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# The Effectiveness of Tirzepatide (GIP/GLP-1 Receptor co-Agonist) vs GLP-1 Receptor Agonists on Lowering A1C in Adults with Type 2 Diabetes Mellitus

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# The Effectiveness of Tirzepatide (GIP/GLP-1 Receptor co-Agonist) vs GLP-1 Receptor Agonists on Lowering A1C in Adults with Type 2 Diabetes Mellitus

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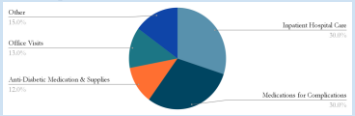
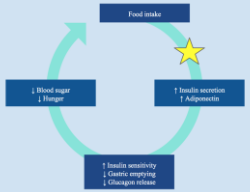
## Introduction

In the United States, 34.2 million people are currently diagnosed with diabetes mellitus, which accounts for 10.5% of the total population.[1] Type 2 diabetes mellitus (T2DM) holds 94.2% of all diabetes diagnoses. The American Association of Diabetes estimates approximately $327 billion annually and is broken up as follows:[1]




## Tirzepatide

Tirzepatide (Mounjaro) is a novel dual medication that was recently approved in May 2022 for treatment of T2DM. It modulates both gastric inhibitory polypeptide (GIP) activity and glucagon-like peptide-1 (GLP-1), becoming the first dual GIP/GLP-1 receptor co-agonist on the market.[5]




## Why?

Although metformin remains the mainstay first-line treatment for T2DM, it is often discontinued due to adverse gastrointestinal side effects.[4] GLP-1 receptor agonists have become a common second-line agent due to superior reduction in A1C, cardio-protective properties, and associated weight loss.[4] Even with GLP-1 receptor agonists growing popularity, T2DM remains a disease with high morbidity and has been classified by the CDC as the 8th leading cause of death in the US (100,000 deaths/year).[2] The focus of this review is to discuss whether tirzepatide's dual GLP-1/GIP mechanism offers greater glycemic control and could be considered the first alternative second-line agent.

## Methods

Five randomized control trials were found usingthe following criteria on PubMed:

**Inclusion criteria:**

- Key phrases such as "tirzepatide" AND "diabetes"
- ≤ 5 years old
- Full texts, as well as randomized controlled trials and clinical trials.

**Exclusion criteria:**

- No GLP-1 RA comparison
- No glycemic control measurement
- Treatment of T2DM complications

## Results

| Drug | Dose (Mg) | % A1C Reduction | Estimated Difference | P-Value |
|---|---|---|---|---|
| Semaglutide | 1 | 1.86% | | |
| Tirzepatide | 5 | 2.01% | −0.15% | P=0.02 |
| | 10 | 2.24% | −0.39% | P<0.001 |
| | 15 | 2.30% | −0.45% | P<0.001 |

**Table 1.** Results of the first paper showing % A1C reduction in doses ranging from 5-15 mg of tirzepatide versus 1 mg dosing of semaglutide.[5]

| Compound | Baseline CDI (pmol m−2 L min−2 kg−1) | 28-week CDI (pmol m−2 L min−2 kg−1) | CDI Difference (pmol m−2 L min−2 kg−1) | Standard Error |
|---|---|---|---|---|
| Placebo | 0.4 | 0.3 | 0 | 0.04 |
| Tirzepatide | 0.3 | 2.3 | 1.9 | 0.16 |
| Semaglutide | | | 0.84 | |

**Table 2.** Primary measurements showing clamp disposition index differences over a 28-week dosing period for tirzepatide as compared with the placebo. A secondary measurement was done to add in a semaglutide comparator.[7]

| Drug | Dose (mg) | 52-week Hg A1C Reduction (MD) | Mean Treatment Differences (against dulaglutide) | Dose-dependent Weight Reduction (LBS-kg) |
|---|---|---|---|---|
| Tirzepatide | 5 | 2.4 | 1.1 (P<0.0001) | 8.8 |
| | 10 | 2.6 | 1.3 (P<0.0001) | 8.6 |
| | 15 | 2.8 | 1.5 (P<0.0001) | 10.7 |
| Dulaglutide | 0.75 | 1.3 | | 0.5 |

**Table 3.** Results of tirzepatide in doses ranging from 5-15 mg versus dulaglutide at 0.75 mg for the 52-week Hg A1C reduction as well as dose-dependent weight reductions in both the drugs.[7]

| Compound | Dose (mg) | % Hg A1C Reduction | Estimated Treatment Difference | P-Value |
|---|---|---|---|---|
| Tirzepatide | 5 | 1.87% | -1.91% | P<0.0001 |
| | 10 | 1.89% | -1.93% | P<0.0001 |
| | 15 | 2.07% | -2.11% | P<0.0001 |
| Placebo | | 0.00% | | |

**Table 4.** Tirzepatide dosed at ranges of 5-15 mg over 40 weeks compared to a placebo in regard to Hg A1C percent reduction.[8]

| Compound | Dose (mg) | Significant HOMA 2-B Increase (+/-) | Significant Insulin Resistance Decrease (+/-) | Significant Insulin Sensitivity Increase (+/-) | Significant Proinsulin/insulin & Proinsulin/C-peptide Ratio Decrease (+/-) |
|---|---|---|---|---|---|
| Tirzepatide | 1 | + (P ≤ .02) | - | + | - |
| | 5 | + | - | + | - |
| | 10 | + | + (P ≤ .004) | + | + (P ≤ .007) |
| | 15 | + | - | + | + (P ≤ .007) |
| Dulaglutide | 1.5 | + | + | + | + |
| Placebo | | Baseline | Baseline | Baseline | Baseline |

**Table 5.** Table 5. Tirzepatide doses ranging from 1-15 mg vs dulaglutide at 1.5 mg and a placebo, comparing increase and decreases in multiple biological markers of insulin as related to type 2 diabetes.[9]

| | Adverse Drug Reaction | | | | | |
|---|---|---|---|---|---|---|
| Compound | Nausea | Vomiting | Diarrhea | Constipation | Nasopharyngitis | Hypoglycemia |
| Tirzepatide | 18.40% | 5.70% | 15.10% | 15.70% | 16.00% | 1.30% |
| Semaglutide | 19.00% | 8.00% | 14.00% | | | 0.40% |
| Dulaglutide | 8.00% | | | 11.00% | 16.00% | |
| Placebo | 9.60% | 2.40% | 10.50% | | | |

**Table 6.** Adverse drug reactions in tirzepatide trials including semaglutide, dulaglutide, and the placebo[6,7,8,9]

## Conclusion

The goal of this review was to evaluate whether tirzepatide was superior in glycemic control when compared to GLP-1 receptor agonists in adults with type 2 diabetes mellitus. The current research discussed in the overall findings of this paper suggests that tirzepatide has superior A1C lowering capabilities when compared to GLP-1 receptor agonists.[6,7,8,9,10] Both medications result in similar side effect profiles. Therefore, when clinicians prescribe pharmaceutical treatments in patients with T2DM tirzepatide should be considered the mainstay second-line treatment for those who do not achieve glycemic control or cannot tolerate metformin before initiating alternative GLP-1 or insulin treatments.

## Future Research

1. The effect of tirzepatide on specific races, ethnicities, and genders to see if it is superior in one group versus another.
2. Evaluation in efficacy against many comorbid conditions commonly found in patients diagnosed with T2DM.
3. Tirzepatide vs. Metformin in efficacy of glycemic control and patient adherence.

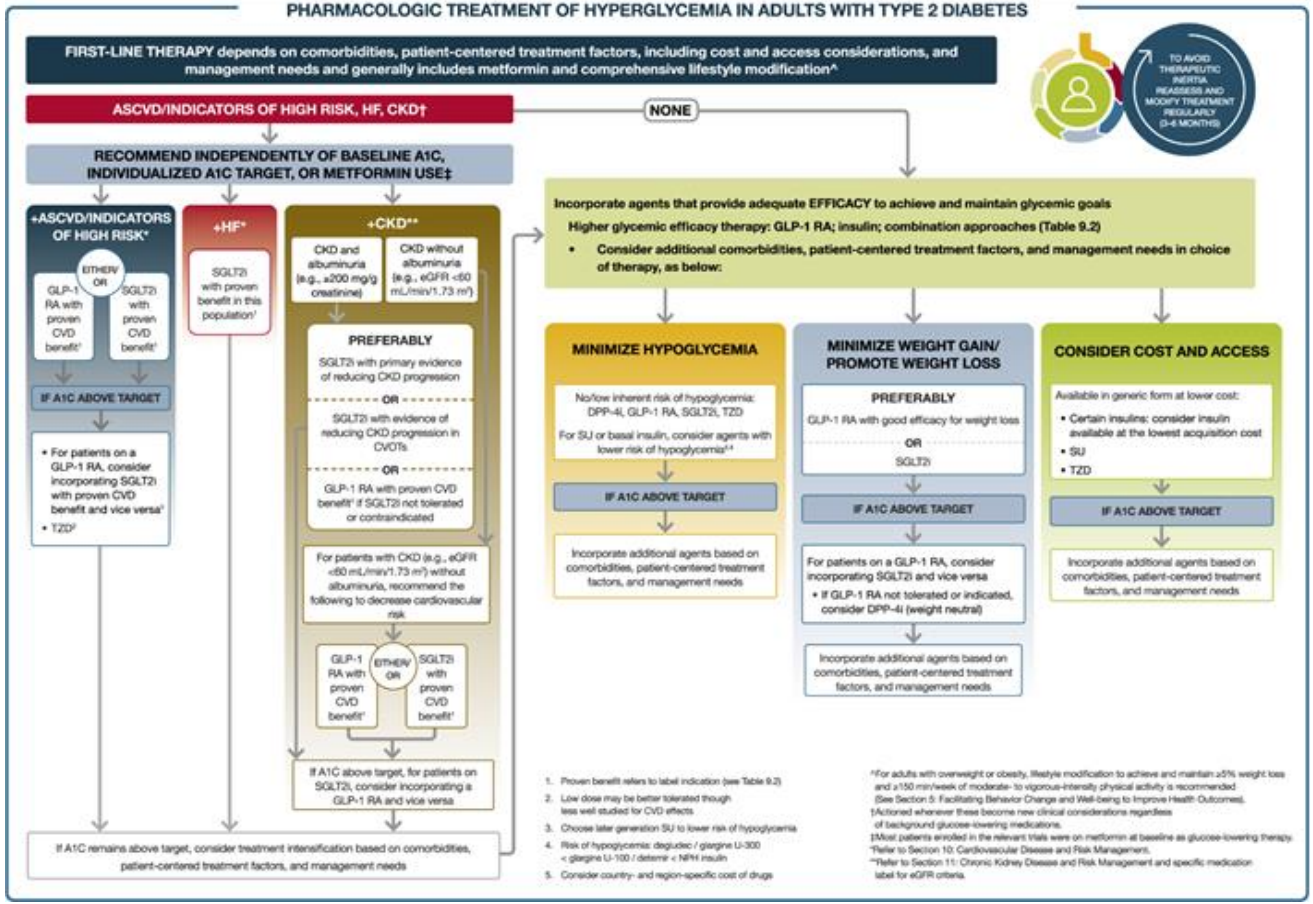



***Figure 1.*** *A flowchart showing the 2022 pharmaceutical treatment guidelines for hyperglycemia in adults with type 2 diabetes mellitus.*[14]

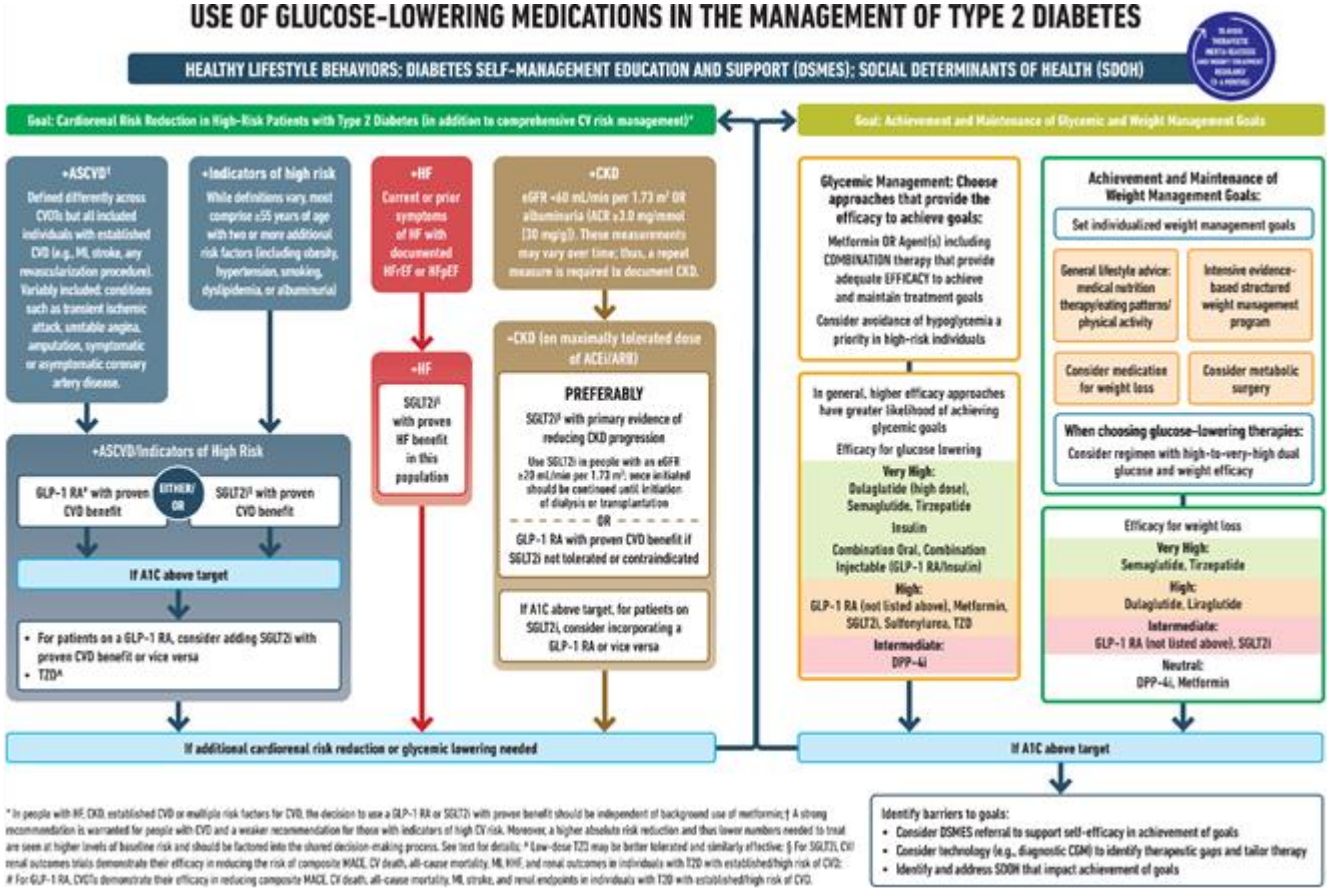



***Figure 2.*** *A flowchart showing the 2023 pharmaceutical treatment guidelines for hyperglycemia in adults with type 2 diabetes mellitus.*[45]

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