



Diabetes Mellitus Masterclass  
Chapter 5

# USING ORAL MEDICATIONS



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# AVOIDING HYPOGLYCEMIA



For patients at high risk of hypoglycemia, we want to use medications that are low risk for causing low blood sugars. These typically include the medications that do not increase insulin and primarily target insulin resistance.

## Stepwise approach to adjusting medications when goal is to avoid hypoglycemia

1. **Metformin** is the first-line therapy for nearly all patients, including those at high risk of hypoglycemia.

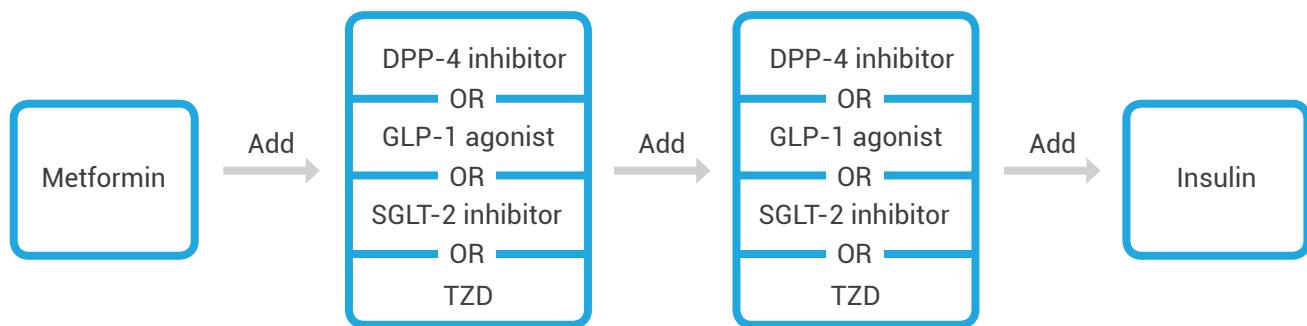
2. If A1c is still above goal after three months on the maximum dose of metformin, add a second agent.

- DPP-4 inhibitors have the fewest side effects
- GLP-1 receptor agonists to minimize weight gain
- SGLT-2 inhibitors minimize weight gain
- TZDs for patients with significant insulin resistance

3. If A1c is still above goal after three months on two medications, consider adding a third agent.

- If currently on Metformin + DPP-4 inhibitor—consider switching to GLP-1 agonist (more effective than a DPP-4 inhibitor)
- If currently on Metformin + GLP-1 RA or DPP-4 inhibitor—add SGLT-2 inhibitor
- If currently on Metformin + SGLT-2 inhibitor—add GLP-1 agonist or DPP-4 inhibitor
- If currently on Metformin + GLP-1 agonist, DPP-4 inhibitor or SGLT-2 inhibitor—add TZD

4. If not at goal after three months on three medications, you need to consider starting insulin.



*When trying to minimize hypoglycemia,  
sulfonylureas should be avoided.*

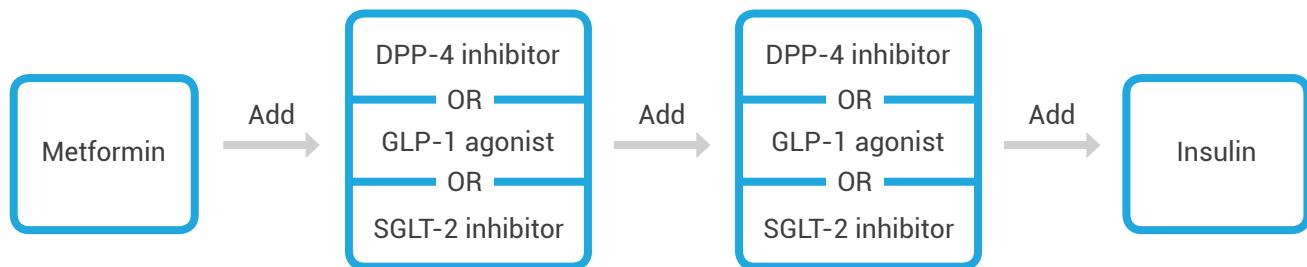
# AVOIDING WEIGHT GAIN



For patients who are concerned with weight gain (which unfortunately is a side effect of many diabetes medications), we want to use medications that minimize weight gain, or may even aid in weight loss.

## Stepwise approach to adjusting medications when goal is to minimize weight gain

1. **Metformin** is the first-line therapy, as it is weight neutral, and may even result in weight loss for some patients. It is important to emphasize lifestyle interventions as well.
2. If A1c is still above goal after three months on the maximum dose of metformin, add a second agent
  - DPP-4 inhibitors have the fewest side effects—no weight loss (these are considered weight neutral)
  - GLP-1 receptor agonists for some weight loss (associated with nausea)
  - SGLT-2 inhibitors for weight loss (associated with urinary symptoms)
3. If A1c is still above goal after three months on two medications, consider adding a third agent.
  - Metformin + GLP-1 agonist (or DPP-4 inhibitor) + SGLT-2 inhibitor—best option for weight loss
4. If not at goal after three months on three medications, you need to consider starting insulin. Unfortunately, nearly all patients will gain weight on insulin, but with continued efforts at diet and lifestyle, you can minimize this while improving glucose control.



# MINIMIZING CARDIOVASCULAR RISK

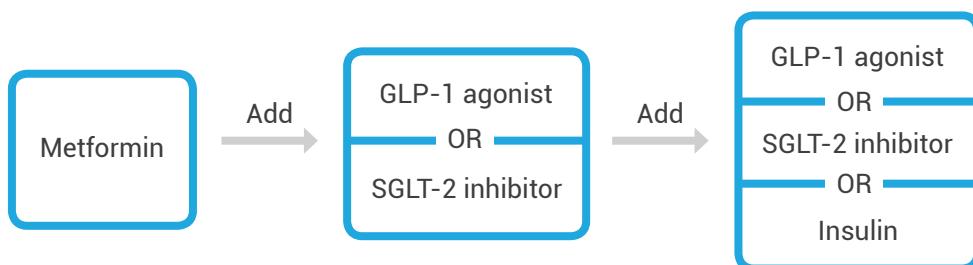


The leading cause of death for patients with diabetes is cardiovascular disease.

For patients at high risk of cardiovascular disease, choosing diabetes medications that have the additional benefit of protecting against heart disease, should be a high priority.

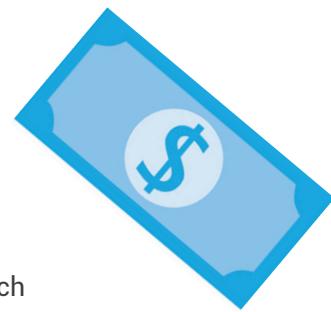
## Stepwise approach to adjusting medications when goal is to minimize cardiovascular risk

1. As with all patients with type 2 diabetes, **metformin** is first-line therapy. Compared to lifestyle changes alone, metformin can reduce cardiovascular events by as much as 30%.
2. If A1c is still above goal after three months on the maximum dose of metformin, add a second agent.
  - SGLT-2 inhibitors (empagliflozin) have been shown to decrease cardiovascular events in patients with established cardiovascular disease. Similar effects were seen with canagliflozin, but unexplained increase in lower extremity amputations for the treatment group (not seen with empagliflozin).
  - GLP-1 receptor agonists (liraglutide) are associated with a decrease in cardiovascular events. Similar results were seen with semaglutide, but with an increased risk of retinopathy. No benefit seen with lixisenatide (but no increased risk).
3. If A1c is still above goal after three months on two medications, consider adding a third agent.
  - Metformin + SGLT-2 inhibitor + GLP-1 agonist has not been studied for cardiovascular protection, but is an effective combination for glucose lowering and reasonable to consider.
  - Insulin has not shown cardiovascular benefit, but is effective at lowering blood glucose, which may help lower cardiovascular risk.
  - DPP-4 inhibitors and sulfonylureas are likely safe, although no benefit for cardiovascular disease.



*Avoid TZDs in patients with high cardiovascular risk and congestive heart failure.*

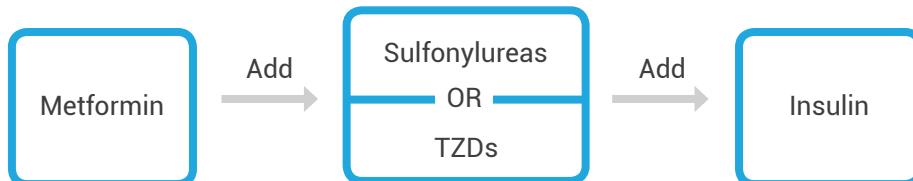
# MINIMIZING COST



Many patients with type 2 diabetes will require multiple medications to manage their diabetes. For many patients, the cost of these medications can be a significant concern, and minimizing the cost may be a priority when selecting which medications to use.

## Stepwise approach to adjusting medications when goal is to minimize cost

1. As with all patients with type 2 diabetes, **metformin** is first-line therapy. It is an effective low-cost medication, accessible to nearly all patients.
2. If A1c is still above goal after three months on the maximum dose of metformin, add a second agent.
  - Sulfonylureas are generally well tolerated, but have an increased risk of hypoglycemia (risk is minimized by avoiding glyburide).
  - TZDs have low risk of hypoglycemia, but significant side effects including weight gain and osteoporosis.
3. If A1c is still above goal after three months on two medications, consider adding a third agent:
  - Insulin is the most cost-effective third agent.
  - Metformin + sulfonylureas + TZDs are an option, but side effects are usually limiting.



# READING LIST

**Review of pharmacologic therapies for type 2 diabetes**

Wright, JJ and Tylee, TS. 2016. Pharmacologic Therapy of Type 2 Diabetes. *Med Clin North Am.* **100**: 647–663.  
<https://www.ncbi.nlm.nih.gov/pubmed/27235609>

**Review of cardiovascular effects of diabetes medications**

Younk, LM, Lamos, EM, and Davis, SN. 2016. Cardiovascular effects of anti-diabetes drugs. *Expert Opin Drug Saf.* **15**: 1239–1257.  
<https://www.ncbi.nlm.nih.gov/pubmed/27268470>

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