trulicity)**
High A1c lowering, high weight loss potential, low hypoglycemic risk		

Step 2: Review and Evaluate for Contraindications and Potential Adverse Effects

Contraindications		Important Considerations for specific populations	
SGLT-2is	**GLP-1RAs:**	**SGLT-2is:**	**GLP-1RAs:**

• Patients on dialysis
• Pregnancy/lactation
• Type 1 diabetes
	***FDA Black Box Warning*:** Personal or family history of Medullary Thyroid Cancer or Multiple Endocrine Neoplasia Syndrome Type 2 (MEN2)
	• Pregnancy/Lactation
	• Type 1 Diabetes *(for glycemic control)*
		• Less glucose-lowering benefit in patients with more severe kidney disease at initiation (e.g. eGFR < 45 mL/min/1.73m^2)
		• Frequent genitourinary infections
		• Volume depletion/hypotension
		• The following patients are at increased risk for adverse effects and close monitoring is recommended:
		  • Severe peripheral neuropathy, severe PVD
		  • Risk/history of lower extremity ulcers/amputation
		  • Risk/history of diabetic ketoacidosis – consult a specialist
			• History/risk of pancreatitis or severe gastroparesis – consult a specialist

Step 3: Choose the medication within the preferred therapeutic class

See therapeutic class dosing charts (Table 1 and Table2) which contain **medication specific considerations** and highlight preferred formulary agents. **Consider insurance coverage and cost**, and refer to manufacturer programs and other medication access resources if needed.

Step 4: Assess impact on current regimen

See Table 3 for select changes that may be required in certain drug classes.

Step 5: Establish follow-up and monitoring to achieve therapeutic goals

- Ensure f/u visits at regular intervals
- Review blood glucose log, follow up A1c at 3 months if not at goal
- See additional info to address barriers

Recommended monitoring

SGLT2i: assess renal function, electrolytes, and volume status See Table 1 for important details

GLP1-RA: titrate to maintenance dose after recommended initiation period

Step 6: Insulin and Combination Therapy

- **Intensifying to injectable therapies**: Consider GLP1-RA in most patients prior to insulin. See algorithm from the ADA Guide: Pharmacologic Therapy for Adults with Type 2 Diabetes.
- **Prescribing both an SGLT-2i and GLP-1RA when clinically indicated**: Data suggests some independence in effect, and addition of SGLT-2i to GLP-1RA therapy demonstrated additive effects on glycemic control, weight loss, and cardiovascular benefit. Patient out of pocket costs may be very high.

Therapeutic Class Dosing and Considerations for use in Type 2 Diabetes

Table 1
SGLT-2 Inhibitors Comparison Chart for use in Type 2 Diabetes
This section highlights the medications with the most robust clinical evidence

Contraindications

- Patients on dialysis
- Pregnancy/lactation
- Type 1 diabetes

Precautions and Important Considerations

- Less glucose-lowering benefit in patients with more severe kidney disease at initiation (e.g. eGFR < 45 mL/min/1.73m^2)
- Frequent genitourinary infections
- Volume depletion/hypotension
- The following patients are at increased risk for adverse effects and close monitoring is recommended:
  - Severe peripheral neuropathy, severe PVD
  - Risk/history of lower extremity ulcers/amputation
  - Risk/history of diabetic ketoacidosis – consult a specialist

Agents → *(including links to Package Inserts)*	**Empagliflozin (Jardiance)**	**Dapagliflozin (Farxiga)**	**Canagliflozin (Invokana)**
Starting Dose	10 mg once daily	5 mg once daily *Concomitant HF: start at 10 mg daily*	100 mg daily Prior to first meal of the day
Target Dose (consider ↑after 4-12 wks. if needed to achieve glycemic goals)	May increase to 25 mg once daily	May increase to 10 mg once daily	May increase to 300 mg once daily
Renal Considerations	**Glucose lowering effect is reduced and varies by drug in patients with eGFR < 45 ml/min/1.73m^2**		
Treatment of Hyperglycemia	**Not recommended in patients with** eGFR < 30 mL/min/1.73m^2	**Not recommended in patients with** eGFR < 45 mL/min/1.73m^2	**DOSE ADJUSTMENT recommended:** eGFR 30-60 mL/min/1.73m^2: 100 mg daily **Not Recommended**: eGFR < 30 mL/min/1.73m^2
Treatment for HF / CKD	**CKD/HF:** Established patients with eGFR ≥ 20 mL/min/1.73m^2 may continue 10 mg daily	**CKD/HF:** Established patients with eGFR < 25 mL/min/1.73m^2 may continue on 10 mg daily	**CKD:** Established patients with eGFR < 30 mL/min/1.73m^2 and urinary albuminuria ≥ 300 mg/day may continue 100 mg daily
Formulary Coverage (Commercial and MassHealth ACO risk contracts) BILHPN cost/coverage chart	BCBS, HPHC, Tufts: Covered MassHealth: Covered	BCBS, HPHC, Tufts: Covered MassHealth: Covered	BCBS, HPHC, Tufts: Not Covered MassHealth: Covered
Manufacturer Savings Programs	https://www.jardiance.com/type-2-diabetes/support-and-savings/savings/	https://www.farxiga.com/savings-support.html	https://www.janssencarepath.com/hcp/invokana/affordability
Patient Counseling Points	• Mechanism of action, expect increased urination • Risk for genitourinary infections and proper hygiene • Maintain adequate hydration to avoid risk of volume depletion • Monitor blood pressure • Advise women considering pregnancy of possible risks to fetus		

Monitoring	• Asses volume status and renal function in patients at risk for volume depletion
	• Ketoacidosis:
	  ○ Consider factors that may predispose patient to ketoacidosis; pancreatic insulin deficiency from any cause, caloric restriction, alcohol abuse
	  ○ Hold therapy 3 days prior to surgery; do not restart until risk has been resolved
	• Review glucose readings regularly, follow up A1c at 3 months
	• Incorporate foot exams to assess risk of amputation especially in patients with peripheral vascular disease, peripheral neuropathy, etc.		

Important Note: This guide does not replace clinical judgment. Always consider consultation with a specialist if clinical circumstances are not addressed within this guide or if clarification is needed for an individual patient scenario.

Therapeutic Class Dosing and Considerations for use in Type 2 Diabetes

Table 2
GLP-1 Receptor Agonist Comparison Chart for use in Type 2 Diabetes
Semaglutide SQ, liraglutide and dulaglutide have the most robust clinical evidence for cardiorenal benefits

Contraindications

- ***Black Box Warning***: Personal or family history of Medullary Thyroid Cancer or Multiple Endocrine Neoplasia Syndrome Type 2 (MEN2)
- Type 1 Diabetes *(for glycemic control)*
- Pregnancy/Lactation

Precautions and Important Considerations

- History/risk of pancreatitis
- History/risk of severe GI disease/gastroparesis
- Active gallbladder disease
- Risk of worsening diabetic retinopathy due to rapid improvement in glycemic control

	Semaglutide SQ (Ozempic)	**Liraglutide (Victoza)**	**Dulaglutide (Trulicity)**	**Semaglutide PO (Rybelsus)** *NOTE: neutral cardiorenal benefits*
Weight loss potential	**+++**	**++**	**+**	**+++**
Starting Dose: *Intended to reduce GI symptoms, does not provide effective glycemic control*	0.25 mg SQ weekly x 4 weeks then titrate	0.6 mg SQ daily x 1 week then titrate	0.75 mg SQ weekly then titrate	3 mg daily x 30 days, then titrate ***Must take on empty stomach; with max 4 oz water at least 30 minutes before food, beverage or other medications***
Target Dose (titrate after 4-12 weeks to achieve glycemic goals) ***Renal Considerations*** *No renal dose adjustment necessary, use is not recommended in ESRD due to limited clinical evidence*	0.5 mg weekly, may increase to 1 mg weekly after 4 weeks if needed **Max dose 2 mg weekly**	1.2 mg daily, may increase to 1.8 mg after 1 week if needed **Max dose 1.8 mg daily**	May increase to 1.5 mg weekly after 4 to 8 weeks, continue to titrate every 4-8 weeks **Max dose 4.5 mg weekly**	7 mg daily, may increase to 14 mg after 30 days **Max dose 14 mg daily** **SWITCHING FROM OZEMPIC:** May initiate on 7 mg dose starting 7 days post last Ozempic dose
Formulary Coverage (Commercial and MassHealth ACO risk contracts) BILHPN cost/coverage chart	BCBS: Not Covered HPHC, Tufts: Covered MassHealth: Not Covered	BCBS: Not Covered HPHC, Tufts: Covered MassHealth: Covered	BCBS, HPHC, Tufts: Covered MassHealth: Preferred/Covered	BCBS: Not Covered HPHC, Tufts: Covered MassHealth: Covered
Device and Pen Needle	 No additional pen needles required, NovoFine Plus 32G 4mm pen needles included	 **Additional Rx needed for pen needles,** NovoFine 32G pen needles recommended *but ANY pen needle will work*	 No additional pen needles required, includes a pre-attached, hidden needle	Tablets must be stored in closed Rybelsus bottle. Do not use pill box or other storage container. Swallow tablet whole; do not split, crush or chew. See additional administration instructions under starting dose section above.
Manufacturer Savings Programs	https://www.novocare.com/ozempic/savings-card.html	https://www.victoza.com/victoza-support-and-savings/save-on-your-prescription.html	https://www.trulicity.com/savings-resources	https://www.novocare.com/rybelsus/savings-card.html
Instructions for Use	Video / Website	Video / Website	Video / Website	Video / Website

Patient Counseling Points *(Refer to manufacturer sites to review proper administration)*	• Purpose of starting dose (to improve tolerability) and need for titration: review titration schedule with patient
	  ○ Expected, and likely transient, gastrointestinal side effects; consider individualized titration schedules when needed
	  ○ Encourage patients to eat smaller meals, and avoiding fatty foods to help minimize nausea/vomiting
	• Advise women considering pregnancy of possible risk to fetus			

Monitoring	• Frequent visits/follow up to ensure up titration for maximum benefit (*dose titrations should occur 4 weeks after starting dose*) • Review glucose readings regularly, follow up A1c at 3 months			

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Management of Concurrent Therapies

Table 3	Adding SGLT-2i to Therapy	Adding GLP-1RA to Therapy
Sulfonylurea (SU)	**Consider dose reduction/discontinuation to minimize risk of hypoglycemia based on current glycemic control**	
Insulin Therapy	**Consider dose adjustment to minimize risk of hypoglycemia based on current glycemic control.** If glucose levels are at goal, consider the following recommendations. Reassess once on a stable dose of new medication. Basal insulin: • ≥ 20 units: reduce basal dose by 20-50% • < 20 units: discontinue Mealtime insulin: Consider 50% reduction or discontinue	
DPP-4i	Consider discontinuing due to limited cost/benefit ratio	**Discontinue upon initiation**
Diuretics	May require empiric dose reduction in patients at risk for volume depletion	N/A
Antihypertensives	Empiric dose reduction generally not recommended; encourage patients to monitor BP closely	N/A

Avoiding Clinical Inertia – Critical in Preventing Suboptimal Glycemic Control

Please refer to the American Diabetes Association website "Overcoming Therapeutic Inertia" for patient engagement resources

Therapy intensification for patients not meeting treatment goals should not be delayed. Some reminders:

- Evaluate medication regimen, adherence, and medication costs/patient burden at regular intervals
  - Consider deprescribing of other medications that may not have clinical value
  - Blood glucose monitoring is an important component in evaluating treatment response; medication adjustments may be warranted prior to follow-up HbA1c. Consider follow-up within 4-6 weeks with each medication change/adjustment
- GLP-1RA's need to be up titrated 4 weeks after starting; additional titration to maximum tolerated dose should be addressed
- Evaluate need and refer for diabetes self-management education and support (DSMES) at critical time points as defined within ADA Guidelines (e.g. annually and/or when not meeting targets)
- Optimize treatment with multiple non-insulin options before adding insulin

Consider referrals to specialty prescribers when patient specific factors suggest drug therapy needs may be unique/complex (e.g. Pregnancy/breastfeeding, women considering pregnancy, Type 1 Diabetes, ESRD/ESLD, CKD Stage 3B or higher, inadequate response to two or more therapies, hepatology for persistent elevated LFTs, organ transplant, etc.)

Additional Resources:

- Standards of Medical Care in Diabetes-2022 Living Standards Updates: Sections 10 and 11 have been updated to include evidence from trials of medication effects in patients with type 2 diabetes on heart failure, cardiovascular, and chronic kidney disease outcomes: https://diabetesjournals.org/care/article/doi/10.2337/dc22-ad08/147053/Addendum-10-Cardiovascular-Disease-and-Risk
- Cardiovascular Disease and Risk Management: https://diabetesjournals.org/care/article/45/Supplement_1/S144/138910/10-Cardiovascular-Disease-and-Risk-Management
- Chronic Kidney Disease and Risk Management: https://diabetesjournals.org/care/article/45/Supplement_1/S175/138914/11-Chronic-Kidney-Disease-and-Risk-Management
- Older Adults-Standards of Medical Care in Diabetes-2022: https://diabetesjournals.org/care/article/45/Supplement_1/S195/138920/13-Older-Adults-Standards-of-Medical-Care-in
- Intensifying to Injectable Therapy: https://ada.silverchair-cdn.com/ada/content_public/journal/care/44/supplement_1/10.2337_dc21-s009/3/m_dc21s009f9-2.jpeg?Expires=1660837460&Signature=d7Imj0YTtL3ZgOv2OR7t1o0t-HK1LkB3f1R9AeHLr2NJYsLFAq9mg3lMIyd3U5xEq0gLtR5cYEaFSod8InLUqqVntsLNpITKxhGr-ZhSCygQICfpRdx9Rj7rs0A~PO4zB0OcMyEcdIJFzpDRA0wtkc6K6oVupwhCL9aMJSScjOKinpP-PxVJ65R8MFc5EkZggdNV94gCel3T7xmATPsw-XU~vu6Dgi3zpdkHbZXHw0p1KezPtAxwSYFMMvLbmFTYmak96A3EM-ioV089TGflq9JetEB-5NEZjE0OH2HT3shiRfZ2v1-hM1Lo8fFqfKRm781tc-edvIzwN48ctyIc2g__&Key-Pair-Id=APKAIE5G5CRDK6RD3PGA
- Facilitating Behavior Change and Well-being to Improve Health Outcomes: https://ada.silverchair-cdn.com/ada/content_public/journal/care/issue/45/supplement_1/7/standards-of-care-2022-copyright-stamped-updated01062022.pdf?Expires=1662667627&Signature=LpTPBaWmvirLjGgb2dLNbx8ctARpkDVCS9G8PcLs0YYBipLSkl2o7j1W5O2Q6frIojIkC1OKjKjww4kvJAohAXxOQG1tmhl1omDFXxblU2PI4Td6lFHq9xSkd~ybtx4jx2sHdCwtMmeoLsXbnqYJ1B2J~eu-VhcNciVeN4Q60L~q-zmy4N4HrdaTy0aBo6wxzqppd2IYe0osD-Cty3velpcFJ70FfXXCHQOPUp5faffDXOqV8A6VcK6kY~uEENE5f7c--uq-JhCGZVTtN5PkhquwSZJSca0-fW8X8MAbyqaYL09NxO~07r-ChsTeD2pw1G6QMIEaWc4HN4I0nYaDHg__&Key-Pair-Id=APKAIE5G5CRDK6RD3PGA

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Abbreviations:

ASCVD: Atherosclerotic cardiovascular disease	ESLD: End-stage liver disease	LFTs: Liver function tests
BCBS: Blue Cross Blue Shield of Massachusetts	ESRD: End-stage renal disease	MACE: Major adverse cardiovascular event
BP: Blood pressure	GLP-1RA: Glucagon-like peptide-1 receptor agonist	SGLT-2i: Sodium–glucose cotransporter-2 inhibitors
CKD: Chronic kidney disease	HF: Heart failure	SU: Sulfonylurea
CVD: Cardiovascular disease	HFrEF: Heart failure with reduced ejection fraction	Tufts: Tufts Health Plan (Commercial)
D/C: Discontinue	HHF: Hospitalization for heart failure	TZD: Thiazolidinediones
DPP-4i: Dipeptidyl peptidase-4 inhibitor	HPHC: Harvard Pilgrim Health Care	

Definitions:

*ASCVD: coronary heart disease, cerebrovascular disease or peripheral arterial disease	**Indicators of cardiovascular risk: patients ≥55 years of age with coronary, carotid, or lower-extremity artery stenosis >50% or left ventricular hypertrophy	^MACE: Composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke

References:

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Approval:

BILH System P&T Executive Committee 9/2022
BILH/BILHPN Ambulatory P&T Subcommittee: 10/2022
BILH System P&T Committee: Pending