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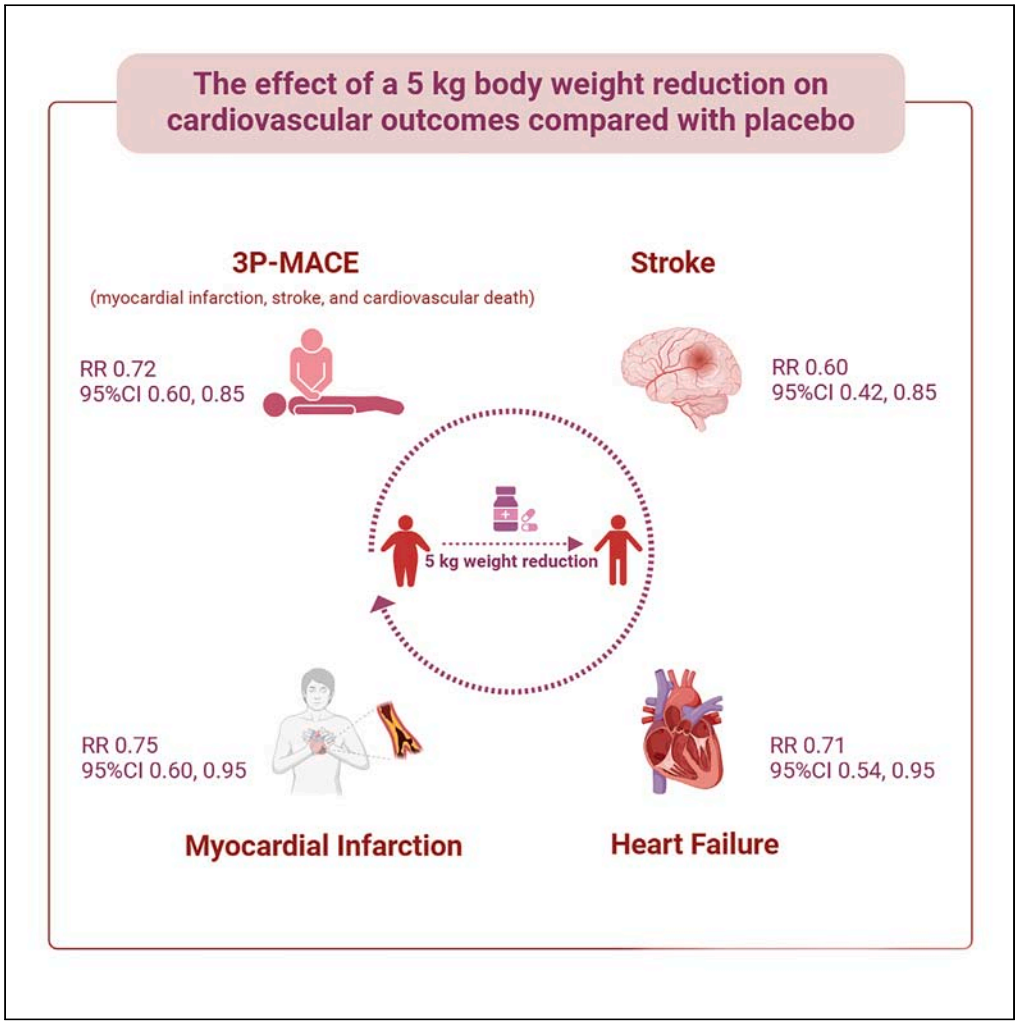

Yuchen Guo, Chu Lin, Xiaoling Cai, ..., Geling Liu, Xiaolin Yang, Linong Ji

dr_junel@sina.com (X.C.)
jiln@bjmu.edu.cn (L.J.)

Highlights

Weight reduction by AOM was associated with the cardiovascular benefits in AOM users

Weight-reduction associated cardiovascular benefits were observed in GLP-1RA users

Further investigations are needed to validate the findings and casual associations

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The weight reduction mediated by anti-obesity medication and the cardiovascular outcome

Yuchen Guo,[1,3] Chu Lin,[1,3] Xiaoling Cai,[1,4,*] Han Wu,[1] Jingya Yan,[1] Zonglin Li,[1] Ruoyang Jiao,[1] Shuzhen Bai,[1] Wenjia Yang,[1] Fang Lv,[1] Geling Liu,[2] Xiaolin Yang,[2] and Linong Ji[1,*]

SUMMARY

The association between anti-obesity medications (AOMs) as well as their weight-loss effects and cardiovascular outcomes need to be comprehensively investigated. We searched PubMed, Embase, the Cochrane Center Register of Controlled Trials for Studies, and Clinicaltrial.gov website from the inception to April 2024 and included 129 randomized controlled trials (RCTs) of AOMs. When compared with placebo, every 5 kg weight reduction mediated by AOMs was associated with the reduced risks of 3-point major adverse cardiovascular events (relative risk [RR] 0.72, 95% confidence interval [CI] 0.60–0.85), myocardial infarction (RR 0.75, 95% CI 0.60–0.95), stroke (RR 0.60, 95% CI 0.42–0.85), and heart failure (RR 0.71, 95% CI 0.54–0.95). As for glucagon-like peptide 1 receptor agonist (GLP-1RA)-users, similar cardiovascular benefits were also observed with 5 kg weight loss. This study indicated that the weight reductions mediated by AOMs were associated with cardiovascular benefits observed in AOM-users.

INTRODUCTION

There is a growing pandemic of overweight and obesity worldwide, with over 2.6 billion people equated to 38% of the whole population.[1] For years, a pyramid of evidence demonstrated that obesity was associated with the increased risk of cardiovascular events.[2–4] Therefore, the management of the cardiovascular prognosis has become a heated agenda for patients with overweight or obesity.

So far, there is little evidence indicating that any pharmacologic or lifestyle therapy could definitely reduce the cardiovascular risk conferred by overweight or obesity. Lifestyle interventions, including healthy dietary patterns and physical activity are the first-line treatment for obesity, but the effects of lifestyle interventions on cardiovascular outcomes might be below our expectations.[5] As indicated by the Look AHEAD (Action for Health in Diabetes) study, compared with standard care, although an intensive lifestyle intervention resulted in a significant weight loss, no reduction in the incidence of cardiovascular events was found in adults with overweight or obesity.[6]

Anti-obesity medications (AOMs), as an important treatment for obesity,[7] could achieve certain weight reduction in patients with overweight or obesity, but their cardiovascular effects still remain to be unclear. A meta-analysis, which was conducted to assess the effects of obesity pharmacotherapy on cardiovascular mortality (CVM), demonstrated a significant improvement in CVM in patients treated by orlistat, lorcaserin, phenteramine/topiramate, or naltrexone/bupropion when compared with the controls.[8] Conversely, another two meta-analyses reached different conclusions. Zhang's study, involving randomized placebo-controlled trials of liraglutide 3.0 mg, naltrexone/bupropion, lorcaserin, orlistat, and phentermine/topiramate indicated that AOMs did not show a benefit in lowering MACEs (major adverse cardiovascular events, defined as a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke).[9] The other systematic review, enrolling the same medications as Zhang's study, found that there was no difference in the risk of cardiovascular death, stroke, myocardial infarction or heart failure between the AOMs and placebo treatment.[10] We assumed that the discrepancy may be attributed to the type of medications and the number of trials included.

The rise of glucagon-like peptide 1 receptor agonist (GLP-1RA), is leading to a revolution in the field of obesity, whose metabolic benefits have been verified in numerous studies.[11–13] The latest encouraging publication of the Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity (SELECT) trial have further refreshed our cognition of GLP-1RA as an AOM,[14] which might lead to a revolution in the current pharmacotherapy of obesity. The rapidly emerging and growing clinical evidence provides us with the opportunity to reexamine the association between AOMs and cardiovascular diseases and more importantly to explore the relationship between the weight reductions mediated by AOMs and cardiovascular outcomes. Therefore, we design and perform this meta-analysis to address the aforementioned issues.

[1]Department of Endocrinology and Metabolism, Peking University People's Hospital, No. 11, Xizhimen South Street, Xicheng District, Beijing 100044, P.R. China
[2]Department of Endocrinology and Metabolism (Section 1), Tangshan Gongren Hospital, No. 27 Wenhua Road, Tangshan, Hebei 063000, P.R. China
[3]These authors contributed equally
[4]Lead contact
*Correspondence: dr_junel@sina.com (X.C.), jiln@bjmu.edu.cn (L.J.)
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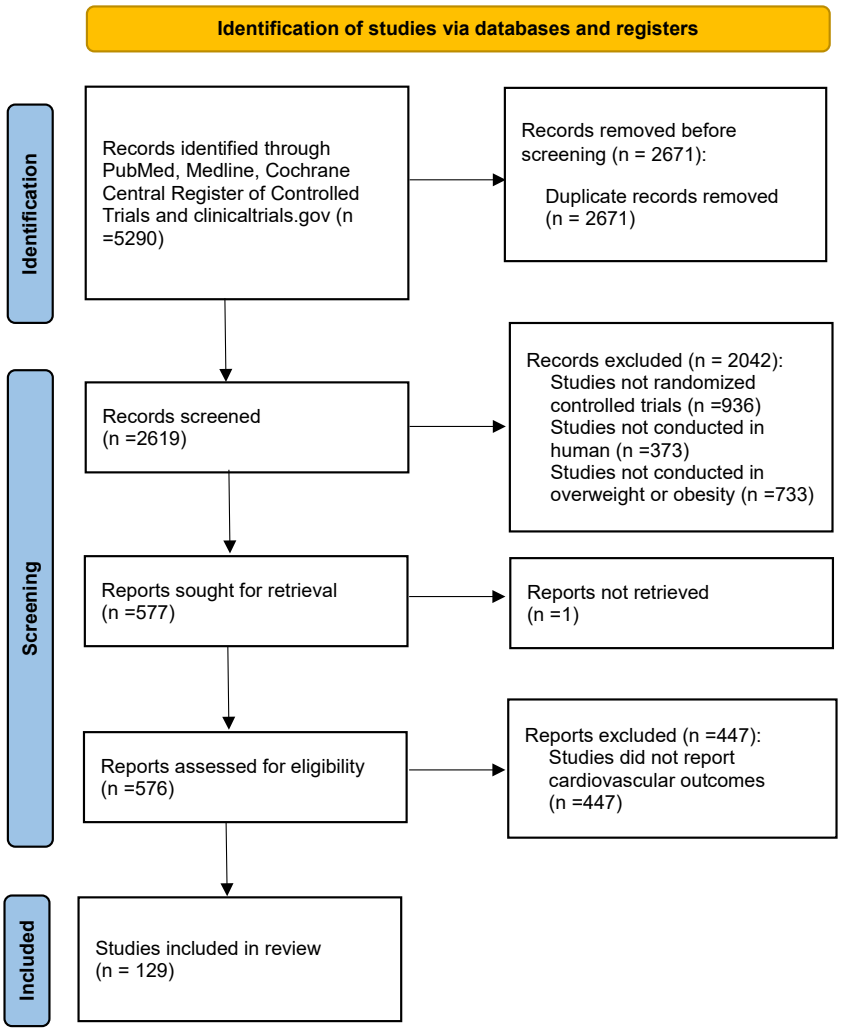

Figure 1. PRISMA flow diagram of included studies

RESULTS

Characteristics and quality assessment of included studies

Overall, 129 randomized controlled trials (RCTs) involving 163,456 patients were included in this meta-analysis, among which 82 RCTs with 131,390 patients compared AOMs with placebo and 49 RCTs with 32,066 patients compared AOMs with active controls (Figure 1). There were 104 trials investigating GLP-1RAs, 14 trials investigating GLP-1 and glucose dependent insulinotropic polypeptide (GIP) receptor coagonist (tirzepatide), 1 trials investigating GLP-1 and glucagon (GCG) receptor coagonist (efinopegdutide), 1 trials investigating GLP-1 and amylin receptor coagonist (CagriSema), 2 trials investigating GLP-1, GIP and GCG receptor triagonist (retatrutide), 2 trials investigating phentermine/topiramate, 4 trials investigating naltrexone/bupropion, 1 trials investigating bimagrumab, and 2 trials investigating orlistat. Baseline characteristics of included studies were systematically summarized in Table S1.

There were 32/129 RCTs with high risks of bias in blinding of participants and caregivers, 22/129 RCTs with high risks of bias in blinding of outcome assessors and adjudicators, and 22/129 RCTs with high risks of bias in missing outcome data (Table S2). The Begg's tests generally showed symmetrical distributions (Figure S1) while Egger's tests indicated potential publication bias in only a few of individual endpoints, including myocardial infarction, heart failure and cardiovascular death (Table S3).

The associations between AOM treatments and cardiovascular outcomes

As for the types of AOMs, the administration of GLP-1RA was associated with a significant reduction in the incidence of 3P-MACE (relative risk [RR] 0.89, 95% confidence interval [CI] 0.85–0.92), myocardial infarction (RR 0.89, 95% CI 0.84–0.95), stroke (RR 0.87, 95% CI 0.79–0.95), cardiovascular death (RR 0.89, 95% CI 0.83–0.95), heart failure (RR 0.88, 95% CI 0.81–0.95) and angina unstable (RR 0.87, 95% CI 0.77–0.99) when

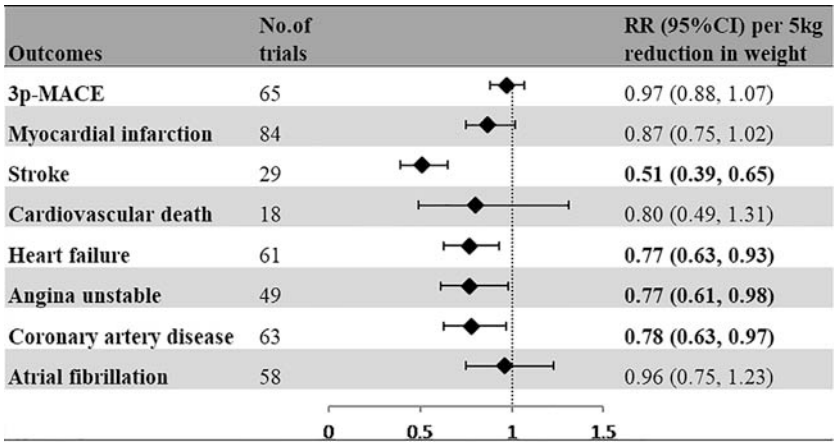

Figure 2. Standardized effects of a 5 kg reduction in body weight with AOM treatments compared with active controls or placebo

AOM, anti-obesity medication; RR, relative risk; 3P-MACE, 3-point major adverse cardiovascular event. For detailed information, see Table S4.

compared with active agents or placebo. When compared with placebo only, the GLP-1RA treatments were associated with the risk reduction of 3P-MACE (RR 0.88, 95% CI 0.84–0.93), myocardial infarction (RR 0.89, 95% CI 0.84–0.95), stroke (RR 0.87, 95% CI 0.79–0.95), cardiovascular death (RR 0.89, 95% CI 0.83–0.95), and heart failure (RR 0.86, 95% CI 0.77–0.97). No significant risk reductions concerning cardiovascular outcomes were observed in patients with other AOM treatments.

The effect of a 5 kg body weight reduction on cardiovascular outcomes

Overall, every 5 kg weight reduction mediated by AOMs was associated with the reduced risk of stroke (RR 0.51, 95% CI 0.39–0.65), heart failure (RR 0.77, 95% CI 0.63–0.93), angina unstable (RR 0.77, 95% CI 0.61–0.98), and coronary artery disease (RR 0.78, 95% CI 0.63–0.93) compared with active agents or placebo (Figure 2). When compared with placebo only, every 5 kg weight reduction mediated by AOMs was associated with a decreased risk of 3P-MACE (RR 0.72, 95% CI 0.60–0.85), myocardial infarction (RR 0.75, 95% CI 0.60–0.95), stroke (RR 0.60, 95% CI 0.42–0.85), and heart failure (RR 0.71, 95% CI 0.54–0.95) (Figure 3).

As for GLP-1RA-users, a significant reduction in the risk of 3P-MACE (RR 0.70, 95% CI 0.57–0.87), myocardial infarction (RR 0.77, 95% CI 0.60–0.98), stroke (RR 0.52, 95% CI 0.33–0.83), heart failure (RR 0.67, 95% CI 0.52–0.87), and angina unstable (RR 0.69, 95% CI 0.48–0.98) was found when body weight lowered by every 5 kg in contrast with active agents or placebo (Figure 4). Compared with placebo, every 5 kg weight reduction mediated by GLP-1RA was associated with reductions in the risk of 3P-MACE (RR 0.65, 95% CI 0.53–0.81), myocardial infarction (RR 0.71, 95% CI 0.55–0.91), stroke (RR 0.50, 95% CI 0.32–0.78), heart failure (RR 0.70, 95% CI 0.50–0.98) (Figure 5). As for other AOMs, no significant risk reduction in any cardiovascular outcomes was observed with a 5 kg weight loss (Table S4).

Subgroup analyses of the risk of cardiovascular events with AOM treatments

In diabetic patients with overweight or obesity, every 5 kg weight reduction mediated by AOMs was associated with the reduced risk of 3P-MACE (RR 0.71, 95% CI 0.54–0.93), myocardial infarction (RR 0.73, 95% CI 0.56–0.96), stroke (RR 0.47, 95% CI 0.28–0.79), and angina unstable (RR 0.65, 95% CI 0.44–0.98) in contrast to those who received placebo treatment. However, in patients without diabetes, no significant reduction in the incidence of these cardiovascular outcomes was found as body weight reduced by 5 kg. However, the differences between two strata were not statistically significant (all $p_{interaction} > 0.05$; Table S5).

As for follow-up duration, a 5 kg weight loss with AOM treatments was associated with a decreased risk of 3P-MACE (RR 0.72, 95% CI 0.58–0.90), myocardial infarction (RR 0.78, 95% CI 0.61–0.99), and stroke (RR 0.55, 95% CI 0.37–0.81) in patients with follow-up more than 52 weeks, when compared with placebo. In patients with follow-up less than 52 weeks, no significant reduction in the risk of any cardiovascular outcomes was found. Still, the differences between two strata did not reach statistical significance (all $P_{interaction} > 0.05$).

When stratified by baseline BMI, in patients with baseline BMI around 30–35 kg/m^2, every 5 kg weight reduction was associated with reductions in the incidence of 3P-MACE (RR 0.63, 95% CI 0.50–0.79), myocardial infarction (RR 0.66, 95% CI 0.50–0.87), stroke (RR 0.47, 95% CI 0.28–0.79), and heart failure (RR 0.64, 95% CI 0.45–0.92) when receiving AOM treatments versus placebo. In patients with baseline BMI over 35 kg/m^2, a 5 kg weight reduction mediated by AOMs was associated with a reduced risk of coronary artery disease (RR 0.50, 95% CI 0.29–0.85). But in patients with baseline BMI less than 30 kg/m^2, no significant reduction in the risk of any cardiovascular outcomes was found. However, such differences among patients with different BMI were insignificant (all $P_{interaction} > 0.05$).

As for age, every 5 kg weight reduction mediated by AOMs was correlated with the reduced risk of 3P-MACE (RR 0.62, 95% CI 0.45–0.87), myocardial infarction (RR 0.69, 95% CI 0.52–0.91), stroke (RR 0.47, 95% CI 0.28–0.81), and angina unstable (RR 0.65, 95% CI 0.43–0.99) in AOM-users over 60 years old compared with whom received placebo. And in patients below 60 years old, a 5 kg weight loss was associated with a decreased risk of heart failure (RR 0.62, 95% CI 0.40–0.97) and coronary artery disease (RR 0.60, 95% CI 0.39–0.94) with AOM treatments. No

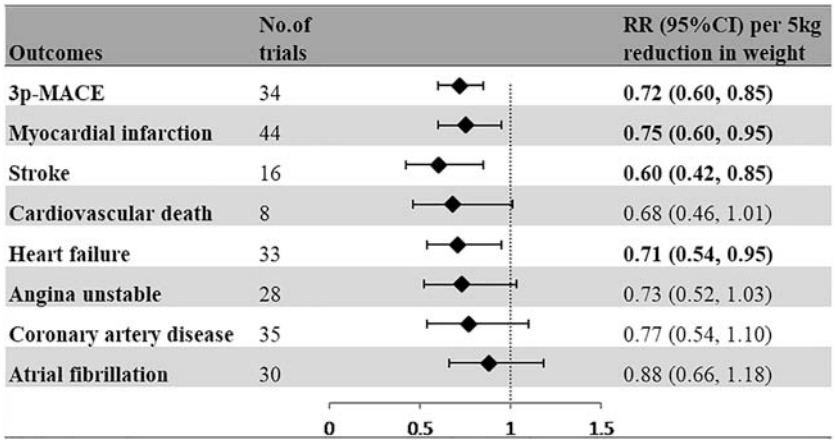

Figure 3. Standardized effects of a 5 kg reduction in body weight with AOM treatments compared with placebo

AOM, anti-obesity medication; RR, relative risk; 3P-MACE, 3-point major adverse cardiovascular event. For detailed information, see Table S4.

significant differences in the risk of any cardiovascular outcomes with a 5 kg weight reduction mediated by AOMs was found between subgroups stratified by age (all $P_{interaction} > 0.05$).

When stratified by sex, a 5 kg weight loss with AOM treatments was associated with a decreased risk of 3P-MACE (RR 0.66, 95% CI 0.50–0.87), myocardial infarction (RR 0.69, 95% CI 0.54–0.89), and stroke (RR 0.55, 95% CI 0.36–0.84) in subgroup with male percentage more than 50% in contrast to placebo. In subgroup with male percentage below 50%, a reduction in the risk of heart failure (RR 0.57, 95% CI 0.33–0.98) was found when body weight lowered by every 5 kg in contrast with placebo. There were no significant differences in the risk of cardiovascular events between the two subgroups (all $P_{interaction} > 0.05$).

Similar outcomes of subgroup analyses were observed in patients who received GLP-1RA treatments, when compared with those who received placebo (Table S6).

DISCUSSION

Involving 129 anti-obesity pharmacological trials, our meta-analysis indicated that among current AOMs, the use of GLP-1RA was associated with the reduced risk of cardiovascular outcomes in patients with overweight or obesity. More importantly, weight reduction mediated by the treatments of AOM was associated with the reduced risk of cardiovascular events in AOM-users.

The cardiovascular benefits of AOMs have been reported previously but with inconsistent results. A meta-analysis involving 7 studies with orlistat, lorcaserin, phentermine/topiramate or naltrexone/bupropion, indicated potential cardiovascular benefits of AOMs in terms of CVM.[8] Moreover, Leite's meta-analysis conducted in 2022 showed that the treatment effect of GLP-1 RA versus placebo resulted in a statistically significant reduction in the risk of any cardiovascular event, but was not associated with a decrease in the risk of MACE.[15] Conversely, another two meta-analyses found no superior performance in reducing the risk of myocardial infarction, stroke, heart failure, hospitalization for angina, or MACE in patients with overweight or obesity under the treatment of AOMs.[9,10] Our meta-analysis, involving medications with weight-loss effects as comprehensively as possible, indicated that the treatments of AOM, especially GLP-1RA, were associated with reduced risk of cardiovascular events in patients with overweight or obesity. This finding was consistent with the conclusion of SELECT study, further confirming the cardiovascular protective effects of AOMs, represented by GLP-1RA. For the different aforementioned conclusions, we speculated that the reasons might stem from the discrepancy in the type of drugs and the number of trials included among different analyses.

More importantly, according to the results of our standardized meta-analyses, the weight loss mediated by AOMs was significantly associated with the risk reductions in cardiovascular outcomes, suggesting that the cardiovascular benefits of the AOM treatments in patients with overweight or obesity might be partially attributed to their weight-loss effect. This conclusion could also apply to the reduced risk of cardiovascular events in patients with the treatment of GLP-1RA. Although increased risk of gallbladder or biliary diseases have been indicated in the treatment of GLP-1RA especially when used for weight loss,[16] it outperformed the other AOMs with superior weight loss effects in the RCTs.[17] Meanwhile, our analyses suggested that the substantial weight reductions GLP-1RA caused were associated with the cardiovascular benefits conferred by itself. Previously, the Look AHEAD study showed that no reduction in the rate of cardiovascular events was found although the intensive lifestyle intervention contributed to significant weight loss when compared with standard care.[6] However, a post-hoc analysis of the Look AHEAD trial showed that individuals who lost at least 10% of their body weight in the first year of the study had a 21% lower risk of primary cardiovascular outcomes and a 24% reduced risk of the secondary cardiovascular outcomes.[18] This result had demonstrated that there was an association between the magnitude of weight loss and incidence of cardiovascular disease in people with obesity and type 2 diabetes. Therefore, it is suggested that the weight-loss effects of AOMs may exert an important role in the cardiovascular improvements in patients with overweight or obesity.

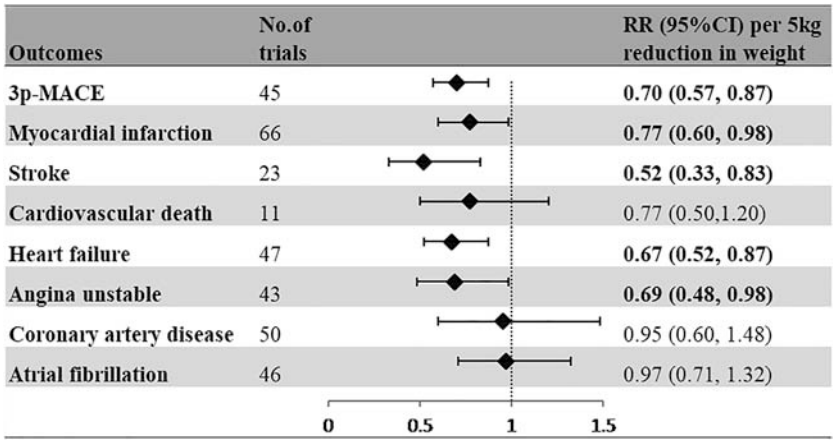

Figure 4. Standardized effects of a 5 kg reduction in body weight with GLP-1RA treatments compared with active controls or placebo
GLP-1RA, glucagon like peptide 1 receptor agonist; RR, relative risk; 3P-MACE, 3-point major adverse cardiovascular events.

As a cardiovascular outcome trial (CVOT) conducted in overweight or obesity without diabetes, SELECT trial has recently reported a significantly reduced incidence of cardiovascular adverse events with weekly subcutaneous semaglutide at a dose of 2.4 mg, though the magnitude of weight loss observed at endpoint was less than 10%.[14] Early in the SELECT trial, a difference in cardiovascular risks between semaglutide and placebo was found, which suggested that more rapid treatment-induced physiological or metabolic changes had exerted earlier cardiovascular protective effects beyond the magnitude of body weight reduction. Furthermore, the event curves in this trial started to diverge very soon, which preceded the maximal weight loss due to semaglutide. And when the weight-loss effect reached a plateau, the cardiovascular benefits still continued. This difference between the trends of weight loss and cardiovascular benefits further corroborated that the cardiovascular protection of AOMs (mainly GLP-1RA) may not entirely depend on the weight-loss effect. Based on previous studies exploring the effects of AOMs on cardiovascular system,[12,19–21] we speculated that the part of cardiovascular benefits beyond weight-loss effects probably derived from the direct cardiovascular protection or indirect cardiovascular risk improvement of AOMs themselves.

The directly protective effects on the cardiovascular systems of AOMs have been systematically documented both in animal experiments and clinical studies. As for GLP-1RA, it can exert anti-atherosclerotic effects through multiple mechanisms and pathways.[22] Liraglutide and semaglutide were found to significantly attenuate plaque lesion formation by improving endothelial dysfunction,[23–26] inhibiting macrophage foam cell formation and suppressing platelet activation and aggregation,[27,28] which were the key components of atherosclerosis. GLP-1RA could also increase plaque fibrous cap thickness and inhibit vascular smooth muscle cell alterations to suppress the progression of plaque.[28,29] Another pathway GLP-1RA exerting cardioprotective effects may be via its anti-inflammatory actions. Exenatide was demonstrated to suppress several inflammatory factors associated with atherosclerosis and insulin resistance.[30] It was shown that GLP-1 analogue therapy was able to reduce the frequency of inflammatory macrophages.[31] Besides, GLP-1RA could cf. cardiovascular protective effects directly by

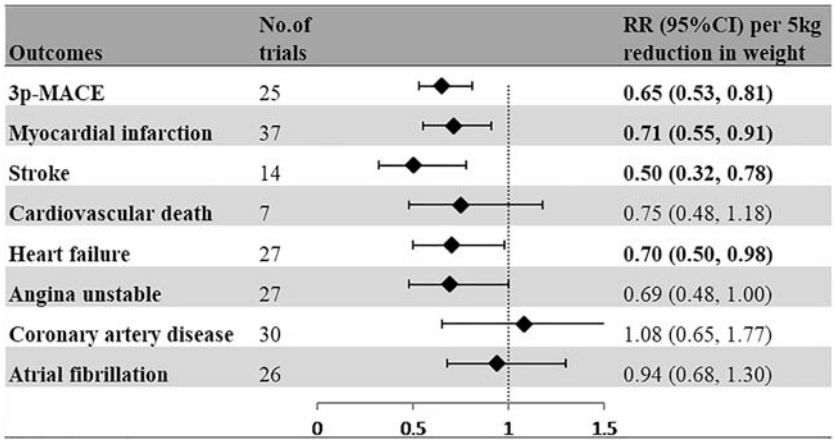

Figure 5. Standardized effects of a 5 kg reduction in body weight with GLP-1RA treatments compared with placebo
GLP-1RA, glucagon like peptide 1 receptor agonist; RR, relative risk; 3P-MACE, 3-point major adverse cardiovascular events.

promoting the glucose uptake in myocardium, enhancing myocardial contractility, improving tolerance of ischemia and the secretion of atrial natriuretic factor.[19,31] Orlistat has been reported to exert cardiovascular protection through anti-inflammatory and antioxidative effects, restoring the balance between pro-inflammatory and anti-inflammatory cytokines.[32–34]

Most AOMs could also benefit the management of cardiovascular risk factors. GLP-1RA was able to improve the control of blood glucose, blood pressure, and blood lipids and inhibit inflammatory responses to reduce cardiovascular events.[35] The use of orlistat, naltrexone/bupropion and phentermine/topiramate also contributed to the improvement of cardiometabolic indicators, such as blood pressure, lipid profiles, fasting glucose and waist circumference.[36,37] However, this indirect cardiovascular protection through modulation of these risk factors might be limited.[19]

We also conducted the subgroup analyses to deal with the potential heterogeneity. And the results showed there were no statistically significant differences among predefined subgroups. These analyses indicated that the weight reductions mediated by AOMs might be consistently associated with cardiovascular benefits among patients with different characteristics. Certainly, more investigations are still required to verify these findings.

Besides, meta-regression analyses were performed to evaluate influencing factors of cardiovascular outcomes in patients with diabetes. As for the severity of diabetes, we found that longer duration of diabetes was associated with a reduced incidence of 3P-MACE ($\beta = -0.42 \times 10^{-3}$, 95% CI −0.069 to −0.011, $p = 0.009$) and myocardial infarction ($\beta = -0.048$, 95% CI −0.081 to −0.015, $p = 0.005$) while higher baseline HbA1c was associated with the reduction in the risk of myocardial infarction ($\beta = -0.105$, 95% CI −0.195 to −0.014, $p = 0.023$) (Table S7). Since the duration and severity of diabetes were the influencing factors for the outcomes, they should be considered when interpreting the results. Meanwhile, the analyses indicated that HbA1c reduction was associated with the reduction in the risk of angina unstable ($\beta = 0.604$, 95% CI 0.167–1.041, $p = 0.008$, Table S7). Other than angina unstable, no significant associations were revealed between HbA1c reduction and the rest of cardiovascular outcomes (Table S7). In another word, improvements in most of the cardiovascular outcomes in AOM users were not associated with HbA1c reduction.

In conclusion, this meta-analysis indicated that among current AOMs, the use of GLP-1RA was associated with the reduced risk of cardiovascular events in patients with overweight and obesity. Weight reductions mediated by AOMs were associated with the cardiovascular benefits observed in patients with AOM treatments. Such association also applied for patients with GLP-1RA treatments. These findings might provide with insights for the future management of cardiovascular prognosis in patients with overweight or obesity.

Limitations of the study

There were also some limitations in our study. Firstly, the heterogeneity was inevitable, as the included trials differed in terms of participants, study design, types of AOMs. To deal with the heterogeneity, we categorized the trials by drug type, conducted standardized analyses focusing on the magnitude of weight-loss and performed multiple sensitivity analyses. Secondly, the cardiovascular benefits observed in our study were mainly driven by GLP-1RA. The roles of non-GLP-1RA agents still need to be further explored in the future. Meanwhile, due to the lack of data regarding cardiovascular outcomes stratified by the baseline cardiovascular diseases, we were unable to distinguish the effects of AOMs on the primary and secondary prevention for cardiovascular events. Hopefully it will be enriched in further investigations. Moreover, most previous CVOTs of AOMs were conducted in overweight or obesity with diabetes. The SELECT trial, as a CVOT of AOM truly dedicated to obesity without diabetes, makes a landmark for the exploration to the cardiovascular outcomes of AOM treatments. Inspired and encouraged by SELECT trial, more CVOTs should be expanded to a wilder population with nondiabetic obesity to characterize the cardiovascular effects of AOMs in this very population. In addition, most trials included in our study had a follow-up duration of 24–108 weeks. Therefore, the results of our study might not be able to explain the effect of a transient weight loss on cardiovascular outcomes. However, a difference in cardiovascular risks between semaglutide and placebo was found early in the SELECT trial without a significant weight reduction, which suggested that more rapid treatment-induced physiological or metabolic changes had exerted earlier cardiovascular protective effects beyond the magnitude of body weight reduction. This indicated that the cardiovascular protection of AOMs (mainly GLP-1RA) may not entirely depend on the weight-loss effect. Besides, the analysis for the cardiovascular benefits of AOMs was based on the continuous administration of AOMs during the trials. Therefore, we are unable to clarify whether the cardiovascular benefits would still remain after patients stopped the AOMs treatment or even started gaining weight again with current evidence. Further investigations are required to address this issue. To note, our study preliminarily investigated the association between the AOMs-mediated weight loss and the risk of cardiovascular events. Therefore, the findings from this study only applied to AOMs but probably not to interventions like diet, exercise, and metabolic surgeries. To fully characterize the associations between weight reduction and cardiovascular outcomes, additional weight-losing interventions including lifestyle modifications and bariatric surgeries, should also be considered, and analyzed in further investigations.

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources and reagents should be directed to and will be fulfilled by the lead contact, Xiaoling Cai (dr_junel@sina.com).

Materials availability

This study is a meta-analysis and did not use or generate any reagents.

Data and code availability

- This meta-analysis used data from published studies which are available in the key resources table.
- This study did not report the original code.
- Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon reasonable request.

ACKNOWLEDGMENTS

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AUTHOR CONTRIBUTIONS

L.J., Y.G., and X.C. conceptualized this study and designed the systematic review protocol; Y.G., .H.W, J.Y., Z.L., R.J., S.B., X.Y., and G.L. performed the study selection and data extraction; C.L., F.L. and W.Y. performed the statistical analyses; Y.G., C.L., and X.C. prepared the outlines and wrote the manuscript. All authors contributed to the critical revision of manuscript drafts.

DECLARATION OF INTERESTS

L.J. has received fees for lecture presentations and for consulting from AstraZeneca, Merck, Metabasis, MSD, Novartis, Eli Lilly, Roche, Sanofi-Aventis and Takeda.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.isci.2024.110867.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited data		
Studies For Meta-analysis	PubMed, Embase, the Cochrane Center Register of Controlled Trials for Studies and Clinicaltrial.gov website	The studies included are referenced in Table S2
Software and algorithms		
STATA software, version 17.0	Downloaded STATA Software	https://www.stata.com/products/
EndNote X9	Downloaded EndNote X9 Software	https://endnote.com/downloads
Microsoft Word 2013	Downloaded Microsoft Word Software	https://www.microsoft.com/en-us/microsoft-365/word
Microsoft Excel 2013	Downloaded Microsoft Excel Software	https://www.microsoft.com/en-us/microsoft-365/word

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

This is a systematic review and meta-analysis of RCTs. The subject recruitment for each RCT was carried out according to the methodology of study protocol. The total sample size of this study is 163,456 as the sum of the subjects from the included RCTs.

METHOD DETAILS

Study design and registration

This systematic review and meta-analysis was conducted according to the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) protocol. It has been registered in International Prospective Register of Systematic Reviews (PROSPERO) with the number of CRD42023459379.

Data sources and searches

According to the recommendations from the Cochrane Handbook for Systematic Reviews for meta-analysis, pairs of investigators (YG, CL, HW, and JY) independently conducted systematic searches of PubMed, Embase, the Cochrane Center Register of Controlled Trials for Studies and Clinicaltrial.gov Website for RCTs of AOMs conducted in patients with overweight or obesity from the inception to November 2023. And later the literature search was updated in April 2024. Both searches were conducted with terms relating to obesity, weight loss, investigated drugs, cardiovascular outcomes and RCTs (Table S8). Any discrepancies were resolved by a senior reviewer (XC).

Study selection and data extraction

The inclusion criteria for eligible studies were as follows: 1) RCTs enrolling adults with overweight or obesity, whose body mass index (BMI) was $\geq$25 kg/m^2 or $\geq$ 30 kg/m^2; 2) RCTs comparing AOMs with active controls or placebo; 3) RCTs reporting any cardiovascular outcomes of interest, including 3P-MACE, myocardial infarction, stroke, cardiovascular death, heart failure, atrial fibrillation, angina unstable or coronary artery disease. The 3P-MACE referred to a composite of myocardial infarction, stroke and cardiovascular death. The AOMs in our study included traditional medications (orlistat, phentermine/topiramate, bupropion/naltrexone),[38] GLP-1RAs with weight-loss effects, and other medications (tirzepatide, orforglipron, danuglipron, survodutide, mazdutide, efinopegdutide, pemvidutide, retatrutide, cagrilintide, pramlintide, CagriSema, bimagrumab, VK2735, SCO-094, CT-388, AZD6234, ZP8396, NNC0487-0111, YY 1875, NNC0165-1562, Y-14, AMG 133). We excluded RCTs with follow-up duration less than 6 months or using rimonabant, lorcaserin, or sibutramine, as these drugs had been withdrawn from market for safety concerns. Observational studies, reviews, meta-analyses, or cross-over design studies were also deemed ineligible.

The paired investigators (HW, JY, YG, and CL) independently reviewed the titles, abstracts, and full texts of the research articles. They excluded any duplicate or ineligible items and extracted data from eligible studies with a standardized form: publication data, study design, baseline characteristics, treatment arms, study duration, efficacy endpoints if presented such as HbA1c change, weight change and blood pressure change, and cardiovascular outcomes of interest. If the above data were not found in both articles and supplementary files, the data from ClinicalTrials.gov Website would be extracted. Another three investigators (RJ, SB, and ZL) checked the results of extractions, with any disagreements or discrepancies resolved by a senior reviewer (XC).

QUANTIFICATION AND STATISTICAL ANALYSIS

Assessment of risk of bias

The risk-of-bias of the included trials was independently assessed by paired reviewers (HW, JY, ZL, XY, and GL) using the Cochrane risk-of-bias tool,[39] including seven domains: adequate randomization sequence generation, adequate allocation concealment, blinding of participants and caregivers, binding of outcome assessors and adjudicators, free of frequent missing outcome data, free of selective outcome reporting and free of other bias. For each domain, we rated definitely yes (low risk of bias), probably yes, probably no, and definitely no (high risk of bias) based on the description in the articles. A senior reviewer (XC) resolved discrepancies.

Statistical analysis

The primary endpoint of this meta-analysis was the association between AOM treatments as well as their weight-loss effects and the risk of cardiovascular outcomes in patients with overweight or obesity. For each outcome, we calculated the RR and 95% CI compared with overall controls or placebo in different types of medications. We standardized the analyses to assess the cardiovascular effects associated with a 5 kg weight reduction by multiplying the log of the summary statistic of each trial (and its standard error) by 5/d, where "d" was the average body weight reduction in the trial. For example, if the logRR was −0.1 and the body weight reduction was 5 kg, the standardized logRR would be $-0.1 \times (10/5) = -0.2$. The statistical methods for standardization analysis have been reported in previous studies.[40] Besides, subgroup analyses were conducted according to indication, follow-up duration, age, sex ratio, and baseline BMI. Meta-regression analyses were performed to evaluate the influencing factors of cardiovascular outcomes. The heterogeneity between included studies was evaluated by Higgins I^2 statistics. For estimated I^2 values of 0%–40%, 30%–60%, 50%–90%, and 75%–100%, heterogeneity was defined as low, moderate, substantial, or considerable, respectively. The random-effect model was consistently adopted in this meta-analysis due to the potential heterogeneity. Publication bias was assessed via Begg's test and Egger's test.

Statistical analyses were conducted by STATA software, version 17.0 (STATA, College Station, TX, USA). Statistical significance was considered at $p < 0.05$.

ADDITIONAL RESOURCES

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