An Ob**E**sity-centric Approach with and without Anti-obesity **M**edications Com**P**ared to the Usual-care Appr**O**ach to Management of Patients **W**ith Obesity and Type 2 Diabetes in an **E**mployer Setting: A Pragmatic **R**andomized Controlled Trial (EMPOWER-T2D)

Rationale for the trial

Cleveland Clinic is one of the largest hospital systems in the United States, employing approximately 55,000 individuals, most of whom are enrolled in the Cleveland Clinic's Employee Health Plan for their medical insurance. Of the approximately 75,000 adult employees and their spouses on the Health Plan, approximately 25,000 have obesity, defined by BMI $\geq$ 30 kg/m^2, and more than 8,000 suffer severe obesity (BMI $\geq$ 35 kg/m^2).

Cleveland Clinic's Employee Health Plan (EHP) provides employees diagnosed with obesity support for participating in a weight management program (part of our Healthy Choice program). The Healthy Choice program is a way for Cleveland Clinic's Health Plan members to take charge of their well-being. Caregivers and their spouses who participate can improve their health and get up to 30% off their premiums by meeting personalized annual medical, nutrition or fitness goals. In 2019, approximately 50% of employees with obesity signed up for the Healthy Choice program. It is concerning that in spite of the significant prevalence of obesity among our employees and having the opportunity to participate in a program to improve their health, just a limited number of individuals sign up for this program.

In the US, employers are the ultimate purchasers of health care for the majority (56%) of employees. Recommendations support addressing obesity in the workplace; however, real-world evidence of best practices for chronic weight management in the employer context is lacking. More specifically, the impact of aggressively managing obesity (i.e., the primary problem) compared to addressing its comorbidities in the workplace is still unknown.

In order for medications for chronic weight management to be included in the health care offered to employees, employers have to "opt-in" or deliberately decide to pay for these medications for employees, even when payers have added them to their formulary. In part, this is due to questions regarding the cost/benefit ratio of these drugs in a real-world setting.

This lifestyle intervention program in this trial will be administered through SMAs (monthly in year 1, quarterly in year 2), which is a concept based on the chronic care model that combines group appointments for patients with clinical intervention, consisting of encounters with a nutritionist, exercise physiologist, and endocrinologist/obesity medicine specialist. If needed, patients are also referred to a mental health provider and sleep clinic[1]. Medications approved for chronic weight management by the United States Food and Drug Administration (FDA) will also be utilized in a subset of patients that participate in this clinical trial. Five AOMs are currently approved by the FDA for chronic weight management[2]. Patients with type 2 diabetes (T2D) will be encouraged to increase their level of physical activity, improve their nutrition and also potentially receive therapy with medications such as metformin, glucagon-like peptide (GLP)-1

receptor agonists and sodium-glucose co-transporter 2 (SGLT2) inhibitors. These anti-diabetes medications, in addition to improving glucose control, are associated with weight loss[3].

Cleveland Clinic provides a unique environment to investigate the impact of a weight-centric program, including the utilization of approved medications for chronic weight management, in patients with obesity and T2D, in the context of an employer-based weight management program. The use of a pragmatic clinical trial design will afford the opportunity to study the effects of an obesity-centric program that includes treatment with medications for chronic weight management in one arm, in an employer-based real-world setting, while affording a prospective comparison between three randomly assigned interventions in employees with obesity and T2D, as well as many other comorbidities, including hypertension, hyperlipidemia, osteoarthritis, depression, and fatty liver disease. In order to increase the generalizability of the study findings, the trial will also include an Employee or the significant other of an employee of Medical Mutual of Ohio, or Bravo Health, that is covered by the Employee Health Plans of Medical Mutual of Ohio and Bravo Health, respectively.

Background and significance

Obesity affects nearly 40% of adults in the US and it is responsible for important medical problems including hypertension, dyslipidemia, T2D, depression, coronary heart disease, stroke, osteoarthritis, obstructive sleep apnea (OSA), fatty liver disease, and some cancers, to name a few[4,5].

Obesity is responsible for the development of T2D and hypertension in more than 90% and 50% of cases, respectively[6-7]. Also more than 70% of patients with obesity have dyslipidemia. The prevalence of depression in patients with obesity is more than 50% and obesity is responsible for causing osteoarthritis in more than 25% of the patients[8]. Also, in the adult population, the prevalence of OSA is estimated to be ~25%, and as high as 45% in subjects with obesity[9].

Patients with obesity have an increased risk of all-cause and cardiovascular death. In recognition of the biologic basis and seriousness of obesity, several professional health associations and organizations worldwide recognize obesity as a disease[10].

Even though there is clear evidence in the literature that weight loss is associated with a dramatic improvement of obesity-related comorbidities and the patient's quality of life, in general, clinicians all over the world focus their attention on treating the diabetes, hypertension, hyperlipidemia and other comorbidities rather than the obesity itself, concentrating their efforts on improving blood glucose indices, blood pressure and LDL as well as triglycerides, and in many instances, prescribing anti-diabetes and antihypertensive medications that potentiate further weight gain[11,12]. As a result, clinicians are faced with a rising epidemic of obesity, perpetuating a preexisting epidemic of diabetes, hypertension, dyslipidemia, and metabolic syndrome.

Obesity is one of the biggest drivers of preventable chronic diseases and healthcare costs in the United States. Currently, estimates for these costs are $210 billion per year. In addition, obesity is associated with job absenteeism and with lower productivity while at work costing approximately $4.3 billion annually[12,13].

As a person's BMI increases, so do the number of sick days, medical claims and healthcare costs. Individuals who suffer obesity spend 42% more on direct healthcare costs than adults who have a healthy weight. Individuals with grade 1 obesity (BMI between 30 and 35) are more than twice as likely as individuals with BMI < 30 to be prescribed prescription pharmaceuticals to manage medical conditions[14].

Reducing obesity, improving nutrition, increasing physical activity, and making lifelong meaningful lifestyle changes can help lower costs through fewer doctor's office visits, tests, prescription drugs, sick days, emergency room visits and admissions to the hospital and lower the risk for a wide range of diseases.

A 2008 study by the Urban Institute, The New York Academy of Medicine and Trust for America's Health found that an investment of $10 per person in proven community-based programs to increase physical activity, improve nutrition, and prevent smoking and other tobacco use could save the country more than $16 billion annually within five years. That's a return of $5.60 for every $1 invested[15].

In spite of these important facts there is a significant, yet much-underutilized role, for structured weight management programs, both with and without use of anti-obesity medications, to improve metabolic control for patients with obesity who have developed comorbidities such as hypertension hyperlipidemia and T2D. Unfortunately, these patients have a much higher risk of developing coronary artery disease and cancer.

The medical literature contains ample evidence which demonstrates the positive impact that a lifestyle intervention program augmented by FDA approved AOMs can have on anthropometric and metabolic parameters in patients with obesity who have developed significant comorbidities[16-17]. Lifestyle intervention, in the form of improving diet, eating behaviors and increasing physical activity, is first-line treatment for obesity and overweight, but the majority of people with obesity and overweight struggle to achieve and maintain their weight loss long-term. We hypothesize that an obesity-centric approach delivered through a medically-supervised and comprehensive weight loss program[18], augmented by AOM, as the primary treatment of patients with obesity and T2D, will result in greater and sustainable weight loss, a better metabolic profile, (including glycemic blood pressure and cholesterol control) and improved quality of life (QOL) and treatment satisfaction when compared to an obesity-centric approach without AOM therapy or the current usual care/standard of care comorbidity-centric approach to general health management in patients with obesity and T2D. If confirmed, these findings would be expected to change our future approach to chronic diseases management, and reduce the rates of T2D, hypertension, and hyperlipidemia related complications (including heart disease and cancer) as well as the development of other obesity-related comorbidities, potentially reducing the long-term cost of care.

Type of trial

This is a pragmatic, 24 month, single-center, randomized, open-label, parallel-group trial comparing an obesity-centric approach with a medically-supervised and comprehensive weight loss program (Cleveland Clinic's Endocrinology and Metabolism Institute's Integrated Weight Management Program) augmented by AOMs, vs. an obesity-centric approach with a medically-

supervised and comprehensive weight loss program without AOMs, vs. the current usual care approach to general health management.

Informed consent will be obtained. IRB approval of the study will be obtained. 300 subjects (employees or spouses covered by our EHP or the EHPs of Medical Mutual or Bravo Health) will be randomized 1:1:1 to receive either an obesity-centric approach with AOM therapy (N=100), an obesity-centric approach without AOM therapy (N=100), or the current usual care approach to general health management (N=100).

Specific aim 1:
In a population of employees with a BMI ≥ 30 and A1C >7.5%, determine if the body weight loss and A1C improvement obtained via the obesity-centric approach with AOM therapy are both non-inferior to that obtained via the obesity-centric approach without AOM therapy, and to demonstrate that at least one of these endpoints is superior in the obesity-centric approach with AOM therapy relative to the obesity-centric approach without AOM therapy. We aim to show similar non-inferiority in both endpoints and superiority in at least one endpoint in the comparisons between both obesity-centric approach groups with usual care. Primary analyses will be performed at 1 year.

Hypothesis: In a population of employees with a BMI ≥ 30 and A1C >7.5%, the obesity-centric + AOM approach to management will prove to be non-inferior in weight loss and A1C improvement vs. the obesity centric approach without AOM or usual care approach, and superior in at least one of these endpoints . The obesity-centric approach without AOM therapy will be non-inferior in both weight loss and A1C improvement vs. the usual care approach and superior in at least one of these endpoints.

Specific aim 2:
In a population of employees with a BMI ≥ 30 and A1C >7.5%, determine if the percentage of patients that achieve a > 5% body weight loss or the A1C treatment target of < 7.0% observed with the obesity-centric approach + AOM is greater than what is observed in the obesity-centric approach without AOM therapy or with the usual care approach.

Hypothesis: In a population of employees with a BMI ≥ 30 and A1C >7.5%, the obesity-centric + AOM approach to management will afford a greater percentage of patients that achieve a > 5% body weight loss or the A1C treatment target of <7% vs. the obesity-centric approach without AOM or with the usual care approach. The obesity-centric approach without AOM therapy will result in a greater percentage of patients that achieve a > 5% body weight loss or the A1C treatment target of <7% vs. the usual care approach.

Specific aim 3:
In a population of employees with a BMI ≥ 30 and A1C >7.5%, determine if the effect on serum LDL, HDL and triglycerides are different between the groups of patients who received care under the obesity-centric approach with or without AOM therapy, vs those who received care under the usual care approach.

Hypothesis: In a population of employees with a BMI ≥ 30 and A1C >7.5%, the obesity-centric + AOM approach to management will afford greater mean reductions in serum LDL and

triglycerides, and a mean increase in HDL, compared to that obtained via the obesity-centric approach without AOM therapy, or the usual care approach. The obesity-centric approach without AOM therapy will result in a greater mean decrease in LDL and triglycerides, and mean increase in HDL vs. the usual care approach, but it will result in a lower mean decrease in LDL and triglycerides, and lower mean increase in HDL, than what is achieved with the obesity-centric + AOM approach.

Specific aim 4:
In a population of employees with a BMI ≥ 30 and A1C >7.5%, determine if the obesity-centric approach to management + AOM improves the rate of blood pressure goal attainment (< 140/90 mmHg) when compared to the blood pressure goal attainment rate observed with an obesity-centric approach to management without AOM therapy, or the usual care approach.

Hypothesis: In a population of employees with a BMI ≥ 30 and A1C >7.5%, the obesity-centric + AOM approach to management will afford a greater percentage of patients that attain a blood pressure of < 140/90 compared to that obtained via the obesity-centric approach without AOM therapy, or the usual care approach. The obesity-centric approach without AOM therapy will result in a higher percentage of patients that attain a blood pressure of < 140/90 mmHg vs. the usual care approach, but it will result in a percentage that is lower than what is achieved with the obesity-centric + AOM approach.

Specific aim 5:
To determine if QOL and treatment satisfaction are different between the groups of patients who received care under the obesity-centric approach with or without AOM therapy vs. those who received care under the usual care approach.

Hypothesis: The obesity-centric approach to management with or without AOM therapy will afford greater quality of life and treatment satisfaction compared to the quality of life and treatment satisfaction observed within the group managed via the usual care approach. The observed improvements in QOL and treatment satisfaction will be greater in the obesity-centric approach + AOM therapy when compared the group managed with an obesity-centric approach without AOM therapy.

Specific aim 6:
In a population of employees with a BMI ≥ 30 and A1C >7.5%, determine if the total cost of care are different between the groups of patients who received care under the obesity-centric approach with or without AOM therapy vs. those who received care under the usual care approach.

Hypothesis: The obesity-centric approach to management with or without AOM therapy will afford an average total cost of care per patient that is lower than what is observed under the usual care approach. The observed reduction in total cost of care per patient will be greater with the obesity-centric approach + AOM therapy vs the obesity-centric approach without AOM therapy.

Research design and methods
Study Type: Interventional
Study Design: Allocation: Prospective, Pragmatic, Randomized
Endpoint Classification: Safety/Efficacy Study

Intervention Model: Parallel Assignment
Masking: Open Label
Primary Purpose: Treatment

Study Population/Sample

Patients with documented T2D with an A1C > 7.5% and BMI ≥ 30 kg/m^2 will be screened for inclusion/exclusion criteria.

Patients will be included in the study if these criteria are met and their clinical data will be recorded.

Inclusion Criteria:
1. Gender: men and women
2. Ethnicity: all ethnic groups
3. Age: ≥18, < 75 years
4. Diagnosis of T2D -A1C within the last 90 days must be >7.5%
5. Obesity, BMI ≥30
6. An Employee, or the significant other of an employee, that is covered by the Cleveland Clinic Employee Health Plan, or an Employee or the significant other of an employee of Medical Mutual of Ohio, or Bravo Health, that is covered by the Employee Health Plans of Medical Mutual of Ohio and Bravo Health, respectively

Exclusion Criteria:
1. Type 1 diabetes or known latent autoimmune diabetes of adulthood (LADA)
2. Glomerular Filtration Rate <30 mL/min/1.73 m^2 (calculated by the Chronic Kidney Disease Epidemiology Collaboration Equation, CKD-EPI)
3. Current glucocorticoid therapy
4. Currently or within the past 3 months receiving an anti-obesity medication, or any other medication used for the primary intent of weight loss
5. Any condition, unwillingness or inability, not covered by any of the other exclusion criteria, which, in the study clinician's opinion, might jeopardize the subject's safety or compliance with the protocol
6. Mental incapacity or language barrier
7. Pregnancy or plans to become pregnant within the next 2 years
8. Personal or family history of medullary thyroid carcinoma
9. Personal or family history of Multiple Endocrine Neoplasia syndrome type 2
10. History of acute pancreatitis, severe liver disease (Cirrhosis), or severe disease of digestive tract
11. History of congestive heart failure
12. History of bariatric or metabolic surgery/procedure
13. Visit with an endocrinologist within the past 1 year for treatment of type 2 diabetes
14. Prior participation in the Endocrinology and Metabolism Institutes Integrated Weight Management Program

Sample Size
This initial sample size of 300 patients
-100 patients randomized to the obesity-centric approach with a prescription for an AOM
-100 patients randomized to the obesity-centric approach without a prescription for an AOM

-100 patients randomized to the current usual care approach

This sample size should be adequate to detect moderate effect size differences in the primary endpoints between groups.

Assumptions for sample size calculations included:

- Two sample one sided t-test with equal variances.

- Overall 5% significance level for non-inferiority, and adjusted 2.5% significance level for superiority testing. Superiority is only claimed if estimated difference in mean weight loss favors the obesity-centric approach.

- To account for multiple comparisons across the three groups, a Bonferroni adjustment of $\alpha/3$ was applied to both non-inferiority and superiority comparisons.

- 1:1:1 randomization
    - 40% of subjects in all arms are expected to be non-compliant with assigned treatment
    - Among subjects who were non-compliant, 50% are expected to return for a month 24 (visit 25) assessment.
    - Non-compliant subjects in the comorbidity-centric (usual care) arm are assumed to have the same effect as subjects who complete the comorbidity-centric approach (usual care) arm.
    - Non-compliant patients who follow-up in the obesity-centric arm are assumed to have an effect corresponding to half the weight loss difference (compared to comorbidity-centric [usual care] arm) of subjects who complete the study in the obesity-centric arm.

- The following expected distribution of AOM prescriptions in the obesity-centric arm (based on input from our obesity medicine providers):
    - 5% Orlistat (Xenical®)
    - 15% Phentermine/Topiramate extended-release (Qsymia®)
    - 15% Naltrexone/Bupropion extended-release (Contrave®)
    - 15% Liraglutide (Saxenda®)
    - 50% Semaglutide 2.4 (Wegovy®)

Preliminary Data

An EHR study performed by our team (manuscript in press) identified patients that participated in our SMA program, 2 years from baseline, vs. controls, and had the following observed changes in A1C (Table 1). The majority of these patients did not have prescriptions for AOM therapy. Table 2 demonstrates the weight loss differences, between a propensity matched group of SMA participants and controls.

Table 1: Change in A1C observed in SMA program in patients with T2D and Obesity

	N of patients	**SMA**	**Control**	**P-value**

Baseline	91 SMA and 709 control	7.64(1.70)	8.23(2.12)	0.012
1 year	79 SMA and 551 control	7.32 (1.78)	7.75 (1.72)	0.038
2 year	82 SMA and 486 control	7.26 (1.69)	7.84 (1.80)	0.007

SMA, shared medical appointments; Patients in the SMA group attended at least 1 SMA during this study period with the option of scheduling supplemental individual medical appointments, as needed. Patients in the control group were those who had an ICD-9 encounter diagnosis code for obesity or morbid obesity during an individual medical appointment with an endocrinologist during the same study period.

Table 2: Weight Loss Outcomes after Propensity Matching, SMA vs. Control

	SMA (N=301)		**Control** (N=301)		**P-value**
	N	Weight loss (%) Mean (SD)	N	Weight loss (%) Mean (SD)	
6-months	264	4.17 (5.79)	143	1.51 (5.91)	<0.001
1-year	217	5.18 (7.05)	140	1.76 (7.54)	<0.001
2-years	207	3.78 (7.95)	151	1.64 (9.06)	0.02

SMA, shared medical appointments; Patients in the SMA group attended at least 1 SMA during this study period with the option of scheduling supplemental individual medical appointments, as needed. Patients in the control group were those who had an ICD-9 encounter diagnosis code for obesity or morbid obesity during an individual medical appointment with an endocrinologist during the same study period.

This data suggests that a change in A1C of about 0.4-0.5% is expected to accompany changes in body weight on the order of 4-5%.

Table 3 presents several sample size scenarios and power calculations based on the above assumptions, assuming that (treatment effect) at 1 year is 5% for weight loss in the AOM group relative to non-AOM groups, and improvement in A1C is 0.5% for the same comparisons. Power calculations further assumed a per comparison significance level of 0.0167 for one-sided non-inferiority tests and 0.0083 for one-sided superiority tests to account for the multiple comparisons across all pairs of groups. Non-inferiority regions of 1% for weight loss and 0.5% for A1C were also assumed, as was a small positive correlation (r=0.25) between weight loss and A1C change within subject. Standard deviations (SD) reflect the variation of weight loss and A1C between subjects within the same treatment arm. SD of 8, 9, and 10% for weight loss were chosen based on the NN8022 (SCALE) program[19-21] and the TRAMOMTANA[18] study as well as the preliminary data above. Standard deviations of 1.5%, 1.75% and 2% for A1C were assumed based on preliminary data.

Table 3. Power calculations for selected total N, treatment effects, and standard deviations

A1C SD (%)	1.5			1.75			2.0		
Wt. SD (%)	8	9	10	8	9	10	8	9	10

Final N									
70	0.89	0.81	0.73	0.83	0.76	0.67	0.74	0.67	0.60
80	0.93	0.91	0.81	0.88	**0.82**	0.77	0.80	0.75	0.69
90	0.96	0.91	0.86	0.93	0.88	0.83	0.86	0.82	0.77
100	0.98	0.94	0.89	0.96	0.92	0.87	0.90	0.88	0.83

Final N = sample size per group after loss to follow-up; standard deviation (SD) =variation in weight loss between subjects within the same treatment arm; assumed treatment effect of 5% for weight and 0.5% for A1C, with non-inferiority regions of 1% for weight loss and 0.5% for A1C. Power estimates are based on a simulation with 2000 runs per observation, and assume normality of the outcome measures.

Power calculations were performed using a simulation approach [22]. Based on the above mentioned assumptions and results from the referenced studies, if we assume that 20% of patients will be lost and not able to complete the evaluation at 1 year, then with 80 completers per group, and assuming a weight loss standard deviation of 9% and an HbA1c standard deviation of 1.75%, there will be 82% power to detect non-inferiority in both measures and superiority in weight loss.

Interim Analysis
No interim analysis is planned for this study.

Study Period
24 months

Primary endpoint

Comparison of the joint hypotheses comparing study groups on mean weight loss and A1C improvement at year 1. Specifically, the goal will be to demonstrate non-inferiority of the AOM therapy group in both measures relative to non-AOM therapy groups separately, and superiority versus each group on at least one of these endpoints at year 1 (month 12). Similarly, non-inferiority of the SMA alone vs. usual-care group on both mean weight loss and A1C improvement, and superiority on at least one of these endpoints, at 1 year will be evaluated.

Protocol

Patients determined to meet the study inclusion/exclusion criteria will be consented, baseline characteristics will be recorded. Patients will be randomized to one of the following three study arms:

1) Obesity-centric approach + AOM: a comprehensive weight management program comprised of SMAs[1] (monthly in year 1, quarterly in year 2) with an obesity-medicine specialist lead team to treat their obesity and review issues related to stress, mental health, nutrition, sleep, physical activity, and appetite control (including a prescription for an AOM). Please see Tables 4 and 5.

Patients will be seen and evaluated by one of our obesity-medicine specialists in a 1:1 face-to-face consultation. The plan of care will be determined, and the subjects will choose one of two dietary programs (Mediterranean-style Diet or Ketogenic-style Diet). They will see a registered dietitian (between visit 1 and 2), either individually or in the setting of a shared nutrition appointment, to review the chosen dietary plan.

Subjects will then initiate a series of 12 monthly study visits (year 1) followed by 4 quarterly study visits (year 2) in the context of SMAs with up to approximately 4-5 subjects each. The SMAs will be run by a health care provider and a nutritionist and will be approximately 75-90 minutes in length. The 5 main areas of the SMA program will be reviewed at every SMA and include: nutrition, physical activity, appetite control, sleep issues, and anxiety/depression/stress. SMA content will focus on accomplishing a healthier lifestyle, including rotating topics related to nutrition (meal plan education, self-monitoring/record-keeping, emotions related to eating such as comfort foods, "fear" foods, etc., stimulus control, problem-solving, eating competence skills, mindful eating, weight set point, internal regulation skills relating to hunger/fullness/satisfaction, how to choose and prepare healthy food, trying new foods, social eating and eating outside of the home); information and advice regarding different exercise programs and compliance with exercise physiologist referral; issues related to healthy sleep habits; and specific topics regarding behavior modification and stress management (goal setting, accountability, relapse prevention).

As part of the obesity-centric approach weight management program, subjects will be referred to an exercise physiologist for a personalized physical activity program. Subjects who are considered high-risk for underlying CVD will be referred for exercise stress testing. Additionally, if assessed relevant by the study clinician, subjects may also be referred to a mental health specialist and/or sleep clinic. Concomitant medications for medical conditions other than obesity are allowed in both treatment arms at the discretion of the investigator.

Obesity medication

After randomization, subjects randomized to the obesity-centric approach + AOM therapy arm will be eligible to initiate treatment with prescription medication indicated for chronic weight management. Prescription may be provided at the time of randomization (visit 1) or at visit 2, as agreed between the investigator and the subject, consistent with usual clinical practice and standard of care. Medication choice, dose, and dose escalation will be at the discretion of the investigator. Loose combination therapy with medications for weight management, on- or off-label, is not allowed. Subjects in the obesity-centric approach arm may switch to another medication indicated for chronic weight management or discontinue temporarily or permanently taking medication for chronic weight management during the trial, according to standard clinical practice at the discretion of the investigator. If subjects choose to stop their obesity medication treatment, they will be asked to notify the investigator of their decision to ensure a safe withdrawal. In case of discontinuation of one of the medications for chronic weight management, subjects will be encouraged to initiate treatment with another medication for chronic weight management. Subjects who discontinue medication for chronic weight management should be encouraged to continue attending the trial visits.

The medications for chronic weight management will be acquired on the regular US market and 100 dispensed by one of Cleveland Clinic's ambulatory pharmacies. In order for the trial to remain as close as possible to real world condition, subjects randomized to obesity-centric arm will be required to pay a fee for the obesity medication of choice simulating the co-pay the subject would have to pay at a retail pharmacy if the medication was covered by their employer. The fee will be the same for all medications for chronic weight management. All prescription medications approved in the US for chronic weight management will be made available for the subjects. Use of any medication for the primary intent of weight loss, besides the four FDA-approved AOMs, is

not allowed. Intensification of anti-diabetes, hypertension and hyperlipidemia therapy occurs as indicated via A1C, blood pressure and lipid profile values, and therapies chosen will be at the discretion of the investigator. Patients may be referred for a diabetes self-management and education consultation with a certified diabetes educator, at the discretion of the investigators. The need and frequency for point of care (POC) glucose testing will be determined by the investigator/treating physician, as part of usual care. The patients will continue to remain under the care of their primary care provider and/or any other usual physicians.

2) Obesity-centric approach without AOM: a comprehensive weight management program comprised of SMAs[1] (monthly in year 1, quarterly in year 2) with an obesity-medicine specialist lead team to treat their obesity and review issues related to stress, mental health, nutrition, sleep, physical activity, and appetite control (excluding a prescription for an AOM). Please see Tables 4 and 5.

Patients will be seen and evaluated by one of our obesity-medicine specialists in a 1:1 face-to-face consultation. The plan of care will be determined, and the subjects will choose one of two dietary programs (Mediterranean-style Diet or Ketogenic-style Diet). They will see a nutritionist (between visit 1 and 2), either individually or in the setting of a shared nutrition appointment, to review the chosen dietary plan.

Subjects will then initiate a series of 12 monthly study visits (year 1) followed by 4 quarterly study visits (year 2) in the context of SMAs with up to approximately 6-8 subjects each. The SMAs will be run by a health care provider and a nutritionist and will be approximately 75-90 minutes in length. The 5 main areas of the SMA program will be reviewed at every SMA and include: nutrition, physical activity, appetite control, sleep issues, and anxiety/depression/stress. SMA content will focus on accomplishing a healthier lifestyle, including rotating topics related to nutrition (meal plan education, self-monitoring/record-keeping, emotions related to eating such as comfort foods, "fear" foods, etc., stimulus control, problem-solving, eating competence skills, mindful eating, weight set point, internal regulation skills relating to hunger/fullness/satisfaction, how to choose and prepare healthy food, trying new foods, social eating and eating outside of the home); information and advice regarding different exercise programs and compliance with exercise physiologist referral; issues related to healthy sleep habits; and specific topics regarding behavior modification and stress management (goal setting, accountability, relapse prevention).

As part of the obesity-centric approach weight management program, subjects will be referred to an exercise physiologist for a personalized physical activity program. Subjects who are considered high-risk for underlying CVD will be referred for exercise stress testing. Additionally, if assessed relevant by the study clinician, subjects may also be referred to a mental health specialist and/or sleep clinic. Concomitant medications for medical conditions other than obesity are allowed in both treatment arms at the discretion of the investigator.

Use of any medication for the primary intent of weight loss, including the four FDA-approved AOMs, is not allowed. Intensification of anti-diabetes, hypertension and hyperlipidemia therapy occurs as indicated via A1C, blood pressure and lipid profile values, and therapies chosen will be at the discretion of the investigator. Patients may be referred for a diabetes self-management and education consultation with a certified diabetes educator, at the discretion of the investigators. The need and frequency for point of care (POC) glucose testing will be determined by the

investigator/treating physician, as part of usual care. The patients will continue to remain under the care of their primary care provider and/or any other usual physicians.

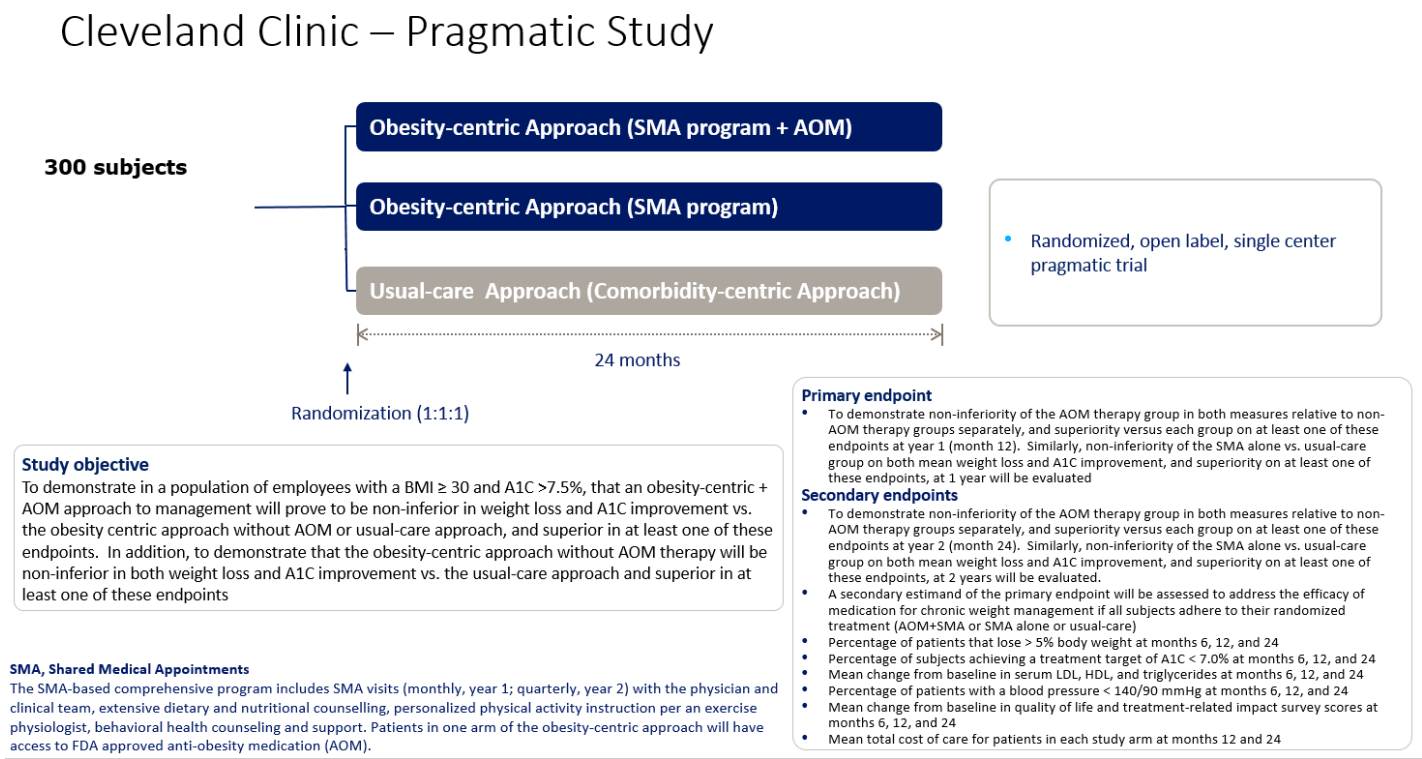
3) Usual care approach (Comorbidity-centric approach): the traditional usual care/standard of care approach to T2D, hypertension, hypercholesterolemia management comprised of a consultation with an endocrinologist, along with office encounters every 3 months with an endocrinology specialist. Intensification of anti-diabetes, hypertension and hyperlipidemia therapy occurs as indicated via A1C, blood pressure and lipid profile values, and therapies chosen will be at the discretion of the treating physician. Patients may be referred for a nutrition consultation with a registered dietitian, or for diabetes self-management and education consultation with a certified diabetes educator, at the discretion of the investigators. The need and frequency for point of care (POC) glucose testing will be determined by the treating physician, as part of usual care. The patients will continue to remain under the care of their primary care provider and/or any other usual physicians. Use of any medication for the primary intent of weight loss, including the four FDA-approved AOMs, is not allowed. Please see Tables 6 and 7.

All lab values obtained during this study are considered standard of care and will be extracted from the Cleveland Clinic Electronic Health Record.

Baseline Characteristics

The following patient baseline characteristics/variables will be recorded: age, gender, ethnicity, weight, height, BMI, A1C (%), LDL (mg/dL), HDL (mg/dL), triglycerides (mg/dL), blood pressure (mmHg), GFR (calculated by CKD-EPI formula), self-reported duration of diabetes (years). QOL and the treatment-related impact on patients will be assessed using the EQ-5D-5L[23-24], TRIM-D[25-26], WPAI:SHP[27] and WLQ-SF[28] questionnaires, respectively.

Figure 1: Study Design



Schedule of Events

Table 4: Time and Events Schedule, Obesity-centric Approach, Year 1

	Screening and Randomization	Obesity-centric Approach to Management Program (with or without AOM therapy)[f]											
Visit (V)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13
Timing of visit (months)	0	1	2	3	4	5	6	7	8	9	10	11	12
Visit window (days)	0	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14
SUBJECT-RELATED INFORMATION AND ASSESSMENTS													
Informed consent	X												
Demographics[a]	X												
Inclusion criteria	X												
Exclusion criteria	X												
Urine pregnancy test	X												
HbA1c Point of Care test[b]	X												
Randomization	X												
Medical history/concomitant illness, self-reported duration of diabetes	X												
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X
Disallowed medication[c]		X	X	X	X	X	X	X	X	X	X	X	X
EFFICACY													
Height	X												
Body weight	X	X	X	X	X	X	X	X	X	X	X	X	X[d]
Questionnaires: EQ-5D-5L, TRIM-D, WPAI:SHP and WLQ-SF	X						X						X

	Screening and Randomization	Obesity-centric Approach to Management Program (with or without AOM therapy)[f]											
Visit (V)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13
Timing of visit (months)	0	1	2	3	4	5	6	7	8	9	10	11	12
Visit window (days)	0	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14
SMA attendance		X	X	X	X	X	X	X	X	X	X	X	X
SAFETY													
Adverse event	X[e]	X	X	X	X	X	X	X	X	X	X	X	X
Labs/Blood Pressure & Reminders													
HbA1c/Lipids/Blood Pressure	X			X			X			X			X
Schedule nutritionist appointment	X												
Refer to exercise physiologist	X												

[a] Demographics consists of date of birth, sex, ethnicity, and race
[b] POC HbA1c will be obtained during screening visit and used for assessment of eligibility/study inclusion and randomization. A lab HbA1c will be obtained along with lipids within study visit window. The lab HbA1c will be used for purposes of the analyses.
[c] Disallowed medications: Any medication on- or off-label prescribed for weight loss other than the anti-obesity medication (AOM) prescribed by the study clinician for chronic weight management (Xenical®, Saxenda®, Qsymia®, Contrave® Wegovy®). Use of these medications will be assessed during routine medication review at SMAs.
[d] If a subject does not attend the SMA at visit 13, a stepwise approach to obtaining weight data will be applied to obtain a month 12 weight measurement (-14 days, +14 days from scheduled month 12/visit 13): calling subject in for a month 12/visit 13 weight measurement, extract recent weight data from the electronic medical record, or use recent subject-reported weight.
[e] Screening and randomization are one visit. Serious adverse event and pregnancy collection will begin after informed consent and randomization.
[f] There will be two arms of patients in the obesity-centric approach cohort, one arm (N=100) will receive AOM therapy, the other arm (N=100) will not. In the non-AOM therapy arm, any medication, on- or off-label prescribed for the primary intent of weight loss will be disallowed, including the chronic weight management medications (Xenical®, Saxenda®, Qsymia®, Contrave®, Wegovy®).
QOL: EQ-5D-5L. Five level health status measure; SMA: Shared Medical Appointment
TRIM-D. 28 item measure with 5 domains assessing Treatment Burden, Daily Life, Diabetes Management, Compliance and Psychological Health.
WPAI:SHP Work Productivity as measured by Work Productivity and Activity Impairment Questionnaire Specific Health Problem
WLQ-SF Work limitation as measured by Work Limitations Questionnaire 8-Item Self-administered Short Form

Table 5. Time and Events Schedule, Obesity-centric Approach, Year 2

	Obesity-centric Approach to Management Program (with or without AOM therapy)[a]									
Visit (V)	V14			V15			V16			V17
Timing of visit (months)	15			18			21			24
Visit window (days)	±14			±14			±14			±14
SUBJECT-RELATED INFORMATION AND ASSESSMENTS										
Concomitant medication	X			X			X			X
Disallowed medication[b]	X			X			X			X
EFFICACY										
Height										
Body weight	X			X			X			X[c]
Questionnaires: EQ-5D-5L, TRIM-D, WPAI:SHP and WLQ-SF				X						X
SMA attendance	X			X			X			X
SAFETY										
Adverse event	X			X			X			X
Labs/Blood Pressure & Reminders										
HbA1c/Lipids/Blood Pressure	X			X			X			X

[a]There will be two arms of patients in the obesity-centric approach cohort, one arm (N=100) will receive AOM therapy, the other arm (N=100) will not. In the non-AOM therapy arm, any medication, on- or off-label prescribed for the primary intent of weight loss will be disallowed, including the chronic weight management medications (Xenical®, Saxenda®, Qsymia®, Contrave®, Wegovy, ®).
[b] Disallowed medications: Any medication on- or off-label prescribed for weight loss other than the anti-obesity medication (AOM) prescribed by the study clinician for chronic weight management (Xenical®, Saxenda®, Qsymia®, Contrave® Wegovy ®). Use of these medications will be assessed during routine medication review at SMAs.
[c] If a subject does not attend the SMA at visit 17, a stepwise approach to obtaining weight data will be applied to obtain a month 24 weight measurement (-14 days, +14 days from scheduled month 24/visit 17): calling subject in for a month 24/visit 17 weight measurement, extract recent weight data from the electronic medical record, or use recent subject-reported weight.
QOL: EQ-5D-5L. Five level health status measure; SMA: Shared Medical Appointment
TRIM-D. 28 item measure with 5 domains assessing Treatment Burden, Daily Life, Diabetes Management, Compliance and Psychological Health.
WPAI:SHP Work Productivity as measured by Work Productivity and Activity Impairment Questionnaire Specific Health Problem
WLQ-SF Work limitation as measured by Work Limitations Questionnaire 8-Item Self-administered Short Form

Table 6. Time and Events Schedule, Usual Care Approach, Year 1

	Screening and Randomization	Usual Care Approach to Management Program									
Visit (V)	V1	V2			V3			V4			V5
Timing of visit (months)	0	3			6			9			12
Visit window (days)	0	±14			±14			±14			±14
SUBJECT-RELATED INFORMATION AND ASSESSMENTS											
Informed consent	X										
Demographics[a]	X										
Inclusion criteria	X										
Exclusion criteria	X										
Urine pregnancy test	X										
HbA1c Point of Care test[b]	X										
Randomization	X										
Medical history/concomitant illness, self-reported duration of diabetes	X										
Concomitant medication	X	X			X			X			X
Disallowed medication[c]		X			X			X			X
EFFICACY											
Height	X										
Body weight	X	X			X			X			X[d]
Questionnaires: EQ-5D-5L, TRIM-D, WPAI:SHP and WLQ-SF	X				X						X

	Screening and Randomization	Usual Care Approach to Management Program									
Visit (V)	V1	V2			V3			V4			V5
Timing of visit (months)	0	3			6			9			12
Visit window (days)	0	±14			±14			±14			±14
Endocrinology visit attendance		X			X			X			X
SAFETY											
Adverse event	X[e]	X			X			X			X
Labs/Blood Pressure & Reminders											
HbA1c/Lipids/Blood Pressure	X	X			X			X			X
Schedule nutritionist appointment	X										

[a] Demographics consists of date of birth, sex, ethnicity, and race

[b] POC HbA1c will be obtained during screening visit and used for assessment of eligibility/study inclusion and randomization. A lab HbA1c will be obtained along with lipids within study visit window. The lab HbA1c will be used for purposes of the analyses.

[c] Disallowed medications: Any medication on- or off-label prescribed for weight loss, including the anti-obesity medications (AOMs) approved for chronic weight management (Xenical®, Saxenda®, Qsymia®, Contrave®, Wegovy ®). Use of these medications will be assessed during routine medication review at scheduled appointments.

[d] If a subject does not attend the visit 5, a stepwise approach to obtaining weight data will be applied to obtain a month 12 weight measurement (-14 days, +14 days from scheduled month 12/visit 5): calling subject in for a month 12/visit 5 weight measurement, extract recent weight data from the electronic medical record, or use recent subject-reported weight.

[e] Serious adverse event and pregnancy collection will begin after informed consent and randomization.

QOL: EQ-5D-5L. Five level health status measure.

TRIM-D. 28 item measure with 5 domains assessing Treatment Burden, Daily Life, Diabetes Management, Compliance and Psychological Health.

WPAI:SHP Work Productivity as measured by Work Productivity and Activity Impairment Questionnaire Specific Health Problem

WLQ-SF Work limitation as measured by Work Limitations Questionnaire 8-Item Self-administered Short Form

Table 7. Time and Events Schedule, Usual Care Approach, Year 2

	Usual Care Approach to Management Program									
Visit (V)	V6			V7			V8			V9
Timing of visit (months)	15			18			21			24
Visit window (days)	±14			±14			±14			±14
SUBJECT-RELATED INFORMATION AND ASSESSMENTS										
Concomitant medication	X			X			X			X
Disallowed medication[a]	X			X			X			X
EFFICACY										
Body weight	X			X			X			X[b]
Questionnaires: EQ-5D-5L, TRIM-D, WPAI:SHP and WLQ-SF				X						X
Endocrinology visit attendance	X			X			X			X
SAFETY										
Adverse event	X			X			X			X
Labs/Blood Pressure & Reminders										
HbA1c/Lipids/Blood Pressure	X			X			X			X

[a] Disallowed medications: Any medication on- or off-label prescribed for weight loss, including the anti-obesity medications (AOMs) approved for chronic weight management (Xenical®, Saxenda®, Qsymia®, Contrave®, Wegovy ®). Use of these medications will be assessed during routine medication review at scheduled appointments.

[b] If a subject does not attend the visit 9, a stepwise approach to obtaining weight data will be applied to obtain a month 24 weight measurement (-14 days, +14 days from scheduled month 24/visit 9): calling subject in for a month 24/visit 9 weight measurement, extract recent weight data from the electronic medical record, or use recent subject-reported weight.

QOL: EQ-5D-5L. Five level health status measure

TRIM-D. 28 item measure with 5 domains assessing Treatment Burden, Daily Life, Diabetes Management, Compliance and Psychological Health.

WPAI:SHP Work Productivity as measured by Work Productivity and Activity Impairment Questionnaire Specific Health Problem

Follow-up

1) Obesity-centric approach (with or without AOM): patients will attend monthly SMAs in year 1, followed by quarterly SMAs in year 2, with an endocrinology specialist/obesity medicine lead team to treat their obesity and review issues related to stress, mental health, nutrition, physical activity, and appetite control. Weight, body mass index, and blood pressure will be assessed at baseline and at the SMAs. A1C will be assessed at baseline and weeks 12, 24, 36, 48, 60, 72, 84 and 96. Serum LDL, HDL and triglycerides will be assessed at baseline and at 24, 48, 72 and 96 weeks. QOL and treatment-related impact surveys will be administered again at weeks 24, 48, 72, and 96. Background standard of care labs and procedures pertaining to T2D management will be obtained (CMP at baseline and every 6 months, yearly urine albumin:Cr), yearly dilated eye exams. Intensification of anti-diabetes therapy occurs as indicated via A1C values, and therapies chosen will be at the discretion of the investigator.

2) Usual care approach (Comorbidity-centric approach): patients will attend office encounters every 3 months with an endocrinology specialist. A1C, weight, body mass index, and blood pressure will be assessed at baseline and at weeks 12, 24, 36, 48, 60, 72, 84 and 96. Serum LDL, HDL and triglycerides will be assessed at baseline, at weeks 24, 48, 72 and 96. QOL and treatment-related impact surveys will be administered again at weeks 24, 48, 72 and 96. Background standard of care labs and procedures pertaining to T2D management will be obtained (CMP at baseline and every 6 months, yearly urine albumin:Cr), yearly dilated eye exams. Intensification of anti-diabetes therapy occurs as indicated via A1C values, and therapies chosen will be at the discretion of the investigator.

At the end of the trial, subjects, who potentially have stopped attending the appointments, will be encouraged to attend the last visit for a lab assessment, weight measurement, and completion of questionnaires within the visit window, unless they have withdrawn consent.

Data collection

A file database will be created for data collection accessible only by authorized study personnel. Information will be entered into the database as it is collected and patients finish the study. Each patient will be assigned a study number consecutively as they are enrolled. Only the study number will be used to identify all study-related documents such as case report forms. A master list of study numbers linked to patient identifiers will be maintained by the study coordinator in a secured location. Study data will be collected and managed using REDCap (Research Electronic Data Capture); this will include patient identification number, medical record number, age, gender, and ethnicity**.**

Biorepository: Serum and urine
Included in the informed consent process and documentation will be an 'opt in/out' for collection of biospecimens. From consenting subjects, the following specimens will be collected at baseline, 3, 12, and 24 months to support future ancillary research studies in this population:
• Blood (plasma): 24 ml will be drawn along with the rest of the labs, then processed, aliquoted, and stored at -80 degrees Celsius. Samples will be processed according to the lab processing manual

• Clean catch urine: samples will be processed, aliquoted and stored according to the lab processing manual

Statistical analysis

The primary analysis will be performed using the intent-to-treat cohort. Categorical factors will be described using frequencies and percentages, while continuous measures will be summarized using means, standard deviations, and percentiles of interest. Changes in primary continuous measures from baseline to the pre-specified times during the follow-up periods will be compared using linear mixed effect models that include baseline levels of these variables as well as stratification factors as covariates. In these models, all commonly observed study times will be used, and interactions between time and group will be included. For the primary endpoints, non-inferiority will be tested at the 0.05 level at 1 year. If both primary endpoints are non-inferior, superiority testing at the 0.025 overall error level for each endpoint at 1 year will be performed [27]. A similar analysis will be performed based on 2-year results from this model as a secondary endpoint. Other secondary endpoints will be performed using similar models, but determination of whether to evaluate time points separately will depend on model fit. If the interactions in these mixed effect models are not significant, overall differences in each endpoint over time will be evaluated. Otherwise, contrasts will be used to compare groups at pre-specified time points. If necessary, transformations of continuous measures will be performed prior to analysis to meet assumptions of the models. These mixed effect models account for data missing at random through maximum likelihood estimation, and do not require additional imputation approaches. The correlation structure used will be chosen based on comparisons of model fits using likelihood ratio tests. Select categorical variables will be compared between groups using mixed effect Poisson regression and logistic regression models, as appropriate. Cost data will be evaluated for normality and then analyzed with Gamma regression, if non-normal distributions are observed. These models will also incorporate multiple time points and evaluate overall and time specific differences between groups. Each endpoint will be tested assuming an overall 0.05 significance level. Non-inferiority tests will be performed pairwise, and therefore will employ Bonferroni adjusted significance levels for each paired comparison. For all tests of superiority, if overall tests are significant, Bonferroni adjustments for pairwise comparisons between groups will be made to preserve the overall significance level. Secondary endpoints will be each evaluated independently with error level control being employed at the Aim level, such that for each aim, the error will be controlled at the 0.05 level. As a sensitivity analysis, a per-protocol analysis, among those patients that meet minimum compliance standards with their assigned treatment will be performed as above.

Adverse events and data monitoring

The PI or one or more study team members designated by the PI will have sole responsibility to monitor adverse events and safety.

Safety

For the purposes of this study, adverse events (AEs) will only be required to be collected if they meet the definition of an SAE. An SAE is defined as any AE which results in at least one of the following outcomes:

- Initial inpatient hospitalization or prolongation of existing inpatient hospitalization
- A life-threatening event, i.e., an event in which the subject was at immediate risk of dying at the time of the event; not an event that hypothetically could have caused death had it been more severe
- Persistent or significant disability or incapacity
- Congenital anomaly or birth defect in offspring
- Death
- Is deemed serious for any other reason, i.e., if it is an important medical event based on appropriate medical judgement which may jeopardize the subject and may require medical or surgical intervention to prevent one of the other listed outcomes.

Study clinicians are responsible for reporting all SAEs and following the subject until the outcome of the event is closed out. All SAEs will be reported from randomization until EOS at month 12, or until the subject withdraws from the study. Study clinicians are also responsible for recording all pregnancies in female subjects from randomization until EOS at month 12 or subject study withdrawal. The subject will be followed for the duration of the pregnancy until one month post-delivery to report the pregnancy outcome and any AEs or SAEs observed in the fetus or newborn until 1 month of age. Safety will be summarized descriptively.

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