Considerations for Initiating Pharmacotherapy in Patients Diagnosed with Type 2 Diabetes

Executive Summary: Select initial pharmacotherapy based on your patient's baseline A1c. Metformin should be initiated in all patients unless contraindicated, and should not be discontinued until an honest effort was made to ensure tolerability. Remember to recheck the A1c in 3 months to assess response and adjust pharmacotherapy.

AMG Type 2 Diabetes Treatment Algorithm recommends selecting initial treatment based on baseline A1c value.

A1c 6.5-7.5%	A1c 7.6-9.0%	A1c >9.0%
Initiate monotherapy Always metformin unless contraindicated or not tolerated	Initiate dual therapy Usually metformin + non-insulin agent *Consider an SGLT2i as first add on due to CVD, HF, renal, and weight benefits	Initiate triple therapy Usually metformin + GLP-1 RA + SGLT2i +/- basal insulin

Before discontinuing metformin due to intolerance, ensure the following:

- Patient is taking dose(s) with a meal
- Patient has tried metformin extended release
- Start on a low dose and slowly titrate up
    - Can start with 250mg once daily for immediate release tablets (cut 500mg tablets in half)
    - Start with 500mg once daily for extended release tablets
- Slow titration of metformin occurred, e.g.
    - 250mg PO once daily x 1 week, then
    - 500mg PO once daily x 1 week, then
    - 500mg PO BID x 1 week, then
    - 1000mg PO QAM and 500mg PO QPM x 1 week, then
    - 1000mg PO BID
    - Do not increase dose while patient is experiencing side effects, can maintain at a lower dose until side effects diminish
    - If side effects do not diminish, decrease dose to maximally tolerated dose

What is the evidence for metformin in impaired renal function?

Metformin is cleared through the kidneys and lactic acidosis has been associated with very high circulating levels of metformin, however the occurrence is very rare and the evidence that lactic acidosis will actually occur is weak. A study published in Diabetes Care in 2018 provides evidence that metformin can safely be continued in patients with moderate or severe CKD, although a stepwise decrease in dose should be employed as eGFR decreases in order to prevent excessive drug concentrations.

Kidney function	Metformin dosing	Monitoring
eGFR ≥60 ml/min	Maximum dose 2550mg/day	Monitor eGFR at least annually
CKD stage 3a (eGFR 45-59 ml/min)	Labeling states no dosage adjustment necessary – Consider maximum dose 1500mg/day in divided doses	Monitor eGFR every 3-6 months
CKD stage 3b (eGFR 30-44 ml/min)	Maximum dose 1000mg/day in divided doses	Monitor eGFR every 3 months

In fragile patients, consider measuring lactate. Discontinue metformin if result is >5 mmol/L. If result is >2.5 mmol/L, consider repeating and discontinuing metformin if two consecutive results are >2.5 mmol/L.

When choosing pharmacologic agents, a patient-centered approach should be used to guide the decision. Place considerations on the pharmacologic agent's effect on cardiovascular and renal comorbidities, efficacy, hypoglycemia risk, impact on weight, cost, risk for side effects, and patient preferences. Refer to the AMG Type 2 Diabetes Treatment Algorithm to help guide decision. Due to various positive clinical benefits and long term decreased overall health care costs associated with SGLT2i, this class would be preferred initial add on to metformin.

A1c should be rechecked in 3 months to assess pharmacotherapy and lifestyle changes implemented by the patient. Continue to recheck A1c 3 months after changes in treatment. Once patient is at goal, recommend monitoring A1c every 6 months.

Avera Health Plan considerations for clinical scenarios

- Combination of a DPP-4i and GLP-1 RA is not recommended and provides little additional clinical benefit
    - Additional co-pay for patient with little clinical benefit
    - Additional cost to Avera Health Plan with little clinical benefit
- Titrate non-insulin therapies to maximum doses before adding additional agents
    - One copay for patient instead of two
    - Lower cost to Avera Health Plan
- Combination oral products can be used to decrease pill burden, decrease co-pay burden, and provide lower cost to Avera Health Plan
    - Metformin – alogliptin: generic
    - Janumet, Janumet XR (metformin and Januvia): preferred brand
    - Synjardy (metformin and empagliflozin): preferred brand
    - Trijardy XR (metformin XR, linagliptin, and empagliflozin): preferred brand
    - Glyxambi (empagliflozin and linagliptin): preferred brand
    - Qtern (dapagliflozin and saxagliptin): preferred brand

Links to internal and/or external resources:

AMG Type 2 Diabetes Treatment Algorithm

Pharmacologic Approaches to Glycemic Treatment: *Standards of Medical Care in Diabetes – 2021*

Cardiovascular Risk Reduction in Type 2 Diabetes

Executive Summary: If your patient is at high risk for ASCVD, or has clinical ASCVD, HF, and/or CKD, a GLP-1 RA or SGLT2i should be on board regardless of A1c based on proven cardiovascular benefits. Tailor medication selection based on individual patient co-morbidities.

Regardless of baseline A1c, the patient's A1c goal, or metformin use, the ADA Standards of Care 2021 recommend the use of a Glucagon-Like Peptide-1 Receptor Agonist (GLP-1 RA) or Sodium-Glucose Cotransporter 2 Inhibitor (SGLT2i) if the patient has any of the following:

- Established ASCVD or indicators of high ASCVD risk (such as patients ≥55 years of age with coronary artery disease, carotid artery disease, peripheral vascular disease, or left ventricular hypertrophy)
- Chronic kidney disease
- Heart failure

Clinical ASCVD	Heart Failure	Kidney Disease	
		Diabetic kidney disease and albuminuria	Chronic kidney disease
GLP-1 RA *or* SGLT2i	SGLT2i	SGLT2i	GLP-1 RA *or* SGLT2i

Select agents that have proven cardiovascular benefit

GLP-1 RA with proven cardiovascular benefit:

- Dulaglutide (Trulicity)*
- Liraglutide (Victoza)*
- Semaglutide SubQ (Ozempic)*

SGLT2i with proven cardiovascular benefit:

- Canagliflozin (Invokana)
- Dapagliflozin (Farxiga)*
- Empagliflozin (Jardiance)*

*Covered by Avera Health Plans

Renal dosing for SGLT2is

- Canagliflozin
  - eGFR ≥60 ml/min: no dosage adjustment
  - eGFR 30 to <60 ml/min: 100mg PO daily
  - eGFR <30 ml/min: do not initiate, may be continued in patients with urinary albumin excretion >300 mg/day at 100mg PO daily
- Dapagliflozin
  - eGFR ≥45 ml/min: no dosage adjustment
  - eGFR 30 to <45 ml/min:
    - For heart failure use: no dosage adjustment

        - For hyperglycemia: manufacturer recommends against use
    - eGFR <30 ml/min: not recommended
- Empagliflozin
    - eGFR <45 ml/min: do not initiate, discontinue use if eGFR is persistently below this threshold

Avera Health Plan considerations for clinical scenarios:

- If patient is on a DPP4i and you are adding a GLP-1 RA for cardiovascular benefit, discontinue the DPP4i
    - Combination of a DPP-4i and GLP-1 RA is not recommended and provides little additional clinical benefit
    - Additional co-pay for patient with little clinical benefit
    - Additional cost to Avera Health Plan with little clinical benefit
- When either an SGLT2i or GLP-1 RA is indicated, consider starting with the SGLT2i
    - Likely similar or lower co-pay for patient
    - Lower cost to Avera Health Plan
    - Similar glycemic efficacy and CVD benefit
    - Additional CHF benefit with SGLT2i
- For patients on basal insulin plus a GLP-1 RA, or you are considering adding on one of these agents, consider use of a combination product
    - One copay for patient instead of two
    - Lower cost to Avera Health Plan
    - Similar glycemic efficacy
    - Xultophy (insulin degludec + liraglutide)
        - Maximum insulin dose = 50 units/day

Evidence Summary:
See review of evidence supporting the use of SGLT2i and GLP-1 RA in these patient populations.

Links to internal and/or external resources:
AMG Type 2 Diabetes Treatment Algorithm

Sources:
Pharmacologic Approaches to Glycemic Treatment: Standards of Medicare Care in Diabetes – 2021
EMPA-REG OUTCOME trial
The CANVAS Program
CREDENCE trial
Patorno E, et al. *BMJ*. 2018;360:k119
DECLARE-TIMI 58
LEADER
SUSTAIN-6
REWIND
DAPA-HF

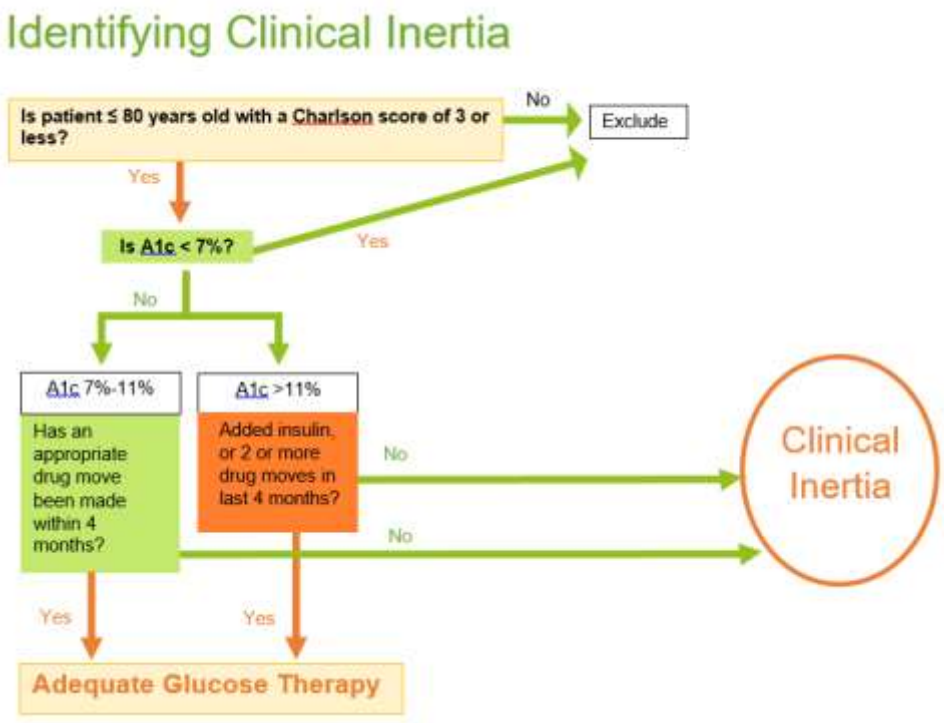
Identifying and Resolving Clinical Inertia in Diabetes Care

Executive Summary: Clinical inertia can be defined as failure to intensify treatment or delay treatment in patients who are not meeting their clinical goals of care. Many factors may contribute to clinical inertia. Clinicians should utilize the tools that are already in place to work towards reducing clinical inertia (guidelines and algorithms, disease registries, obtaining labs in advance of appointments, and team based care).

Clinical inertia is a major factor that contributes to inadequate care in patients with chronic diseases, including diabetes, and is defined as lack of treatment intensification in a patient not at evidence-based goals for care. In a systematic review published in Diabetes, Obesity and Metabolism in 2018, the median time to treatment intensification after an A1c measurement above target was found to be longer than one year. Multiple other real-world findings confirm a high prevalence of clinical inertia in diabetes management and extended periods of time to intensify treatment in those not meeting clinical goals.

The consequences of treatment delays involve microvascular and macrovascular complications, including shorter time to development of complications and increased rates of complications and/or events.

The following algorithm can be used to identify clinical inertia in diabetes care:



Source: O'Connor PJ, Sperl-Hillen JAM, Johnson PE, et al. Clinical Inertia and Outpatient Medical Errors. In: Henriksen K, Battles JB, Marks ES, et al., editors. Advances in Patient Safety: From Research to Implementation (Volume 2: Concepts and Methodology). Rockville (MD): Agency for Healthcare Research and Quality (US); 2005 Feb. Available from: https://www.ncbi.nlm.nih.gov/books/NBK20513/

It has been proposed that clinical inertia has 3 main sources – physician factors, patient factors, and office system factors – which may interact in complex ways.

Physician factors

- Goal setting pathologies
- Fail to initiate treatment; lack of knowledge/resource for initiating injectable agents
- Fail to titrate treatment
- Fail to identify and manage comorbid conditions
- Insufficient time, competing demands
- Reactive vs proactive care

Patient factors

- Deny having disease
- Believe disease not serious
- Low health literacy
- Cost of treatment
- Polypharmacy
- Side effects of medication
- Poor communication with physician
- Do not trust physician
- Multiple diagnoses, concerns at visits

Office system factors

- No clinical guideline
- No disease registry
- No visit planning
- No active outreach
- No decision support
- No team approach to care
- Lack of access to diabetes education programs
- Poor communication between physician and staff

Reducing clinical inertia

- Use a more proactive than reactive approach – ensure diabetic registry is being utilized in clinic
  - Consider identifying a nurse diabetic registry manager for a pod or small group of physicians
  - Diabetic Registry
- Initiate and titrate treatment more rapidly
- Order labs in advance of next appointment so they are available to review with patient while in clinic. This also serves as a reminder if patients fail to follow up.
- Utilize resources that are available, e.g., AMG guidelines and algorithms
- Utilize other members of the care team to assist with each patient's unique needs. These team members can connect with patients' in-between office visits to help ensure implementation of the care plan and identify and address additional needs the patient may have.
- **Coordinated Care team** serves as a direct connection with the primary care provider; dedicate time to answering questions and further explaining the education provided by other team members; remind patients of upcoming appointments, arrange transportation if needed; help connect with community resources
- **Diabetes educator** provides in-depth counseling and education on all aspects of diabetes complications, preventative care, and lifestyle modifications

- **Dietitian** provides in-depth counseling and education on diet, assessment for food insecurities, and assistance in managing multiple different dietary concerns
- **Pharmacist** serves as the medication expert; assessment of medications for appropriateness, efficacy, safety, adherence, and cost; recommendations for medication management; assessment and management of self-monitored blood glucose; continuous glucose monitor initiation and assessment
- **Social worker** to assist with finding and providing resources for patients

Links to internal and/or external resources:
AMG Type 2 Diabetes Treatment Algorithm
Data Repository – Diabetes Registry

Sources:

1. O'Connor PJ, Sperl-Hillen JAM, Johnson PE, et al. Clinical Inertia and Outpatient Medical Errors. In: Henriksen K, Battles JB, Marks ES, et al., editors. Advances in Patient Safety: From Research to Implementation (Volume 2: Concepts and Methodology). Rockville (MD): Agency for Healthcare Research and Quality (US); 2005 Feb. Available from: https://www.ncbi.nlm.nih.gov/books/NBK20513/
2. Khunti K, Gomes MB, Pocock S, et al. Therapeutic inertia in the treatment of hyperglycaemia in patients with type 2 diabetes: a systematic review. Diabetes Obes Metab 2018;20:427–437.
3. Strain WD, Cos X, Hirst M, et al. Time to do more: Addressing clinical inertia in the management of type 2 diabetes mellitus. *Diabetes Research and Clinical Practice*. 2014;105(3):302-12.
4. Karam SL, Dendy J, Polu S, Blonde L. Overview of Therapeutic Inertia in Diabetes: Prevalence, Causes, and Consequences. *Diabetes Spectrum*. 2020;33(1):8-15

Reducing Total Cost of Care through Optimal Pharmacologic Treatment

Executive Summary: The total cost of care in patients with diabetes exceeds any other chronic disease. The use of SGLT2is in patients with ASCVD or at high risk for ASCVD has been shown to reduce the total cost of care despite potentially increasing the cost for pharmacotherapy when compared to sulfonylureas and DPP-4is. Appropriate blood glucose monitoring, intensive management of glycemia, and cardiovascular preventative measures (statin and aspirin use) have also been found to be cost-effective when managing type 2 diabetes.

Diabetes is the most expensive chronic condition in the United States and accounts for $237 billion total medical costs in addition to $90 billion in lost work and wages for people diagnosed with diabetes, and medical costs for people with diabetes are more than twice as high as for people without diabetes. The rise of new pharmacotherapy and technologies has provided mechanisms to better optimize diabetes control, reduce the risk of complications, and improve patient's quality of life, however they also come at a price. When developing diabetes care plans, it is important to understand not only the price of the intervention, but also the cost-savings that may be realized.

To help inform value-based contracting and targeted prescribing interventions to improve care and reduce total cost of care, Garry et al conducted a population-based cohort study utilizing real-word evidence in new users of SGLT2i, DPP-4i, or sulfonylureas. The authors defined three patient subgroups:

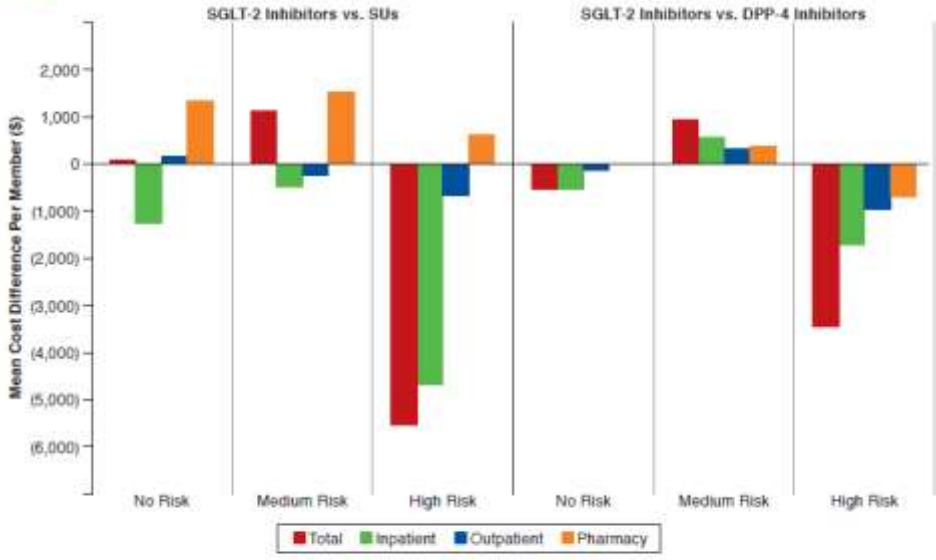
- High-risk CVD status (patients with CVD-related hospitalization any time before cohort entry)
- Medium-risk CVD status (patients with previous CVD-related office visits but no hospitalization)
- No recorded risk

This study was performed in commercially insured patients with a median age of 56 years and 53.5% male. The most common comorbidities among patients were CVD (55.1%); or CVD risk factors, hyperlipidemia (56.3%), hypertension (50.2%), and obesity (20.3%). For patients on sulfonylureas, 42% were on statin therapy, statin use in patients on DPP-4i was 46%, and 52% for SGLT2i.

In patients in the high-risk CVD subgroup, SGLT2i use was associated with an average increased pharmacy cost of $1,527 compared to SU, however SGLT2i use lead to an estimated savings of $5,520 with six months of use. This cost savings was primarily attributed to reduced total medical cost, driven by inpatient cost savings. Comparing SGLT2i with DPP4i in patients in the high-risk CVD subgroup, the average cost difference per patient with six months of use was $3,419 favoring SGLT2i use.

Be aware that this study was limited to regional data representing commercially insured patients and may not be generalizable to Medicare or Medicaid populations. Also, the lower CVD risk subgroups showed no clear patterns in cost savings for SGLT2i.

FIGURE 3 Mean Cost Difference Per Member Stratified by Cardiovascular Risk



Note: Second-line comparisons included initiators of SGLT-2 inhibitors (n = 3,626) versus SUs (n = 6,709) and SGLT-2 inhibitors (n = 3,529) versus DPP-4 inhibitors (n = 5,232) without exposure to either drug in the comparison during the 180-day baseline period. These initiators were aged at least 18 years, had no previous exposure to basal insulin, and had at least 1 medical claim in order to identify medical benefit. Second-line treatment with GLP-1 receptor agonists was additionally considered but omitted from the analysis due to small sample size.
DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; SGLT-2 = sodium-glucose co-transporter-2; SU = sulfonylurea.

A literature evaluation published in Diabetes Care in 2020 sought to classify diabetes interventions based on the strength of evidence and the level of cost-effectiveness. This review provides an understanding of the potential value of interventions for managing diabetes and its complications.

Intervention	Comparison	Cost-effectiveness
Self-monitored blood glucose (SMBG)	SMBG 3x/day vs SMBG 1x/day	$3,719/QALY
Intensively managing glycemia according to age and duration of diabetes	Intensive vs conventional management in young newly diagnosed Type 2 diabetes	$4,318/QALY
	Intensive vs conventional management in older individuals (50 years or older)	$15,398/QALY
Statin therapy for secondary prevention	Statin vs no statin	$4,627/QALY
Statin therapy for primary prevention	Statin vs no statin	$67,873/QALY
Aspirin for primary prevention	Aspirin vs no aspirin	$2,395/QALY

QALY = Quality-adjusted life year
<$25,000/QALY = very cost-effective
$25,000-$50,000/QALY = cost-effective
>$50,000-$100,000/QALY = marginally cost-effective

Sources:
Cost-Effectiveness of Diabetes Interventions. CDC – National Center for Chronic Disease Prevention and Health Promotion. Last reviewed: Sept 29, 2020. Accessed on: Mar 22, 2021. Available at: https://www.cdc.gov/chronicdisease/programs-impact/pop/diabetes.htm.

Garry EM, Schneeweiss S, Eapen S, et al. Actionable Real-World Evidence to Improve Health Outcomes and Reduce Medical Spending Among Risk-Stratified Patients with Diabetes. *J Manag Care Spec Pharm*. 2019;25(12):1442-52. https://doi.org/10.18553/jmcp.2019.25.12.1442

Siegel KR, Ali MK, Zhou X, et al. Cost-effectiveness of Interventions to Manage Diabetes: Has the Evidence Changed Since 2008? *Diabetes Care*. 2020;43(7):1557-92. https://doi.org/10.2337/dci20-0017