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"WEGOVY (SEMAGLUTIDE) AND CARDIAC HEALTH: A REVIEW OF THE LATEST CLINICAL TRIAL FINDINGS"

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ABSTRACT

Cardiovascular disease remains a leading cause of death worldwide, and obesity and overweight are significant risk factors. Recent evidence suggests that semaglutide (Wegovy), a glucagon-like peptide-1 (GLP-1) receptor agonist, may have a role in reducing cardiovascular risk. This review article provides a comprehensive overview of the latest research on the effects of Wegovy on heart health. As a glucagon-like peptide-1 receptor agonist, Wegovy has been shown to improve glycaemic control and reduce cardiovascular risk in individuals with obesity or over weight. We summarize the findings from recent clinical trial and additionally, we discuss the potential mechanisms by which semaglutide exerts its weight management effect. Recent clinical trial proves that Wegovy significantly reduced the risk of major adverse cardiovascular events by 20% (6.5% vs 8% in the placebo group), cardiovascular death by 15%, and all-cause mortality by 19%. Additionally, semaglutide showed improvements in secondary endpoints, including significant reductions in body weight, blood pressure, and lipid levels. Based on the results obtained on those clinical trials, on 8th March 2024 the U.S. Food and Drug Administration approved a new indication for use for Wegovy (semaglutide) injection to reduce the risk of cardiovascular death, heart attack and stroke in adults with cardiovascular disease and either obesity or overweight.

KEYWORDS: Wegovy, Semaglutide, Cardiovascular diseases, Obesity, GLP-1, SELECT trial

1. INTRODUCTION

Obesity and cardiovascular disease (CVD) are two of the most pressing public health concerns of the 21st century, with far-reaching consequences for individuals, communities, and healthcare systems worldwide. Overweight refers to excess body fat, while obesity is a chronic condition where excess fat can lead to serious health problems, including diabetes, heart disease, and certain cancers. It can also impact daily life, making it harder to sleep, move around, and maintain overall well-being.[1] Cardiovascular diseases (CVDs) is a term that encompasses a range of conditions and disorders that impact the heart and blood vessels The coexistence of these two conditions is not coincidental, as obesity is a major risk factor for the development and progression of CVD. The relationship between obesity and CVD is complex and multifaceted, involving a web of interrelated factors that contribute to the development of this comorbidity. Compared to individuals with a healthy BMI, people with obesity not only had a higher risk of heart disease but they also had a higher risk of death due to heart disease. Excess adiposity, particularly visceral adiposity, triggers a cascade of metabolic and inflammatory changes that increase the risk of CVD. These changes include insulin resistance,

dyslipidaemia, hypertension, and endothelial dysfunction, which collectively create a perfect storm for the development of CVD. Recent evidence highlights the importance of abdominal obesity, as measured by waist circumference, as a distinct cardiovascular risk marker that is independent of body mass index (BMI). Advanced imaging modalities have enabled the precise assessment of body composition, including visceral adiposity, which has emerged as a key predictor of cardiovascular outcomes. Studies have consistently shown that excess visceral adiposity is associated with poor cardiovascular outcomes, independent of other risk factors. [1,2]

Moreover, obesity leads to the development of CVD and CVD mortality independently of other cardiovascular risk factors, emphasizing the need for a comprehensive understanding of the relationship between obesity and CVD. Lifestyle modification and weight loss have been shown to improve metabolic syndrome, systemic inflammation, and endothelial dysfunction, underscoring the importance of addressing obesity in the prevention and management of CVD. Despite the gravity of this situation, there is hope for prevention and treatment. A comprehensive understanding of the relationship between obesity and CVD can inform evidence-based strategies for risk reduction, early intervention, and effective management of these conditions. [3,4] In this review, we discuss details of Wegovy (semaglutide) in weight loss, as well as the latest clinical trial findings on its association with reduced major adverse cardiac events.

2. METHODOLOGY OF REVIEW

The literature search was performed using search engines such as google & google scholar, publishing sites of National Library of Medicine, PubMed, FDA. Two search items, Wegovy and cardiac health were used to search the literature sources. Other literature sources included are international and national news and Govt. reports.

3. WEGOVY (SEMAGLUTIDE) IN WEIGHT LOSS

Wegovy (semaglutide) is a medication prescribed for weight loss in specific individuals. Semaglutide is an antidiabetic medication used for the treatment of type 2 diabetes and an anti-obesity medication used for long-term weight management. It is a peptide similar to the hormone glucagon-like peptide-1 (GLP-1), modified with a side chain. It is administered via injection under the skin, using a prefilled pen that contains a single dose of the drug in liquid form. It is recommended with exercise and a low calorie diet for long-term weight loss in:

- Adults with a body mass index (BMI) of 30 or higher (obesity).
- Adults with a BMI of 27 or higher (which is considered overweight) plus a health condition that's related to weight.
- Children 12 years and older whose BMI is in the 95th percentile or higher (which is considered obesity).[5]

Wegovy functions by imitating the action of a natural hormone called GLP-1, which interacts with the brain's appetite and food consumption centers, helping to reduce hunger and calorie intake.[6]

3.1 Mechanism of Action:

Wegovy (semaglutide) is a medication that mimics the natural hormone GLP-1, which regulates appetite and calorie intake. It works by binding to GLP-1 receptors in the brain, reducing hunger and leading to weight loss. This weight loss is thought to contribute to the reduction in cardiovascular risk associated with Wegovy. In simpler terms, Wegovy acts like a natural hormone to help regulate appetite and weight, leading to cardiovascular benefits. Some of the ways which Wegovy works to reduce weight are:

i. Wegovy works in the gut to induce feelings of fullness and reduce hunger:
   Wegovy works by slowing gastric emptying, keeping food in the stomach for longer, and prolonging feelings of fullness. This leads to eating fewer calories and weight loss. However, research suggests that this effect on the gut tends to decrease after 5 months, reducing side effects like nausea.[7]

ii. Wegovy targets areas in your brain that regulate appetite:

Wegovy not only slows down digestion in the gut but also acts on the brain to reduce hunger and increase feelings of fullness, leading to lower food intake. Additionally, it may help quiet "food noise" in the mind, reducing constant thoughts about food.[7]

iii. Wegovy may help reduce cravings for certain foods, leading to a decrease in unhealthy eating habits and an increase in weight loss:

Wegovy's impact on the brain can lead to changes in food preferences, reducing cravings for unhealthy foods like sweets and salty snacks. It may also decrease the pleasure associated with eating these foods. In clinical trials, Wegovy significantly reduced food cravings for nearly two years, including cravings for savory foods. While this may be beneficial for some, others may experience a loss of taste for favourite foods, making it essential to find nutritious alternatives to maintain adequate nutrition during treatment.

iv. Wegovy may counteract certain hunger hormones that affect weight gain:

Wegovy works by mimicking the gut hormone GLP-1, which helps regulate appetite, metabolism, and weight. Other hormones like ghrelin (the "hunger hormone") and leptin (the "fullness hormone") also play a role. When you lose weight, ghrelin levels increase, stimulating appetite and fat storage, while leptin levels decrease, making it harder to maintain weight loss. Wegovy may counteract these hormonal changes, helping individuals maintain weight loss over time. However, this effect is reversed when Wegovy treatment is stopped.[7]

3.2 Adverse Reactions:

The use of Wegovy may be associated with the following adverse reactions:

- Common Side Effects:
  - Gastrointestinal: nausea, diarrhoea, vomiting, constipation, abdominal pain, dyspepsia, abdominal distension, eructation, flatulence, gastroenteritis, and gastroesophageal reflux disease
  - General: fatigue, headache, dizziness
  - Metabolic: hypoglycaemia (in patients with type 2 diabetes)

- Serious Side Effects:
  - Allergic Reaction: Hives, Itching, Difficulty breathing, Swelling of face, lips, tongue, or throat
  - Vision changes
  - Unusual mood changes or suicidal thoughts
  - Pounding heartbeats or fluttering in the chest
  - Light headedness or fainting
  - Thyroid tumour symptoms:
    - Swelling or lump in the neck
    - Trouble swallowing
    - Hoarse voice
    - Shortness of breath
  - Pancreatitis symptoms:
    - Severe stomach pain
    - Nausea and vomiting
    - Fast heart rate
  - Gallbladder problems:
    - Upper stomach pain
    - Fever
    - Clay-coloured stools
    - Jaundice (yellowing of skin or eyes)
  - Kidney problems:
    - Swelling
    - Decreased urination
  - Stomach flu symptoms:
    - Stomach cramps
    - Vomiting

- Loss of appetite
- Diarrhoea (may be watery or bloody) [5]

Fig 1: Wegovy (Semaglutide) Injection

3.3 Black Box Warning

Thyroid C-Cell Tumours and Medullary Thyroid Carcinoma (MTC)

Semaglutide, the active ingredient in Wegovy, has been shown to cause thyroid C-cell tumours in rodents at exposures relevant to human clinical use. However, it is uncertain whether Wegovy causes thyroid C-cell tumours, including MTC, in humans. The relevance of semaglutide-induced rodent thyroid C-cell tumours to human risk has not been determined.

3.4 Contraindications

Wegovy is contraindicated in patients with:

- A personal or family history of MTC
- Multiple Endocrine Neoplasia syndrome type 2 (MEN 2)
- Pregnancy
- Breast feeding

3.5 Administration

Wegovy dosing starts low and gradually increases to minimize stomach side effects. The initial schedule is:

- 0.25 mg (weeks 1-4)
- 0.5 mg (weeks 5-8)
- 1 mg (weeks 9-12)
- 1.7 mg (weeks 13-16)

The maintenance dose is 2.4 mg once a week, starting from week 17. If adults have trouble tolerating this dose, they can temporarily decrease to 1.7 mg for up to 4 weeks before increasing back to 2.4 mg. If the 2.4 mg dose is still not tolerated, discontinue use. For paediatric patients (12+ years), the maintenance dose is also 2.4 mg once a week, with the option to reduce to 1.7 mg if not tolerated. [5,8]

4. WEGOVY AND CARDIAC RISK REDUCTION

The FDA approved Wegovy (semaglutide) in March 2024 to reduce the risk of cardiovascular death, heart attack, and stroke in adults with cardiovascular disease and overweight or obesity, based on the SELECT trial results. [9] The SELECT trial showed that, once-weekly subcutaneous semaglutide significantly reduced the risk of major adverse cardiac events, including cardiovascular death, nonfatal

myocardial infarction (MI), and stroke, in patients with overweight or obesity and established cardiovascular disease (CVD) without diabetes, compared to placebo. The SELECT trial, which enrolled over 17,600 adults, demonstrated that Wegovy significantly reduced the risk of cardiovascular events by 20% compared to placebo. Additionally, Wegovy decreased the risk of death from cardiovascular disease by 15% and death from any cause by 19%. The drug is meant to be used in addition to a reduced-calorie diet and increased physical activity. This approval is significant because cardiovascular disease is a leading cause of death, and obesity and overweight are major risk factors. Wegovy is the first weight loss medication to also be approved to help prevent life-threatening cardiovascular events in adults with cardiovascular disease and either obesity or overweight. [10,11]

4.1. Clinical trial summary

The clinical trial for Wegovy (semaglutide) was conducted to study its efficacy in reducing cardiac risk. The official title of the trial is SELECT - Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity.[16] This trial led to FDA approval for the following reasons:

- **Study duration and population**: The study lasted for approximately 40 months and involved over 17,600 participants, making it a large-scale and long-term trial.
- **Study design:** The trial was a multicentered, randomized, double-blind, placebo-controlled study, which is considered the gold standard in clinical trials.
- **Participants:** The study included overweight or obese (BMI ≥27 kg/m2) adults with established cardiovascular disease without diabetes.
- **Treatment groups**: Participants were divided into two groups: one receiving Wegovy (semaglutide) and the other receiving a placebo.
- **Intervention:** Once-weekly subcutaneous semaglutide (2.4 mg) vs. placebo.
- **Primary endpoint:** The primary endpoint was the reduction of major adverse cardiovascular events (MACE), including cardiovascular death, non-fatal heart attack, and non-fatal stroke.
- **Results:** Wegovy significantly reduced the risk of MACE by 20% compared to the placebo group. The results showed that 6.5% of participants in the Wegovy group experienced MACE, compared to 8% in the placebo group. [18,19]
- **Additional findings:** The study also found that Wegovy reduced the risk of death from any cause by 19% and the risk of cardiovascular death by 15%.
- **Side effects:** Common side effects of Wegovy included gastrointestinal issues like nausea, diarrhoea, and vomiting, as well as injection site reactions.
- **Diversity and limitations**: The study had some limitations, including a lack of diversity in the participant population (84% white and 72% male). However, the study's large size and long duration help to compensate for these limitations.
- **Conclusion:** Semaglutide reduced major adverse cardiac events by 20% compared to placebo in patients with overweight or obesity and established CVD without diabetes, with a favourable safety profile. These findings support the potential use of semaglutide in secondary CVD prevention in this population. [12,3,14,16,20]

5. CONCLUSION

The FDA's approval of Wegovy (semaglutide) for heart disease prevention marks a significant milestone in the management of cardiovascular risk. The robust evidence from clinical trials, demonstrates Wegovy's efficacy in reducing major adverse cardiovascular events, cardiovascular death, and all-cause mortality. The consistent benefits observed across various subgroups underscore Wegovy's potential as a valuable adjunct therapy for high-risk populations.

The mechanisms underlying Wegovy's cardioprotective effects, including weight loss, improved glycaemic control, and favourable changes in lipid profiles and blood pressure, support its use as a comprehensive approach to cardiovascular risk management. While potential side effects and limitations should be considered, the overall benefit-risk profile of Wegovy is robust.

As the first GLP-1 receptor agonist approved for heart disease prevention, Wegovy paves the way for a new era in cardiovascular therapeutics. Its approval expands treatment options for patients with cardiovascular

disease and overweight/obesity, offering hope for improved outcomes and enhanced quality of life. As research continues to uncover the full potential of Wegovy and GLP-1 receptor agonists, their impact on cardiovascular health is likely to be significant.

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