# Review of the Algorithm for Adding Different Medications in DM

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# Diabetes Medications – Case Based Approach Care

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# Disclosures of Interest

- I am one of the specialists for Well-Ahead Louisiana's Diabetes ECHO Hub Team.

# Learning Objectives

1. Review new screening guidelines and diagnostic criteria for Type 2 Diabetes
2. Recognize the importance of an individualized approach
3. Acknowledge provider-related barriers leading to poor diabetes control
4. Recognize different goals for optimal glycemic control
5. Review algorithms and medication profiles per updated guidelines from American Diabetes Association (ADA) and American Association of Clinical Endocrinology (AACE) with use of case examples.

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Clin Diabetes.
2020;38(4):371-381.
doi:10.2337/cd20-0053

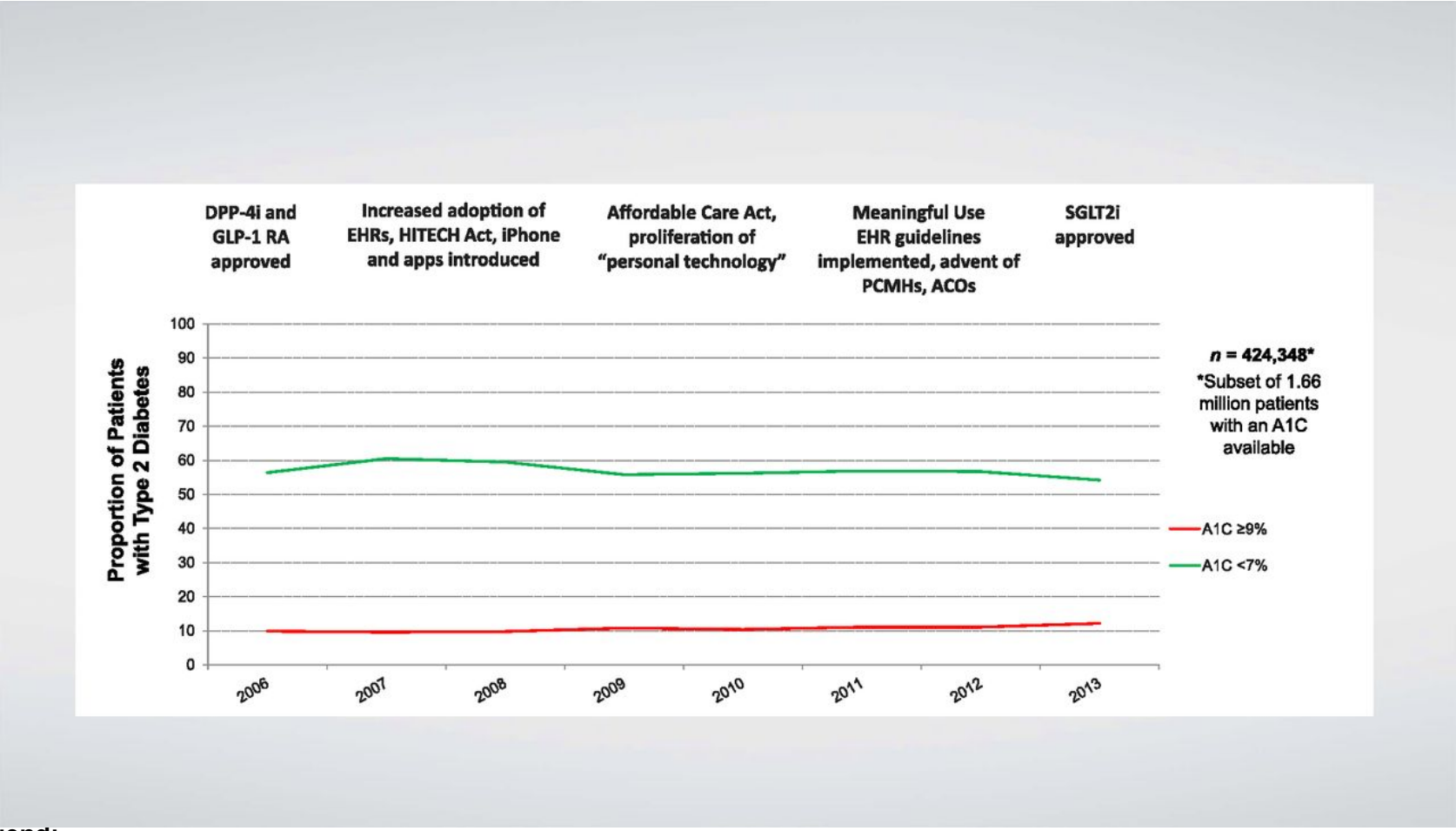


**Figure Legend:**

Type 2 diabetes trends in the United States, 2006–2013. Advances in health technologies, drug therapies, and public policy have not translated to improvements in diabetes care quality. ACO, accountable care organization; DPP-4i, dipeptidyl peptidase 4 inhibitor; GLP-1RA, glucagon-like peptide 1 receptor agonist; HITECH, Health Information Technology for Economic and Clinical Health; PCMH, patient-centered medical home; SGLT2i, sodium–glucose cotransporter 2 inhibitor. Adapted from ref. 24.

# Barrier to Care – Clinical Inertia

- Most often time we focus a lot on medical nonadherence and blame poor control due to limitations of our patients.
- It's also important to recognize our role in poor control of diabetes as well.
- Failure of healthcare providers to initiate or intensify therapy can be due to lack of education, training or having programs or clinical practices aimed at achieving therapeutic goals (Gabbay, 2020).
- Therapeutic inertia is common – affecting as many as 50% of patients with type 2 diabetes (McCoy, 2021).
  - Driven by wide range of barriers (Rattelman, 2021).
    - Clinician
    - Patient
    - Health system levels

Clin Diabetes. 2022;40(1):10-38. doi:10.2337/cd22-as01


**Figure Legend:**

Decision cycle for patient-centered glycemic management in type 2 diabetes. $HbA_{1c}$, glycated hemoglobin. Adapted from Davies MJ, D'Alessio DA, Fradkin J, et al. Diabetes Care 2018;41:2669–2701.

# When should we start screening

- New guidelines include screening adults without diabetes symptoms for both prediabetes and diabetes at the age of 35 (Kenney, 2022).

# Criteria for Screening and Diagnosis of Prediabetes and Diabetes

| | Prediabetes | Diabetes |
|---|---|---|
| A1C | 5.7–6.4% (39–47 mmol/mol)* | ≥6.5% (48 mmol/mol)† |
| Fasting plasma glucose | 100–125 mg/dL (5.6–6.9 mmol/L)* | ≥126 mg/dL (7.0 mmol/L)† |
| 2-hour plasma glucose during 75-g OGTT | 140–199 mg/dL (7.8–11.0 mmol/L)* | ≥200 mg/dL (11.1 mmol/L)† |
| Random plasma glucose | — | ≥200 mg/dL (11.1 mmol/L)‡ |

- **TABLE 2.2/2.5** Criteria for the Screening and Diagnosis of Prediabetes and Diabetes

- Adapted from Tables 2.2 and 2.5 in the complete 2022 Standards of Care.

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# Diabetes glycemic control goals

| | |
|---|---|
| A1C | <7.0% (53 mmol/mol)*# |
| Pre-prandial capillary plasma glucose | 80–130 mg/dL* (4.4–7.2 mmol/L) |
| Peak post-prandial capillary plasma glucose† | <180 mg/dL* (10.0 mmol/L) |

- **TABLE 6.3**Summary of Glycemic Recommendations for Many Nonpregnant Adults With Diabetes

- *More or less stringent glycemic goals may be appropriate for individual patients. #CGM may be used to assess glycemic target as noted in Recommendation 6.5b and Figure 6.1. Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations.
- †Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals. Postprandial glucose measurements should be made 1–2 hours after the beginning of the meal, generally peak levels in patients with diabetes.

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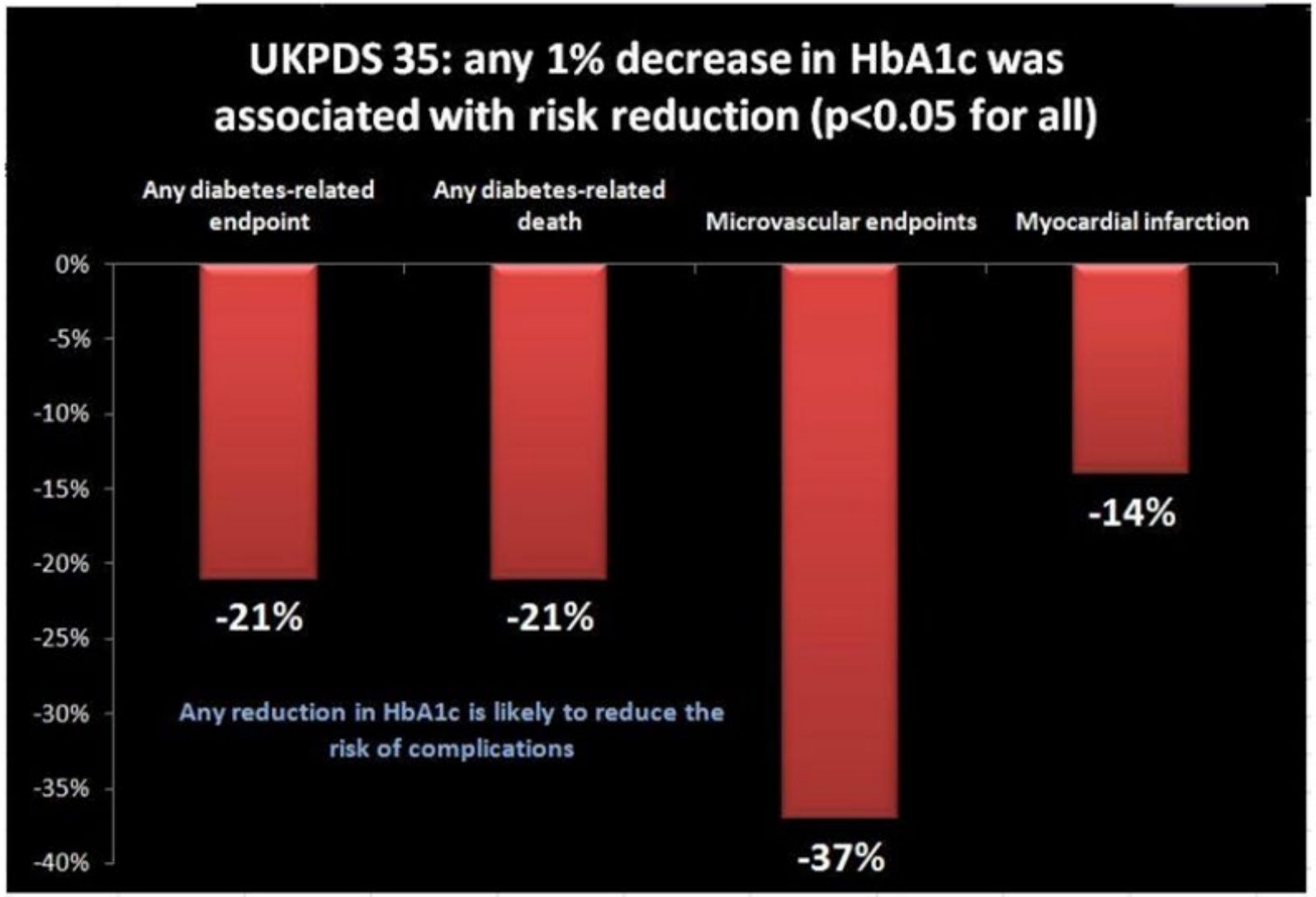



(Clore, 2019)

American Diabetes Association.

*British Medical Journal 2000; 321: 405-412*

# Foundation of Diabetes Therapy

- Comprehensive lifestyle management is important when initiating care for all individuals with diabetes
  - Exercise
    - Engage in about 150 minutes or more of moderate to vigorous intense aerobic activity per week spread over 3 days per week; no more than 2 days without activity.
    - Engage in 2-3 sessions/week of resistance training.
  - Weight management
  - Healthy eating
    - Emphasize a variety of nutrient dense foods and appropriate portion sizes.
    - Maintain pleasure of eating while providing nonjudgmental messages about food choices.
    - Provide practical tools for healthy eating patterns.
  - Decrease sedentary behavior
    - Interrupt prolonged sitting every 30 minutes

(American Diabetes Association, 2022)

# Foundations of Diabetes Therapy

- Metformin is usually still the initial therapy for patients with type 2 diabetes.
  - Recommended dose is 1000 mg twice daily if tolerated
  - Titrate slowly over 1-2 weeks in 500 mg increments
  - Extended release formulation is highly recommended
  - Medication must be renally dosed and should not be used if GFR less than 30 cc/min

    (Clore, 2019)
- New guidelines are now recommending an individualized approach at the time of diagnosis.
- From the Chief Science and Medical Officer of American Diabetes Association – Robert A. Gabbay, MD, PhD:
  - “We know now that many of these medications that lower cardiovascular [heart] and renal [kidney] disease can be quite effective, often literally life-saving,” said Gabbay. “Metformin is still a good drug, but it should not be a deterrent to work quickly and start medications we know will be effective” (Kenney, 2022).

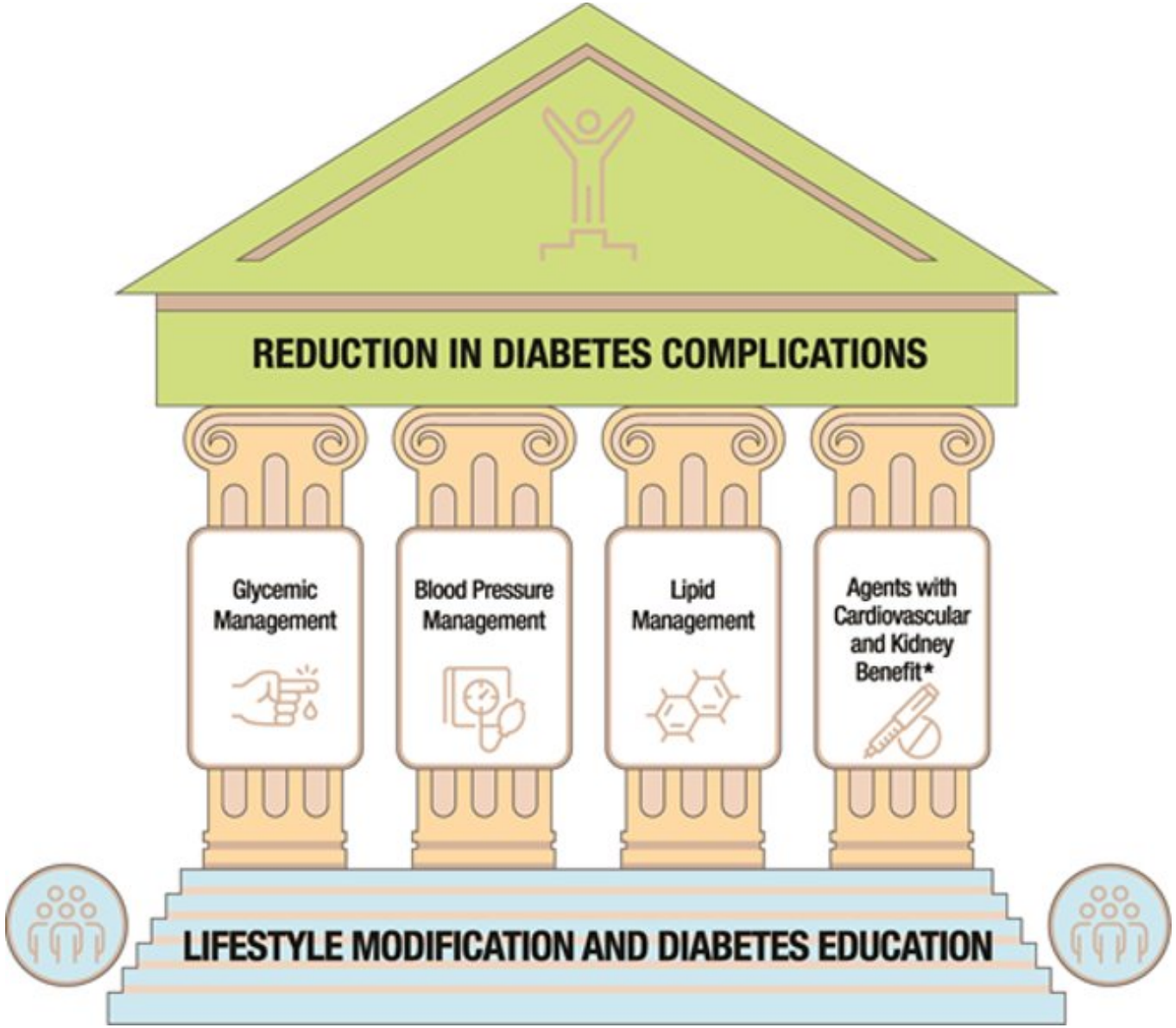
# Combination therapy

Treatment therapy that uses 2 or more medications to address medical conditions including type 2 diabetes.

Often utilized as one medication alone is not always enough to keep glycemic control within target range.

"Early combination therapy can be considered in some patients at treatment initiation to extend the time to treatment failure."

*(Combination therapy for type 2 diabetes, n.d)*




https://diatribe.org/your-guide-2022-changes-ada-standards-care#glucose

From: **Standards of Care in Diabetes—2023 Abridged for Primary Care Providers**

Clin Diabetes. 2022;41(1):4-31. doi:10.2337/cd23-as01

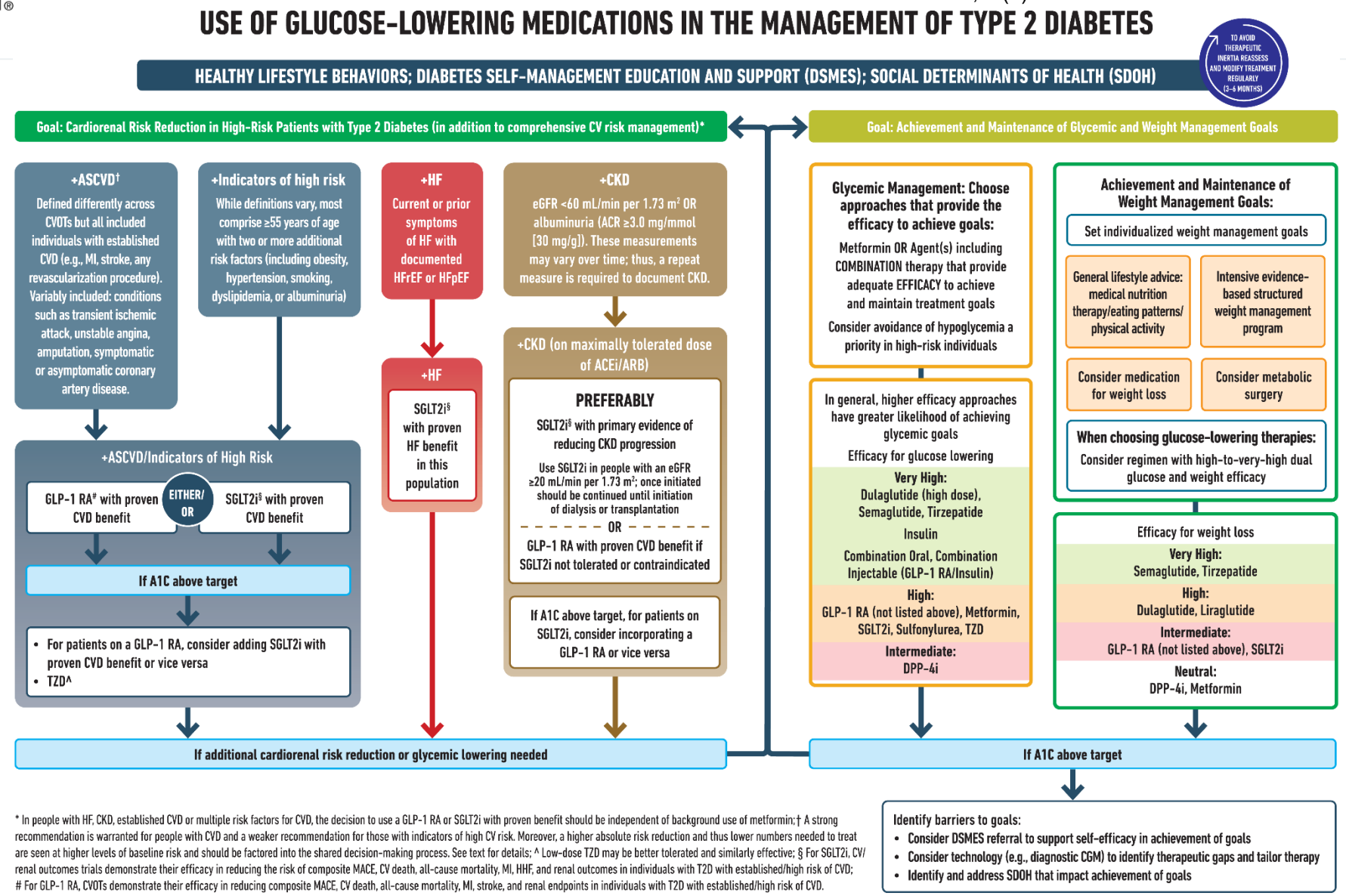


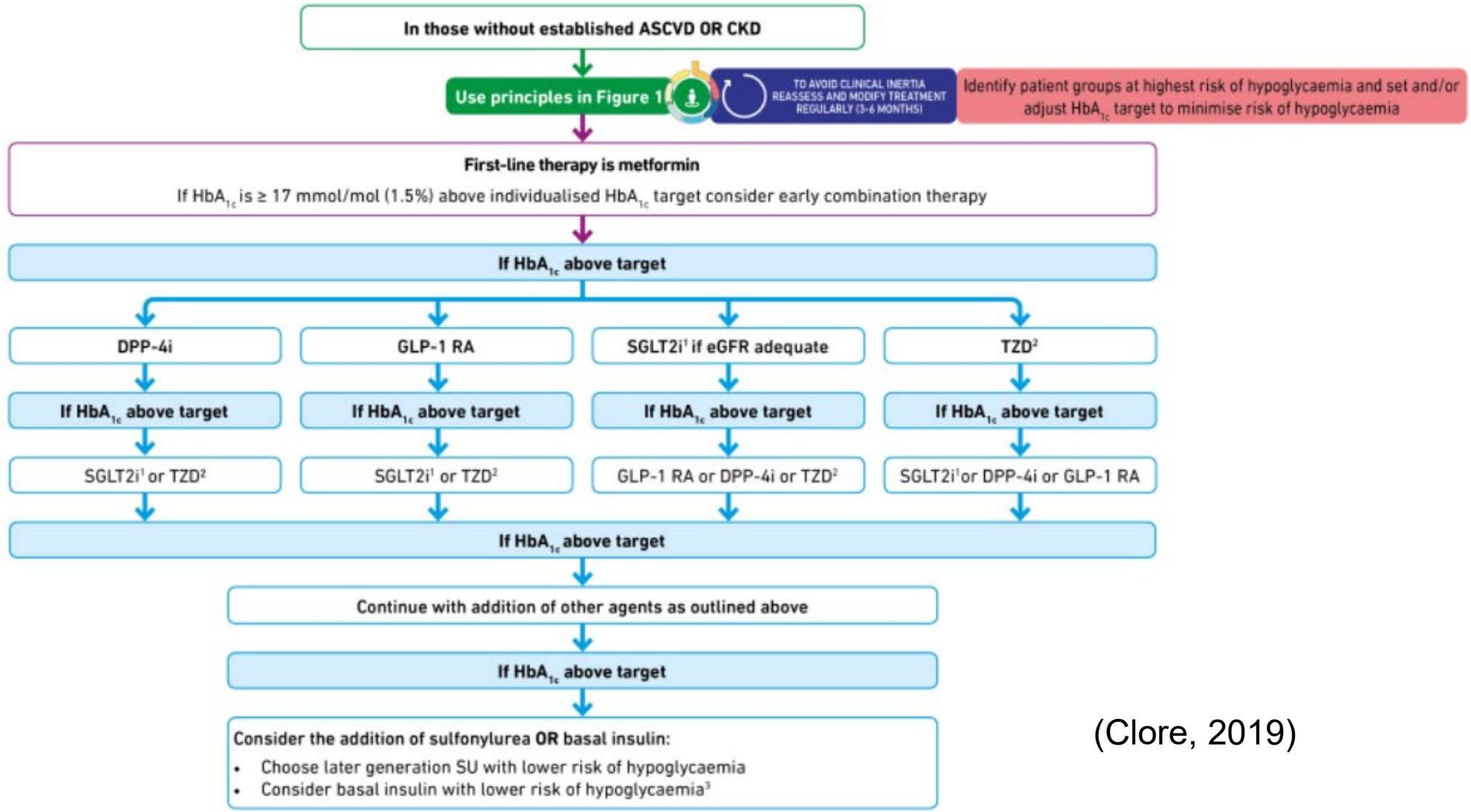

**Figure Legend:**

Use of glucose-lowering medications in the management of type 2 diabetes. ACEi, ACE inhibitor; ACR, albumin-to-creatinine ratio; CVOT, cardiovascular outcomes trial; DPP-4i, dipeptidyl peptidase 4 inhibitor; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HHF, hospitalization for heart failure; SGLT2i, sodium-glucose cotransporter 2 inhibitor; T2D, type 2 diabetes. Adapted from Davies MJ, Aroda VR, Collins BS, et al. Diabetes Care 2022;45:2753–2786.

# Case 1

- A newly diagnosed 38-year-old male without comorbidities presents to your clinic with an A1c of 7.8%.  After counseling patient and attempts to counsel on healthy diet and exercise, patient remains above his therapeutic goal of less than 7%. He is already on metformin 1000 mg extended release twice daily. What other medications would you consider for this patient?

# CHOOSING GLUCOSE-LOWERING MEDICATION IF COMPELLING NEED TO MINIMISE HYPOGLYCAEMIA



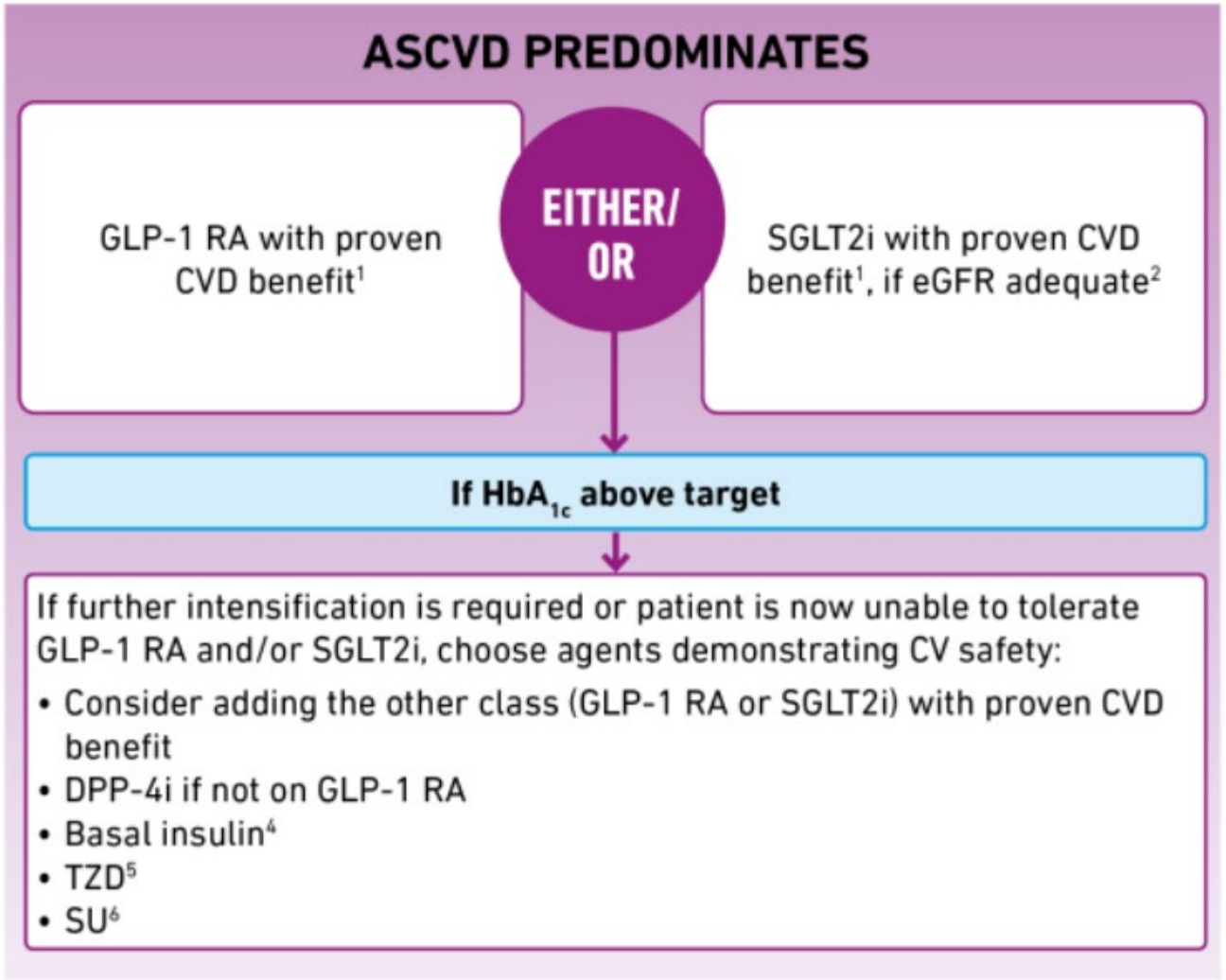

1. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
2. Low dose TZDs are better tolerated
3. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin

(Clore, 2019)

# Case 2

- 59-year-old male with a past medical history significant for type 2 diabetes and prior history of ischemic stroke in 2016 presents the clinic with an A1c of 8.9%. He is already on extended-release metformin 1000 mg twice daily and has been actively working towards a healthy lifestyle. He has lost 10 pounds over the past two months with healthy exercise and diet. He has a BMI of 31. What other medications would you consider adding to help achieve glycemic control?

# Step 1: Assess Cardiovascular Disease




1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence of liraglutide > semaglutide > exenatide. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU with lower risk of hypoglycaemia

(Clore, 2019)

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# Case 3

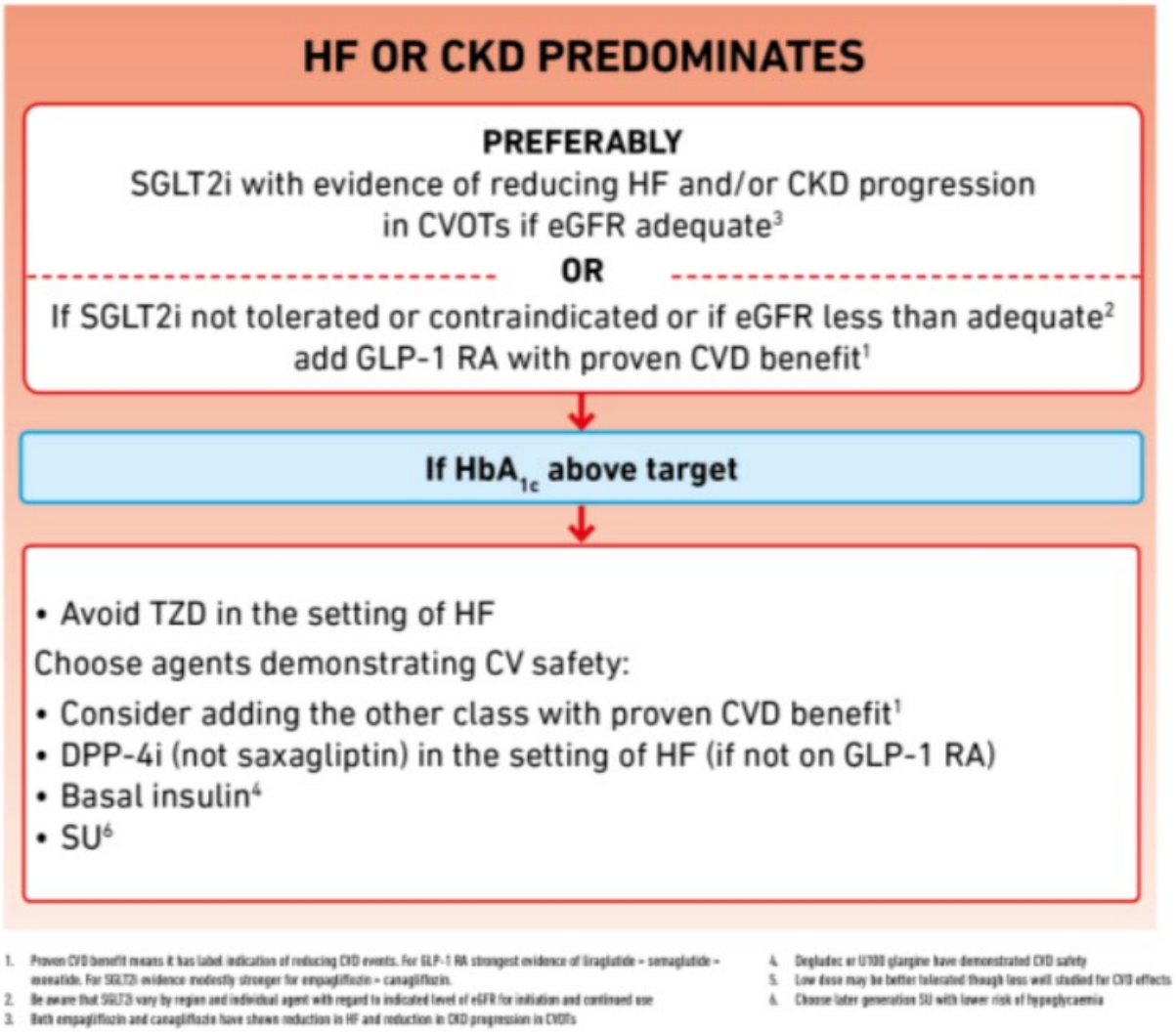
- 68-year-old female with a past medical history significant for type 2 diabetes and heart failure with reduced ejection fraction of 25%, chronic kidney disease stage 3bA2 and hyperlipidemia who presents to clinic with an A1c of 9.2%. She is on Metformin and has tried an SGLT-2 inhibitor but was unable to tolerate medication due to recurrent yeast infections. She is on a GLP-1 receptor agonist. What other medications would you consider in this patient?

**Prognosis of CKD by GFR and Albuminuria Categories**

| GFR categories (ml/min/1.73 m²) Description and range | | | | Albuminuria categories Description and range | | |
|---|---|---|---|---|---|---|
| | | | | **A1** | **A2** | **A3** |
| | | | | Normal to mildly increased | Moderately increased | Severely increased |
| | | | | <30 mg/g <3 mg/mmol | 30-299 mg/g 3-29 mg/mmol | ≥300 mg/g ≥30 mg/mmol |
| | **G1** | Normal or high | ≥90 | | | |
| | **G2** | Mildly decreased | 60-90 | | | |
| | **G3a** | Mildly to moderately decreased | 45-59 | | | |
| | **G3b** | Moderately to severely decreased | 30-44 | | | |
| | **G4** | Severely decreased | 15-29 | | | |
| | **G5** | Kidney failure | <15 | | | |

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.
KDIGO 2012

https://www.kidney.org/kidneydisease/siemens_hcp_quickreference

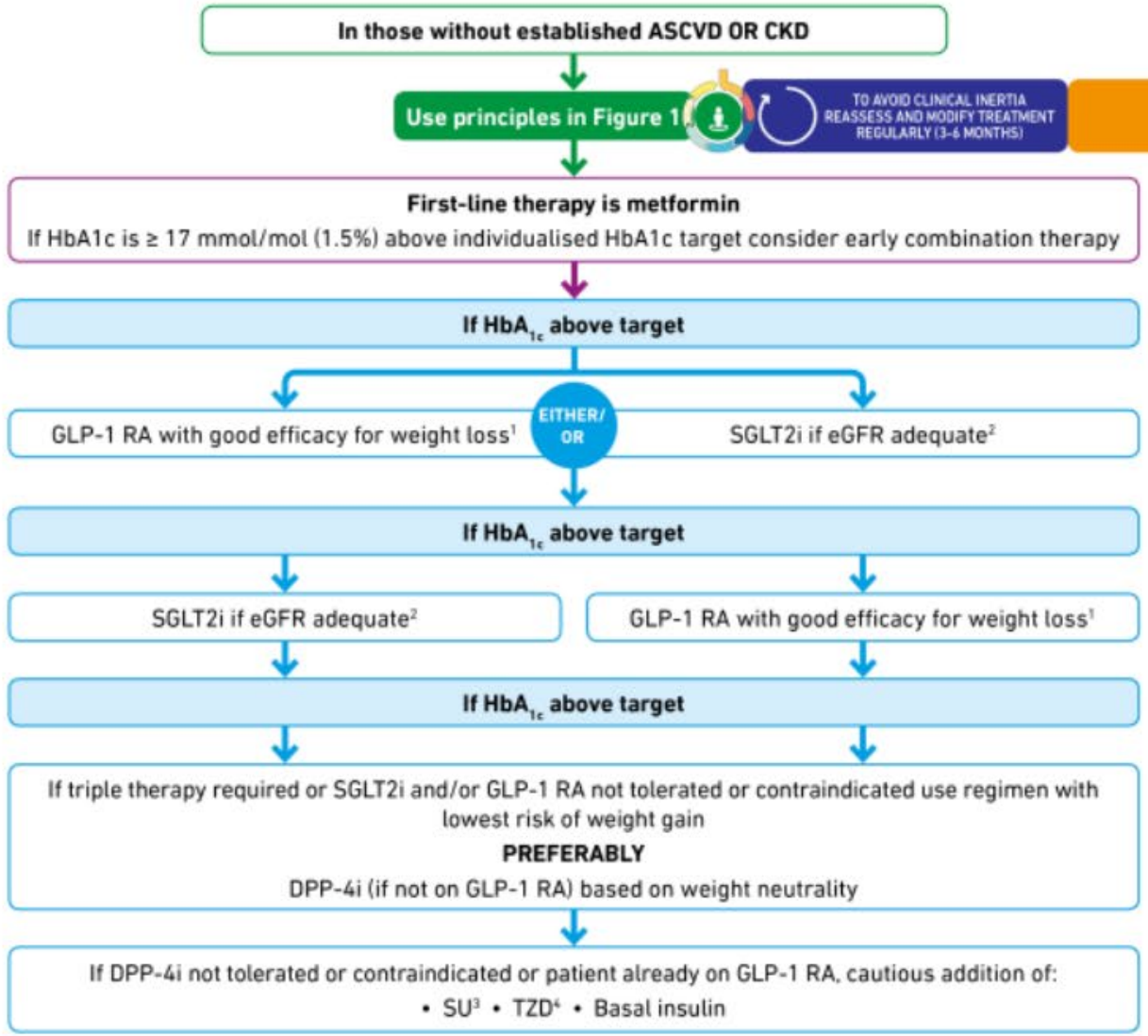

HF OR CKD PREDOMINATES
PREFERABLY
SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate3
OR
If SGLT2i not tolerated or contraindicated or if eGFR less than adequate2 add GLP-1 RA with proven CVD benefit1
If HbA1c above target
• Avoid TZD in the setting of HF
Choose agents demonstrating CV safety:
• Consider adding the other class with proven CVD benefit1
• DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
• Basal insulin4
• SU6
1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence of liraglutide > semaglutide > exenatide. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU with lower risk of hypoglycaemia

(Clore,2019)

# Case 4

- A 47-year-old female with a past medical history significant depression is establishing care at your facility. This is her first time seeing an outpatient provider and she wishes to establish care. Laboratory evidence show an initial A1c of 8.9%, repeat labs were drawn that also confirms the same result. Her BMI is 45 and she wishes to also lose weight. What medications would you initiate for this patient?

# CHOOSING GLUCOSE-LOWERING MEDICATION IF COMPELLING NEED TO MINIMISE WEIGHT GAIN OR PROMOTE WEIGHT LOSS





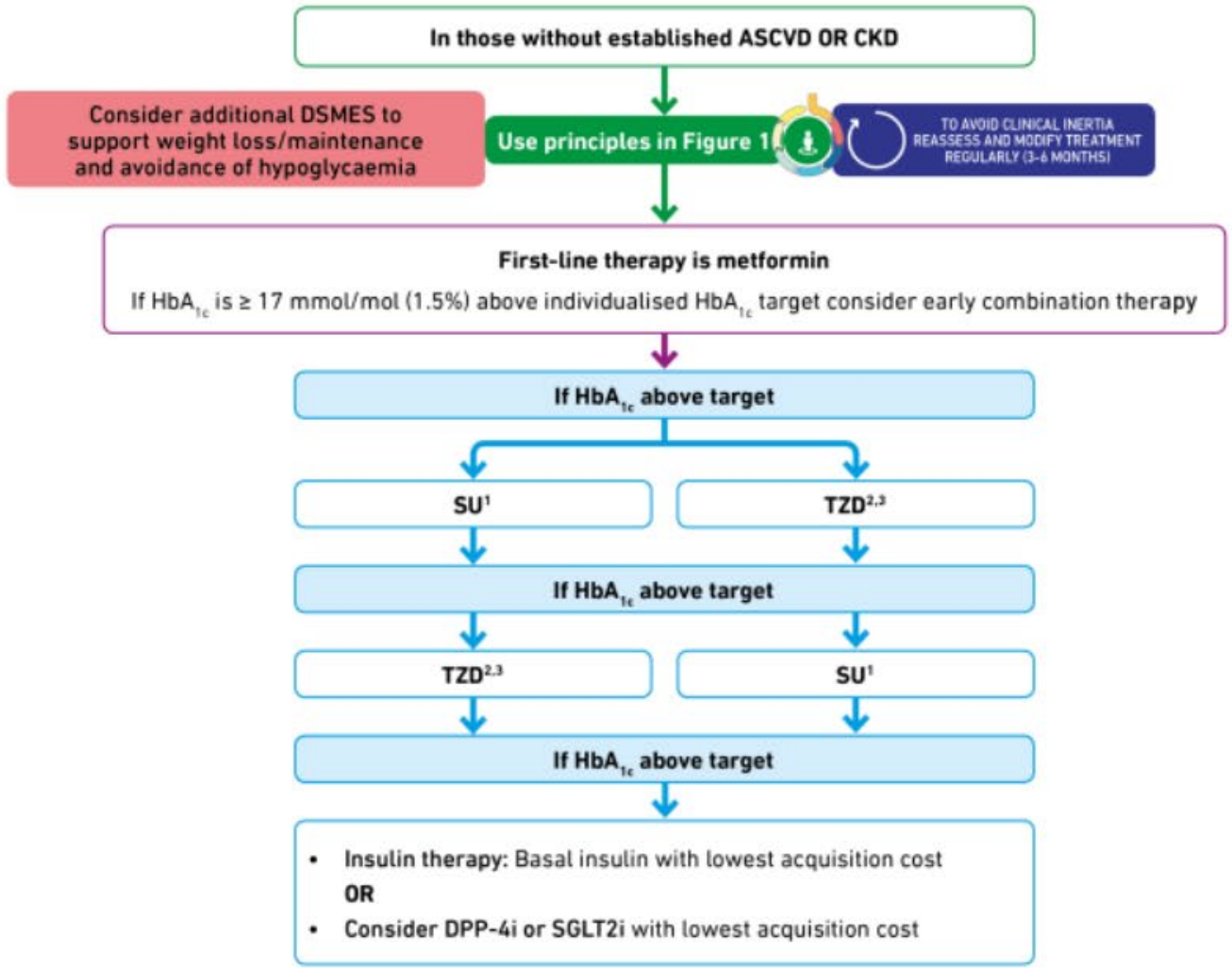
1. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Choose later generation SU with lower risk of hypoglycaemia
4. Low dose may be better tolerated though less well studied for CVD effects

(Clore,2019)

# Case 5

- A 77 y/o male presents to clinic due to concerns of financial ability to obtain medications. He is retired and has very little to no benefits from his health insurance. He can afford metformin but has an A1c of 9%. What additional medications would you consider?

# CHOOSING GLUCOSE-LOWERING MEDICATION IF COST IS A MAJOR ISSUE




1. Choose later-generation SU to minimise risk of hypoglycaemia
2. Consider country- and region-specific cost of drugs. In some countries, TZD relatively more expensive and DPP-4i relatively cheaper
3. Low-dose TZDs are better tolerated

# Wal-Mart Diabetes Medication List

30-day supply

- GLIMEPIRIDE 1MG, 2MG, 4MG (30 tablets, $4)
- GLIPIZIDE 5MG, 10MG (60 tablets, $4)
- METFORMIN 500MG, 850MG, 1000MG (60 tablets, $4),
- METFORMIN ER 500MG TAB (120 tablets, $4)
- METFORMIN ER 750MG TAB (60 tablets, $4)
- GLIPIZIDE ER 2.5MG, 5MG, 10MG (30 tablets, $9)
- GLYBURIDE/METFORMIN 2.5/500MG, 5/500MG (60 tablets, $9)
- PIOGLITAZONE 15MG, 30MG, 45MG (30 tablets, $15)

(Walmart 2022)

# Wal-Mart Diabetes Medication List

- GLIMEPIRIDE 1MG, 2MG, 4MG (90 tablets, $10)
- GLIPIZIDE 5MG, 10MG (180 tablets, $10)
- METFORMIN 500MG, 850MG, 1000MG (180 tablets, $10)
- METFORMIN ER 500MG TAB (360 tablets, $10)
- METFORMIN ER 750MG TAB (180 tablets, $10)
- GLIPIZIDE ER 2.5MG, 5MG, 10MG (90 tablets, $24)
- GLYBURIDE/METFORMIN 2.5/500MG, 5/500MG (180 tablets, $24)
- PIOGLITAZONE 15MG, 30MG, 45MG (90 tablets, $38)

(Walmart 2022)

# Other ways to help with affording medication costs

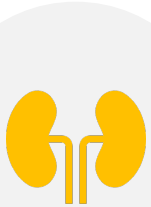
- Pharmaceutical Assistance Programs
  - Examples include Lily Cares Foundation Patient Assistance Program, Pfizer RxPathways Program, Merck Patient Assistance Program.
- Coupon cards
  - GoodRx, coupons directly from the manufacturer/drug company, InsideRx are a few examples.
- Device Assistance Programs
- Nonprofit assistant programs
- Mail-order pharmacies
- Pharmacy loyalty programs
- Government assistance
- Insurance programs
  - Medicare Extra Help
- Medication utility
  - Example including generic Instead of brand-name, use of a combination medication rather than two separate medications and 90 day supplies.

(Behring, 2021)

# Insulin Caps!

Eli Lilly announced on March 1, 2023 that it plans on reducing cost of insulin by 70%

Automatic cap on out of pocket costs of $35 or less for those with those with private insurance and use of participating pharmacies



The company will cut the cost of its non branded insulin to $25 a vial as of May 1, 2023.

People who don't have insurance can continue to go to InsulinAffordability.com and immediately download the Lilly Insulin Value Program savings card to receive Lilly insulins for $35 per month.

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# Lilly Updates on reducing insulin costs as of March 1, 2023

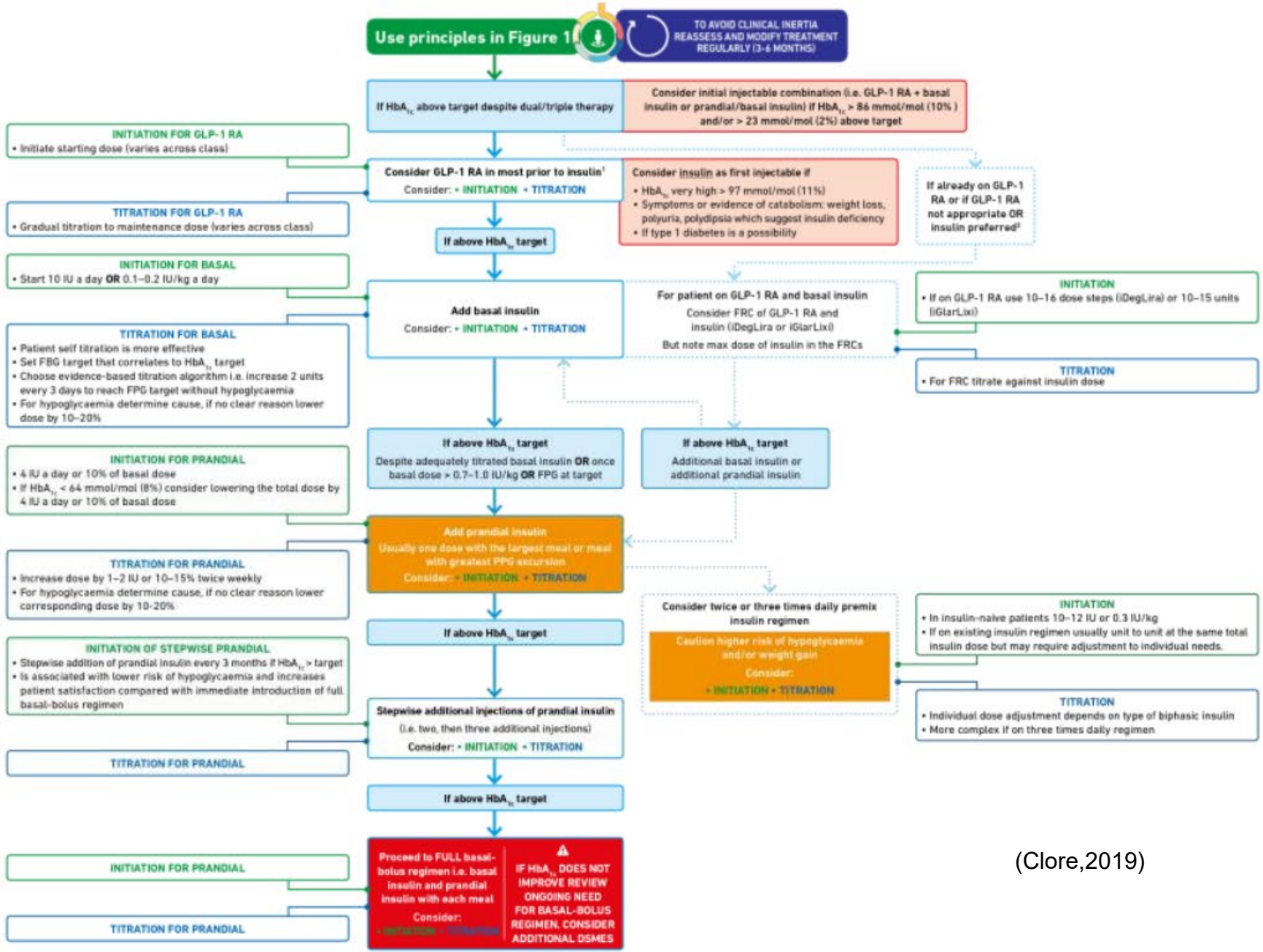
- Cutting the list price of its non-branded insulin, Insulin Lispro Injection 100 units/mL, to $25 a vial. Effective May 1, 2023, it will be the lowest list-priced mealtime insulin available, and less than the price of a Humalog® vial in 1999.
- Cutting the list price of Humalog® (insulin lispro injection) 100 units/mL1, Lilly's most commonly prescribed insulin, and Humulin® (insulin human) injection 100 units/mL2 by 70%, effective in Q4 2023.
- Launching RezvoglarTM (insulin glargine-aglr) injection, a basal insulin that is biosimilar to, and interchangeable with, Lantus® (insulin glargine) injection, for $92 per five pack of KwikPens®, a 78% discount to Lantus, effective April 1, 2023.

# Case 6

- A 39-year-old female has an A1c of 11.5%, transitioning care to you because she hasn't noticed significant changes with her last provider. She is motivated in changing her lifestyle due to a recent death in her family from diabetes complications. She is concerned about having hypoglycemic episodes as it has happened to her in the past. She is only on oral medications including Metformin, Glipizide and Sitagliptin. What other medications would you consider in this patient?

Figure 7

# INTENSIFYING TO INJECTABLE THERAPIES




1. Consider choice of GLP-1 RA considering patient preference: $HbA_{1c}$ lowering, weight-lowering effect or frequency of injection. If CVD, consider GLP-1 RA with proven CVD benefit
2. Consider insulin as preferred to GLP-1 RA if symptoms of hyperglycaemia are present, or evidence of ongoing catabolism (polyuria, polydipsia or weight loss)

(Clore,2019)

Figure 8

# CONSIDERING ORAL THERAPY IN COMBINATION WITH INJECTABLE THERAPIES

## METFORMIN

Continue treatment with metformin

## SGLT2i

If on SGLT2i, continue treatment

Consider adding SGLT2i if

- Established CVD
- If $HbA_{1c}$ above target or as weight reduction aid

Beware

- DKA (euglycaemia)
- Instruct on sick-day rules
- Do not down-titrate insulin over-aggressively

## TZD[1]

Stop TZD when commencing insulin OR reduce dose

## SULFONYLUREA

If on SU, stop or reduce dose by 50% when basal insulin initiated

Consider stopping SU if prandial insulin initiated or on a premix regimen

## DPP-4i

Stop DPP-4i if GLP-1 RA initiated

1. Contraindicated in some countries, consider lower dose. This combination has a high risk of fluid retention and weight gain

American Diabetes Association.

(Clore,2019)

(Garber 2020)

# PROFILES OF ANTIHYPERGLYCEMIC MEDICATIONS

| | MET | GLP1-RA | SGLT2i | DPP4i | AGi | TZD (moderate dose) | SU / GLN | COLSVL | BCR-QR | INSULIN | PRAML |
|---|---|---|---|---|---|---|---|---|---|---|---|
| HYPO | Neutral | Neutral | Neutral | Neutral | Neutral | Neutral | Moderate/Severe / Mild | Neutral | Neutral | Moderate to Severe | Neutral |
| WEIGHT | Slight Loss | Loss | Loss | Neutral | Neutral | Gain | Gain | Neutral | Neutral | Gain | Loss |
| RENAL / GU | Contra-indicated if eGFR <30 mL/min/1.73 m² | Exenatide Not Indicated CrCl <30<br>Potential Benefit of LA GLP1-RA | Not Indicated for eGFR <45 mL/min/1.73 m²<br>See #1<br>Genital Mycotic Infections<br>Potential CKD Benefit; See #1 | Dose Adjustment Necessary (Except Linagliptin)<br>Effective in Reducing Albuminuria | Neutral | Neutral | More Hypo Risk | Neutral | Neutral | More Hypo Risk | Neutral |
| GI Sx | Moderate | Moderate | Neutral | Neutral | Moderate | Neutral | Neutral | Mild | Moderate | Neutral | Moderate |
| CHF | Neutral | Neutral | Prevent HF Hospitalization Manage HFrEF; See #2 | See #4 | Neutral | Moderate | Neutral | Neutral | Neutral | CHF Risk | Neutral |
| CARDIAC ASCVD | | Potential Benefit of LA GLP1-RA | See #3 | | | May Reduce Stroke Risk | Possible ASCVD Risk | Lowers LDL-C | Safe | Neutral | |
| BONE | Neutral | Neutral | Neutral | Neutral | Neutral | Moderate Fracture Risk | Neutral | Neutral | Neutral | Neutral | Neutral |
| KETOACIDOSIS | Neutral | Neutral | DKA Can Occur in Various Stress Settings | Neutral | Neutral | Neutral | Neutral | Neutral | Neutral | Neutral | Neutral |

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

1. Canagliflozin indicated for eGFR ≥30 mL/min/1.73 m² in patients with CKD 3 + albuminuria.
2. Dapagliflozin—potential primary prevention of HF hospitalization & demonstrated efficacy in HFrEF.
3. Empagliflozin—FDA approved to reduce CV mortality. Canagliflozin—FDA approved to reduce MACE events.
4. Possible increased hospitalizations for heart failure with alogliptin and saxagliptin.


DOI 10.4158/CS-2019-0472

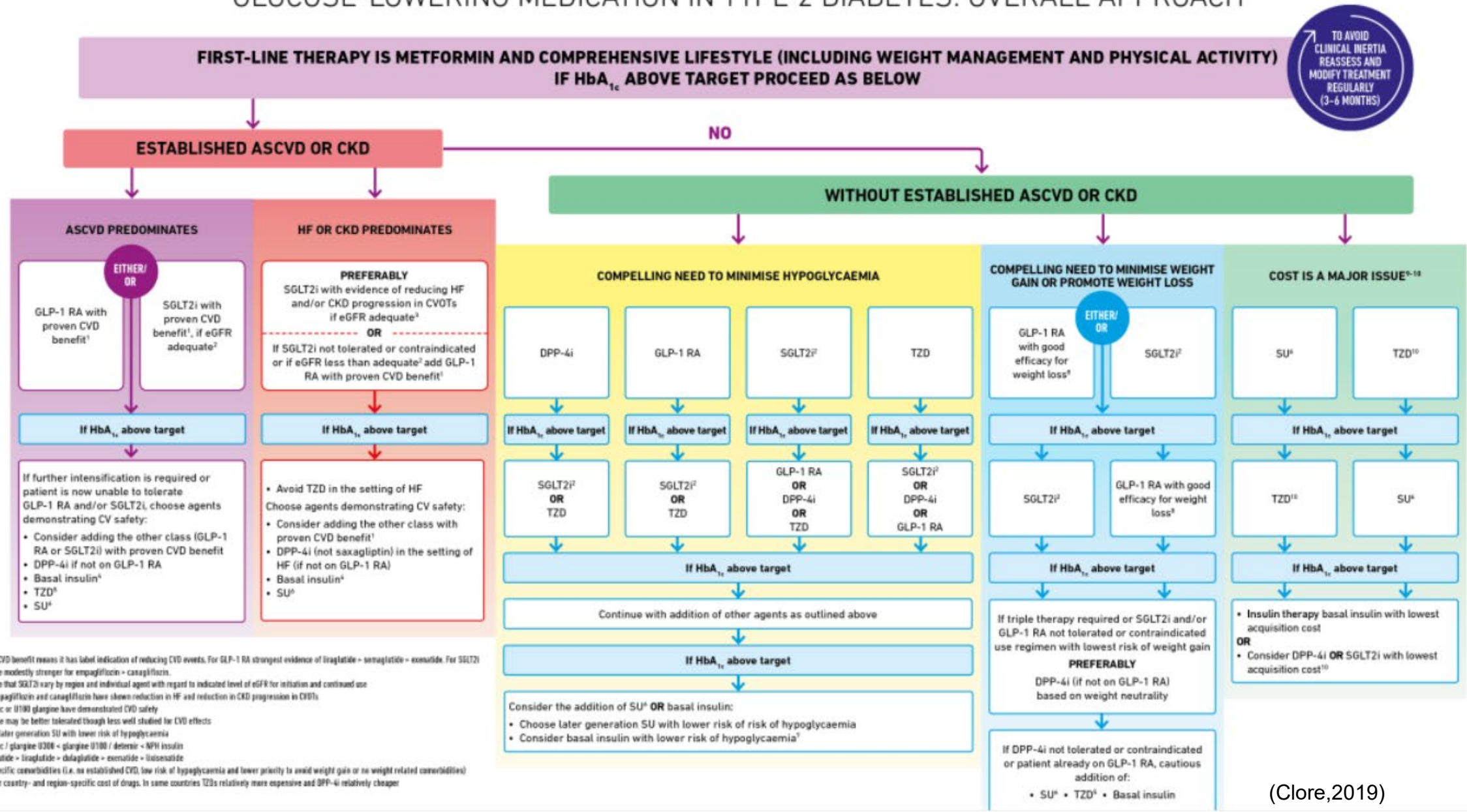




Diabetes Management Algorithm, *Endocr Pract.* 2020;26(No. 1) 139

Figure 2

# GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH

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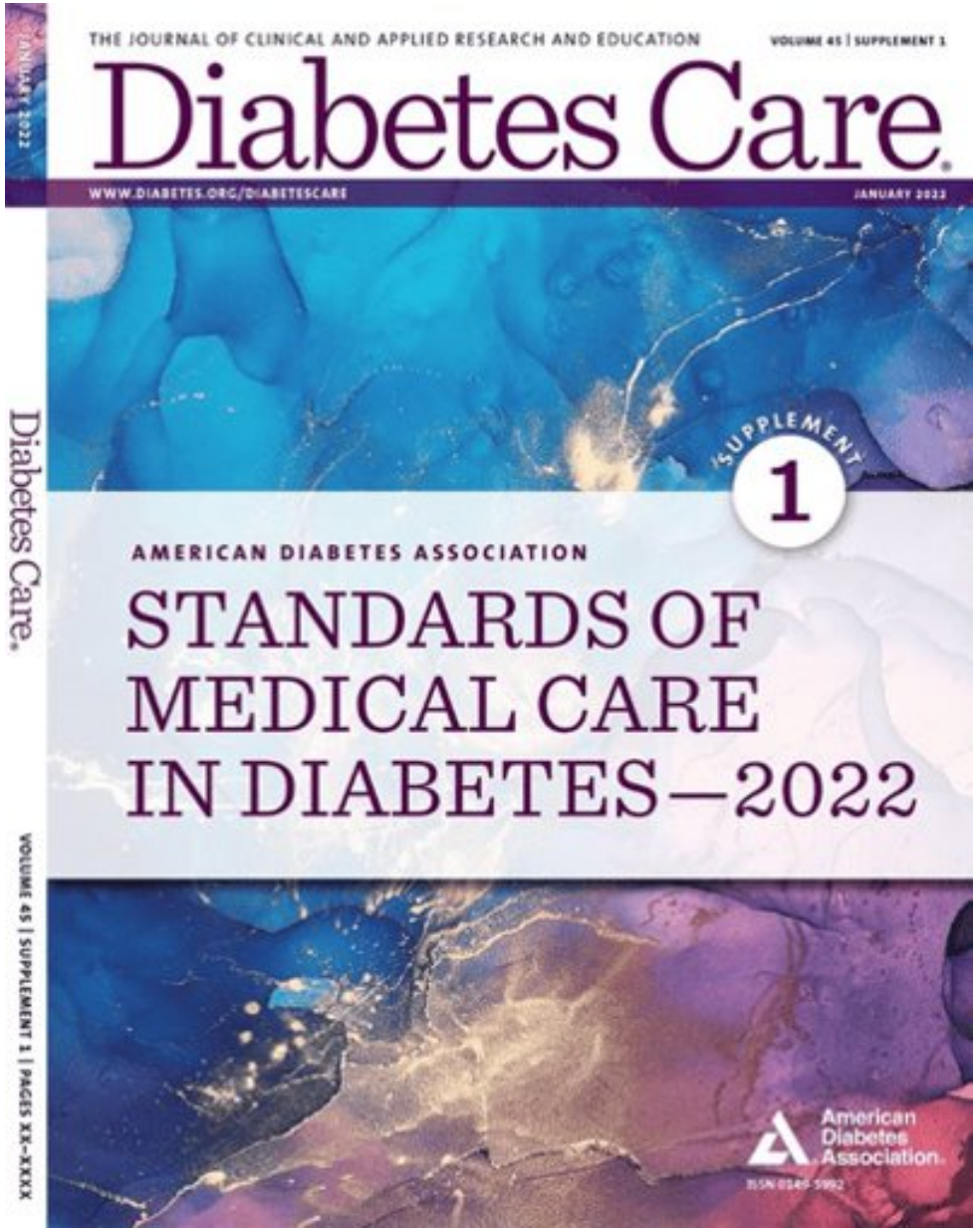
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU with lower risk of hypoglycaemia
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e. no established CVD, low risk of hypoglycaemia and lower priority to avoid weight gain or no weight related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

(Clore,2019)




(American Diabetes Association, 2022)

# 2022 AACE Diabetes Guideline Update

**NEW** FROM

AACE

## 2022 Diabetes Guideline Update

September 27, 2022

**American Association of Clinical Endocrinology Clinical Practice Guideline: Developing a Diabetes Mellitus Comprehensive Care Plan—2022 Update** https://pro.aace.com/disease-state-resources/diabetes/clinical-practice-guidelines/2022-aace-clinical-practice-guideline (Blonde, 2022)

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# Questions?

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