Administration of Canagliflozin for the Remission of Metabolic Syndrome in Nondiabetic Adults

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ADMINISTRATION OF CANAGLIFLOZIN FOR THE REMISSION OF
METABOLIC SYNDROME IN NONDIABETIC ADULTS

A Thesis Presented to
The Faculty of the School of Medicine
Yale University

In Candidacy for the degree of
Master of Medical Science

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Abstract

Metabolic syndrome is a critical risk factor for the development of type 2 diabetes mellitus and cardiovascular disease, two of the leading causes of death in the United States. With over one third of the adult population currently affected, this syndrome poses a serious health and economic burden. Lifestyle modification is the primary treatment, however only 50% maintain adherence. A single pharmacological therapy such as canagliflozin may overcome this lack of treatment adherence. **Our purpose is to establish a difference between canagliflozin 300 milligrams daily plus lifestyle modification education and lifestyle modification education alone for the remission of metabolic syndrome in nondiabetic adults after one year.** We will conduct a double-blind, randomized placebo-controlled trial in order to assess for this primary endpoint. This study has the capability to improve the current treatment of metabolic syndrome and potentially prevent the development of type 2 diabetes mellitus and cardiovascular disease.
Chapter 1 – Introduction

1.1 Background:

Metabolic syndrome (MetS) is a cluster of cardiovascular risk factors comprised of obesity, dyslipidemia, hypertension, and glucose intolerance.\(^1,^2\) The United States (US) prevalence of MetS in adults (≥18 years) is reaching pandemic proportions, increasing from 25.3% in 1988-1994 to 34.2% in 2007-2012, and is still expected to rise.\(^3,^4\) Further, data from the Third National Health and Nutrition Examination Survey (NHANES III) indicates that prevalence increases with age, with 44% of the US population over 50 years old meeting MetS criteria.\(^5\)

Identifying MetS in the population is clinically beneficial for several reasons. The discovery allows for the recognition of those with an increased risk of cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM), with a higher risk being associated with a greater number of risk factors.\(^6\) Plus, the reversible nature of MetS allows for a unique opportunity to intervene and reduce the health and economic burdens of CVD and T2DM on the US population.\(^4\)

The cost of MetS to both the patient and the healthcare system is substantial. One study found that those with MetS spend on average about $2,000 more annually than those without ($5,732 vs. $3,581).\(^7\) When examining the financial burden of the syndrome on those 65 years and older, one study found that total cost to Medicare for those with MetS was 20% higher than those without ($40,873 vs. $33,010).\(^8\) Once there is progression to CVD or T2DM, these costs can be expected to rise. As chronic diseases, they take a huge economic toll, costing hundreds of billions of dollars to the healthcare system and billions lost in productivity.\(^9\)
In order to appropriately address MetS, it is important to understand its etiology. Though the exact underlying cause is unknown, the syndrome is widely considered to be a result of insulin resistance. Factors contributing to insulin resistance include both genetic predispositions and environmental components. Over time, insulin resistance leads to hyperglycemia and salt overload, which can then result in hypertension, lipogenesis, and a worsened lipid profile. Treatment targeted towards these initial causes of the syndrome will likely relieve some of the harm and improve outcomes.

Ultimately, the goals of management for MetS are to reduce the risk of progression to CVD and T2DM, two of the leading causes of death and disability in the US. The current primary treatment is lifestyle modification, which includes weight loss, moderately intense physical activity, and a highly structured antiatherogenic diet. Generally, a 10% reduction in weight is encouraged through lifestyle modification; however, the higher the risk of progression to additional diseases, the more likely weight loss drugs will be considered for use.

If tightly followed and maintained, lifestyle modification offers the greatest potential for controlling the pandemic of MetS and has been shown to improve all metabolic abnormalities of the syndrome. But in spite of this promising evidence, nonadherence to lifestyle changes is near 50%, and many patients end up requiring risk-reducing drugs that target each individual risk factor. But this presents a consequential problem of polypharmacy, which comes with its own risks of increased costs, decreased compliance, and adverse drug reactions.

The inverse relationship of number of medications to medication adherence has been cited numerous times in the literature. Drugs frequently noted in these studies were
those that would target the risk factors of MetS: antihypertensives, antidiabetics, and lipid-lowering agents.\textsuperscript{18-25} Consequently, the ideal pharmacologic solution to improve MetS outcomes would be a single drug that simultaneously reduces weight, glucose levels, blood pressure, triglycerides, and raises high-density lipoprotein (HDL) cholesterol.\textsuperscript{14,26}

Sodium-glucose cotransporter 2 inhibitors (SGLT2is), are novel oral antidiabetic drugs that work by inhibiting the sodium-glucose cotransporter 2 in the proximal collecting tubule of the kidney. The inhibition of this transporter prevents the reabsorption of both sodium and glucose, facilitating their excretion into the urine. Through this mechanism, SGLT2is have the potential to target all five components of MetS, thereby reducing the rate of progression to poor outcomes such as CVD and T2DM.\textsuperscript{27}

\textbf{1.2 Statement of the Problem}

Thus far, there has been no randomized controlled trial (RCT) in the US to assess the efficacy of SGLT2is as the single pharmacologic therapy for the treatment of MetS. Any evidence for this potential indication is found in preclinical trials, retrospective analyses or inferred from studies with different primary objectives. While evidence from these studies and analyses is promising,\textsuperscript{28} an RCT is required to evaluate SGLT2is in comparison to what is currently being practiced as the primary treatment: lifestyle modification education. Such an RCT is particularly pressing given the noncompliance and nonadherence rates to the primary treatment, as well as the increased risk of progression to T2DM and CVD with a MetS diagnosis. In comparison to other Food and Drug Administration (FDA)-approved
SGLT2is, canagliflozin has shown slightly more beneficial effects on metabolic abnormalities and is therefore the most promising SGLT2i for the proposed study.29-31

1.3 Goals and Objectives

The purpose of the proposed study is to establish a difference between canagliflozin 300 mg daily plus lifestyle modification education and lifestyle modification education alone for the remission of MetS in nondiabetic adults. This potential difference will be measured using the following primary outcome: remission of MetS in nondiabetic adults after one year (represented as incidence proportions). The results of this primary outcome will serve as a foundation for the use of canagliflozin in the treatment of nondiabetic adults with MetS and inform the drug’s role in the prevention of T2DM and CVD development.

Secondary outcomes will include fasting plasma glucose (FPG), waist circumference, blood pressure, triglyceride level, HDL cholesterol, C-reactive protein (CRP) level, insulin resistance, glycated hemoglobin (hA1C), and change in diet and exercise. Adverse events to be monitored include genital mycotic infection and amputations, among others. Measuring these outcomes and events will achieve our goal of quantifying the effect of canagliflozin 300 mg on metabolic abnormalities in nondiabetic adults after one year, identify possibly modifying effects on the outcome, and clarify canagliflozin’s safety profile.

1.4 Hypothesis

There will be a difference in the proportion of nondiabetic adults who achieve remission of MetS after one year of initiation of canagliflozin 300 mg daily plus lifestyle modification education compared to lifestyle modification education alone.
1.5 Definitions

- **MetS**: meeting 3 or more of the following criteria:
  
  o Impaired Fasting Glucose (IFG) (FPG 100-125 mg/dL)
  
  o Abdominal obesity (waist circumference > 40 inches in men and > 35 inches in women)
  
  o Blood pressure ≥ 135/85 mmHg
  
  o Triglycerides ≥ 150 mg/dL
  
  o HDL cholesterol < 40 mg/dL in men and <50 mg/dL in women

- **Remission of MetS**: meeting ≤ 2 MetS criteria (listed above)

- **Lifestyle modification education**: Unstructured advice delivered by our research team’s physicians emphasizing the importance of a healthy lifestyle. Topics to be discussed include smoking and alcohol cessation, as well as proper exercise, eating, and sleeping habits. All research team physicians will be educated on the Centers for Disease Control and Prevention’s (CDC) National Diabetes Prevention Program curriculum before delivering the lifestyle modification education.
1.6 References

Chapter 2 – Literature Review

2.1 Introduction

To date, there are no studies in the US evaluating the use of SGLT2is as the single pharmacologic therapy versus the current primary recommendations for the treatment of metabolic syndrome (MetS). The purpose of this literature review is to summarize and critically evaluate prior research pertaining to this topic. The review of literature was performed from August 2019 to June 2020 using PubMed, Ovid and Embase databases. Systematic reviews, meta-analyses, and RCTs were included. Only results written in the English language were reviewed. The following MeSH terms were utilized:

Metabolic syndrome, Syndrome X, MetS, Type 2 Diabetes Mellitus, T2DM,
Impaired Fasting Glucose, Gliflozins, SGLT2i, SGLT2 inhibitor, Sodium Glucose Cotransporter-2 Inhibitor, Empagliflozin, Canagliflozin, Dapagliflozin

2.2 Brief overview of Metabolic Syndrome and Its Implications

MetS, as defined by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III), is a constellation of three or more risk factors for T2DM and CVD, which include obesity (waist circumference >40 inches for men and >35 inches for women), high triglycerides (≥150 mg/dL), low HDL cholesterol (<40 mg/dL in men and <50 mg/dL in women), hypertension (blood pressure ≥130/85 mmHg), and glucose intolerance (fasting plasma glucose ≥100 mg/dL). The syndrome results from a lack of physical activity, poor diet, and genetic predisposition. These habits and inherent susceptibility, over time, lead to insulin resistance and a chronic inflammatory state, which ultimately presents as the vascular damage and autonomic dysfunction consistent with MetS.
The strong association between MetS and the risk of development of T2DM has been well-documented. In a meta-analysis of prospective cohort studies, the relative risk (RR) of developing T2DM with a diagnosis of MetS ranged from 3.53 to 5.17 depending on the criteria used to define MetS. This risk also increases with the number of metabolic abnormalities one has. The same meta-analysis found that compared to those without any abnormality, the RR for developing T2DM for those with four or five abnormalities using the NCEP/ATPIII definition ranged from 10.88 to 24.4. This meta-analysis incorporated multiethnic prospective studies to draw these conclusions, which allows these results to be applied to a considerably heterogeneous population.\textsuperscript{4}

Evidence for the risk of CVD with a MetS diagnosis is well-supported in the literature. In a national cross-sectional study examining the association between MetS and CVD, Ninomiya et al. found that those with MetS were twice as likely to have a stroke or myocardial infarction (MI) (odds ratio [OR] 2.05; 95% confidence interval [CI], 1.64 to 2.57) than those without the syndrome. These results, though significant, are limited by both poor internal validity due to potential recall biases and its inherent inability to draw a causal relationship between the predictor variables and outcomes.\textsuperscript{5} Lakka et al. sought to better identify a causal relationship between MetS and death due to CVD and coronary heart disease (CHD) by conducting a prospective study following \textasciitilde1200 Finnish men over the average course of 11.4 years. They concluded that men with MetS were almost 3 times more likely to die of CHD and 2.5 times more likely to die of CVD. Though this study is difficult to generalize, major strengths include its longitudinal design and exclusion of men with T2DM and CVD at baseline.\textsuperscript{6}
For those who achieve remission of MetS, the risk of T2DM and CVD are significantly reduced. This phenomenon was observed by Huh et al. (2019) with a large prospective cohort study investigating change in MetS status on 10-year risk of incident T2DM in a Korean population. The authors followed 7,317 subjects to determine their change in MetS status after a two-year period and group them into four categories: non-MetS, incident MetS, resolved MetS, and persistent MetS. Using a Cox proportional-hazards analysis, Huh et al. found that the persistent MetS group showed the highest incidence risk of T2DM (hazard ratio [HR] 1.98; 95% CI, 1.50 to 2.61), and the resolved MetS group showed a decreased incidence risk of T2DM (HR 1.28; 95% CI, 0.92 to 1.79). The difference between these two groups was statistically significant (p <0.0001).

Seeing as T2DM is a known risk factor for CVD, it may be inferred from these results that the resolved MetS group not only had a decreased incidence risk of T2DM, but also of CVD. These results may even be underestimated due to loss to follow-up. Because of the homogenous sample, these results should be applied to more diverse populations with caution. However, the findings of this study should not be downplayed, as they suggest that treating MetS may prevent T2DM in practice.

Park et. al. further demonstrated the favorable effects of achieving remission of MetS in a 2019 retrospective cohort study investigating the association between MetS status and major adverse cardiovascular events (MACE), including MI, stroke, and revascularization. From the health data of 9,553,042 Koreans, Park et. al. concluded that those who achieved remission of MetS had a significantly lower (p <0.001) MACE risk (adjusted incidence rate ratio [IRR] 1.48; 95% CI, 1.44 to 1.51) than those with persistent MetS (adjusted IRR 2.01; 95% CI 1.98 to 2.04). The major strength of this study is that
the findings came from a large nationwide database. At the same time, this serves as a limitation because the findings have only come from one nation. Nonetheless, the results of this study are noteworthy as they highlight the potential benefits of achieving remission of MetS.

The importance of this syndrome is evident due to its striking prevalence and association with an increased risk of both T2DM and CVD and their complications. Therefore, effective treatment strategies are needed that target the components of the syndrome to prevent associated morbidity and mortality.\textsuperscript{8,10} Current management strategies practiced by clinicians include recommending lifestyle modification, as well as prescribing antihypertensives, lipid-lowering agents, and antidiabetics if felt necessary. These options will be reviewed in the following section.\textsuperscript{11}

2.3 Review of Current Strategies and Their Limitations

2.3.1 Lifestyle Modification Therapy

Although genetics play a role in the development of MetS, the syndrome often coincides with poor diet and physical inactivity. Therefore, initial treatments tend to focus on lifestyle modification therapy (diet, physical activity, behavioral strategies, etc.) before beginning drug therapy.\textsuperscript{11} If patients are motivated and willing to adhere to the recommendations, these changes offer substantial benefit.\textsuperscript{12-15} Pettman et al. demonstrated this in a 2008 RCT that compared a 16-week lifestyle program (intervention) to education on the national guidelines for healthy eating (control) for the treatment of MetS. The lifestyle program provided strategies in diet, exercise, and behavior, peer group support, free gym access, and one supervised exercise session each week. The results revealed that the intervention was effective in targeting the risk factors
of MetS, including obesity, blood pressure, total cholesterol, and plasma glucose. The study further demonstrated that greater attendance at information and exercise sessions was associated with greater reductions in body fat (p <0.001), diastolic blood pressure (p<0.001), systolic blood pressure (p = 0.01), total cholesterol (p <0.001), and plasma glucose (p < 0.001). While this study speaks to the benefits of lifestyle intervention, it was limited by its loss of 33 participants to follow-up (21.5%) and its assessment of compliance, which consisted of self-reported food and physical activity logs.16

While the patients’ recognition of the benefits of lifestyle modifications is important, receiving brief information on healthy diet and exercise practices from a provider alone is not typically sufficient to inspire weight loss habits or lead to health benefits. A 2007 RCT conducted by Bo et al. demonstrated this by comparing a recommendation-based program of lifestyle intervention facilitated by trained professionals to advice given by family physicians to evaluate change in MetS prevalence after one year. The authors found that the intervention significantly reduced the prevalence of MetS compared to the controls (p <0.001). This emphasizes the inefficacy of advice given by primary care providers (PCPs), which was shown by the control group’s worsening metabolic variables and increasing cardiovascular risk over the year. These results were strengthened by the similarity of the two groups after randomization and by the sample size of 375 participants.17

Not only is there a problem regarding noncompliance to lifestyle modification recommendations, but there is also the issue of nonadherence for those who do receive active interventions.18 For example, the Diabetes Prevention Program (DPP) Research Group determined that only about 20% of overweight individuals are successful at
maintaining weight loss after participating in intensive lifestyle intervention. Utilizing an RCT, the DPP Research Group followed approximately 1000 overweight individuals in an intensive lifestyle intervention for up to 4.6 years and found that the group, on average, maintained a weight loss of about 7 kg at 6 months, but only about 3 kg at 4 years. This study upholds external validity by including a well-sized population that was racially and ethnically diverse, allowing the results to be generalized to the larger US population.19,20

Noncompliance and nonadherence to lifestyle modifications illustrate a need for other forms of therapy in the treatment of chronic illnesses such as MetS. Providers typically move towards pharmacotherapy when lifestyle modification proves to be inadequate, as it often does.21 Current drug therapies will be briefly reviewed in the following section.

2.3.2 Pharmacotherapy

The American Heart Association and National Heart, Lung, and Blood Institute released practice guidelines regarding the choice of drug for each component of the syndrome for those with risk factors that are not controlled adequately by a patient’s lifestyle changes, as is the case for many.11,22 Such drugs typically include antihypertensives, lipid-lowering agents, and antidiabetics.11 As risk factors worsen, the number of drugs required to treat each risk factor tends to increase. For instance, once IFG has progressed to the diagnosis of T2DM in patients with MetS, often ≥10 medications are required for treatment. At this point, a patient may not only be prescribed medications for the risk factors of MetS and its complications, but also for closely related conditions that follow (kidney disease, peripheral neuropathy, etc.).22
While the risk factors and complications of MetS must be treated, polypharmacy comes with its own dangers. In a systematic review, Rollason and Vogt identified six major clinical consequences of polypharmacy, for all of which the risk increases with number of medications taken: patient nonadherence, drug-drug interactions, increased risk of hospitalizations, medication errors, adverse drug events, and increased cost.\(^\text{23}\) These unfavorable possibilities emphasize the need for a single drug that can target the five metabolic abnormalities of the syndrome and prevent further complications.

Some argue that metformin is the single drug that can accomplish this task, however studies have shown that metformin is not equipped to significantly reduce the incidence of MetS when compared to placebo in an adult population.\(^\text{24}\) In a large RCT conducted by the DPP, 1711 volunteer participants were shown to have MetS at baseline and were equally randomized to three groups: intensive lifestyle intervention, metformin 850 mg twice daily, and placebo. After a 3-year follow-up, resolution of MetS was only found to be significant in the intensive lifestyle intervention group (38%; \(p = 0.002\)) when compared to placebo. In the metformin group, only 23% of those with MetS at baseline had resolution (not significant, no \(p\) value provided). Importantly, it is possible that the only reason the intensive lifestyle found significant resolution when compared to placebo was due to the volunteer population, which arguably could have higher motivation to restore health than the general population.\(^\text{24}\)

2.4 The Promise of Sodium-Glucose Cotransporter 2 Inhibitors

The first SGLT2i, canagliflozin, was approved in 2013 by the FDA for the improvement of glycemic control and treatment of T2DM in adults. The following SGLT2is, dapagliflozin and empagliflozin, were approved for the same indication shortly
thereafter.\textsuperscript{25} As the class of the drug describes, SGLT2is work by inhibiting the sodium-glucose cotransporter 2 in the proximal convoluted tubule of the nephron. Inhibition of this transporter primarily reduces the reabsorption of filtered glucose, but has also been noted to increase urinary sodium excretion.\textsuperscript{26} Through this mechanism, SGLT2is have been shown to positively influence not only fasting plasma glucose levels, but also body weight, blood pressure, and lipid levels.\textsuperscript{25} This section will review the current understanding of how SGLT2is are potential sole treatments for MetS.

2.4.1 Impaired Fasting Glucose (Fasting Plasma Glucose $\geq$100 mg/dL)

SGLT2is are currently indicated to treat T2DM and improve glycemic control.\textsuperscript{27} Multiple studies have documented a larger decrease in FPG as an outcome of treatment with SGLT2is, regardless of which FDA approved drug, when compared to placebo.\textsuperscript{28-46} To illustrate one study, Abdul-Ghani et al. identified eight subjects with IFG and assigned them empagliflozin 25 mg daily (treatment) for two weeks. FPG concentration was measured both 2 days and 14 days after the start of treatment. The results showed a statistically significant decrease in FPG in the IFG subjects at day 2 (from 110 ± 2 mg/dL to 103 ± 3 mg/dL; $P < 0.01$). This decrease was maintained at day 14.\textsuperscript{46} Although the short follow-up period and small sample size limit the impact of the aforementioned results, the CANTANA-M trial found a similar outcome but with a larger sample and longer length of study.\textsuperscript{47}

The CANTANA-M study was a randomized, double-blinded clinical trial evaluating the effects of canagliflozin 100 or 300 mg versus placebo over a 52-week period. From baseline to week 52, the authors found a dose-dependent reduction in least squares FPG mean changes (-27.4 mg/dL, 95% CI -31.8, -23.0 and -39.1 mg/dL, 95% CI
-43.6, -34.7 for 100 mg and 300 mg, respectively), and changes were seen as early as 6 weeks into treatment. A total of 452 participants spanning 17 countries completed the entire 52-week study. This multi-country recruitment method serves this study well, as its results are more easily applied to a greater population.47

2.4.2 Obesity (Waist Circumference: Men >40 inches, Women >35 inches)

SGLT2is have also been shown to reduce weight from 1 kg to up to 5 kg, with a greater reduction in weight seen in those with a higher weight at baseline.37,48,49 While the weight loss might be attributable to volume depletion, it has also been shown to have come from visceral fat.48,50-52 The ASSIGN-K study demonstrated this reduction of visceral fat with 50 mg ipragliflozin (an SGLT2i currently approved in Japan) given to 257 patients over 24 weeks, where in the first 4 weeks both body water and body fat decreased significantly, but from weeks 4-24, body fat continued to decrease while body water seemed to remain relatively unchanged. This study was both strengthened and limited by the sample population, which consisted only of Japanese patients with T2DM who had inadequate glycemic control with a hA1C >6% despite diet and exercise therapy or diet and exercise plus antidiabetic drug therapy for at least 12 weeks. This population strengthened the study by demonstrating an SGLT2i to be more effective than lifestyle modification. At the same time, this population only included one ethnicity, making it difficult to generalize to the US population.53

In a different prospective intervention study conducted by Lee et. al., it was found that more than 70% of weight loss from ipragliflozin was attributable to reduction in body fat, while only about 20% was attributable to water loss. However, this was a single-arm study without placebo control, making the evaluation of the results more
difficult. Further, the body composition analyzer used in the study could not distinguish between visceral fat and subcutaneous fat.\textsuperscript{54} Nonetheless, these results are promising in that SGLT2is could effectively reduce waist circumference and address the obesity component of MetS.\textsuperscript{55,56}

\textbf{2.4.3 Hypertension (Blood Pressure $\geq$130/85 mmHg)}

SGLT2is are not indicated as antihypertensive drugs. However, the blood pressure-lowering effect of SGLT2is has been documented in numerous studies and is thought to be due to the drug class’s mechanism of action, which facilitates both glucose- and sodium-induced osmotic diuresis.\textsuperscript{57} Regardless of the mechanism, these drugs have been noted to lower systolic blood pressure more than placebo.\textsuperscript{58} For instance, in a meta-analysis of 38 clinical trials, Zaccardi et. al. found a reduction of up to -4.9 mmHg in systolic blood pressure and up to -2.0 in diastolic blood pressure in all SGLT2is versus placebo, with canagliflozin 300 mg producing the largest reduction.\textsuperscript{59}

The EMPA-REG OUTCOME trial was the first major double-blinded, placebo-controlled RCT documenting the cardiovascular benefit of an SGLT2i. The study quantified blood pressure reduction as a consequence of empagliflozin at either 10 mg or 25 mg. Regardless of the dose, empagliflozin reduced the mean systolic blood pressure by about 4 mmHg more than placebo after 52 weeks.\textsuperscript{60} The CANVAS Program study found similar results, as canagliflozin was noted to produce a mean difference systolic blood pressure of -3.93 mmHg more than placebo ($p < 0.001$, 95\% CI, -4.30 to -3.56).\textsuperscript{61} Though both the CANVAS Program and EMPA-REG OUTCOME trials included primarily white males, the large sample sizes (10,142 and 7,020, respectively) are able to provide more accurate mean values and smaller margins of error.
The blood pressure-lowering effect of SGLT2is has even been recognized by the FDA and is reported in the respective labeling documents.\textsuperscript{48} For example, the prescribing information for INVOKANA (canagliflozin) warns about the risk of hypotension for those who already have low blood pressure and supports this advisory with a double-blind, placebo-controlled study. The study enrolled 584 patients and revealed statistically significant (p<0.001) mean changes from baseline in systolic blood pressure relative to placebo.\textsuperscript{58} This evidence further supports the use of SGLT2is as a mediator for a blood pressure-lowering effect.

2.4.4 Lipid Disorders (Triglycerides $\geq$150 mg/dL; HDL Cholesterol: Men <40 mg/dL, Women <50 mg/dL)

RCTs and meta-analyses have shown SGLT2is can address the last two components of MetS: low HDL cholesterol and high triglycerides. With regard to the former, the EMPA-REG OUTCOME and CANVAS trials both found small increases (~2 mg/dL) in HDL cholesterol after 52 weeks of treatment with empagliflozin and canagliflozin, respectively.\textsuperscript{60,61} Another study found small improvements in HDL cholesterol (+2.1% to +9.3%) and small reductions in triglycerides (-0.9% to -10.6%) in patients receiving dapagliflozin.\textsuperscript{62} In the Zaccardi et. al. meta-analysis of 38 clinical trials, all SGLT2is slightly increased HDL cholesterol when compared with placebo, with the highest increase being 1.26 mg/dL. The same meta-analysis revealed that canagliflozin at all doses reduced triglyceride levels when compared with placebo.\textsuperscript{59} These results support the beneficial effects of SGLT2is on lipid disorders.

2.5 Limitations of Sodium-Glucose Cotransporter 2 Inhibitors
No drug comes without report of adverse events, and SGLT2is are no exception. Though these drugs are generally well-tolerated, reported adverse events for this drug class range from non-serious, easily treatable infections to life-threatening complications. Genital mycotic infection with candida species is the most frequently reported adverse event and is observed in all FDA approved SGLT2is. The EMPA-REG OUTCOME trial reported a 3-4x increase in genital infection with candida species with pooled treatment of empagliflozin versus placebo. The increase in genital infection was statistically significant when compared with placebo (p <0.001) and was observed in both men and women. Similar statistically significant (p <0.001) outcomes were found in the CANVAS study, where the incidence of genital mycotic infections per 100 patient years for both men (3.5) and women (6.9) were 3-4x higher than men and women in the placebo group (1.1 and 1.8, respectively). The DECLARE study, which randomized 17,160 participants with T2DM to dapagliflozin or placebo to evaluate the cardiovascular safety profile of dapagliflozin, also found a statistically significant (p <0.001) increase in genital infections in the treatment group. Seventy-six participants receiving 10 mg of dapagliflozin developed a genital infection, while only 9 participants receiving placebo developed a genital infection. While genital mycotic infections are the most frequently reported adverse event, they remain relatively uncommon, are easily treated, and rarely lead to discontinuation of the drug.

Urinary tract infections (UTIs) also seem to be a cited adverse event in the literature. In 2015, the FDA even issued a Drug Safety Communication warning of the risk of complicated UTIs. However, when compared to placebo in RCTs, SGLT2is do not seem to significantly increase the risk of UTIs. This may be because SGLT2is are
typically prescribed to diabetic patients, and diabetic patients are at an increased risk of developing UTIs.\textsuperscript{63} Neither the EMPA-REG OUTCOME, CANVAS, nor the DECLARE study found statistically significant differences in reported UTIs in the treatment versus placebo groups.\textsuperscript{60,61,64}

Other adverse events of concern include hypoglycemia, ketoacidosis, kidney injury, cancer (breast and bladder), urosepsis, bone fracture, and perineal necrotizing fasciitis (Fournier’s gangrene).\textsuperscript{63} Importantly, the EMPA-REG OUTCOME, CANVAS, and DECLARE studies (all large RCTs with a type 2 diabetic population) did not find any statistically significant differences in the incidences of these adverse events in the treatment versus placebo groups.\textsuperscript{60,61,64} Hypotension due to intravascular volume depletion was also noted to be balanced between the treatment and placebo groups.\textsuperscript{60,64} Reports of these adverse events might be due to other drugs or a combination of SGLT2is plus other drugs that the type 2 diabetic population could be prescribed (i.e. insulin, diuretics, etc.). They might also be due to intercurrent stressors, such as illness or major surgery, or because of incorrect use of the drug, such as skipping days of treatment.\textsuperscript{63}

Of note, canagliflozin has a black box warning (BBW) for lower limb amputations (LLA) in type 2 diabetics with established CVD as a consequence of results from the CANVAS study.\textsuperscript{58} Patients in this study were followed for an average of 5.7 years, and those taking canagliflozin were found to be about twice as likely to have a LLA than those taking placebo (6.3 vs. 3.4 participants with amputation per 1000 patient-years; HR 1.97; 95\% CI, 1.41 to 2.75). These amputations most often occurred at the levels of the toe or metatarsal and in those with a history of amputation or peripheral vascular disease.\textsuperscript{61} No significant difference in amputations in empagliflozin or
dapagliflozin versus placebo were found in the EMPA-REG OUTCOME or DECLARE studies, respectively.\textsuperscript{60,64}

Despite the BBW for LLA with the use of canagliflozin, SGLT2is have a relatively good safety profile. The most commonly reported adverse event, genital mycotic infections, is rather minor and can be easily treated. Serious adverse events are infrequent and can potentially be avoided with diligent prophylactic measures and patient education.

2.6 Methodology Considerations for the Proposed Study

2.6.1 Choice of Intervention Group

Existing studies assessing for remission of MetS all do so following demanding interventions, including diet, exercise, combinations of both, bariatric surgery, and medications such as metformin.\textsuperscript{66} However, data regarding remission of MetS using the promising SGLT2is are scarce, with only one study of this nature being identified in the literature. Using the SGLT2i dapagliflozin, González-Ortiz et al. found a favorable remission rate of 58.3\% in 12 participants after 12 weeks of intervention.\textsuperscript{67} The small sample size and short intervention period of this study prompt further investigation of SGLT2is for the remission of MetS.

Following a thorough review of the literature, it has been determined that empagliflozin, canagliflozin, and dapagliflozin have consistent class effects and similar safety profiles. However, slight differences in their effects on metabolic abnormalities have been noted between them in various meta-analyses. For example, even though all SGLT2is are shown to reduce blood pressure, indirect data from a meta-analysis demonstrated that canagliflozin 300 mg daily led to greater reduction of systolic blood
pressure when compared with other SGLT2is, while no differences were reported for diastolic blood pressure among several SGLT2is.\textsuperscript{68} Two other meta-analyses both showed that canagliflozin had the largest favorable effects on lipid profiles (increased HDL and decreased triglycerides) when compared to empagliflozin and dapagliflozin.\textsuperscript{69,70}

For the purposes of this study, canagliflozin 300 mg tablet daily will be used due to its slightly more beneficial outcomes as evidenced in the aforementioned meta-analyses. Because our study population consists of nondiabetics, the BBW for LLA with canagliflozin will likely not be of concern as it is noted specifically for patients diagnosed with T2DM and have or are at risk for CVD.\textsuperscript{58} Although 100 mg is the starting dose of canagliflozin, 300 mg has been shown to offer a greater benefit and will therefore be the dose offered in this study.\textsuperscript{71} In addition to canagliflozin 300 mg tablet daily, the intervention group will receive lifestyle modification education. This education will be identical to that given to the control group to ensure blinding of the participants and investigators.

While González-Ortiz et al. found encouraging results after only 12 weeks of SGLT2i administration, the authors note that longer-term studies need to be performed to confirm the findings.\textsuperscript{67} Landmark studies of SGLT2is have administered treatment for close to 5 years, but all were able to find notable results after 52 weeks.\textsuperscript{60,61,64} In an effort to maintain both feasibility and reliability, the duration of the intervention for the proposed study will be 52 weeks. In this achievable time frame, we expect well-founded results that can translate to clinical practice.

\textit{2.6.2 Choice of Control Group}
Most studies evaluating the potential benefit of SGLT2is as monotherapy, regardless of the study population, compare the drug class to either a placebo drug, another antidiabetic drug, or an intensive lifestyle intervention. None of these studies have compared the drug class to lifestyle modification education alone, which is what might typically be offered initially to nondiabetic adults with MetS. Such a control group is necessary to establish the efficacy of SGLT2is compared to current clinician practices.

Bo et al. managed to compare the role of recommendation-based lifestyle intervention program given by trained professionals to unstructured advice given by family physicians (“usual care”) in the remission of MetS. This study demonstrated that usual care is insufficient to treat MetS, and alternative therapies are necessary.17

Thus, our RCT will employ lifestyle modification education as our control for the purposes of comparing SGLT2is to the reality of standard treatment for MetS in nondiabetic adults. Modeled off of Bo et al.’s RCT, participants will receive the lifestyle modification education from our research team’s physicians once at the start of the intervention period, with no further material offered for the entirety of the 52 weeks.17 This education will be identical to that given to the intervention group. The control group will also receive a placebo pill that appears identical to the canagliflozin 300 mg tablet to keep in accordance with a double-blinded clinical trial. This control group will serve to demonstrate whether there is a difference between an SGLT2i and actual everyday practice and help direct future clinical management.

2.6.3 Study Population: Inclusion and Exclusion Criteria

The NCEP/ATPIII definition of MetS is the most widely accepted and utilized classification for diagnosis. When experts in the field discuss the implications of a MetS
diagnosis, the risk of progression to T2DM is frequently cited.\(^2\) This reported risk of progression to T2DM implies that those with MetS who would benefit considerably from an intervention are in a state of prediabetes (FPG 100-125 mg/dL). Therefore, adults (aged 18-65 years) meeting a modified NCEP/ATPIII definition of MetS will be recruited as the study population for our proposed RCT, where the modified definition is as follows:

Participants must have any three or more of the following:

- IFG (FPG 100-125 mg/dL)
- Abdominal obesity (waist circumference > 40 inches in men and > 35 inches in women)
- Blood pressure \(\geq 135/85\) mmHg
- Triglycerides \(\geq 150\) mg/dL
- HDL cholesterol < 40 mg/dL in men and < 50 mg/dL in women

In addition to T2DM, other diseases to be excluded include type 1 diabetes mellitus, CVDs, chronic liver or kidney disease, and advanced cancer. These diseases, which require medications and specific diet and exercise recommendations, would likely bias the results of the study.\(^{17,67}\) In efficacy and safety studies of 300 mg canagliflozin, participants with moderate renal impairment (estimated glomerular filtration rate [eGFR] 30-50 mL/min/1.73m\(^2\)) experienced increases in serum potassium levels. This population may also be more susceptible to complications such as hypotension or acute kidney injury with canagliflozin at any dosage. Due to the increased potential for adverse events with moderate renal impairment and the 300 mg dose of canagliflozin used for this proposed study, those with an eGFR of <60 mL/min/1.73m\(^2\) will be excluded from the
study. Canagliflozin is contraindicated in dialysis patients, and thus dialysis patients will be excluded as well.\textsuperscript{58}

Elderly participants (\textgreater 65 years) will be excluded to not only maintain consistency with several other relevant studies,\textsuperscript{17,67} but also to limit the number of adverse events. Due to its mechanism of action, canagliflozin has the ability to reduce intravascular volume. This process was shown to cause more adverse events (i.e. orthostatic hypotension, syncope, dehydration, etc.) in those \textgreater 65 years more often than in younger individuals in 13 clinical trials of canagliflozin.\textsuperscript{58}

While there is existing human data to speak to the effects of canagliflozin on the elderly, the same cannot be said for pregnant or breastfeeding women and breastfed infants. Any efficacy or safety data for these populations comes from animal studies.\textsuperscript{58} Due to the lack of human evidence, pregnant and breastfeeding women will be excluded from the study. Further, any women of childbearing age must agree to use an acceptable birth control method. These include tubal ligation, transdermal patch, intrauterine device/system, oral, implantable, or injectable contraceptives, sexual abstinence, double barrier method, or vasectomy of partner. This requirement is adapted from the EMPA-REG OUTCOME study.\textsuperscript{60}

In accordance with the landmark CANVAS study, current or prior users of SGLT2is will be excluded from the study.\textsuperscript{61} All participants being SGLT2i-naïve allows the outcomes between participants to be more accurately compared.

\textbf{2.6.4 Primary and Secondary Outcomes}

Several studies investigating SGLT2is look at the drugs’ effects on the five abnormalities of MetS as distinct secondary outcomes.\textsuperscript{59,67} Despite the evidence of its
metabolic effects, there is no evidence supporting the use of canagliflozin as a single treatment for MetS. Therefore, remission of MetS will be the dichotomous primary outcome of this study.

Many secondary outcomes will be measured in this study, including the five distinct metabolic abnormalities of MetS: fasting plasma glucose (mg/dL), waist circumference (inches), blood pressure (mmHg), triglyceride level (mg/dL), and HDL cholesterol (mg/dL). Evaluating these abnormalities separately will quantify the metabolic effects of canagliflozin 300 mg in nondiabetic adults after one year of treatment. It will also allow for the analysis of which improved metabolic abnormality contributes most to the remission of MetS.

Additional secondary outcomes will include CRP level (mg/L), change in diet, change in exercise, insulin resistance, and hA1C. Numerous studies have linked elevated CRP levels with MetS, and there is evidence to support that elevated CRP levels contribute to an increased cardiovascular risk. In 2004, Yudkin et al. found strong associations between the CRP levels and metabolic abnormalities, including insulin resistance, blood pressure, low HDL, and triglycerides in nondiabetes with MetS. There is limited evidence suggesting SGLT2is reduce CRP levels. One study conducted by Garvey et al. found a trend of decreasing CRP levels in participants with T2DM (on metformin) receiving canagliflozin 300 mg for 52 weeks; however, this trend was not statistically significant. Because there is a strong association between CRP levels and MetS, and there is currently insufficient evidence to ascertain a relationship between SGLT2is and CRP levels, CRP levels make for an important secondary outcome in establishing the effect of SGLT2is (in this case, canagliflozin) on MetS.
Change in diet and exercise over the 52-week intervention period are two variables that may influence the primary outcome of our proposed study, and thus they must be included as secondary outcomes to evaluate for a modifying effect. To monitor for changes in diet, participants will complete a Food Frequency Questionnaire (FFQ) on both the first and last day of the intervention period. The FFQ is a fixed list of foods and beverages with areas to indicate the usual frequency of consumption of specific portion sizes over a stated period of time. The FFQ to be used for this proposed study is the Diet History Questionnaire III (DHQ III) developed by the National Cancer Institute, which includes 135 food and beverage line items and 26 dietary supplement questions. In 2003, the OPEN study evaluated the validity of the “Past Year with Portion Size” DHQ III and determined that underreporting is a significant problem. Because recall accuracy declines as the time between the reference period and the administration of a FFQ increases, the “Past Month with Portion Size” DHQ III will be administered in hopes of limiting measurement error and recall bias. The Healthy Eating Index-2015 (HEI) is a data output of the “Past Month with Portion Size” DHQ III that measures alignment with the Dietary Guidelines for Americans, and it has demonstrated both construct validity and reliability for this purpose.

To monitor for changes in exercise, the Stanford 7-day Physical Activity Recall (PAR) self-report questionnaire will be used. Categories of activity included in this well-studied questionnaire are sleep and moderate, hard, and very hard physical activity. Although this questionnaire is subject to recall and social desirability bias, it is cost effective and easy to administer among groups. In *A Practical Guide to Measuring Physical Activity*, Sylvia et al. reports that adults have adequate recall ability for a self-
report questionnaire,\textsuperscript{80} and thus the Stanford 7-Day PAR should be sufficient in measuring our secondary variable. Energy expenditure, measured in kcal/kg/day, is a data output of the questionnaire, making the results of the questionnaires easily comparable amongst study participants.

Seeing that insulin resistance is the leading mechanism proposed for the development of MetS, it is important to quantify this value and monitor changes in the participants.\textsuperscript{67} In our study, insulin resistance will be estimated using the modified homeostasis model assessment (HOMA-IR). HOMA-IR is a simple index based on fasting levels of glucose and insulin that has been validated for the estimation of insulin resistance. Simple indices assess hepatic insulin resistance (the chief contributor to the pre-diabetic state) more than they do peripheral insulin sensitivity, and is consequently unreliable for populations with uncontrolled T2DM or type 1 diabetes mellitus. While it has been argued that this method of assessment is a limitation of simple indices such as HOMA-IR,\textsuperscript{81} in the case of our proposed study it may actually serve as a strength, given that our population will include those in a pre-diabetic state.

T2DM is a significant consequence of MetS, and therefore its risk and potential progression over time should be measured as a secondary outcome in our sample population. T2DM risk and progression is typically measured by hA1C as a percentage, and thus our study will do the same.\textsuperscript{82,83}

\textit{2.6.5 Monitoring of Side Effects and Adverse Events}

In their 12-week RCT evaluating dapagliflozin for the remission of MetS, González-Ortiz et al. had participants record side effects in a diary and present the diary at monthly visits, where the investigator would inquire further if needed.\textsuperscript{67} Although the
intervention and primary outcome of González-Ortíz et al.’s study is most similar to those of the one being proposed, their method of identifying adverse events leaves room for error. For instance, it is unclear whether the participants were aware of which symptoms to be concerned about and document, or whether investigators conducted thorough physical exams and testing regardless of participants’ diary recordings. Consequently, it is possible some side effects or adverse events were missed.

In a better effort to account for safety outcomes and adverse events, the three large phase 3 trials evaluating the effect of SGLT2is on cardiovascular outcomes had participants return for in-person follow-up appointments at pre-specified periods during the course of the studies.\textsuperscript{60,61,64} For example, the DECLARE study had participants follow-up every 6 months, while the CANVAS study had participants follow-up every 3 months in the first year, and every 6 months thereafter (each study also conducted telephone follow-ups in between in-person visits).\textsuperscript{61,64} Because the proposed study will last for only 52 weeks, monitoring of side effects and adverse events will take place during in-person follow-ups every 3 months with telephone follow-up occurring every month, as modeled after the CANVAS study.\textsuperscript{61} Safety outcomes as previously mentioned in “Limitations of Sodium-Glucose Cotransporter 2 Inhibitors” will be followed throughout the course of this study.

\textbf{2.6.6 Confounding Variables}

Due to the nature of RCTs, the effects of any variables related to both the exposure (canagliflozin) and the primary outcome (remission of MetS) should be reduced and likely insignificant. However, there are effect modifiers that have often been noted in relevant studies, including age, education level, smoking habits, alcohol consumption,
LDL levels, change in diet and exercise, and independent prescriptions for specific MetS abnormalities. \textsuperscript{6,66}

**2.7 Conclusion**

Existing literature backs the use of SGLT2is as a single drug catalyst for remission of MetS. To date, only one study has evaluated such a proposal, with the results being limited by a small sample size and short follow-up period. Due to its documented superiorities over other drugs in its class, canagliflozin is a sensible SGLT2i for further study. Remission of MetS is a logical primary outcome because the results could have additional implications for canagliflozin’s ability to prevent T2DM and CVD. Important secondary variables to consider include FPG, waist circumference, blood pressure, triglycerides, and HDL cholesterol, as well as CRP, HEI, energy expenditure, HOMA-IR, and hA1C. Important adverse events to monitor include number of genital mycotic infections and amputations, among others. These variables will not only provide further insight into the effect of canagliflozin on individual metabolic abnormalities, but also reveal potentially modifying effects on the primary outcome and further clarify the drug’s safety profile.
2.8 References


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65. U.S. Food and Drug Administration. Drug Safety Communication: FDA warns that SGLT2 inhibitors for diabetes may result in a serious condition of too much acid in the blood; . In.
70. Zhang X-L, Zhu Q-Q, Chen Y-H, et al. Cardiovascular Safety, Long-Term Noncardiovascular Safety, and Efficacy of Sodium-Glucose Cotransporter 2 Inhibitors in Patients With Type 2 Diabetes Mellitus: A Systemic Review and


Chapter 3 – Study Methods

3.1 Study Design

Our study will be a 52-week, multi-center, double-blinded, placebo-controlled randomized clinical trial.

3.2 Study Population and Sampling

The study population will include adults aged 18-65 years who meet our modified NCEP/ATPIII definition of metabolic syndrome (MetS). Both English- and Spanish-speakers will be included. PCPs in the greater New Haven area will be asked to identify eligible patients meeting our inclusion criteria and exclusion criteria and refer them to our team. Recruitment will take place over an 11-month period to ensure an adequate pool from which to select our final sample. This sampling method is partially biased by the initial convenience sampling of those who visit a provider. Given the risks associated with canagliflozin, the SGLT2i is most safely used in those who have access to and make use of regular monitoring, and thus this limitation is reasonable. Participants selected will undergo a final screening, including blood tests and a physical exam, conducted by team members to ensure all meet criteria as delineated below. If criteria are met and informed consent is signed, this final screening will serve as the participants’ baseline values and will mark the beginning of the intervention period.

3.3 Inclusion Criteria

In order to be considered for participation, subjects must meet our modified NCEP/ATPIII definition of MetS:

- IFG (FPG 100-125 mg/dL)
• Abdominal obesity (waist circumference > 40 inches in men and > 35 inches in women)
• Blood pressure ≥ 135/85 mmHg
• Triglycerides ≥ 150 mg/dL
• HDL cholesterol < 40 mg/dL in men and < 50 mg/dL in women

These criteria will be confirmed with blood testing and a physical exam prior to the start of the study.

3.4 Exclusion Criteria

In addition to T2DM (defined as FPG >125 mg/dL), subjects diagnosed with type 1 diabetes mellitus, CVD, chronic liver or kidney disease (eGFR <60 mL/min/1.73m²), and advanced cancer will be excluded from the study. The reason for the exclusion of these diseases stems from their specific diet and exercise recommendations that could potentially interfere with the results of the study. Elderly patients (>65 years), pregnant and breastfeeding women will be excluded to reduce the risk of adverse events. Any women of childbearing age not agreeable to acceptable birth control will be excluded. Acceptable forms of birth control include tubal ligation, transdermal patch, intrauterine device/system, oral, implantable, or injectable contraceptives, sexual abstinence, double barrier method, or vasectomy of partner. Current or prior users of SGLT2is will be excluded in order to compare the outcomes of the study more accurately. Non-English and non-Spanish speakers will be excluded.

3.5 Subject Protection and Confidentiality

Institutional Review Board (IRB) approval will be obtained prior to recruitment to ensure the personal information of all participants is kept private and confidential during
the recruitment, screening, and conduct of the research as appropriate. Keeping in accordance with IRB’s policy will establish the trust of our participants and facilitate their willingness to share information. All participants will be required to sign a written informed consent, as detailed by Yale University’s IRB Policy 200. Contents of the informed consent will be available in both English and Spanish, and will include the following elements: an explanation of the purpose of the research, duration of participation, description of procedures, foreseeable risks and benefits, methods of protecting confidentiality, limits to confidentiality, a statement that participants may withdraw at any time without explanation, and more. All participants will be informed should significant new findings develop during the course of the research that may affect their willingness to proceed. Participants will be made aware that, if necessary, the principal investigators may terminate their involvement at any time. Contact information will be provided should participants have any comments, questions, or concerns. See Appendix A for a sample consent form.

In conformity with IRB approval requirements, our study will comply with all relevant privacy standards and regulations as specified by the Health Insurance Portability and Accountability Act (HIPAA). This includes the method of blinding both investigators and participants, as well as the creation, collection, and storage of health information.

3.6 Recruitment

PCPs in the greater New Haven area will be asked to recruit patients from their outpatient clinics and refer them to the research team. Recruits will receive a small information flyer from their PCPs describing relevant study details, contact information,
and compensation for participations ($100 at each in-person follow-up visit and $200 at the final visit, totaling $500). Participants will begin the study as they are being recruited. A sample information flyer for recruitment is included in Appendix B.

3.7 Study Variables and Measures

3.7.1 Independent Variable: Intervention and Placebo Control

The intervention group will receive one canagliflozin 300 mg tablet to be taken once every morning for 52 weeks. Similarly, the active control group will receive a placebo tablet to be taken once every morning for 52 weeks. Both the intervention and active control groups will receive lifestyle modification education one time from a research team physician at the start of the 52 weeks. Participants will receive 90 tablets at a time and are expected to attend an in-person follow-up visit with an investigator every 3 months for a refill and debrief. Monthly telephone follow-ups will also occur in between the in-person visits to address any comments, questions or concerns.

3.7.2 Dependent Variable: Primary and Secondary Outcomes

The primary outcome of this study is remission of MetS after 52 weeks, with remission of MetS being defined as two or less of the five metabolic abnormalities as previously described. This is a dichotomous variable, with the two categories being ‘yes’ or ‘no.’

The secondary outcomes of this study will include the five distinct measures of MetS – FPG (mg/dL), waist circumference (inches), blood pressure (mmHg), triglyceride level (mg/dL), and HDL level (mg/dL) – operationalized as within-person changes in medians between groups. Additional secondary outcomes will include within-person changes in median CRP level (mg/L), median HOMA-IR (µU/mL x mg/dL), and median
hA1C (%) between groups. Diet will be measured by within-person changes in median HEI calculated from the “Past Month with Portion Size” DHQ III, and exercise will be measured by within-person changes in median energy expenditure (kcal/kg/day) calculated from the Stanford 7-day PAR.

3.8 Blinding of Intervention and Outcome

To ensure that the principal investigators are blinded, control and intervention groups will be designated with either an ‘A’ or a ‘B’ for the duration of the study as well as the analysis. Participants will also be blinded to their respective groups by receiving identically appearing pills and lifestyle modification education. To blind the outcome of the study, analysis will occur before groups ‘A’ and ‘B’ are revealed as either intervention or control.

3.9 Assignment to Intervention

Using computer-generated randomization, participants will be randomized into their respective groups labeled ‘A’ and ‘B’ in a 1:1 ratio.

3.10 Data Collection

Various methods for data collection will be utilized during this study. First, participating subjects will undergo blood testing and a physical examination at the start of the study to establish baseline values that both define our primary outcome and serve as individual secondary outcomes: FPG, waist circumference, blood pressure, triglycerides, and HDL cholesterol. Other secondary outcomes requiring blood testing, which include CRP levels, HOMA-IR, and hA1C will also be collected at this time. As for assessment of diet and exercise practices, participants will be expected to complete the “Past Month with Portion Size” DHQ III online, and the Stanford 7-Day PAR questionnaire will be
administered by a research team physician at the start of the study. A link to an example of the “Past Month with Portion Size” DHQIII can be found in Appendix C. A copy of the Stanford 7-Day PAR and a link to its protocol can be found in Appendix D. Pre-menopausal women will also receive a pregnancy test. These same measures, with the exception of the diet and exercise questionnaires, will be tested and collected at each in-person follow-up (every 3 months) and at the end of the 52-week intervention. The diet and exercise questionnaires will only be collected at the first and last visits.

Data on adverse events will be collected every 3 months at in-person follow-up visits. At these visits, a research team physician will conduct a thorough interview and physical examination to identify signs and symptoms that may be consistent with side effects or adverse events. Monthly telephone follow-ups will occur in order to maintain communication regarding any questions or concerns (such as side effects/adverse events) that may arise between the in-person visits. Participants will be encouraged, but not required, to keep track of any signs or symptoms in a daily diary so nothing is missed. All participants will have the contact information of the research team and will be encouraged to reach out should there be any questions or concerns. This information will be documented and analyzed at the end of the 52-week intervention period.

3.11 Adherence

Adherence to the canagliflozin 300mg/placebo tablets will be confirmed at the in-person follow-up visits by method of pill counting and self-report.

3.12 Sample Size

The calculation for our sample size is adapted from that of Bo et. al,¹ who’s study also aimed to find the difference in the proportion of MetS between two groups after one
year. In the calculation of their sample size, Bo et. al. assumed an absolute difference in effect of 15% between their control group (unstructured lifestyle education) and their intervention group (detailed written and verbal individualized recommendations from trained professionals). The results of their study revealed that 9.1% of the control group no longer had MetS (defined by the NCEP/ATPIII criteria) at the end of the one-year study. To calculate our sample size, we used 9.1% as the estimated incidence proportion of remission we expect to see in our own control group, and used an absolute effect size of 15% to come to a predicted incidence proportion of remission of 24.1% in our intervention group. The sample size has also been calculated as a two-tailed test, using a power of 80% and an alpha of 0.05. These assumptions have led to a sample size of 190, as calculated by Power and Precision Version 4.0.BioStat, Englewood NJ. This means that, with 190 participants, 80% of studies would be expected to generate a significant effect that would reject the null hypothesis. Since we will assume a 15% loss to follow-up, our final sample size will be 228. Because Bo et. al.’s intervention group was nonpharmacologic, we might actually find an even larger effect size in our study. Our sample size calculation is conservative in this way. The full sample size calculation is included in Appendix E.

3.13 Analysis

Variables to describe the population will include age, sex, smoking status, alcohol consumption, body mass index (BMI) and other baseline laboratory and clinical values (see Table 1 below). Analysis will be performed under both the intention-to-treat and per-protocol methods. Results will be statistically significant if $p \leq 0.05$. The Chi-squared statistical test will be used to analyze the dichotomous primary outcome (remission of
MetS: yes or no). The results of the primary outcome will be presented in Table 2. With regard to the secondary variables, all will be represented by a median and will be analyzed by the Wilcoxon Rank Sum test (Mann-Whitney U test). Such variables include within-person changes in median FPG (mg/dL), waist circumference (inches), blood pressure (mmHg), triglycerides (mg/dL), HDL cholesterol (mg/dL), CRP (mg/L), HOMA-IR (μU/mL x mg/dL), hA1C (%), HEI, and energy expenditure (kcal/kg/day) between groups.

### Table 1: Clinical and Laboratory Baseline Characteristics of the Participants

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<th>Control Group</th>
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<tr>
<td>Diastolic blood pressure, mmHg</td>
<td></td>
<td></td>
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<tr>
<td>Triglycerides, mg/dL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
HDL cholesterol, mg/dL

CRP Level, mg/L

HOMA-IR, µU/mL x mg/dL

hA1C, %

HEI

Energy Expenditure, kcal/kg/day

Data are n (%) or medians (25th percentile, 75th percentile)

Table 2: Results of the Primary Outcome for the Proposed Study

<table>
<thead>
<tr>
<th></th>
<th>Remission of MetS (n)</th>
<th>No Remission of MetS (n)</th>
<th>Total (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td></td>
<td></td>
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<tr>
<td>Control</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>228</td>
</tr>
</tbody>
</table>

3.14 Timeline and Resources

Two years will be required to complete the recruitment (11 months) and intervention periods (12 months) of this study (1 month buffer period). After a participant has been recruited, he/she will undergo a final screening to determine eligibility. At this final screening, the research team physicians will ensure every participant meets the inclusion and exclusion criteria and has signed the informed consent. This will also be the time that baseline values (lab data, physical examination data, questionnaire data, and pregnancy test if applicable) are collected and the intervention period begins. Eligible patients will then receive lifestyle modification education as provided by one of the research team physicians, as well as a 90-day supply of either the canagliflozin 300mg or control tablets.
Every 3 months, the participants are expected back in the office for another physical exam and lab data collection, as well as an adherence assessment. At this time they will also receive their next 90-day supply of tablets, as well as their $100 incremental compensation. Telephone follow-up will occur monthly to address any comments, questions or concerns. At the last visit, they will receive their final $200 for completing the study. This is also when final physical exam, questionnaire, and lab data collection for analysis will occur. Analysis is estimated to take about 6 months after all participants have completed the 12-month intervention period.

The study will be conducted at the Church Street Research Unit (CSRU). This facility can be rented as needed at low cost, offers six physical examination rooms, provides access to core lab services, and is staffed with a full-time nurse and a bilingual medical assistant. The hours of operation are flexible, making it simple for our participants to schedule appointments.

Personnel required for the study include 2 managerial team members, 10 research team physicians that speak both English and Spanish, as well as 10 research assistants for data input and analysis. The research team physicians will be in charge of conducting the in-person visits and telephone follow-ups, confirming adherence by pill counting, collecting questionnaire data, and ordering labs. The full-time nurse staffed by CSRU will collect blood work from participants. In addition to office space and personnel salaries, the budget will include the cost of lab testing, printing small recruitment flyers, and compensation for participants. Janssen Pharmaceuticals, Inc will be approached and asked to provide canagliflozin 300 mg/placebo tablets for study participants free of charge, as well as any additional funding support the company can provide.
3.15 References

Chapter 4 – Conclusion

MetS is a critical risk factor for the development of T2DM and CVD, two of the leading causes of death and disability in the US.\(^1\) Currently, lifestyle modification education is the primary treatment, but 1 in 2 people do not adhere to the recommendations.\(^2\) Nonadherence for this population eventually results in multiple drug prescriptions to target each individual MetS risk factor,\(^3\) but this presents new problems of increased costs, decreased compliance, and adverse drug reactions.\(^4,5\) Such difficulties with current treatment options for MetS justifies a search for a better solution. SGLT2is are novel oral antidiabetic agents that have been shown to target all 5 metabolic abnormalities of MetS. Thus, SGLT2is have the potential to allow for remission of MetS and to reduce the rate of progression to T2DM and CVD as a single pharmacologic therapy.\(^6\) So far, there has been no RCT in the US to evaluate such potential. Hence, the aim of the proposed study is to establish a difference between canagliflozin as an adjunct to lifestyle modification education versus lifestyle medication education alone for the treatment of MetS in nondiabetic adults. Results of this study will elucidate canagliflozin’s role in the remission of MetS and in the prevention of T2DM and CVD.

4.1 Advantages

Advantages of the proposed study include its RCT study design. RCTs help to strengthen internal validity by random allocation of the intervention and control groups. In theory, this will ensure equal characteristics of the intervention and control groups to avoid the influence of confounding factors and minimize allocation bias. The utilization of double blinding in this study also minimizes potential information bias. The purpose of including both English- and Spanish-speakers in the proposed study is to maximize
external validity and reach wider populations that may benefit from canagliflozin as a treatment for MetS. This serves as an advantage by making the results of our study more applicable and relevant.

4.2 Disadvantages

Despite the numerous advantages of the proposed study, there are several disadvantages that must be considered as well. First, the location of the study will be limited to the greater New Haven area, which will limit the generalizability of the results. Secondly, the RCT study design itself requires trust in the participants to comply with the intervention and placebo treatments. Noncompliance from either of these groups could threaten the validity and reliability of the study results. In anticipation for potential noncompliance, the participants will receive a total of $500 compensation for completion of the study, to be given in increments at each in-person follow-up visit. This will hopefully serve as a motivator to take the intervention/placebo drug as prescribed and prevent loss to follow-up. However, as a study with a moderately large sample population, this compensation for each participant becomes costly. Adding to this expense is the salary for all personnel, office space rent, lab testing, canagliflozin and placebo tablets, and other expenditures that make the proposed study a costly one.

In terms of our definition of MetS, it could be argued that restricting the criteria to a FPG of 100-125 mg/dL rather than ≥100 mg/dL will limit the study results. However, given that one of our study aims is to prevent the progression of MetS to T2DM with canagliflozin, this limitation is acceptable.

Another disadvantage of the proposed study is that our intervention group will receive canagliflozin 300 mg tablets, whereas in clinical practice they would be started on
100 mg first. Further, our intervention period is limited to just 52 weeks in length while other large clinical trials evaluating the effects of SGLT2is followed participants for an average of 3-4 years. Our relatively short intervention period will limit us from understanding how long canagliflozin would be effective in our study population.

4.3 Clinical and/or Public Health Significance

As a predictor for the development of costly and burdensome chronic diseases, MetS is certainly a syndrome to be targeted for effective treatment. With current treatment strategies proving unsuccessful due to nonadherence and noncompliance, a search for a novel treatment approach that is easy to maintain is warranted. The proposed study offers a potential solution with canagliflozin – a once-a-day tablet that has been shown to target all five components of the syndrome.

If canagliflozin 300 mg plus lifestyle modification education is shown to have a significant benefit over lifestyle modification education alone for the remission of MetS in nondiabetic adults, it would be reasonable to consider the medication for use in clinical practice. Such results may lead to a slowed progression of MetS, a syndrome which affects over a third of the US adult population, to T2DM and CVD. Such results would also speak to the inefficacy of lifestyle modification education alone and may prompt revision to current strategies.

If the results were to suggest that lifestyle modification education alone has a significant benefit over the intervention for the remission of MetS, or suggest no difference at all, it may be wise to consider an alternative novel treatment, or to improve the current treatments available.
Regardless of the outcome, the proposed study has significant implications for the future treatment of MetS. It is also likely that the results could have a ripple effect on not only the health complications of the syndrome, but also the financial toll the syndrome places on the economy.

4.4 Future Directions

Given the limitations of this study, there are several directions for future clinical research to explore. To start, the current study could be replicated for a period longer than 52 weeks in order to better understand the long term effects of canagliflozin 300 mg. Should the results of our proposed study be promising, it would be reasonable to conduct a study that further informs a dose-response relationship and help to guide treatment protocols. This would be particularly important given our study is testing the effects of canagliflozin 300 mg rather than the starting dose of 100 mg. Seeing that those in the greater New Haven area are not representative of all those diagnosed with MetS, it would also be wise to replicate this study in different populations or across a wider geographic area. Regardless of the study outcomes, our proposed trial will provide productive information concerning the use of canagliflozin for the remission of MetS and will guide future research.
4.5 References

Appendices

Appendix A: Sample Consent Form

Created using “Compound Authorization and Consent Template_Biomedical Research_1-21-2019”

COMPOUND AUTHORIZATION AND CONSENT FOR PARTICIPATION IN A RESEARCH STUDY

YALE UNIVERSITY
YALE UNIVERSITY SCHOOL OF MEDICINE, PHYSICIAN ASSOCIATE PROGRAM
YALE-NEW HAVEN HOSPITAL

Study Title: Administration of Canagliflozin 300 mg for the Remission of Metabolic Syndrome in Nondiabetic Adults

Principal Investigator (the person who is responsible for this research): Francis P. Wilson, MD, MSCE

Co-Principal Investigator: Corrie Asseo, PA-SII

24-Hour Phone Number: 203-xxx-xxxx

Research Study Summary:

- We are asking you to join a research study.
- The purpose of this research study is to understand the role of canagliflozin (a medication indicated for type 2 diabetes mellitus) for the treatment of metabolic syndrome
- Study procedures will include: 5 in-person visits over a 52-week period. The first visit will provide lifestyle modification education and a 90-day supply of either canagliflozin or the placebo drug. The first and last visits will include a physical examination, blood draws, diet and exercise questionnaires, and a pregnancy test if applicable. Each visit in between the first and the last will provide another 90-day supply of canagliflozin or the placebo drug and include a physical examination, blood draws and a pregnancy test if applicable. Canagliflozin is to be taken one time every day for the full 52 weeks.
- 5 visits of approximately 1 hour each are required.
- Each visit will take approximately 1 hour total.
- There are some risks from participating in this study. The most common risks are genital mycotic infection, urinary tract infections, and increased urination. Other risks include volume depletion, low blood sugar, allergic reaction, kidney injury, and bone fracture. Less common risks include acid production. A rare, but serious risk is a flesh-eating bacteria infection of the skin between the anus and the genitals.
Canagliflozin has a Black Box Warning for lower limb amputations. Other risks can be found later in the document.

- The benefits you may experience include improved health outcomes.
- There are other choices available to you outside of this research. These choices include lifestyle changes, seeking treatment from your physician, partaking in another study, or not seeking treatment at all. Alternative treatments that may be provided by your physician include an array of drugs to target each of your metabolic abnormalities (statins, weight loss drugs, diuretics, etc). Please note that the treatment being offered in this study is not currently available as a treatment for metabolic syndrome in the United States.
- Taking part in this study is your choice. You can choose to take part, or you can choose not to take part in this study. You can also change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.
- If you are interested in learning more about the study, please continue reading, or have someone read to you, the rest of this document. Take as much time as you need before you make your decision. Ask the study staff questions about anything you do not understand. Once you understand the study, we will ask you if you wish to participate; if so, you will have to sign this form.

**Why is this study being offered to me?**

We are asking you to take part in a research study because you meet the criteria for the diagnosis of metabolic syndrome and you do not have type 2 diabetes mellitus. We are looking for 228 participants to be part of this research study.

**Who is paying for the study?**

[insert organizations/entities]

**What is the study about?**

The purpose of this study is to test how well canagliflozin works for the treatment of metabolic syndrome. Canagliflozin is not currently approved for the use or treatment of metabolic syndrome in the United States.

**What are you asking me to do and how long will it take?**

If you agree to take part in this study, this is what will happen:

- This study is expected to take place over 52 weeks (12 months).
- Women of childbearing age are required to practice an acceptable method of birth control: tubal ligation, transdermal patch, intrauterine device/system, oral, implantable, or injectable contraceptives, sexual abstinence, double barrier method, vasectomy of partner
First, you will meet with one of our study physicians who will conduct an interview and physical examination to determine the status of your health and your baseline criteria. Women of childbearing age will take a pregnancy test. You will also meet with a lab assistant who will draw approximately four tablespoons of blood. This process will occur at each in-person visit, which will occur every 3 months until the end of the 12-month study (a total of 5 visits). At this visit you will also complete two questionnaires. One will be regarding your diet over the past month, and the other will be regarding your exercise habits over the past week. The purpose of these questionnaires is to establish your baseline habits at the start of the study.

At your first visit, you will receive lifestyle modification education, as well as a 90-day supply of either our treatment drug (canagliflozin 300 mg) or our placebo drug. Canagliflozin is a drug typically prescribed to people with type 2 diabetes mellitus. A placebo drug is an inactive drug (without medication) that will appear identical to the treatment drug. You will be asked to take this drug once a day every day until your next in-person visit where you will receive your next 90-day supply.

You can expect each in-person visit to take approximately 1 hour: 20 minutes for interview, 20 minutes for physical examination, 20 minutes for blood draw.

In-person visits will take place at the Church Street Research Unit in New Haven, CT.

You will be asked to speak with a research assistant on the phone once a month (in between the in-person visits) to discuss any questions or concerns you may have. This could include side effects that you may be experiencing.

At your last visit, you will again participate in an interview and physical examination conducted by a physician, as well as have your blood drawn by a lab assistant. You will also repeat the diet and exercise questionnaires.

To ensure the data collection is not influenced by either the research participants or the researchers, neither you nor the researchers will know whether you are taking canagliflozin or the placebo drug. This method of concealment is called “double blinding.” The decision of whether you receive the treatment or the placebo will be left to a computer-generated randomization technique. Half of the participants will receive the treatment, and half will receive the placebo.

What are the risks and discomforts of participating?

The most common risks associated with the study drug are genital mycotic infection, urinary tract infections, and increased urination. Other risks include volume depletion, low blood sugar, allergic reaction, kidney injury and bone fracture. Less common risks include acid production. A rare, but serious risk of canagliflozin is a flesh-eating bacterial infection of the skin between the anus and the genitals.

Canagliflozin has a Black Box Warning for lower limb amputations (most often of the toe and midfoot). Lower limb amputations are more likely to occur if you
have had a prior amputation, or currently have vascular diseases, a lower limb infection or ulcer.

- Please be aware that some of these risks have occurred more often in people with multiple diseases or taking other drugs known to have an interaction. These people have likely been excluded from this study.
- Risks to pregnant women are unknown. For this reason, use of birth control in women of childbearing age is required for this study.
- There is a small risk of discomfort, bruising, bleeding, redness, and/or swelling at the site of the needle stick during blood draw. Lightheadedness may occur during this event. Rarely, infection at the site can occur.
- There is always a possibility of financial risk if harm or illness occurs. Participants or their insurance would be required to pay for treatment. The cost of getting to and from in-person visits should be considered.

**How will I know about new risks or important information about the study?**

We will tell you if we learn any new information that could change your mind about taking part in this study.

**How can the study possibly benefit me?**

You may experience improved health outcomes as a result of this study.

**How can the study possibly benefit other people?**

The benefits to science and other people may include a better understanding of the use of canagliflozin for the treatment of metabolic syndrome. Benefits also include advancement in the knowledge of canagliflozin’s side effects on certain populations.

**Are there any costs to participation?**

If you take part in this study, you will not have to pay for any services, supplies, study procedures, or care that are provided for this research only (they are NOT part of your routine medical care). However, there may be additional costs to you. These can include costs of transportation and your time to come to the study visits. You or your health insurance must pay for services, supplies, procedures, and care that are part of your routine medical care. You will be responsible for any co-payments required by your insurance.

**Will I be paid for participation?**

You will be paid for taking part in this study. You will be compensated at each in-person follow-up visit. At your first 3 follow-up visits, you will receive $100. At your last (fifth) visit, you will receive $200. Altogether, you are eligible to receive a total of $500 ($100 + $100 + $100 + $200). You are responsible for paying state, federal, or other taxes for
the payments you receive for being in this study. Taxes are not withheld from your payments.

**What are my choices if I decide not to take part in this study?**

Instead of participating in this study, you have some other choices. You could:

- Get treatment without being in a study. The treatment being offered in this study is not currently approved in the United States, and therefore is not available without participating in the study. However, alternative treatments are available. These include lifestyle changes, as well as an array of drugs to target each of your metabolic abnormalities (statins, weight loss drugs, diuretics, etc).
- Take part in another study.

**How will you keep my data safe and private?**

We will keep information we collect about you confidential. We will share it with others if you agree to it or when we have to do it because U.S. or State law requires it. For example, we will tell somebody if we learn that you are hurting a child or an older person.

Your data will be deidentified within 2 weeks of collection of study data and will be kept in this form indefinitely. All data will be store on a password-protected computer. Please note, after identifiers are removed from the identifiable private information, the information could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or the legally authorized representative.

When we publish the results of the research or talk about it in conferences, we will not use your name. If we want to use your name, we would ask you for your permission.

We will also share information about you with other researchers for future research but we will not use your name or other identifiers. We will not ask you for any additional permission.

**What Information Will You Collect About Me in this Study?**

The information we are asking to use and share is called “Protected Health Information.” It is protected by a federal law called the Privacy Rule of the Health Insurance Portability and Accountability Act (HIPAA). In general, we cannot use or share your health information for research without your permission. If you want, we can give you more information about the Privacy Rule. Also, if you have any questions about the Privacy Rule and your rights, you can speak to Yale Privacy Officer at 203-432-5919.
The specific information about you and your health that we will collect, use, and share includes:

- Research study records
- Medical and laboratory records of only those services provided in connection with this Study.
- The entire research record and any medical records held by YNHH created from: [insert start date] to: [insert end date]
- Records about phone calls made as part of this research
- Records about your study visits
- Information obtained during this research regarding
  - Hepatitis infection
  - Sexually transmitted diseases
  - Other reportable infectious diseases
  - Physical exams
  - Pregnancy status
  - Laboratory, x-ray, and other test results
  - Diaries and questionnaires
  - Use of illegal drugs or the study of illegal behavior
  - Records about any study drug you received

How will you use and share my information?

We will use your information to conduct the study described in this consent form. We may share your information with:

- The U.S. Department of Health and Human Services (DHHS) agencies
- Representatives from Yale University, the Yale Human Research Protection Program and the Institutional Review Board (the committee that reviews, approves, and monitors research on human participants), who are responsible for ensuring research compliance. These individuals are required to keep all information confidential.
- The U.S. Food and Drug Administration (FDA). This is done so that the FDA can review information about canagliflozin involved in this research. The information may also be used to meet the reporting requirements of drug regulatory agencies.
- The study sponsor or manufacturer of study drug/device
- Drug regulatory agencies in other countries
- Governmental agencies to whom certain diseases (reportable diseases) must be reported
- Health care providers who provide services to you in connection with this study.
- Laboratories and other individuals and organizations that analyze your health information in connection with this study, according to the study plan.
- Co-Investigators and other investigators
- Study Coordinator and Members of the Research Team
- Data and Safety Monitoring Boards and others authorized to monitor the conduct of the Study
We will do our best to make sure your information stays private. But, if we share information with people who do not have to follow the Privacy Rule, your information will no longer be protected by the Privacy Rule. Let us know if you have questions about this. However, to better protect your health information, agreements are in place with these individuals and/or companies that require that they keep your information confidential.

**Why must I sign this document?**

By signing this form, you will allow researchers to use and disclose your information described above for this research study. This is to ensure that the information related to this research is available to all parties who may need it for research purposes. You always have the right to review and copy your health information in your medical record.

However, this is a double blinded treatment study and if you sign this permission form, you will not be allowed to look at or copy your study related information until after the research is completed.

**What if I change my mind?**

The authorization to use and disclose your health information collected during your participation in this study will never expire. However, you may withdraw or take away your permission at any time. You may withdraw your permission by telling the study staff or by writing to Francis P. Wilson, MD, MSCE at the Yale University, New Haven, CT 06520.

If you withdraw your permission, you will not be able to stay in this study but the care you get from your doctor outside this study will not change. No new health information identifying you will be gathered after the date you withdraw. Information that has already been collected may still be used and given to others until the end of the research study to insure the integrity of the study and/or study oversight.

**Who will pay for treatment if I am injured or become ill due to participation in the study?**

If you are injured or become ill during the course of the study, seek treatment and contact one of the study physicians as soon as possible.

Yale does not provide any form of compensation for injury or loss of income as a result of the study. Should you become ill or injured, treatment will be provided. You or your insurance will be expected to cover the cost of this treatment.

**What if I want to refuse or end participation before the study is over?**
Taking part in this study is your choice. You can choose to take part, or you can choose not to take part in this study. You also can change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.

We would still treat you with standard therapy or, at your request, refer you to a clinic or doctor who can offer this treatment. Not participating or withdrawing later will not harm your relationship with your own doctors or with this institution.

To withdraw from the study, you can call a member of the research team at any time and tell them that you no longer want to take part.

The researchers may withdraw you from participating in the research if necessary. This may occur if you begin to experience serious side effects or adverse events as previously mentioned.

**What will happen with my data if I stop participating?**

Because all data will be deidentified once collected, your data will not be able to be withdrawn from the study should you stop participating.

**Who should I contact if I have questions?**

Please feel free to ask about anything you don't understand.

If you have questions later or if you have a research-related problem, you can call the Principal Investigator at 201-xxx-xxxx

If you have questions about your rights as a research participant, or you have complaints about this research, you call the Yale Institutional Review Boards at (203) 785-4688 or email hrpp@yale.edu.

A description of this clinical trial will be available on [http://www.ClinicalTrials.gov](http://www.ClinicalTrials.gov), as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.
**Authorization and Permission**

Your signature below indicates that you have read this consent document and that you agree to be in this study.

We will give you a copy of this form.

<table>
<thead>
<tr>
<th>Participant Printed Name</th>
<th>Participant Signature</th>
<th>Date</th>
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<table>
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<tr>
<th>Person Obtaining Consent Printed Name</th>
<th>Person Obtaining Consent Signature</th>
<th>Date</th>
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Complete if the participant is not fluent in English and an interpreter was used to obtain consent. Participants who do not read or understand English must not sign this full consent form, but instead sign the short form translated into their native language. This form should be signed by the investigator and interpreter only. If the interpreter is affiliated with the study team, the signature of an impartial witness is also required.

Print name of interpreter: ______________________________________

Signature of interpreter: ________________________________ Date: __________

**An oral translation of this document was administered to the participant in _______________ (state language) by an individual proficient in English and _______________ (state language).**

Print name of impartial witness: ________________________________

Signature of impartial witness: ________________________________ Date: __________

See the attached short form for documentation.
Appendix B: Sample Recruitment Flyer

Volunteers Needed for Participation in Research Study

We are investigating the use of canagliflozin (a type 2 diabetes mellitus medication) for the treatment of metabolic syndrome.

Who can participate?

Adults (18-65 years) with a diagnosis of metabolic syndrome but do not have type 2 diabetes mellitus.

What will be asked of you?

You will be asked to take a medication once a day for 52 weeks. Our research team will contact you once monthly by telephone to check in. Every 3 months you will be asked to come to our office for an in-person follow-up visit and blood will be collected.

How will I be compensated?

You are eligible to receive up to $500 upon completion of the study. This will be distributed in increments throughout the course of the study.

If you are interested in participating or have any questions, please do not hesitate to contact us at:

203-xxx-xxxx or researchteam@yale.edu
Appendix C: Link to “Past Month with Portion Size” DHQIII

The link for the “Past Month with Portion Size” DHQIII can be found here:

Appendix D: Stanford 7-Day PAR and Link to Protocol

7-Day Physical Activity Recall

PAR#: 1 2 3 4 5 6 7

Participant__________________

Interviewer__________________

Today is__________

Today's Date__________

1. Were you employed in the last seven days? 0. No (Skip to Q#4) 1. Yes
2. How many days of the last seven did you work? ____ days
3. How many total hours did you work in the last seven days? ____ hours last week
4. What two days do you consider your weekend days? (mark days below with a squiggie)

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<thead>
<tr>
<th>WORKSHEET</th>
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<td>Hard</td>
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<td>Very Hard</td>
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<th>EVENING</th>
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<tr>
<td>Hard</td>
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<tr>
<td>Very Hard</td>
<td></td>
</tr>
</tbody>
</table>

Total Min Per Day

Strength: _______ _______ _______

Flexibility: _______ _______ _______

4a. Compared to your physical activity over the past 3 months, was last week's physical activity more, less, or about the same?

1. More 2. Less 3. About the same

5. Were there any problems with the PAR interview?

0. No 1. Yes

If YES, go to the back and explain.

6. Do you think this was a valid PAR Interview?

1. Yes 0. No

If NO, go to the back and explain.

7. Were there any special circumstances concerning this PAR?

0. No 1. Yes, If YES, what were they? (circle)

1. Injury all week 2. Illness all week 3. Illness part week
4. Injury part week 5. Pregnancy 6. Other:
The protocol for the Stanford 7-Day PAR can be found here:

https://drjimsallis.org/Documents/Measures_documents/7daypar_protocol.pdf
Appendix E: Sample Size Calculation

The sample size was calculated* using the following parameters:

- Alpha: 0.5 (two-sided hypothesis)
- Beta: 0.20
- Power of 80%
- Effect size of 15%

Factoring in a 15% drop out rate, the final sample size is 228

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