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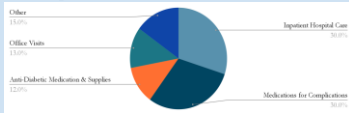
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The Effectiveness of Tirzepatide (GIP/GLP-1 Receptor co-Agonist) vs GLP-1 Receptor Agonists on Lowering A1C in Adults with Type 2 Diabetes Mellitus

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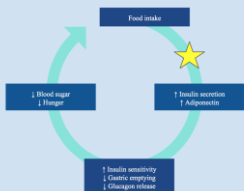
Introduction

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 using the 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%		
	5	2.01%	-0.15%	P=0.02
Tirzepatide	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.⁶

Compound	Baseline CDI (gmol m-2 L min-2 kg-1)	28-week CDI (gmol m-2 L min-2 kg-1)	CDI Difference (gmol m-2 L min-2 kg-1)	Standard Error
Placebo	0.4	0.3	0	0.042
Tirzepatide	0.3	2.3	1.9	0.16
Semaglutide			0.84	

Table 2. Primary measurement showing change 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 comparison.⁷

Drug	Dose (mg)	52-week % A1C Reduction (95% CI)	Mean Treatment Differences (95% CI) (mg/kg)	Dose-dependent Weight Reduction (95% CI)
Placebo	0	2.4	1.1 (P<0.0001)	0.5
Tirzepatide	15	2.1	1.3 (P<0.0001)	0.5
Semaglutide	15	2.8	1.8 (P<0.0001)	0.7
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 % A1C reduction as well as dose-dependent weight reduction in both drugs.⁸

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 doses at ranges of 5-15 mg over 40 weeks compared to a placebo in regard to Hg A1C percent reduction.⁹

Compound	Dose (mg)	Significant HbA1c 5.8-6.5 Increase (%)	Significant Insulin Resistance Increase (%)	Significant Insulin Sensitivity Increase (%)	Significant Proinsulin/Insulin A Proportion Ratio Decrease (%)
Placebo	0	0	0	0	0
Tirzepatide	5	0	0	0	0
	10	0	0	0	0
	15	0	0	0	0
Dulaglutide	1.5	0	0	0	0
Placebo		Baseline	Baseline	Baseline	Baseline

Table 5. Tirzepatide dose ranging from 5-15 mg vs dulaglutide at 1.5 mg over 40 weeks, comparing increase and decrease in multiple biological markers of insulin resistance as stated in table 5 diabetes.¹⁰

Compound	Adverse Drug Reaction				
	Nausea	Vomiting	Diarrhea	Constipation	Nasopharyngitis
Tirzepatide	18.00%	5.70%	15.00%	15.70%	16.00%
Semaglutide	19.00%	8.00%	14.00%	14.00%	8.40%
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.^{11,12}

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.

PHARMACOLOGIC TREATMENT OF HYPERGLYCEMIA IN ADULTS WITH TYPE 2 DIABETES

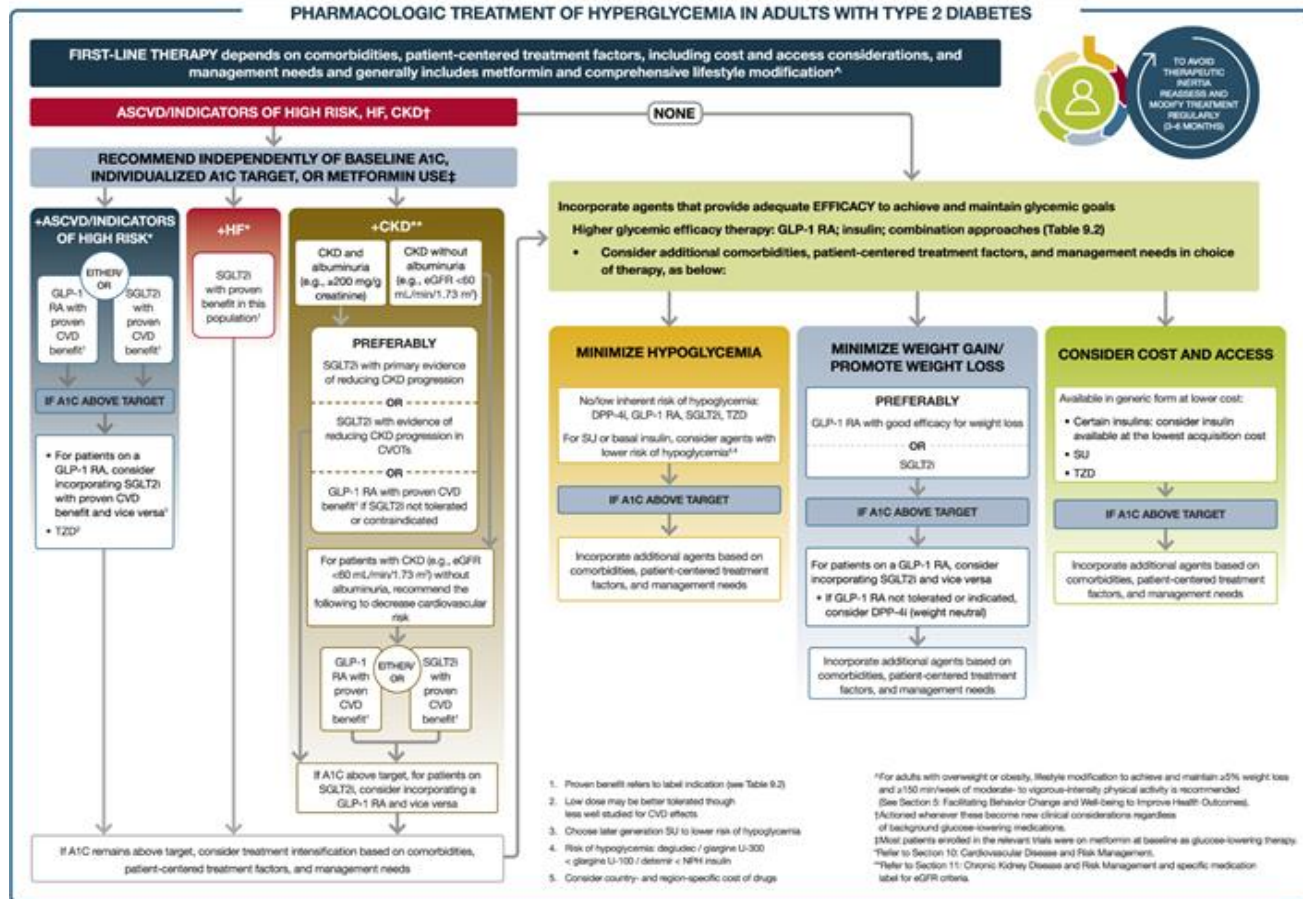
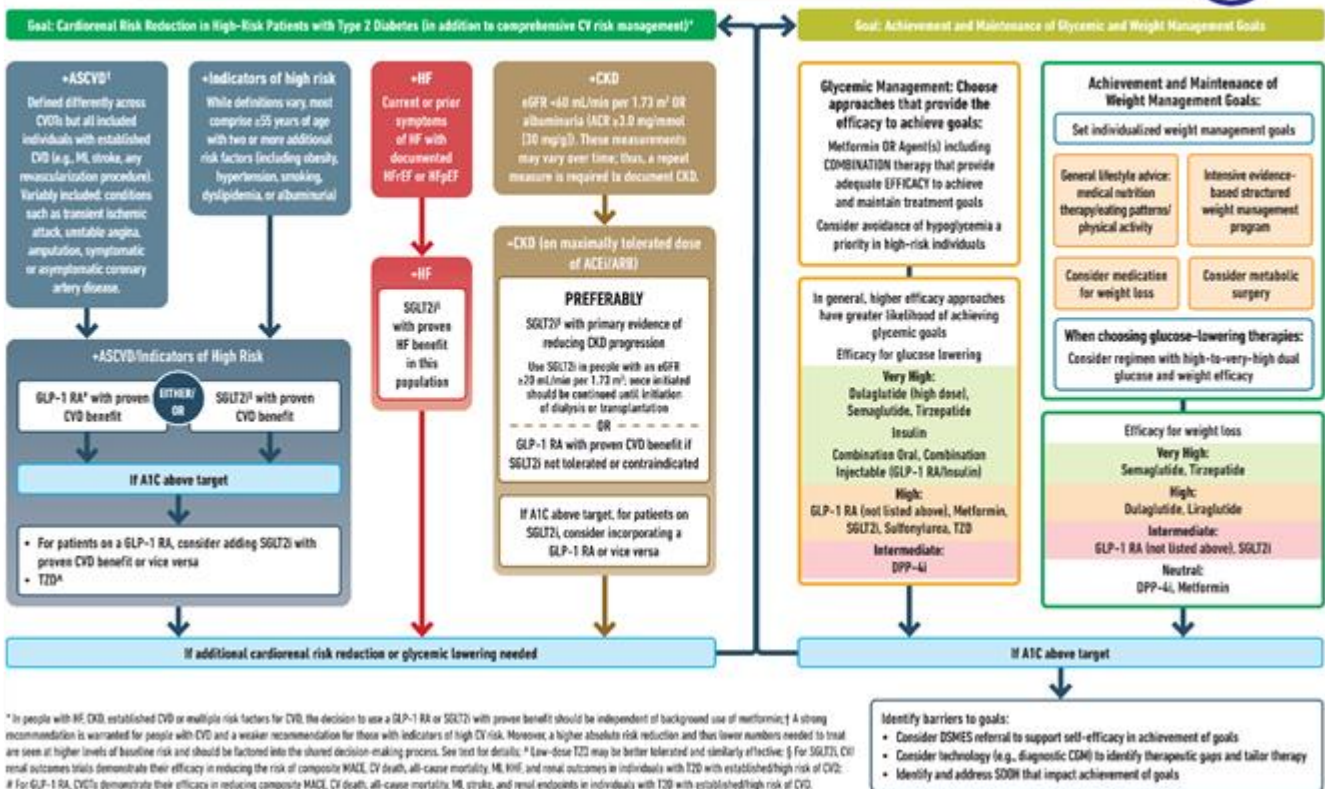


Figure 1. A flowchart showing the 2022 pharmaceutical treatment guidelines for hyperglycemia in adults with type 2 diabetes mellitus.¹⁴

USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES



HEALTHY LIFESTYLE BEHAVIORS: DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)



* In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2 with proven benefit should be independent of background use of metformin. † A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details. ‡ Low-dose TZD may be better tolerated and similarly effective. § For SGLT2, CV renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HF, and renal outcomes in individuals with T2D with established high risk of CVD. ¶ For GLP-1 RA, CVDs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and renal endpoints in individuals with T2D with established high risk of CVD.

Figure 2. A flowchart showing the 2023 pharmaceutical treatment guidelines for hyperglycemia in adults with type 2 diabetes mellitus.⁴³

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