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ORIGINAL RESEARCH

An Obesity-Centric Approach with and Without Anti-Obesity Medications Compared to the Usual-Care Approach to Management of Patients with Obesity and Type 2 Diabetes in an Employer Setting: A Pragmatic Randomized Controlled Trial (EMPOWER-T2D)

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ABSTRACT

Introduction: This study aimed to compare weight loss and glycated hemoglobin (HbA_{1c})-reduction effects of two obesity-centric, weight-loss management approaches (with or without anti-obesity medication) versus usual glucose-centric care in patients with obesity and type 2 diabetes.

Methods: Single-center, randomized, open-label, 3-armed, parallel-group, pragmatic, non-inferiority trial, July 2020 to August 2022. Adults enrolled in the Cleveland Clinic Employee Health Plan (body mass index [BMI] ≥ 30 kg/m^2, type 2 diabetes diagnosis, HbA_{1c} > 7.5%) were randomized to usual glucose-centric management ("Usual-Care" group) or one of two obesity-centric management strategies: participation in a weight management program plus anti-obesity medication ("WMP + AOM" group), or WMP participation without anti-obesity medication ("WMP-Only" group). Primary endpoints were changes in weight and HbA_{1c}, baseline to month 12.

Results: Due to enrollment and retention challenges, largely related to COVID-19, only 74/300 planned participants were randomized and the study was terminated early. Participants were predominantly female (59%), median (interquartile range [IQR]) age 53.5 (47, 60) years, 68% white, with baseline median (IQR) BMI and HbA_{1c} of 37.4 (34.2, 42.7) kg/m^2 and 8.8% (7.9%, 10.4%), respectively. At month 12, mean (90% confidence interval [CI]) percentage

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weight change in the Usual-Care, WMP-Only, and WMP + AOM groups was − 4.5% (− 6.5%, − 2.5%), − 6.7% (− 8.7%, − 4.7%), and − 8.7% (− 10.7%, − 6.8%), respectively; mean (90% CI) HbA_{1c} change was − 1.7% (− 2.1%, − 1.2%), − 2.2% (− 2.7%, − 1.8%), and − 2.2% (− 2.6%, − 1.7%), respectively. WMP + AOM was superior to Usual-Care for weight change ($P = 0.02$); both WMP + AOM and WMP-Only were noninferior ($P \leq 0.01$) to Usual-Care for change in HbA_{1c}.

Conclusions: Including anti-obesity medication was associated with superior weight loss with noninferior HbA_{1c} reductions, warranting further evaluation in larger study populations of obesity-focused approaches to type 2 diabetes management.

Graphical abstract available for this article.

Trial Registration: ClinicalTrials.gov NCT03799198.

Graphical Abstract:

An Obesity-centric Approach With and Without Anti-obesity Medications Compared to the Usual-care Approach to Management of Patients With Obesity and Type 2 Diabetes in an Employer Setting: A Pragmatic Randomized Controlled Trial (EMPOWER-T2D)

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PURPOSE

To compare weight loss and glycated hemoglobin (HbA_{1c})-reduction effects of two obesity-centric, weight-loss management approaches (with or without anti-obesity medication) versus usual glucose-centric care in patients with obesity and type 2 diabetes (T2D)

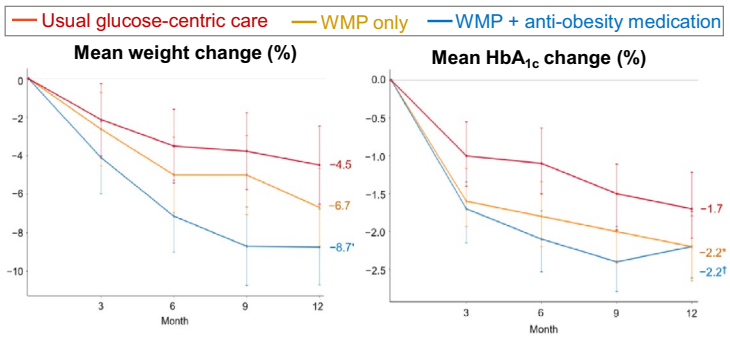
METHODS

Adults with obesity and T2D were randomized to usual glucose-centric management or one of two medically overseen obesity-centric strategies and assessed for changes in weight and HbA_{1c} after 12 months

- Usual "glucose-centric" management of T2D (n=24)
- Weight management program only (n=26)
- Weight management program + anti-obesity medication (n=24)

RESULTS

A weight management program (WMP) + anti-obesity medication produced superior weight loss and noninferior reduction in HbA_{1c} vs glucose-centric care at 12 months; the study was limited by low enrollment and early termination, largely related to COVID-19



*P=0.02 for superiority vs Usual Care

*P=0.007 and †P=0.01 for noninferiority vs Usual Care

CONCLUSIONS

- Despite a small sample size, this study demonstrated **superior weight loss and noninferior HbA_{1c} reductions** with a weight management program with adjunctive anti-obesity medication
- An obesity-focused approach to T2D management, facilitated by the increasing availability of medications with dual weight loss and glucose-lowering effects, provides an opportunity for a broader range of obesity-related health improvements in addition to glycemic control in this population

Keywords: Body mass index; Glycated hemoglobin; Obesity treatment; Type 2 diabetes; Weight change; Weight management

Key Summary Points

Why carry out this study?

Obesity is a major contributory factor in type 2 diabetes; recent American Diabetes Association guidelines emphasize the importance of weight loss, yet disease management remains glucose-centric.

We compared a weight management program, with/without anti-obesity medication, versus usual glucose-centric care for weight loss and glycated hemoglobin (HbA_{1c})-lowering among individuals with obesity and type 2 diabetes.

What was learned from the study?

In this randomized trial, a weight management program plus anti-obesity medication produced superior weight loss (−8.7% vs. −4.5%) and noninferior HbA_{1c} reductions (−2.2% vs. −1.7%) after 12 months, compared with usual, glucose-centric management.

An obesity-centric approach to type 2 diabetes management can achieve a broad range of health-related improvements in addition to glycemic control.

DIGITAL FEATURES

This article is published with digital features, including a graphical abstract, to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.25334650.

INTRODUCTION

Obesity and type 2 diabetes are medically challenging, intertwined epidemics that have been increasing worldwide and contribute to substantial global public health burdens. Obesity is the major driver of type 2 diabetes development, besides other consequential medical conditions such as hypertension, dyslipidemia, depression, coronary heart disease, stroke, osteoarthritis, obstructive sleep apnea, fatty liver disease, and certain cancers [1, 2]. Obesity is an estimated contributory factor in >90% and >50% of type 2 diabetes and hypertension cases, respectively [3, 4]. Since 2013, the American Medical Association has recognized obesity as a complex disease that warrants medical attention using a range of interventions [5].

Despite evidence that weight loss can improve obesity-related comorbidities and even reverse diabetes [6], management of patients with concomitant obesity and type 2 diabetes often remains primarily glucose-centric in nature, with a focus on lowering glycated hemoglobin (HbA_{1c}) levels and mitigating diabetes-related comorbidities rather than facilitating weight loss. Addressing obesity through lifestyle modifications and pharmacotherapy is increasingly recognized as a critical component of type 2 diabetes management. The 2023 American Diabetes Association (ADA) Standards of Care emphasize the need to prioritize obesity and weight management for the treatment of type 2 diabetes [7]. The recommendations encourage lifestyle modification and weight maintenance programs, with adjunctive pharmacotherapy as an option for individuals with BMI ≥ 27 kg/m^2. The recommended weight loss goal is ≥ 5% body weight for glycemic and cardiovascular benefits; weight loss > 10% has the potential to induce remission of type 2 diabetes.

Achieving clinically relevant, sustained weight loss in patients with obesity is notoriously challenging. Intensive lifestyle intervention has been shown to be an effective means of achieving meaningful weight loss in patients with obesity [8], but is often difficult to sustain. Employer-based weight management programs (WMPs) are designed to assist individuals with

achieving weight loss through lifestyle measures, offering expert guidance, encouragement, and accountability, as well as peer support. We previously found significantly improved weight loss outcomes and engagement among participants with obesity participating in an employer-based WMP and who were given access to adjunctive anti-obesity medication (AOM) compared with participants in the same program who did not have such access [9].

Data are relatively lacking on the impact of an obesity-centric approach, with/without adjunctive AOM, on metabolic parameters in patients with obesity and type 2 diabetes. We designed a study to test the hypotheses that in patients with obesity and type 2 diabetes, (1) an obesity-centric approach—delivered through an employer-based, medically supervised, comprehensive weight loss program—would result in greater weight loss and HbA_{1c} lowering than usual, glucose-centric care; and (2) using AOMs as an adjunct to the weight loss program would produce even greater benefits.

METHODS

Study Design and Oversight

This was a single-center, randomized, open-label, 3-armed, parallel-group, pragmatic trial conducted at Cleveland Clinic's Department of Endocrinology, Diabetes, and Metabolism. The study was conducted in accordance with the International Conference on Harmonisation Guideline for Good Clinical Practice, the principles of the Declaration of Helsinki, and all applicable local ethical and legal requirements. The Cleveland Clinic institutional review board approved the study protocol (approval number IRB 20-648). All participants provided written informed consent. Study data were collected and managed using REDCap electronic data capture tools hosted at Cleveland Clinic [10, 11].

Participants

Eligible persons were employees of Cleveland Clinic, and their partners, who had health coverage through Cleveland Clinic, Medical Mutual, or Bravo Health, and who had a BMI ≥ 30 kg/m^2, a diagnosis of type 2 diabetes, and an HbA_{1c} > 7.5% within 90 days preceding screening. Major exclusion criteria included a glomerular filtration rate < 30 mL/min/1.73 m^2; current glucocorticoid therapy; use of AOM within the previous 3 months; medical history that would contraindicate use of AOM (e.g., personal/family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2); history of acute pancreatitis or severe disease of the liver or digestive tract; history of bariatric or metabolic surgery; visit with an endocrinologist within the past year for treatment of type 2 diabetes; and prior participation in the Cleveland Clinic Endocrinology and Metabolism Institutes Integrated Weight Management Program.

Procedures

Participants were randomized 1:1:1 to one of three management arms for a planned duration of 24 months: "Usual-Care" group (glucose-centric approach), or one of two obesity-centric management strategies: participation in a WMP plus adjunctive AOM ("WMP + AOM" group), or participation in a WMP without AOM ("WMP-Only" group). All patients remained under the care of their usual primary care provider and any other regular physicians.

Participants in the Usual-Care arm were managed for type 2 diabetes, hypertension, and hyperlipidemia according to a traditional approach which entailed an initial consultation with an endocrinologist and follow-up visits every 3 months.

Cleveland Clinic's Endocrinology and Metabolism Institute's Integrated Weight Management Program consisted of an initial 1:1 personal evaluation by an obesity medicine specialist to establish a plan of care, then participation in shared medical appointments (SMAs) (4–5 participants per session) once per month during year 1 and once every 3 months during year 2. The SMAs (see electronic Supplementary Materials) were run by an obesity specialist and a nutritionist and were approximately 75–90 min in length. The

five main areas reviewed at every session included nutrition, physical activity, appetite control, sleep issues, and anxiety/depression/stress.

Participants in the WMP + AOM arm were enrolled in the same weight management program, but were also eligible to initiate treatment with one of five US Food and Drug Administration (FDA)-approved medications for chronic obesity treatment (orlistat, phentermine/topiramate, naltrexone/bupropion, liraglutide 3.0 mg, or semaglutide 2.4 mg). Choices of medication and dosage were at the discretion of the investigator, according to routine clinical practice. Participants could discontinue the medication at any time but were encouraged to initiate treatment with a different AOM. AOMs were dispensed by one of Cleveland Clinic's ambulatory pharmacies; to simulate real-world conditions, participants were charged a fee commensurate with a typical retail pharmacy co-pay. Use of weight-loss medications other than the five FDA-approved medications was not allowed.

Participants assigned to the Usual-Care and WMP-Only arms were not allowed to use any medication for the primary intent of weight loss. In all study arms, intensification of antidiabetes, hypertension, and/or hyperlipidemia therapy was allowed as indicated by HbA_{1c}, blood pressure, and lipid profile values, at the discretion of the investigator according to current practice standards.

Body weight, HbA_{1c}, blood pressure, serum low-density and high-density lipoprotein (LDL and HDL) and triglycerides, and blood pressure were assessed at screening/baseline, and at study months 6, 12, and 24.

Primary Outcomes

Primary outcomes were percentage weight loss and change in HbA_{1c} from baseline to month 12. The primary aims were to demonstrate noninferiority of WMP + AOM versus WMP-Only for both outcomes, and to demonstrate superiority in ≥ 1 of the outcomes for WMP + AOM versus WMP-Only. In addition, we aimed to demonstrate similar noninferiority in both outcomes and superiority in ≥ 1 of the outcomes for comparisons between both obesity-centric (weight management program) versus glycemic-centric (usual care) approaches.

Secondary Outcomes

Secondary outcomes included percentage of participants achieving > 5% weight loss (considered clinically relevant [12]) or $HbA_{1c} < 7\%$; changes in serum LDL, HDL, and triglycerides; and percentage of participants with blood pressure < 140/90 mmHg at month 12.

Sample Size Determination

Prior research by our group [13] suggested that a change in HbA_{1c} of 0.4–0.5% was expected to accompany changes in body weight of around 4–5%. Power calculations were performed using a simulation approach [14]. On the basis of the noted assumptions and our prior research findings, a sample size of 300 participants (100 per arm) was planned, assuming 20% of patients would not complete the evaluation at 1 year, leaving 80 completers per group, and assuming a weight loss standard deviation of 1.75%. This sample size would provide 82% power to detect noninferiority in both HbA_{1c} and weight loss, and to detect superiority in weight loss.

Statistical Analysis

The primary analysis was performed using the intent-to-treat group, which included all randomized participants. Primary end points were analyzed using linear mixed-effect models, with baseline body weight and HbA_{1c} as covariates. Time points common to all study arms (months 3, 6, 9, and 12) were used for analysis; time–group interactions were included in the models. The method of joint hypothesis test was applied for this analysis. Noninferiority was tested at the 0.05 level at 1 year and performed pairwise comparison with Bonferroni-adjusted significance levels and *P* values. The noninferiority regions were set to be 1% for weight loss change and 0.5% for HbA_{1c}. When both primary end points were noninferior,

Table 1 Baseline characteristics of study participants

Characteristic	*N*	Usual-Care (*n* = 24)	WMP-Only (*n* = 26)	WMP + AOM[a] (*n* = 24)
Age, years	74	53.5 (48.5, 61.5)	53.5 (47.0, 60.0)	53.0 (45.8, 58.3)
Race, *n* (%)	74			
African American		8 (33.3)	7 (26.9)	7 (29.2)
Asian		0	1 (3.8)	0
White		16 (66.7)	18 (69.2)	16 (66.7)
Hispanic		0	0	1 (4.2)
Ethnicity, *n* (%)	68			
Hispanic or Latino		2 (9.1)	0	4 (16.7)
Not Hispanic/Latino		20 (90.9)	22 (100.0)	20 (83.3)
Sex, *n* (%)	70			
Female		13 (56.5)	13 (56.5)	15 (62.5)
Male		10 (43.5)	10 (43.5)	9 (37.5)
Body weight, kg	74	112.0 (94.9, 118.8)	115.1 (104.9, 127.0)	105.9 (91.5, 122.6)
HbA_{1c}, %	74	8.5 (8.0, 10.5)	8.9 (8.0, 10.1)	8.4 (7.9, 10.5)
BMI, kg/m^2	73	35.8 (33.4, 44.0)	40.7 (36.9, 43.0)	36.2 (34.1, 40.5)
Blood pressure, mmHg				
Systolic	72	127.0 (124.5, 140.0)	131.0 (126.0, 140.0)	128.0 (116.5, 136.3)
Diastolic	72	80.0 (72.5, 82.5)	81.00 (74.0, 84.0)	74.50 (72.0, 82.0)
Lipids, mg/dL				
LDL	66	85.0 (53.0, 112.0)	93.0 (67.5, 133.0)	87.5 (66.3, 99.8)
HDL	68	40.0 (36.0, 46.0)	42.0 (30.5, 54.0)	40.0 (31.5, 51.5)
Triglycerides	68	135.0 (73.0, 186.0)	129.0 (97.5, 181.5)	131.0 (103.8, 169.3)

Data are median (IQR) unless specified otherwise

AOM anti-obesity medication, *BMI* body mass index, *FDA* Food and Drug Administration, *HbA_{1c}* glycated hemoglobin, *HDL* high-density lipoprotein, *IQR* interquartile range, *LDL* low-density lipoprotein, *WMP* weight management program

[a]FDA-approved anti-obesity medication: orlistat, phentermine/topiramate, naltrexone/bupropion, liraglutide 3.0 mg, or semaglutide 2.4 mg

superiority testing at the 0.025 overall error level with Bonferroni adjustment for each end point at 1 year was then performed.

Between-group percentages of participants achieving weight loss > 5%, HbA_{1c} treatment target < 7%, and blood pressure < 140/90 mmHg were compared through separate logistic regression models by odds ratio (OR), with relevant baseline values used as covariates. Linear mixed-effect models were used to analyze changes in serum LDL, HDL, and triglyceride levels, with baseline levels as covariates. Superiority testing at 0.05 overall error level with Bonferroni adjustment at 1 year was performed.

For primary endpoints (changes in HbA_{1C} levels and weight percentage) and secondary

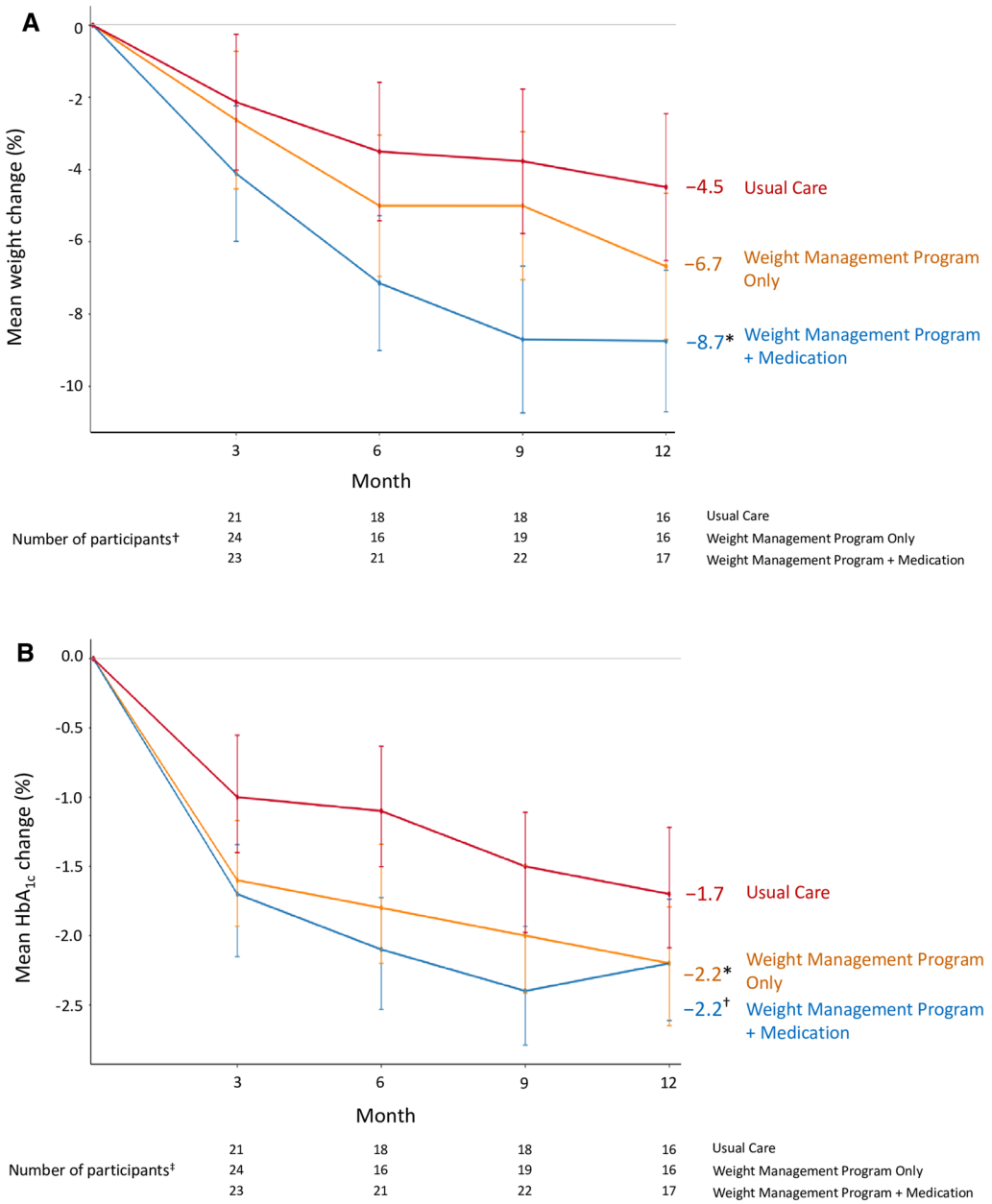
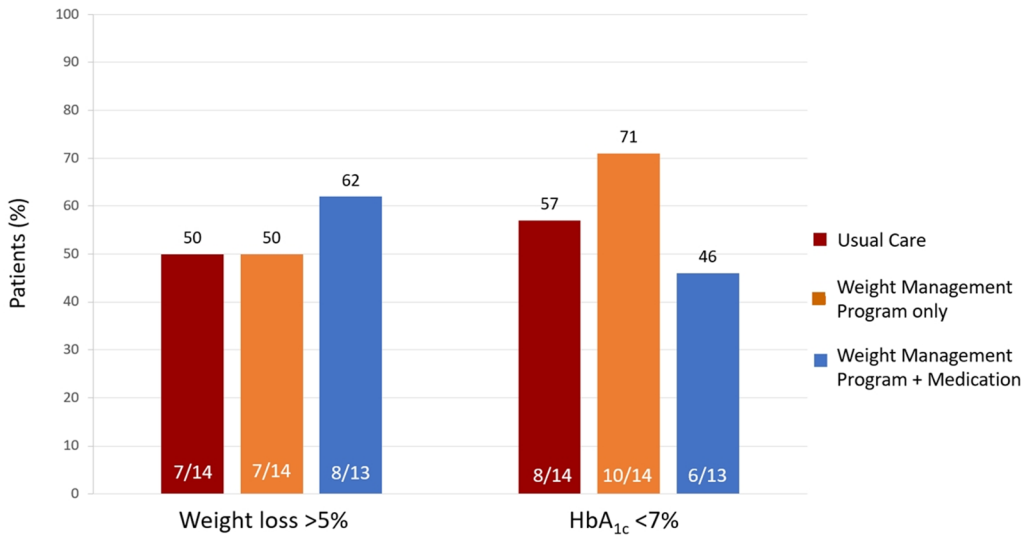


Fig. 1 Changes in **A** body weight and **B** HbA_{1c} at month 12. **A** Whiskers depict 90% confidence intervals (Bonferroni-adjusted). AOMs were FDA approved (orlistat, phentermine/topiramate, naltrexone/bupropion, liraglutide 3.0 mg, or semaglutide 2.4 mg). *AOM* anti-obesity medication, *FDA* Food and Drug Administration, *HbA_{1c}* glycated hemoglobin, *WMP* weight management program. *$P = 0.004$ for noninferiority versus Usual-Care; $P = 0.02$ for superiority versus Usual-Care. †Not all participants had recorded body weight data at every time point. *N* values reflect participants who completed the study through each time point and were included in the linear mixed-effects model which accounts for missing data. **B** *$P = 0.007$ for noninferiority versus Usual-Care. †$P = 0.01$ for noninferiority versus Usual-Care. ‡Not all participants had recorded HbA_{1c} data at each time point. *N* values reflect participants who completed the study through each time point and were included in the linear mixed-effects model which accounts for missing data. Medication = FDA-approved anti-obesity medication: orlistat, phentermine/topiramate, naltrexone/bupropion, liraglutide 3.0 mg, or semaglutide 2.4 mg



	OR (95% CI) versus Usual Care	
	Weight loss >5%	HbA_{1c} <7%
WMP-Only	1.13 (0.22, 5.88)	1.88 (0.40, 9.72)
WMP+AOM	1.71 (0.36, 8.73)	0.65 (0.14, 3.00)
Baseline weight	1.00 (0.98, 1.02)	—
Baseline HbA_{1c}	—	0.91 (0.55, 1.51)

Fig. 2 Patients with weight loss > 5% or HbA_{1c} < 7% at month 12. AOMs were FDA approved (orlistat, phentermine/topiramate, naltrexone/bupropion, liraglutide 3.0 mg, or semaglutide 2.4 mg). *AOM* anti-obesity medication, *CI* confidence interval, *FDA* Food and Drug Administration, *HbA_{1c}* glycated hemoglobin, *OR* odds ratio, *WMP* weight management program

Table 2 Lipid changes from baseline at 12 months

	Usual-Care ($n = 24$)	WMP-Only ($n = 26$)	WMP + AOM[a] ($n = 24$)
Lipids, change from baseline, mean (90% CI)			
LDL, mg/dL	− 4.6 (− 16.0, 6.7)	− 11.2 (− 21.9, − 0.6)	12.6 (1.3, 23.9)
HDL, mg/dL	2.2 (− 1.7, 6.1)	0.7 (− 3.0, 4.3)	6.5 (2.9, 10.2)
Triglycerides, mg/dL	− 45.0 (− 67.3, − 22.8)	− 29.9 (− 50.8, − 9.0)	− 37.2 (− 58.2, − 16.1)

AOM anti-obesity medication, *CI* confidence interval, *FDA* Food and Drug Administration, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *WMP* weight management program

[a]FDA-approved anti-obesity medication: orlistat, phentermine/topiramate, naltrexone/bupropion, liraglutide 3.0 mg, or semaglutide 2.4 mg

endpoints (changes in serum LDL, HDL, triglycerides) where one-sided non-inferiority tests or superiority tests within a significance threshold of 0.05 were performed, 90% Bonferroni-adjusted confidence intervals were presented to ensure the upper confidence limits reflected a one-sided 95% confidence. Data were managed and analyzed using R software (version 4.3.1; Vienna, Austria).

RESULTS

Study Population

Between July 10, 2020 and May 24, 2022, 74 participants were enrolled and randomized to the Usual-Care ($n=24$), WMP + AOM ($n=24$), or WMP-Only ($n=26$) groups. The study was terminated early (August 10, 2022) as a result of recruitment and retention challenges, largely related to the COVID-19 pandemic, as well as changes in the pharmacologic treatment landscape of obesity and type 2 diabetes.

Baseline characteristics of the participants were generally similar (Table 1); of note, median body weight and median HbA_{1c} at baseline were lowest in the WMP + AOM group.

Body Weight

Mean body weight decreased from baseline through month 12 in all groups (Fig. 1A). The mean percentage weight loss in the WMP + AOM group at month 12 (−8.7%; 90% CI −10.7%, −6.8%) was statistically superior to that in the Usual-Care group (−4.5%; 90% CI −6.5%, −2.5%; $P=0.02$). The percentage weight loss in the WMP-Only group was −6.7% (90% CI −8.7%, −4.7%; $P=0.11$ vs. other groups).

Among participants who remained in the study for 12 months ($n=41$), the proportion achieving weight loss > 5% from baseline to month 12 was numerically greatest in the WMP + AOM group (Fig. 2). After adjustment for baseline weight and HbA_{1c}, the OR for achieving weight loss > 5% relative to Usual-Care was 1.71 (95% CI 0.36, 8.73) for the WMP + AOM group and 1.13 (95% CI 0.22, 5.88) for the WMP-Only group. There were no significant differences between groups. From baseline to last visit within 1 year, the proportion of participants who achieved weight loss > 5% was 70% (16/23) in the WMP + AOM group (OR 2.81; 95% CI 0.82, 10.3) and 43% (10/23) in the WMP-Only group (OR 0.85; 95% CI 0.23, 3.02), versus 45% (9/20) in the Usual-Care group.

HbA_{1c}

At month 12, the mean change in HbA_{1c} was −1.65% (90% CI −2.09%, −1.22%) in the Usual-Care group, −2.22% (90% CI −2.65%, −1.79%) in the WMP-Only group, and −2.18% (90% CI −2.61%, −1.74%) in the WMP + AOM group (Fig. 1B). Both WMP groups (with/without AOM) were statistically noninferior to the Usual-Care group ($P \le 0.01$) for change in HbA_{1c}, but superiority testing was not significant for either group versus Usual-Care.

The proportion of participants who achieved $HbA_{1c} < 7\%$ at month 12 was 57% (8/14) in the Usual-Care group, 71% (10/14) in the WMP-Only group, and 46% (6/13) in the WMP + AOM group (Fig. 2). After adjustment for baseline weight and HbA_{1c}, the OR (95% CI) for achieving $HbA_{1c} < 7\%$ relative to Usual-Care was 0.65 (0.14, 3.00) and 1.88 (0.40, 9.72) for the WMP + AOM and WMP-Only groups, respectively. From baseline to last visit within 1 year, the proportion of participants who achieved $HbA_{1c} < 7\%$ was 48% (10/21) in the Usual-Care group, 57% (13/23) in the WMP-Only group, and 43% (10/23) in the WMP + AOM group.

Serum Lipids

Mean changes from baseline to month 12 in serum lipid levels are presented in Table 2. Neither WMP group was statistically superior to the Usual-Care group regarding reductions in LDL, HDL, or triglyceride lipids (all $P > 0.05$).

Blood Pressure

At baseline, the percentages of participants with blood pressure < 140/90 mmHg in the Usual-Care, WMP-Only, and WMP + AOM groups were 70%, 72%, and 88%, respectively. At month 12, the respective percentages were 86%, 79%, and 93%, with no significant differences between treatment groups.

DISCUSSION

In this study involving adults with type 2 diabetes and obesity, an obesity-centric approach characterized by participation in a weight management program including adjunctive AOMs produced superior weight loss as compared to usual glucose-centric care at 1 year. Of note with regard to mean weight loss, WMP + AOM trended more effective than WMP-Only, which trended more effective than Usual-Care, although neither comparison achieved statistical significance. Mean weight loss achieved in both WMP arms met and exceeded the clinically relevant and ADA-recommended goal of ≥ 5% [7], with the WMP-AOM group coming close to the 10% weight loss target. Early termination of the study was a result of patient recruitment and retention difficulties, largely related to the COVID-19 pandemic, as well as the FDA approval (or pending approval) of anti-diabetes medications with notable weight-loss benefits during the study period, which presented a major confounding factor. The consequences were a shortened follow-up period and, most importantly, a final sample size four times smaller than planned. Regardless, because the observed variability in the outcomes was less than anticipated, sufficient statistical power was maintained to identify a significantly greater decrease in body weight in the group managed by an employer-based weight management program plus adjunctive AOM. The two obesity-centric management groups (with/without adjunctive AOM) were statistically noninferior regarding HbA_{1c} reduction versus usual care; however, mean changes from baseline trended lower in the two WMP groups compared with the Usual-Care group and longer-term follow-up would have been of great interest. Early study termination likely precluded identifying other potentially significant differences in secondary outcomes.

Changes in the type 2 diabetes pharmacologic treatment landscape during the study resulted in patients within each group becoming eligible to receive therapies that promote a robust weight loss. Accordingly, the approval of semaglutide 2.4 mg weekly for obesity management, semaglutide 2.0 mg weekly for the management of type 2 diabetes, and impending approval of tirzepatide for the management of type 2 diabetes influenced our decision to terminate the trial early. Patients in the WMP-Only and Usual-Care arms started to receive these therapies for the management of type 2 diabetes, which would have influenced weight outcomes in the WMP-Only and Usual-Care groups, perhaps affording similar or greater weight-loss outcomes to those observed among patients in the WMP + AOM group receiving 2.4 mg semaglutide or other AOM therapy.

The results observed in our study were also heavily influenced by our health plan's diabetes treatment algorithm and formulary coverage, which would differ among other payers, thereby reducing the generalizability of our results. A trial of metformin and utilization of the maximum tolerated dose is required before treatment with a sodium/glucose cotransporter 2 inhibitor (SGLT2i) can be initiated, and a trial of SGTL2i therapy is required before approval of glucagon-like peptide 1 receptor agonist (GLP-1RA) therapy (in the absence of other indications to initiate these classes of drug, e.g., established cardiovascular disease, heart failure, chronic kidney disease). Regardless of study arm, all participants had access to the type 2 diabetes therapies associated with weight loss. Patients were not required to utilize sulfonylureas (SFUs) or insulin therapy before obtaining access to these newer agents. Including participants with other forms of insurance, which may have required the use of SFUs and/or insulin therapy, would certainly have resulted in the potential to observe more substantial differences between groups, in terms of weight- and glycemia-related outcomes. Similarly, "usual care" for type 2 diabetes in many non-US countries relies more heavily on the use

of medications with weight-gain potential (SFUs, insulin, thiazolidinediones), which can perpetuate the underlying obesity. A study of this nature conducted outside the USA might demonstrate even more marked benefits of WMP + AOM therapy.

Treatment guidelines for type 2 diabetes are evolving to include a focus on addressing overweight/obesity as a disease "driver" issue, rather than simply addressing dysglycemia and its consequences. Yet, clinical data addressing an obesity-centric approach to type 2 diabetes care have been limited to date, particularly in a real-world setting. Perhaps the best data come from the Look AHEAD trial [15], which focused primarily on evaluating the effect of intensive lifestyle intervention on cardiovascular events in adults with type 2 diabetes and overweight/obesity. Though the primary analysis of the Look AHEAD study did not identify any overall cardiovascular benefit with intensive lifestyle intervention [16], it did demonstrate that weight loss—and more importantly, long-term maintenance of weight loss—was possible in people with type 2 diabetes. It is worth noting that among Look AHEAD participants who lost > 10% of body weight in the first year, there was a 21% lower risk of cardiovascular death, myocardial infarction, stroke, or angina hospitalization compared to those with stable weight or weight gain [2, 17]. For these same cardiovascular outcomes, there was also a suggestive but nonsignificant benefit of intensive lifestyle intervention for lowering cardiovascular event risk among participants with relevant cardiovascular history at baseline [18]. In the intensive lifestyle intervention group of Look AHEAD, the mean weight loss was 4.7% at 8 years, and approximately 50% and 27% of intensive lifestyle intervention participants lost and maintained > 5% and > 10% of their initial body weight at 8 years, respectively [15]. In addition, the participants assigned to intensive lifestyle intervention required fewer medications to control their blood sugar, blood pressure, and lipid parameters than those receiving standard care [15]. However, results from the control group in the Look AHEAD study confirm that weight-loss or hyperglycemia-reduction benefits are unlikely to be achieved in the absence of a formal program focused on weight loss-related lifestyle changes, including AOMs, even among patients who express willingness. Clinical trials focusing on weight-loss outcomes in patients with obesity and type 2 diabetes are also limited, but studies are increasingly including weight loss as a primary end point [19, 20].

CONCLUSIONS

Despite early termination and a small study sample, we were able to demonstrate that an obesity-centric approach type 2 diabetes management that included a medically overseen, employer-based weight management program with adjunctive AOM was associated with clinically relevant, superior weight loss and noninferior HbA_{1c} reductions compared with usual care. These data support the evolving guidelines for the treatment of type 2 diabetes, which encourage treatment goals to be more intentionally centered on the achievement of weight loss as an imperative objective rather than simply an add-on benefit [7, 21]. Fortunately, the increasing availability of medications with dual benefits of weight loss and glucose-lowering effects greatly simplifies the therapeutic targeting of both disease factors, helping to expand the type 2 diabetes management paradigm to include a focus on obesity. Larger, long-term studies emphasizing an obesity-focused approach to type 2 diabetes management are needed. Such studies should not only prioritize the use of anti-diabetes therapies associated with weight loss (GLP-1RA, gastric inhibitory polypeptide (GIP)/GLP-1RA dual agonists, and SGLT2i) but also fully leverage the armamentarium of anti-obesity pharmacotherapy to augment lifestyle intervention programs leading to quality weight loss in patients with type 2 diabetes with overweight or obesity.

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Declarations

Conflict of Interest. Kevin M. Pantalone has received personal fees from AstraZeneca, Bayer, Corcept Therapeutics, Diasome, Eli Lilly, Merck, Novo Nordisk, and Sanofi; and research support from Bayer, Merck, Novo Nordisk, and Twin Health. He is also an Editorial Board member of *Diabetes Therapy*, but was not involved in the selection of peer reviewers for the manuscript, nor any of the subsequent editorial decisions. Bartolome Burguera has received research support from Novo Nordisk. Bruce Rogen, Patty Zirm, Huijun Xiao, James Bena, Gretchen Barnard, Elena Borukh, Seenia Peechakara, Marcio L. Griebeler, and James B. Young have nothing to disclose.

Ethical Approval. The study was conducted in accordance with the International Conference on Harmonisation Guideline for Good Clinical Practice, the principles of the Declaration of Helsinki, and all applicable local ethical and legal requirements. The Cleveland Clinic institutional review board approved the study protocol (approval number IRB 20-648). All participants provided written informed consent.

REFERENCES

1. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser. 2000;894:i–xii, 1–253.
2. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. Lancet. 2017;390(10113):2627–42
3. Aronow WS. Association of obesity with hypertension. Ann Transl Med. 2017;5(17):350.
4. World Health Organization. Fact sheet: obesity and overweight 2021 Nov 6. 2023. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight. Accessed 1 Mar 2024.

5. American Medical Association. Policy H-440.842: recognition of obesity as a disease. 2023. https://policysearch.ama-assn.org/policyfinder/detail/obesity?uri=%2FAMADoc%2FHOD.xml-0-3858.xml. Accessed 2023.

6. Lean ME, Leslie WS, Barnes AC, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. Lancet. 2018;391(10120):541–51.

7. ElSayed NA, Aleppo G, Aroda VR, et al. 8. Obesity and weight management for the prevention and treatment of type 2 diabetes: Standards of Care in Diabetes—2023. Diabetes Care. 2023;46(Suppl 1):S128–39.

8. Burguera B, Jesús Tur J, Escudero AJ, et al. An intensive lifestyle intervention is an effective treatment of morbid obesity: the TRAMOMTANA study—a two-year randomized controlled clinical trial. Int J Endocrinol. 2015;2015:194696.

9. Pantalone KM, Smolarz BG, Ramasamy A, et al. Effectiveness of combining antiobesity medication with an employer-based weight management program for treatment of obesity: a randomized clinical trial. JAMA Netw Open. 2021;4(7):e2116595.

10. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: building an international community of software platform partners. J Biomed Inform. 2019;95:103208.

11. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377–81.

12. Horn DB, Almandoz JP, Look M. What is clinically relevant weight loss for your patients and how can it be achieved? A narrative review. Postgrad Med. 2022;134(4):359–75.

13. Shibuya K, Ji X, Pfoh ER, et al. Association between shared medical appointments and weight loss outcomes and anti-obesity medication use in patients with obesity. Obes Sci Pract. 2020;6(3):247–54.

14. Mascha EJ, Turan A. Joint hypothesis testing and gatekeeping procedures for studies with multiple endpoints. Anesth Analg. 2012;114(6):1304–17.

15. Look AHEAD Research Group. Eight-year weight losses with an intensive lifestyle intervention: the Look AHEAD study. Obesity (Silver Spring). 2014;22(1):5–13

16. Wing RR, Bolin P, Brancati FL, et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med. 2013;369(2):145–54.

17. Gregg EW, Jakicic JM, Blackburn G, et al. Association of the magnitude of weight loss and changes in physical fitness with long-term cardiovascular disease outcomes in overweight or obese people with type 2 diabetes: a post-hoc analysis of the Look AHEAD randomised clinical trial. Lancet Diabetes Endocrinol. 2016;4(11):913–21.

18. Dutton GR, Lewis CE. The Look AHEAD trial: implications for lifestyle intervention in type 2 diabetes mellitus. Prog Cardiovasc Dis. 2015;58(1):69–75.

19. Davies M, Færch L, Jeppesen OK, et al. Semaglutide 2·4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. Lancet. 2021;397(10278):971–84.

20. Garvey WT, Frias JP, Jastreboff AM, et al. Tirzepatide once weekly for the treatment of obesity in people with type 2 diabetes (SURMOUNT-2): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet. 2023;402(10402):613–26.

21. Burguera B, Ali KF, Brito JP. Antiobesity drugs in the management of type 2 diabetes: a shift in thinking? Cleve Clin J Med. 2017;84(7 Suppl 1):S39–S46.