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RESEARCH ARTICLE

Semaglutide and Tirzepatide Use and Reduction of Cardiovascular Risks in Adults with Overweight and Obesity

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ABSTRACT

Background: Obesity is a prevalent, growing health concern in the United States, affecting over 42% of adults and contributing significantly to the burden of cardiovascular disease (CVD). Recently, approved anti-obesity medications (AOMs) such as semaglutide (Wegovy) and tirzepatide (Zepbound) have emerged as potential interventions to reduce weight and potentially lower cardiovascular risk among individuals with obesity.

Aim: To analyze the impact of AOM on cardiovascular risk among US patients with obesity.

Methods: Utilizing Kythera data, we conducted a retrospective cohort study from November 2022 to June 2024. Patients with obesity and AOM use were identified based on diagnosis claims and prescription claims for tirzepatide or semaglutide (identification period: Nov. 1, 2023–Dec. 31, 2023) with 6 months of follow-up to measure CVD risk. Exclusions included patients with pre-existing CVD and prior AOM use. Cox regression and multivariable analyses adjusted for comorbidities and sociodemographic factors were employed to assess the risk of cardiovascular events, with additional analyses comparing outcomes between tirzepatide and semaglutide users.

Results: We identified 22,620 patients with obesity and AOM use and 84,427 patients with obesity without AOM use. Significant differences were observed in the proportion of patients with an Elixhauser Index Score ≥2, comprising 61.97% in the AOM cohort versus 13.50% in the non-AOM cohort (standardized difference = 1.2868). The AOM cohort demonstrated significantly lower incidence of cardiovascular events (1.77%) than non-AOM users (12.17%, $p<0.0001$). Adjusted analyses confirmed that AOM use was associated with a substantially reduced risk of CVD (hazard ratio=0.37, $p<0.0001$). Differences in specific cardiovascular outcomes between tirzepatide and semaglutide users were observed, with semaglutide users showing a higher hazard of CVD than tirzepatide users (hazard ratio=1.53, $p=0.0215$).

Conclusions: Use of AOM was associated with a significantly lower risk-adjusted likelihood of cardiovascular events than non-use, highlighting these medications as promising interventions in obesity management.

Keywords: anti-obesity medications, cardiovascular disease, obesity, semaglutide (Wegovy), tirzepatide (Zepbound)

Introduction:

Overweight and obesity are highly prevalent conditions. Almost half of the American population lives with obesity, which affects around 40% of U.S. adults.[1] Globally, it is estimated that approximately 604 million adults currently suffer from obesity. [2]

In 1997, the American Heart Association acknowledged that obesity was an independent modifiable cardiovascular risk factor.[3] Since then, the association of obesity with cardiovascular risk factors, such as high blood pressure, high cholesterol, and diabetes, has been well established. [4] [5] Excess fatty tissue in the body promotes altercations in cardiac function. [6] The presence of excess fatty tissue, referred to as adiposity, can lead to a higher blood volume and cardiac output as well as a reduction in systematic vascular resistance. [7] These complications can lead to hypotension, dilated heart tissues, or heart failure. [7] Adiposity can also activate the sympathetic nervous system, thereby increasing blood pressure, overworking the heart, and in turn causing enlargement of the left ventricle, raising the risk of heart failure. [2] Sleep apnea, another complication of obesity, also has significant consequences to the heart and places patients at higher risk for heart failure, high blood pressure, and arrhythmia. [8]

The American College of Cardiology and the American Heart Association have emphasized that weight loss is of paramount importance in the prevention of heart disease. [9] Multiple studies have determined that weight loss can provide a beneficial effect on a number of cardiovascular risk factors. [10] [11] [12]

Historically, pharmacological treatments for weight reduction have had limited availability, been poorly tolerated, and demonstrated only modest efficacy in weight reduction. [13] [14] Semaglutide and tirzepatide are newly approved anti-obesity medications (AOM) that have been proven effective as a means to lose weight and control adiposity. [15,16] Semaglutide was approved in 2017 under the brand name Ozempic, a diabetes treatment found to cause a reduction of up to 15% of body weight. This weight loss effect led to the development of semaglutide, a drug with a higher maximum dose, which the US Food and Drug Administration (FDA) approved for long-term weight management in 2021 under the brand name Wegovy. [15] Tirzepatide, approved by the FDA under the brand name Mounjaro in 2022, later underwent an FDA fast-track investigation for the treatment of adults with overweight/obesity and weight-related comorbidities.[16] Clinical trials had shown promising results, with participants losing around 20% or more of body weight within a year and a half of starting the treatment. [16] In November 2023, the FDA approved tirzepatide for weight loss under the brand name Zepbound. [17]

Recent clinical data have shown that both of these medications can act as cardioprotective agents for patients at high risk for obesity but who do not have diabetes. [18] [19] To our knowledge, there is no outcomes research study comparing the effects of these medications on cardiovascular events.

To address this gap, we conducted a retrospective cohort study to analyze the impact of newly approved anti-obesity medications on CVD. Subgroup analysis is conducted to compare the cardiovascular benefits of semaglutide and tirzepatide.

Materials and Methods:

This retrospective cohort study used Kythera commercial claims data from January 2022 to June 2024. This data set comprises both open and closed versions, encompassing an extensive cohort of approximately 310 million patients, 6.1 million practitioners, 1.6 million organizations, and 1.4 million facilities, yielding a repository of 34 billion healthcare claims.[20] Key variables within the dataset include de-identified patient identifiers, demographic attributes (age, gender), insurance types, geographic information (zip codes), medical diagnoses coded according to the *International Classification of Diseases, Tenth Revision, Clinical Modification* (ICD-10-CM), procedural codes (Current Procedural Terminology), and medication codes (National Drug Codes). This comprehensive data set facilitates longitudinal analysis to explore trends and outcomes over time. Detailed descriptions and assessments of data integrity have been documented and validated against other data sets. [20] [21] [22]

Two cohorts of patients diagnosed with obesity were identified for this study: those receiving treatment with the newly approved AOMs semaglutide (Wegovy) or tirzepatide (Zepbound) and those not receiving such medications (non-AOM). The AOM cohort was defined as patients who had one or more pharmacy claims for semaglutide (Wegovy) or tirzepatide (Zepbound) between October 1, 2023, and December 31, 2023 (identification period). The date of the first prescription claim was designated as the treatment initiation date and served as the index date for the AOM group. Patients in the AOM cohort had documented diagnoses of obesity at baseline, from January 1, 2020, to January 1, 2021, before the index date, and maintained continuous medical and pharmacy benefits for 12 months before and 6 months after the index date. Patients were excluded from the study if they were prescribed any obesity medications during the baseline period, had more than one claim of obesity medication on the same index date, and had a diagnosis of CVD during the baseline period.

For the non-AOM cohort, individuals were identified based on having at least one healthcare claim indicating obesity during the baseline period. The index date for this cohort was randomly selected within the range defined by the earliest and latest index dates observed in the AOM group. Like the AOM cohort, members of the non-AOM cohort were required to maintain continuous enrollment in medical and pharmacy benefits throughout the study period. Exclusion criteria for the non-AOM cohort included individuals who were prescribed any AOM during the baseline period, those with multiple claims for AOM on the same index date, individuals with any cardiovascular disease diagnosed during the baseline period, and those aged 99 years or older. Following the application of these criteria, a random selection procedure was employed to include 1% of

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eligible patients from the non-AOM cohort in the final study sample.

Baseline clinical and demographic characteristics were comprehensively analyzed in this study. Gender, classified as male or female, and age categories were derived from Kythera Medicare claims data. Socioeconomic status (SES) was evaluated using income, education, and occupation data and patients were stratified into SES terciles (low, medium, and high) based on their respective summary SES scores. To adjust for variations in overall patient comorbidities, the revised Charlson Comorbidity Index (CCI) was calculated. [23] This index was utilized to ensure a comprehensive assessment of health status across the study population. [23]

A descriptive analysis was conducted for the AOM and non-AOM cohorts, with a subgroup analysis comparing variables based on medication type. Likelihood ratio tests were utilized to compare differences between two groups, while Wald tests were employed to compare differences among three or more groups. To assess the risk of CVD between the groups, Cox regression and Aalen additive regression models were utilized. Both models controlled for confounding variables, including age, gender, comorbidity scores, SES score, and obesity-related comorbidities. The Aalen model was applied to determine whether the effect of treatment was additive, meaning that it changed over time. For instance, while the Cox regression analysis might not show a significant effect of treatment on the development of CVD, the additive model could reveal a significant effect in the first year, which then diminishes in subsequent years. [24] We identified CVD based on the presence of specific conditions, including coronary artery disease, heart failure, ischemic heart disease, stroke, and peripheral vascular disease using the appropriate ICD-10-CM codes during the follow-up period.

All analyses were conducted on Databricks (https://www.databricks.com/) using PySpark, SparkR (https://spark.apache.org/docs/latest/api/python/index.html) and the R software package.

Ethics approval for this study was not required, as the data used were obtained from an anonymous, de-identified database compliant with the Health Insurance Portability and Accountability Act (HIPAA).

Results:

After applying inclusion and exclusion criteria, 22,620 patients were identified in the AOM cohort and 84,427 patients in the non-AOM cohort.

The mean age of patients in the AOM cohort was significantly lower than that in the non-AOM cohort (45.5 years vs. 50.87 years, $p < 0.0001$). In both cohorts, the majority of patients were female (79.35% vs. 58.56%, $p < 0.0001$). Patients with high comorbidity were defined as those with a comorbidity score of 2 or above. The AOM cohort exhibited a significantly higher proportion of patients with a high CCI (5.098% vs. 2.98%, $p < 0.0001$), a high Chronic Disease Score (52.68% vs. 7.73%, $p < 0.0001$), and a high Elixhauser Index (61.978% vs. 13.508%, $p < 0.0001$). Additionally, a greater proportion of the AOM cohort resided in regions of low SES compared with the non-AOM cohort (27.77% vs. 33.53%, $p < 0.0001$) (Table 1).

At baseline, CVD-related comorbidities were higher in the AOM cohort than in the non-AOM cohort. For example, the prevalence of hypertension was 59.10% in the AOM cohort compared with 48.90% in the non-AOM cohort ($p < 0.0001$). Additionally, the prevalence of diabetes mellitus was 23.40% in the AOM cohort compared with 12.10% in the non-AOM cohort ($p < 0.0001$), followed by dyslipidemia (27.90% vs. 19.00%, $p < 0.0001$) and chronic kidney disease (15.20% vs. 7.30%, $p < 0.0001$) (Table 1).

Characteristics	**With medication (semaglutide or tirzepatide) (N = 22,620)**		**Without medication (N = 84,427)**		***p*-value**
	N/Mean	**%/Std**	**N/Mean**	**%/Std**	
Age (years)	45.50	12.15	50.67	18.15	0.0001
18-40	7,615	33.66%	19,346	22.91%	0.0001
41-60	12,338	54.54%	32,580	38.59%	0.0001
61-80	2,461	10.88%	25,355	30.03%	0.0001
80+	20	0.09%	3,101	3.67%	0.0001
Gender					
Male	4,671	20.65%	34,988	41.44%	0.0001
Female	17,949	79.35%	49,439	58.56%	0.0001
Comorbidity scores					
CCI score ≥2	1,151	5.09%	2,519	2.98%	0.0001
Socioeconomic score					
Low	6,282	27.77%	28,311	33.53%	0.0001
Medium	7,389	32.67%	27,160	32.17%	0.1565
High	8,523	37.68%	27,080	32.08%	0.0001
Baseline CVD-related comorbidities					
Hypertension	7,812	34.54%	8,872	10.51%	0.0001
Hyperlipidemia	4,105	18.15%	4,201	4.98%	0.0001
Diabetes	1,084	4.79%	4,687	5.55%	0.0001
COPD	2,754	12.18%	2,538	3.01%	0.0001
Smoking history	1,076	4.76%	845	1.00%	0.0001
Alcohol use disorder	386	1.71%	291	0.34%	0.0001
Chronic kidney disease	96	0.42%	168	0.20%	0.0001

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Characteristics	With medication (semaglutide or tirzepatide) (N = 22,620)		Without medication (N = 84,427)		*p*-value
	N/Mean	%/Std	N/Mean	%/Std	
Any CVD-related comorbidities	11,844	52.36%	13,087	15.50%	0.0001

Table 1. Baseline characteristics of the study and comparison cohorts.

The unadjusted analysis showed that the proportion of any CVD outcomes was significantly lower in the AOM cohort than in the non-AOM cohort (1.778% vs. 12.178%, $p = 0.0010$). Moreover, the proportion of patients with most of the analyzed conditions, including coronary artery disease (0.55% vs. 5.55%, $p < 0.0001$), heart failure (0.198% vs. 3.37%, $p < 0.0001$), and peripheral vascular disease (0.40% vs. 4.80%, $p < 0.0001$), was significantly lower in the AOM cohort than in the non-AOM cohort (Table 2).

CVD endpoint/outcome	With AOM (semaglutide or tirzepatide), N=22420		Without AOM (semaglutide or tirzepatide), N=84427		*p*-value
	N	%	N	%	
Coronary artery disease	126	0.56	4,687	5.55	0.0001
Heart failure	44	0.19	2,841	3.37	0.0001
Ischemic heart disease	1	0.00	126	0.15	0.0001
Stroke	22	0.10	591	0.70	0.0001
Peripheral vascular disease	91	0.40	4,054	4.80	0.0001
All cardiovascular events	400	1.77	10,276	12.17	0.0001

Table 2. Unadjusted outcome measures among patients in AOM and non-AOM cohorts.

Table 3 presents the results of the Cox regression analysis for the risk of CVD in the AOM and non-AOM cohorts. The use of AOMs among patients with obesity was associated with a significant reduction in the risk of CVD compared with those who did not use AOMs (hazard ratio [HR] = 0.37, 95% CI: 0.34-0.42)

Characteristics	HR	CI		*p*-value
		Lower	Upper	
Treatment				
Yes	0.37	0.34	0.42	0.0001
No	1.00	1.00	1.00	
Age (years)				
18-40	0.12	0.11	0.14	0.0001
41-60	0.57	0.53	0.60	0.0001
61-80	1.76	1.66	1.87	0.0001
80+	1.00	1.00	1.00	
Gender				
Male	0.82	0.80	0.85	0.0001
Female	1.00	1.00	1.00	
Comorbidity scores				
CCI score ≥2	2.11	1.90	2.34	0.0001
Socioeconomic score				
Low	1.16	1.11	1.21	0.0001
Medium	1.11	1.07	1.16	0.0001
High	1.00	1.00	1.00	
Comorbidities				
Hypertension	0.72	0.67	0.77	0.0001
Hyperlipidemia	0.81	0.75	0.88	0.0001
Type 2 diabetes	0.78	0.71	0.85	0.0001
COPD	0.87	0.79	0.96	0.0050
Smoking history	1.18	1.03	1.35	0.0195
Alcohol use disorder	1.15	0.87	1.52	0.3176
Chronic kidney disease	1.15	0.87	1.54	0.3266

Table 3. Cox regression results for time to CVD.

Individuals residing in low-SES (HR: 1.16, $p < 0.0001$, 95% CI: 1.11-1.21) and medium-SES (HR: 1.11, 95% CI: 1.07-1.16) regions exhibited an increased risk of CVD compared with those in high-SES regions. A CCI score of 2 or greater (HR: 2.11, $p < 0.0001$, 95% CI: 1.90-2.34), and smoking (HR: 1.18, $p < 0.0001$, 95% CI: 1.03-1.35), were all associated with an increased risk of CVD.

SUBGROUP ANALYSIS:

Among the 22,620 patients identified in the AOM cohort, 19,801 used semaglutide, and 2,819 used tirzepatide. The semaglutide users were slightly older and had higher comorbidity scores; however, they were less likely to reside in areas with low SES. Both groups exhibited cardiovascular-related comorbidities (Table 4).

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Characteristics	Semaglutide (Wegovy) (N = 19,801)		Tirzepatide (Zepbound) (N = 2,819)		p-value
	N/Mean	%/Std	N/Mean	%/Std	
Age (years)	45.39	12.22	46.23	11.61	0.0004
18-40	6,727	33.97%	888	31.50%	0.0093
41-60	10,723	54.15%	1,615	57.29%	0.0018
61-80	2,150	10.86%	311	11.03%	0.7810
80+	18	0.09%	2	0.07%	0.7387
Gender					
Male	4,054	20.47%	617	21.89%	0.0828
Female	15,747	79.53%	2,202	78.11%	0.0828
Comorbidity scores					
CCI score ≥2	1,032	5.21%	119	4.22%	0.0252
Socioeconomic score					
Low	5,586	28.21%	696	24.69%	0.0001
Medium	6,470	32.68%	919	32.60%	0.9368
High	7,375	37.25%	1,148	40.72%	0.0004
Baseline CVD-related comorbidities					
Hypertension	6,863	34.66%	949	33.66%	0.2983
Hyperlipidemia	3,608	18.22%	497	17.63%	0.4463
Diabetes	977	4.93%	107	3.80%	0.0081
COPD	2,440	12.32%	314	11.14%	0.0721
Smoking history	959	4.84%	117	4.15%	0.1059
Alcohol use disorder	338	1.71%	48	1.70%	0.9870
Chronic kidney disease	90	0.45%	6	0.21%	0.0648
Any CVD-related comorbidities	10,374	52.39%	1,470	52.15%	0.8074

Table 4. Baseline characteristics of the semaglutide (Wegovy) and tirzepatide (Zepbound) cohorts.

Within six months of initiating the medication, and prior to risk adjustment, the incidence of any cardiovascular events was higher among semaglutide users than among tirzepatide users (1.18% vs. 1.14%, $p < 0.01$). Specifically, semaglutide users exhibited a slightly higher rate of coronary artery disease, peripheral vascular disease, and stroke relative to tirzepatide users (Table 5).

Cardiovascular endpoint/outcome	Semaglutide (Wegovy) (N=19801)		Tirzepatide (Zepbound) (N=2818)		p-value
	N/Mean	%/Std	N/Mean	%/Std	
Coronary artery disease	117	0.59%	9	0.32%	
Heart failure	42	0.21%	2	0.07%	0.1115
Ischemic heart disease	1	0.01%	0	0.00%	0.7059
Stroke	22	0.11%	0	0.00%	0.0766
Peripheral vascular disease	85	0.43%	6	0.21%	0.0894
All cardiovascular events	368	1.86%	32	1.14%	0.0064

Table 5. Unadjusted outcome measures among patients using Wegovy and Zepbound

Table 6 presents the results of the Cox regression analysis for the risk of CVD in the semaglutide and tirzepatide cohorts. The use of semaglutide among patients with obesity was associated with a significant increase in the risk of CVD compared with those who used tirzepatide (HR: 1.53, CI:1.06-2.20, $p<0.001$). A CCI score of 2 or greater (HR: 1.81, $p < 0.0001$, 95% CI: 1.28-2.56), hypertension (HR: 1.50, CI:1.18-1.91, $p<0.001$), hyperlipidemia (HR: 1.41, CI:1.14-1.76, $p<0.001$), and smoking history (HR: 1.79, CI:1.32-2.42, $p<0.001$). were all associated with an increased risk of CVD among the AOM cohort.

Characteristics	HR	Confidence limit		p-value
		Lower	Upper	
Treatment				
Wegovy	1.53	1.06	2.20	0.0215
Zepbound	1.00	1.00	1.00	
Age (years)				
18-40	0.52	0.16	1.66	0.2684
41-60	1.05	0.34	3.31	0.9284
61-80	2.81	0.89	8.87	0.0786
80+	1.00	1.00	1.00	
Gender				
Male	0.66	0.53	0.81	0.0001
Female	1.00	1.00	1.00	
Comorbidity scores				
CCI score ≥2	1.81	1.28	2.56	0.0008
Socioeconomic score				
Low	1.16	0.91	1.48	0.2218

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Characteristics	HR	Confidence limit		p-value
		Lower	Upper	
Medium	1.07	0.85	1.36	0.5697
High	1.00	1.00	1.00	
Comorbidities				
Hypertension	1.50	1.18	1.91	0.0010
Hyperlipidemia	1.41	1.14	1.76	0.0018
Type 2 diabetes	1.03	0.70	1.50	0.8949
Chronic obstructive pulmonary disease	1.15	0.87	1.52	0.3339
Smoking history	1.79	1.32	2.42	0.0002
Alcohol use disorder	0.97	0.50	1.90	0.9357
Chronic kidney disease	0.57	0.18	1.80	0.3407

Table 6. Cox regression results for time to CVD (semaglutide [Wegovy] vs. tirzepatide [Zepbound]).

Figure 1 illustrates the results of the Aalen additive regression analysis. The analysis indicates that, compared with semaglutide, tirzepatide had a protective effect against CVD beginning approximately one month after initiation. A sustained increased risk of CVD was observed among patients with a high CCI score, those residing in low- and medium-SES score regions, and those with a history of smoking, hypertension, and hyperlipidemia. In contrast, being female conferred a protective effect against CVD.

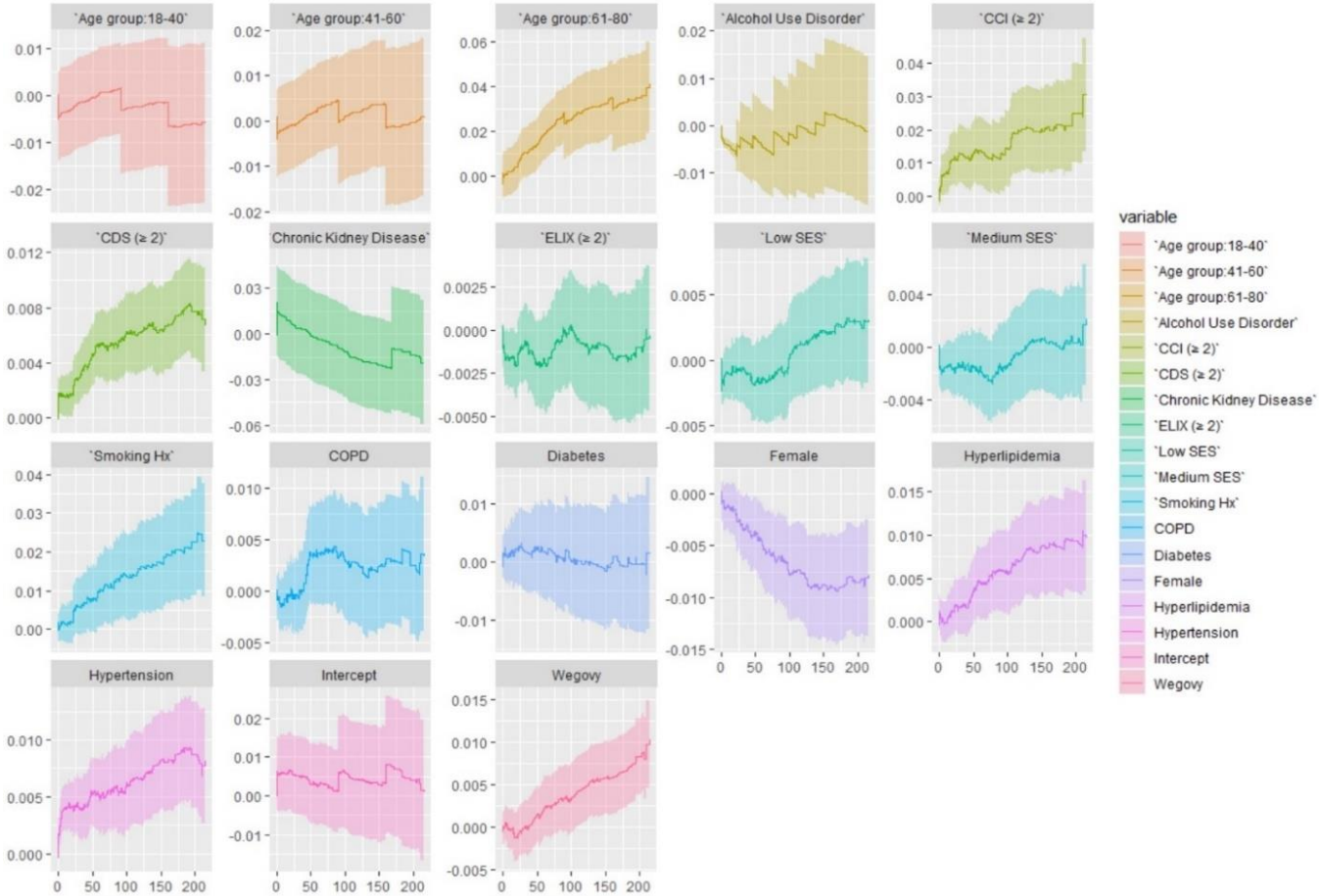

Figure 1. Aalen additive regression analysis.

Discussion:

Obesity is a critical risk factor for cardiovascular disease (CVD), contributing significantly to morbidity and mortality. Obesity-related fatalities are often linked to cardiovascular complications, reflecting the profound impact of excess body weight on heart health. [25,26] The pathophysiological mechanisms connecting obesity to CVD include systemic inflammation, insulin resistance, and dyslipidemia, which exacerbate cardiovascular risk [3][4]. Given the rising prevalence of obesity, effective management strategies are crucial for reducing the associated CVD burden.

Recent advancements in pharmacological treatments, particularly AOMs like semaglutide and tirzepatide, offer promising options for mitigating obesity and its cardiovascular consequences [5][6]. These medications have shown potential in facilitating substantial weight loss, which in turn can improve various cardiovascular risk factors. [27] [28] Evidence supports that even modest weight loss (5% to 10%) can lead to clinically significant reductions in glycated hemoglobin, blood pressure, and cholesterol levels. Nevertheless, to date, no studies have examined the association between these drugs and CVD outcomes using real-world data. Hence, this study offers valuable insights into the impact of AOMs on CVD incidence among individuals affected by obesity.

Our results showed that individuals in the AOM cohort had significantly lower rates of cardiovascular events six

months after the medication initiation (1.77% vs 12.17%). Specifically, individuals in the AOM cohort exhibited substantially lower rates of heart failure (0.19% vs. 3.37%), with those in the non-AOM cohort. Our study also demonstrated a decreased occurrence of heart failure, consistent with prior research indicating the efficacy of AOMs in enhancing health outcomes for heart failure patients. [29] The recent STEP-HFpEFF trial highlighted pharmacotherapy's effectiveness in improving heart failure with preserved ejection fraction in adults with obesity. [30] Additionally, our findings align with the SELECT top-line trial, which reported a 20% reduction in major adverse CVD events with 2.4 mg semaglutide in adult overweight or obesity patients. [31] Moreover, our results agree with previous studies underscoring the increasing prevalence of heart failure and atrial fibrillation in recent years. [32]

Demographic and socioeconomic factors also play a significant role in cardiovascular risk. Our study identified that patients aged 18-40 and 41-60 years, as well as females, had a reduced risk of CVD, which is in line with existing literature suggesting varying cardiovascular risk across age and gender. Conversely, older adults (aged 61-80 years) exhibited a substantially higher risk, consistent with the American Heart Association's reports on age-related increases in CVD incidence .[34,35] Individuals residing in regions with low SES experienced a 16% elevated risk of CVD, whereas those in medium-SES regions had an 11% increased risk. This highlights the profound impact of socioeconomic factors on cardiovascular health. Lower SES often correlates with reduced access to healthcare, lower health literacy, and increased exposure to environmental stressors, exacerbating cardiovascular risk.[33] Our findings align with literature indicating that individuals in lower SES brackets face higher cardiovascular risk due to these compounding factors.

Higher comorbidity scores, indicative of greater illness severity due to a greater number of comorbidities or medications, were correlated with heightened CVD risk. Specifically, individuals with a history of smoking exhibited an 18% elevated risk of CVD, while those with alcohol use disorder and chronic kidney disease each demonstrated a 15% increased risk. These findings align with extensive literature highlighting smoking, alcohol use disorder, and chronic kidney disease as established CVD risk factors

Our study highlights the significant role of comorbidities in influencing cardiovascular risk among individuals with obesity. Smoking, a well-established risk factor for cardiovascular disease (CVD), was associated with an 18% increased risk of CVD in our study, emphasizing the need for smoking cessation efforts. Chronic alcohol consumption also contributed to a 15% higher risk of CVD among those with alcohol use disorder. Chronic kidney disease (CKD) was linked to a 15% increased risk of CVD. Additionally, our study found that hyperlipidemia was associated with a decreased risk of CVD, potentially reflecting effective treatment in the population studied. These findings align with extensive literature highlighting smoking, alcohol use disorder, and chronic kidney disease as established CVD risk factors. It further suggests the need for further research into how management of hyperlipidemia and other comorbidities influences cardiovascular outcomes.[34,35]

It is noteworthy that hyperlipidemia (HR: 0.81, $p < 0.0001$, 95% CI: 0.75-0.88) was associated with a 19% decreased risk of CVD, contrary to prior research. [36]We posit that this discrepancy may stem from the effective treatment of hyperlipidemia among these patients, which is recognized as a significant preventive measure against CVD. [37,38]

Our findings underscore the potential of AOMs as a critical tool in combating the high prevalence of CVD, reflecting their profound impact on reducing CVD risk and incidence. This directly aligns with our aim to analyze the impact of AOMs on cardiovascular risk among US patients with obesity. CVD remains a pervasive and urgent public health challenge, claiming a life every 33 seconds in the United States, as reported by the Centers for Disease Control and Prevention. [39] This issue extends beyond the U.S.; in Europe, CVD accounts for 3.9 million deaths annually, representing 45% of all fatalities, with ischemic heart disease, stroke, and hypertension leading to heart failure being primary contributors. [40] Globally, CVD is a leading cause of mortality, responsible for approximately 18 million deaths each year according to the World Health Organization. [41]

The escalating economic burden of CVD highlights its impact not only on public health but also on healthcare systems. In the United States, expenditures on CVD have surged from $212 billion in 1996 to $320 billion in 2016, reflecting the growing financial strain of managing this condition. [42] Additionally, the economic burden of obesity-related illnesses, including CVD, is substantial, costing $190 billion annually. Given these statistics, the interconnection between obesity and CVD becomes increasingly evident, emphasizing the need for effective interventions.[42] Treatments benefit both weight and comorbidities: the goals of obesity treatment are primary, secondary, and tertiary prevention; that is, to prevent the development or exacerbation of obesity and its complications. Improvements in cardiometabolic risk factors and reduced diabetes risk have been consistently reported in the Phase 3 trials for AOMs.[43]

AOMs, by significantly reducing CVD risk through weight management, offer a promising strategy to alleviate this burden. They provide a valuable opportunity to improve cardiovascular health outcomes and reduce the associated healthcare costs. Our study directly supports this aim by demonstrating the effectiveness of AOMs in mitigating CVD risk among patients with obesity. As CVD is projected to affect half of American adults by 2035, integrating AOMs into obesity treatment plans could play a pivotal role in reversing current trends. [44] This approach aligns with the broader goal of enhancing cardiovascular health and managing the economic impact of CVD, ultimately contributing to more sustainable healthcare solutions and improved quality of life for affected individuals.

This study is subject to multiple limitations due to the utilization of administrative data sets. These data sets, while valuable, are susceptible to inaccuracies in the coding of patient clinical diagnoses and procedures.

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Furthermore, the clinical information available is constrained to conditions and treatments delineated by ICD-10-CM codes. Given that the analysis was conducted using claims data originally intended for purposes other than research, certain critical information may be absent. Consequently, the generalizability of the findings to the entire population remains uncertain, as some relevant data points might have been overlooked during processing or reimbursement procedures. Additionally, it is important to acknowledge that not all health-related data are captured within these claims. Notably, commercial claims data lack information on body size or body mass index, which is particularly relevant for assessing obesity-related medications. Lastly, the reliance on ICD-10-CM codes to identify patients with obesity may lead to an underestimation of the prevalence of such cases, making our estimates biased.

Further, patients with specific comorbidities like hyperlipidemia or diabetes may already be receiving appropriate treatment for these underlying conditions, which could confer a protective effect against CVD. Additional research that carefully accounts for these medications' impact, including AOM on CVD incidence, is recommended.

Utilizing SES also presents several limitations. First, SES is closely intertwined with various factors such as lifestyle choices, access to health care, and environmental conditions, which can independently influence cardiovascular health. This creates difficulties in isolating the specific impact of SES on disease risk without appropriately accounting for these confounding variables. Additionally, SES is complex as it encompasses income, education, occupation, and neighborhood characteristics. All these characteristics may have different effects on health outcomes. Also, the measurement of SES itself can vary largely across studies, which could affect the comparability and generalizability of our findings. Furthermore, SES can change over time, which can make it difficult to access its long-term association with cardiovascular health. To address these limitations, future studies should carefully consider confounding factors, robust measurement strategies, and sensitivity to socioeconomic dynamics across diverse populations.

Conclusion:

Evidence indicates that weight reduction is essential to addressing the incidence, prevalence, and management of CVD. The use of AOMs is a way to alleviate the clinical burden CVD imposes in the United States. Our research findings indicate a correlation between use of newly approved AOMs and reduced prevalence of CVD outcomes, emphasizing the efficacy of these medications in controlling the impact of cardiovascular conditions.

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