Chewing Gum and Saliva Substitute for the Treatment of Thirst in Heart Failure: A Crossover Trial

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CHEWING GUM AND SALIVA SUBSTITUTE
FOR THE TREATMENT OF THIRST IN HEART FAILURE:
A CROSSOVER TRIAL

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

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Master of Medical Science

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# TABLE OF CONTENTS

**TITLE PAGE** ................................................................................................................. i

**TABLE OF CONTENTS** ................................................................................................. ii

**ABSTRACT** ......................................................................................................................... iv

**CHAPTER 1: INTRODUCTION** ....................................................................................... 1
  1.1 Background .................................................................................................................... 1
  1.2 Statement of the Problem .............................................................................................. 4
  1.3 Goals and Objectives .................................................................................................... 6
  1.4 Hypotheses .................................................................................................................... 6
  1.5 Definitions .................................................................................................................... 6
  1.6 References .................................................................................................................. 7

**CHAPTER 2: REVIEW OF THE LITERATURE** ....................................................... 9
  2.1 Introduction .................................................................................................................... 9
  2.2 Review of Empirical Studies ....................................................................................... 9
    2.2a Chewing gum and thirst ......................................................................................... 9
    2.2b Artificial saliva and thirst .................................................................................... 16
    2.2c Chewing gum and artificial saliva ......................................................................... 20
  2.3 Review of Possible Confounding Variables ................................................................ 23
    2.3a Demographics ......................................................................................................... 23
    2.3b Fluid restriction .................................................................................................... 24
    2.3c Heart failure classification and severity ............................................................... 25
    2.3d Preference ............................................................................................................. 26
  2.4 Review of Relevant Methodology .............................................................................. 26
    2.4a Design ................................................................................................................... 26
    2.4b Setting and selection criteria .............................................................................. 27
    2.4c Interventions ......................................................................................................... 28
    2.4d Outcome measurement ....................................................................................... 29
    2.4e Follow-up ............................................................................................................. 33
  2.5 Conclusion .................................................................................................................. 33
  2.6 References ................................................................................................................ 35

**CHAPTER 3: STUDY METHODS** ............................................................................. 37
  3.1 Study Design ................................................................................................................ 37
  3.2 Study Population and Sampling .............................................................................. 37
  3.3 Subject Protection and Confidentiality ....................................................................... 38
  3.4 Recruitment ................................................................................................................ 38
  3.5 Study Variables and Measures .................................................................................. 39
    3.5a Independent variables ......................................................................................... 39
    3.5b Dependent variables ............................................................................................ 39
    3.5c Baseline variables ............................................................................................... 40
  3.6 Methodology Considerations ..................................................................................... 40
    3.6a Assignment of Interventions .............................................................................. 40
    3.6b Blinding of Intervention ...................................................................................... 41
    3.6c Blinding of Outcome ............................................................................................ 41
    3.6d Adherence .............................................................................................................. 41
  3.7 Data Collection .......................................................................................................... 41
ABSTRACT

Heart failure patients are burdened with a variety of pharmacologic and self-care interventions. Diuretic therapy and fluid restriction can cause thirst and dry mouth, which decrease quality of life and adherence to medical recommendations. Prior research has examined saliva stimulants and substitutes to treat thirst and dry mouth in other populations, but has not applied these therapies in heart failure. We propose that chewing gum will decrease thirst to a greater extent than artificial saliva in heart failure patients when compared to baseline. A randomized controlled crossover trial between chewing gum and artificial saliva will be conducted with each intervention lasting two weeks. As thirst is a distressing symptom caused by standard heart failure care and has gone essentially unaddressed, effective treatment of thirst in this population has the potential to increase quality of life and adherence to lifesaving pharmacologic and self-care interventions.
CHAPTER 1: Introduction

1.1 Background

Heart failure (HF) affects over 5.1 million Americans and the prevalence of the disease is increasing. The American Heart Association projects that the total number of Americans living with heart failure will increase 46% from 2012 to 2030. This disease is extremely costly financially as well as in terms of morbidity and mortality. In 2012 alone the direct cost of medical care for HF patients of all ages was $20.9 billion, and that amount is expected to increase to $53.1 billion by 2030. Hospitalization for Acute Decompensated Heart Failure (ADHF) is responsible for 80% of this cost, is the leading cause of hospitalization in the United States, and is associated with a 50%, five-year mortality rate. Increasing size and age of the population, prevalence of the disease, healthcare cost inflation, and high morbidity and mortality has made research on the treatment of HF a top priority.

HF is a chronic and progressive syndrome most often occurring in patients over the age of 65 as a result of cardiovascular injury from myocardial infarction or hypertension, eventually causing remodeling of the myocardium. This results in an inability of the ventricles to properly fill with or eject blood, lowering cardiac output to a point where there is inadequate blood supply to meet circulatory and metabolic demands. The body responds by up-regulating the sympathetic nervous system, renin-angiotensin-aldosterone system, and vasopressin axis to increase cardiac output. Chronic activation of these neurohormonal pathways eventually has the opposite effect, with excessive retention of fluid and sodium causing a paradoxical decline in cardiac output.
This causes the common signs and symptoms of volume overload that often lead to hospitalization such as dyspnea, weight gain, cough, fatigue, and lower extremity edema. Patients with HF are burdened with a substantial number of pharmacologic and self-care interventions to remove fluid and prevent ADHF exacerbations. Medications include diuretics to remove excess fluid, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers to slow the remodeling process in the ventricles, and beta-adrenergic blockers to reduce myocardial oxygen demand. All together, these interventions are directed to improve symptoms and survival. Self-care practices are emphasized in this population as a way to avoid exacerbation, and these include a low sodium and fluid-restricted diet, close monitoring of symptoms and daily weights, appropriate response to new onset of symptoms or weight gain, and adherence to prescribed treatments, which are often numerous and complicated.

For many HF patients, consequences of treatment include secondary symptoms that lead to decreased quality of life. In clinical practice, bothersome thirst is one symptom that nurses and clinicians often encounter in HF patients. HF patients experience a unique combination of factors contributing to the symptom of thirst and dry mouth. Prolonged neurohormonal activation that occurs in HF, including increased vasopressin and angiotensin II, activates central thirst mechanisms. Diuretics contribute to thirst by initiating loss of body water, increase in plasma osmolality, and xerostomia, all of which trigger a desire to drink. Fluid restriction is a long-standing pillar of self-care in HF, with conflicting evidence on its utility, that is correlated with increased perception of thirst. Some recent studies have suggested fluid restriction has no benefit over liberal fluid intake in terms of weight loss, physical capacity, hospitalization, or
mortality.\textsuperscript{6,7,8} Others cite poor adherence to fluid restriction as a common precipitant for readmission to hospital, a measure of morbidity in HF.\textsuperscript{4} In 2013 Philipson et al. conducted a randomized controlled trial with 90 stable HF patients and found that patients on a fluid and sodium restricted diet had significantly better outcomes in New York Heart Association (NYHA) HF functional class and leg edema after 12 weeks compared to controls. Interestingly, thirst was not significantly different between groups but this may have been due to insufficient power to detect a difference.\textsuperscript{8} Despite inconclusive results on the importance of fluid restriction, it is a commonly used self-care intervention that contributes to the problem of thirst in HF.

Thirst is described as a sensation causing a powerful urge to drink.\textsuperscript{5} Xerostomia is an element of thirst that may also alter taste, impair dental health, and make speaking difficult.\textsuperscript{6} It is associated with hyposalivation which is a significant risk factor for dental disease.\textsuperscript{9} The existing studies on HF patients have aimed to describe how thirst is perceived and determine which subset of this population struggles with it the most. A review of the literature suggests that younger age, male sex, higher body mass index (BMI), and higher NYHA classification all correlate to higher likelihood of experiencing thirst.\textsuperscript{10}

The greatest impact of thirst in HF that has been noted in the literature to date is on quality of life. A descriptive pilot study by Reilly et al. (2010)\textsuperscript{11} on 25 stable HF patients aimed at identifying relationships between thirst, fluid intake, and quality of life found that thirst is an issue in patients attempting to follow fluid restricted diets, is indirectly correlated with quality of life, and consistently correlates with all subscales of a HF symptom scale. A 2013 systematic literature review was conducted by Waldreus et
al.\textsuperscript{5} of original research in HF patients, with thirst as a primary or secondary outcome measure, or a patient statement regarding thirst in the results section. They found descriptions of thirst in stable HF patients that included terminology such as “enormously annoying”, “irresistible”, “unquenchable”, and “preoccupying”. More importantly, many studies in the review reported that patients found the only way to alleviate these feelings was to drink more than their fluid restriction allowed. This can lead to a sense of blame for their condition and decreased quality of life.

1.2 Statement of the Problem

The primary barrier to research on thirst is that it is a subjective symptom, experienced and described differently by different people. The Symptom Management Model developed at the University of California San Francisco states that to completely evaluate the experience of a symptom, the four qualities of distress, duration, frequency, and intensity must be assessed\textsuperscript{12}. Currently, there is no framework specifically designed to evaluate thirst. A number of studies have attempted to evaluate thirst in HF, but a 2014 literature review conducted by Allida et al.\textsuperscript{12} found that no single study adequately assessed all four qualities of thirst, with frequency and distress being the most often overlooked. Moreover, there are only three tools designed to assess thirst, all of which rely on self-report, and none are validated specifically for HF.\textsuperscript{4} These are the Visual Analogue Scale (VAS) and the Numeric Rating Scale, which are both commonly used to evaluate pain and breathlessness. The third is a Thirst Distress Scale (TDS), which has most commonly been used to evaluate thirst in hemodialysis (HD) patients.\textsuperscript{12}
As many as 73% of HF patients struggle with fluid restriction for various reasons, and there are currently no intervention studies aimed at reducing or alleviating thirst in these patients. Providers have suggested that their patients who complain of thirst ingest cold drinks, ice chips, peppermint, or buttermilk, and consume less sugar, but none of these remedies have been tested for efficacy.

Thirst management has been most extensively researched in the setting of end-stage renal disease among patients undergoing HD. Attention has been focused on reducing their thirst and xerostomia to help increase compliance with fluid restriction, a self-care requirement that is also prescribed in this population. Treating these symptoms may also help avoid excessive interdialytic weight gain (IWG) and associated complications, and to improve quality of life. The main categories of interventions include saliva stimulants, for example chewing gum, and saliva substitutes. Intervention studies examining the efficacy of chewing gum and artificial saliva have been inconclusive but have suggested chewing gum, and to a lesser extent artificial saliva, may alleviate thirst and dry mouth in HD patients. These patients preferred chewing gum over artificial saliva for its ease of use and taste. Neither intervention was found to have an impact on IWG or net fluid intake, but this may have been because of the short time frame of the interventions. The positive effect of these interventions on alleviating xerostomia and thirst has also been found in patients with rheumatic disease and malignancy. Both chewing gum and artificial saliva are financially reasonable interventions that have proven to be effective in various populations suffering with thirst, and could be an effective treatment for heart failure patients with thirst as well.
1.3 Goals and Objectives

We are proposing a randomized crossover clinical trial, comparing the use of artificial saliva and chewing gum in a sample of stable HF patients to test effects on subjective thirst and dry mouth. Mean VAS scores for thirst intensity will be the primary outcome measure by which we will compare treatments at the end of intervention periods. The TDS and Xerostomia Inventory (XI) will be used to measure thirst distress and xerostomia, respectively, as secondary outcomes. Preference for one intervention over the other will be assessed with two dichotomous questions.

1.4 Hypotheses

1. There will be a difference in thirst intensity (VAS), thirst distress (TDS), and xerostomia (XI) between the chewing gum group and the artificial saliva group after two weeks of each intervention.

2. There will be a difference in preference between chewing gum and artificial saliva.

1.5 Definitions

Xerostomia: dry mouth.
1.6 References


CHAPTER 2: Review of the Literature

2.1 Introduction

An extensive literature search was conducted between August 2015 and June 2016 focusing on thirst in heart failure patients. The aim of the search was to explore the underlying pathophysiology of thirst in this population, how the symptom of thirst is measured in clinical research, and to uncover which thirst treatments were effective.

Ovid, Scopus, and PubMed databases were used to access the relevant literature, and the search terms utilized included *heart failure and thirst or xerostomia or dry mouth, thirst or xerostomia or dry mouth and saliva stimulants or saliva substitutes or mastication or gum or chew or chewing gum*, and *heart failure and self care or fluid restriction or restrict*. Search criteria were limited to “English language” and produced clinical trials, cross sectional studies, prospective cohorts, systematic literature reviews, and meta-analyses pertaining to HF and thirst, as well as interventions to treat thirst.

2.2 Review of Empirical Studies

This section will present the literature that has been reviewed pertaining to chewing gum and artificial saliva and their effect on thirst. This relationship has not yet been studied in HF patients, so literature from other populations suffering from thirst will be utilized.

2.2a Chewing gum and thirst

Bots et al. (2004)\(^1\) completed a randomized clinical trial examining how eight different sugar free chewing gums affect saliva stimulation using a convenience sample of 83 healthy dental students from one school in The Netherlands. The group comprised
41 men and 42 non-pregnant women at an average age of 25 years, taking no medication besides oral contraceptives. Subjects were randomized into eight different groups to receive one of eight different gum flavor and shape combinations including Winterfresh, Peppermint, Sweetmint, or Liquorice, and stick, tab, or pellet shapes. Salivary flow stimulated by parafilm, a tasteless wax, provided a baseline measurement and chewing gum-stimulated salivary flow and pH was measured at intervals up to 10 minutes. MANOVA analysis showed no statistically significant differences between chewing gums in terms of salivary flow rate; each intervention significantly stimulated salivary flow compared to baseline within the first minute of chewing, the average increase being 187%. The different gums subsequently exhibited varying rates of declining salivary flow over time but after 10 minutes had returned to baseline. Salivary pH increased slightly over the 10-minute period, reaching statistical significance in three out of eight chewing gums. However, there was no statistically significant difference in pH change between chewing gums.

A different group of 112 dental students (61 men 23.2±4.1 years of age and 51 women 24.1±3.2 years of age) with the same inclusion and exclusion criteria participated in a crossover design trial to test preference. Participants tested three of the different chewing gums that were randomly selected for two days each, and afterward completed questionnaires with several different VAS on taste, how long participants chewed the gum, and willingness to use it long-term. Overall, subjects preferred the Peppermint stick and Spearmint pellet gums significantly to other options.

This study by Bots et al. (2004) suggests equal efficacy of chewing gum to increase salivary flow and pH regardless of flavor, shape, weight, and manufacturer,
although these variables do seem to influence preference. Subsequent clinical research has offered a choice of gum flavor to participants in an attempt to bolster compliance. Since this was a small sample of healthy young adults from one particular school, there is limited generalizability to our older HF target population. It should also be noted that Wrigley, a gum manufacturing company that provided the majority of the gum, sponsored this research.

Jagodzinska et al. (2011)\(^2\) conducted a three-month prospective study on the effect of sugar free chewing gum on thirst, xerostomia, and hydration of 38 stable chronic HD patients from a dialysis center in Poland. This followed a 2005 crossover trial of chewing gum vs. artificial saliva by Bots et al.\(^3\) that showed chewing gum was effective in reducing thirst in HD patients over a shorter intervention period of two weeks. Those included were over 18 years of age, received HD three times weekly for at least three months, were clinically stable as determined by daily residual diuresis, and had mean IWG \(\geq 1000\) g in the two weeks before the study began. Participants were excluded for acute infections, poor control of DM, and orodental conditions that could impair chewing. Baseline characteristics were similar between the study group and reference group with the exception of IWG, which was significantly greater in the study group. Participants received chewing gum in the flavor of their choice with instructions to slowly chew one piece three times daily after meals for a minimum of 20 minutes, and throughout the day when they perceived thirst or xerostomia. They were given a diary to record the amount of gum and fluids they consumed daily, and returned empty gum packs weekly for assessment of compliance.
Xerostomia and thirst were assessed in a reference group at baseline, and in the intervention group at baseline, after three months of intervention, and after one month of follow-up using a non-validated 19 multiple-choice questionnaire. Neither perceived xerostomia nor thirst was significantly changed from baseline after the intervention or one month follow-up period. However, for xerostomia management the percentage of patients who preferred drinking fluids decreased 26% while those who preferred chewing gum increased 250% (p=.04). Similar trends were seen in thirst management, with a 45% decrease in the number of patients who preferred drinking fluids and a 380% increase in the number of patients choosing gum (p=.004). While the majority had chewed gum prior to the study, only 10% (n=3) had used it to manage symptoms.

There are a variety of limitations in this study design that could account for the lack of treatment effect. The use of multiple-choice questionnaire rather than a validated tool for thirst or xerostomia decreases internal validity. Internal validity may also be decreased by a learning effect of those who had utilized gum to treat thirst previously. The lengthy treatment period could decrease patient compliance compared with other similar trials whose interventions lasted a much shorter time, however it did not result in a high attrition rate (18.5%). Despite being from the same HD unit with identical inclusion criteria, there was a significant difference in xerostomia and thirst perception at baseline between intervention and reference groups, which may reflect poor quality of questionnaire or poor randomization. As patients could not be blinded from chewing gum use, the study design had to be open which introduces reporting bias. Side effects from therapy including diarrhea, abdominal pain, and decreased appetite were reported in 52% of patients, another factor that may have affected compliance. Decreased appetite was the
most commonly reported side effect, which is problematic in a largely malnourished HD population but could potentially be an added benefit of chewing gum for thirst in other settings. Although this was an essentially negative study, the number of patients accepting chewing gum as an alternative tool to fluids for symptom management was significant.

Said et al. (2013) conducted a quasi-experimental study regarding the effect of sugar-free chewing gum on xerostomia, thirst, and IWG in HD patients at the Ain Shams University Specialized Hospital in Cairo, Egypt using the DTI (Dialysis Thirst Inventory), XI, IWG, and salivary flow rates. A group of 60 adult patients with end-stage renal disease, on HD for three months or more, and stable in terms of dry weight and hematocrit were consecutively enrolled and randomized using block randomization 10 patients at a time into evenly divided intervention and control groups. Exclusion criteria were extensive, and included diabetes mellitus, ischemic heart disease, autoimmune disease, malignancy in the oral cavity, microscopic evidence of oral infection, periodontal disease, hemodynamic instability, dementia, anxiety, depression, use of chemotherapy or radiation, and use of known xerogenic medications including anticholinergics, antidepressants, antipsychotics, antihistamines, antiparkinson agents, and diuretics. Data were gathered before and after each dialysis session during the two-week trial. The chewing gum group received strawberry and peppermint flavored gum with instructions to chew one to two pieces for over 10 minutes, six times daily and whenever the mouth felt dry or they felt thirsty.

Kruskal Wallis tests were used to determine if the four main variables changed significantly across six dialysis sessions over a period of two weeks. XI (0-5) decreased
significantly in the intervention group (4.6±0.6 to 1.8±0.8, p<0.001) and increased in the control group (3.3±0.7 to 4.0±0.9, p=0.03). DTI (0-5) decreased with intervention (4.3±0.6 to 1.9±0.7, p<0.001) and increased with control (2.3±1.1 to 4.4±0.8, p<0.001). IWG (kg) also decreased in the intervention group over time (4.4±1.2 to 1.8±0.7, p<0.001) and increased with no intervention (1.8±0.5 to 3.0±1.5, p<0.001). Salivary flow (mL) rate was stimulated by chewing gum (0.4±0.1 to 0.8±0.2, p<0.001) and decreased in the control group (0.5±0.2 to 0.4±0.2, p<0.001).

Chewing gum as an intervention cannot be blinded, and therefore results of the XI and DTI are subject to some degree of reporting bias. There was a large difference in IWG between groups at the first HD session (4.4±1.2 kg in the study group and 1.8±0.5 kg in the control group) despite having no significant difference in baseline dry weight, months on HD, age, or sex. Exclusion criteria were extensive, and eliminated those on any type of drug that could cause thirst or xerostomia as well as those with ischemic heart disease, both of which are common in the HF population. This may have increased internal validity of the study by eliminating potential confounders, but it also greatly limited generalizability.

In 2013 Fan et al. conducted an observational study in No. 5 Hospital of Shanghai dialysis center of 42 maintenance HD patients to assess thirst and xerostomia, as well as a crossover trial with 11 HD patients over the course of six weeks to test the effect that chewing gum versus consuming all liquids through a straw has on the same outcomes. Thirst was measured by VAS and DTI, while VAS and XI measured xerostomia. Those included were at least 18 years of age, had been on HD a minimum of five months, and had stable dry weight and hematocrit. Exclusion criteria were
hospitalization within the past three months, hemodynamic instability preventing sufficient ultrafiltration, dementia, or other terminal disease. Each intervention lasted two weeks with a washout period in between. Sugar-free mint flavored gum was given with instructions to chew a piece for at least 10 minutes, six times daily and additionally as desired for feelings of dry mouth and thirst. Participants were given 3 mm plastic straws to drink water through when they had symptoms.

The use of chewing gum significantly decreased measures of both thirst (VAS 70.7±17.1 to 61.1±22.0, p=0.038 and DTI 19.3±3.4 to 14.3±4.8, p=0.000) and xerostomia (VAS 54.6±19.6 to 44.6±20.0, p=0.001 and XI 32.2±9.4 to 27.3±11.7, p=0.001). The use of straw also had an effect on thirst (VAS 70.7±17.1 to 59.4±21.7, p=0.016 and DTI 19.3±3.4 to 15.6±5.3, p=0.003) but not on xerostomia. Three-day IWG (kg) decreased from a baseline of 3.17±0.89 to 2.88±0.65 with chewing gum (p=0.017), and to 2.94±0.71 with straw (p=0.049), yet there was no change in daily or two-day IWG. When comparing the two treatments directly, the VAS score for xerostomia was significantly decreased by the use of chewing gum compared to straw (p=0.06) but there was no difference in VAS for thirst, DTI, XI, IWG, or salivary flow rates.

Unlike prior studies, this study did not show similar trends between salivary flow and thirst or xerostomia, suggesting that the cause of thirst in this population is more complicated than decreased saliva. The sample size of the crossover trial could also have been insufficient to demonstrate the outcomes. Gum and straws were interventions that made it impossible to blind patients, which may introduce reporting bias, although this effect is partly mitigated by the crossover design as participants received both. A decrease in three-day IWG was a new finding compared with prior studies and would
need to be reevaluated with a longer intervention period in the future. If it is a true finding it could have further implications on the importance of treating thirst to improve objective outcomes in addition to subjective symptoms, a benefit that has been suggested but not supported in previous studies.

2.2b Artificial saliva and thirst

Jellema et al. (2001)\(^6\) examined the effect of Xialine\(^\text{®}\), a xantham gum-based saliva substitute, versus placebo in a double blind crossover pilot study on radiation-induced xerostomia and related symptoms in patients with head and neck cancer. Those included had undergone irradiation for head or neck cancer that began at least three months before the study, had received a minimum radiation dose of 50 Gy to at least 75% of the parotid glands, suffered from subjective xerostomia, and had a WHO performance status of 0-2, a common cutoff for research in cancer patients. Patients were excluded on the basis of alcohol abuse and salivary dysfunction due to other causes, including medication-induced. A total of 30 patients from the Netherlands (19 of whom were male, mean age of 59) were randomized to receive either Xialine or placebo for the first week, then switched and completed a week of the other substance with a one-week washout period in between interventions. Instructions were to use the substance at least four times daily. Placebo composition was similar to the intervention but lacked xantham gum, the active visco-elastic component of Xialine.

A well-validated quality of life questionnaire developed by the European Organization for Research and Treatment of Cancer (EORTC) and specific to head and neck cancer, the EORTC QLQ-H&N35, was used in this study to evaluate xerostomia and related symptoms. The module contains 35 questions, all of which are rated on a
four-point Likert scale and later converted to a scale of 0-100, with higher numbers correlating to a higher burden of symptoms. Data were collected at baseline and after completion of both treatment arms, and mean changes from baseline were compared using repeated measures analysis of variance. Change from baseline of five or more points constituted clinically significant improvement or worsening of symptoms.

Xerostomia was the symptom with the highest EORTC QLQ-H&N35 score at baseline of 84 out of 100, and it improved after Xialine intervention (-14.8) and placebo (-17.2) with no significant difference between the two (p=0.78). The next highest baseline score was for sticky saliva at 71, which also improved with Xialine (-10.7) and placebo (-11.5) a similar amount (p=0.43). Problems with speech mean score at baseline was 30, and although it was again not a statistically significant between-treatment difference (p=0.25), it was demonstrated that Xialine improved it to a clinically significant level (-7.1) whereas placebo did not (-0.6).

Baseline scores were similar at the beginning of each intervention period, suggesting the washout period was sufficient and the order of interventions did not affect results. This study failed to detect a treatment difference between Xialine and placebo in any of the investigated symptoms, but it did show a trend towards Xialine improving problems with speech more than placebo. Both intervention and placebo improved xerostomia and the feeling of sticky saliva. The similar effect in these categories could be due to the similar composition of the two treatments, which would suggest that xantham gum, considered to be the active ingredient in Xialine, has no additional benefit over other saliva substitutes and choice of substitute does not alter results. The short intervention period could also explain their lack of findings. Patients as well as treating
physicians were able to be blinded thereby decreasing information bias since the interventions compared were both saliva substitutes, packaged identically, and with similar composition. The exclusion of patients with salivary dysfunction from medications is one criterion that focused this study on radiation-induced xerostomia to increase internal validity, but limits generalizability.

Alpoz et al. (2007)\textsuperscript{7} examined the efficacy of Xialine versus placebo to treat xerostomia-related symptoms in a single-blind crossover study in patients suffering from Sjögren’s Syndrome, an autoimmune disease that decreases the functional capacity of salivary and lacrimal glands, causing the main symptoms of dry mouth and eyes. A group of 29 patients age 24-77 (mean=45) being treated at the Ege University Faculty of Medicine Department of Rheumatology in Turkey were included in the study. They had diminished salivary function confirmed with salivary flow rates and objective findings of xerostomia on exam, did not use alcohol or tobacco, and had not tried any other intervention for symptoms besides water. Patients completed questionnaires with VAS for 10 different symptoms of dry mouth one hour after first application, and at the end of days 1, 7, and 14 for each intervention. In this crossover design, all participants used placebo six times daily for the first 14 days, then after a washout period of seven days, everyone completed the study with 14 days of Xialine six times daily.

All 10 symptoms of dry mouth decreased with use of Xialine, including burning tongue (21.04%), continuous dry mouth (4.78%), painful oral mucosa (3.93%), diminished taste (25.12%), difficulty with mastication (37.39%), difficulty swallowing (20.93%), the need to sip liquids to aid swallowing (22.95%), difficulty in speaking (2.38%), dryness at night or upon awakening (2.54%), and frequent need to moisten oral
mucosa (3.24%). With use of placebo, there was improvement of only continuous dry mouth (25.42%), difficulty with mastication (27.25%), difficulty swallowing (28.95%), the need to sip liquids to aid swallowing (43.98%), difficulty in speaking (39.61%), dryness at night or upon awakening (35.24%), and frequent need to moisten oral mucosa (33.78%). There was a statistically significant treatment effect favoring Xialine group compared to placebo in the categories of overall satisfaction (p=0.011), swallowing (p=0.027), daily liquid consumption (p=0.019), mouth burning (p=0.025), the need to sip liquids to aid swallowing (p=0.023), and difficulty in speaking (p=0.004). Although continuous dry mouth improved in more cases following Xialine administration than placebo, this result was not statistically significant (p=0.061).

The study by Alpoz et al. (2007) was designed as a crossover trial, but there was no randomization and all participants received the interventions in the same sequence, making it impossible to blind researchers and introducing information bias. This lack of randomization into two different intervention groups also makes it impossible to rule out period effect, so there is no guarantee these results are not affected by the order of intervention. The discussion states that participants were effectively blinded due to similar color, taste, and packaging of the two treatments, however the composition of this placebo (plain water with tea) is much thinner than viscous Xialine, making information bias possible from participants as well. This study was unique in that they used objective means to confirm presence of salivary gland dysfunction, a strategy that is more relevant in Sjögren’s Syndrome than other populations. Participants with this disease are typically younger women (mean age was 45, sex baseline characteristics were not reported), which decreases applicability of these findings to our target population that is primarily
composed of older men.

2.2c Chewing gum and artificial saliva

In a prospective randomized open crossover study, Davies (2000) compared efficacy of Saliva Orthana™, a mucin-based artificial saliva spray, with Freedent™ low-tack, sugar-free chewing gum on xerostomia in patients with advanced cancer. It was conducted in one hospital and one hospice care center in London using both inpatients and outpatients complaining of xerostomia. Exclusion criteria included Sjögren’s Syndrome or other salivary gland disorders, radiation-induced xerostomia, and cognitive impairment. Forty-three patients (mean age 66, range from 32-87 years, 23 of whom were female) were randomized into the two treatment arms for five days of use, followed by two days of washout period, and a final five days of the opposite intervention. The instructions for gum and spray were to use them before each meal and at bedtime, as well as other times throughout the day if the mouth felt dry. Other saliva stimulants or substitutes were not allowed to be used during the study. A questionnaire and VAS for dry mouth were administered at the beginning and end of each treatment period to assess efficacy.

Mean VAS scores in either group were similar at the beginning of the first intervention (32.0 mm in the artificial saliva group and 32.5 mm in the chewing gum group, p=0.95) as well as the second phase of the study (40.7 mm in the artificial saliva group and 31.9 mm in the chewing gum group, p=0.34). Analysis at conclusion of the study showed no evidence of period or carry-over effects (unpaired t-test: P = 0.11). Mean changes in VAS scores were similar; +22.4 mm with the use of artificial saliva and +30.1 mm with the use of chewing gum (paired t-test: p=0.49). More patients preferred
gum (69%) than saliva spray (31%) with the most common reason being a feeling that one was more effective than the other, although these data were not determined to be statistically significant.

Internal validity is questionable in this study due to a large dropout rate of 30%, the majority of which was due to death or deterioration in condition, a common issue in advanced cancer research and likely why the intervention period was kept short. There was no difference in the number of side effects reported between groups (five from saliva spray, seven from chewing gum, \(p=0.75\)), however the three participants that dropped out because of side effects were all due to chewing gum (nausea and mouth irritation). The article reported baseline characteristics on potential confounders such as the use of dentures and drugs that cause xerostomia but did not exclude them, which increases the external validity of their results. Oddly, the VAS scale given to patients in this trial had 0 symbolizing the “worst imaginable oral dryness” and 100 symbolizing “no oral dryness”, which is the opposite of how this common scale is typically implemented. This could have confused participants who were familiar with this type of scale, potentially influencing results.

In 2005, Bots et al.\(^3\) conducted a randomized crossover trial with repeated measures, comparing the efficacy and preference of Freedent chewing gum versus Xialine in HD patients. A total of 89 patients were randomized to receive one of the two interventions to use at least six times daily for two weeks, followed by two weeks using the other intervention in the same manner, with a two-week washout period in between. Inclusion criteria were at least three months on HD, at least 18 years of age, and being mentally and physically capable of completing the study. After 27% of participants
dropped out, a total of 65 patients (42 men, 23 women, mean age 54.65) completed the study. IWG, salivary flow rates, XI and DTI were measured at baseline and after each treatment period.

Chewing gum decreased the XI score from 29.9 to 28.1 (-1.8 difference, p=0.005). Saliva substitute decreased the XI score from 29.9 to 29.0 (-0.9), which was not a significant change. This was a 50% greater treatment effect of chewing gum vs. artificial saliva on XI (p=0.024). Perceived thirst as measured by the DTI significantly improved with chewing gum (p<0.05) from 16.6 to 15.4 (-1.2) and saliva substitute from 16.6 to 15.5 (-1.1). This was an 8% greater treatment effect of chewing gum vs. artificial saliva (p=0.015). IWG and salivary flow were unchanged by either intervention. Age, sex, and dentures had no effect on response to treatment. At the end of both treatment periods, a questionnaire was used to assess efficacy and preference. Chewing gum was significantly superior to Xialine in each category, including ease of use, effect on thirst, effect on dry mouth, judgment of taste, benefit received, and willingness to use the therapy for a longer time period. In a dichotomous assessment of preference, 60% preferred chewing gum and 15.4% preferred Xialine (p<0.001), while the rest did not report a preference or had no preference.

At baseline, data were stratified by gender, age (≤65 or >65), residual urine output (yes/no), and full dentures (yes/no), and there were significant differences found in IWG, XI, and DTI when looking at age and residual urine output. Younger age and no residual urine output, which correlates with more advanced CKD, were associated with high XI, DTI, and IWG. Some other studies chose to exclude denture wearers, but by including them Bots et al.³ was able to show they did not have an effect on response to either gum
or saliva therapy. Consistent with the study by Bots et al. (2004), giving participants a choice of gum flavor did not affect outcomes and is assumed to have increased compliance. The results only included data from the 73% of participants that completed the study, which would not alter characteristics between groups in a crossover design study but may introduce bias. No participant dropped out of the study due to side effects, but unpleasant taste, nausea, irritation of the oral mucosa, diarrhea, sensitivity of the jaw and teeth, and fatigue of muscles were reported.

2.3 Review of Possible Confounding Variables

2.3a Demographics

Age and sex are basic demographics that are reported in all studies to assess their potential influence on results, including those on thirst in HF. In 2011, Waldreus et al. conducted a cohort investigation of thirst in 48 HF patients, 65 years of age or older, half of whom were admitted to the hospital with acute decompensated HF, while the other half were admitted to the hospital for treatment of an acute illness other than HF. Thirst as assessed by VAS was much higher in elderly patients with worsening HF (median 75 mm, interquartile range 56-90) compared with acutely ill elderly patients without HF (median 25 mm, 11-40; p<0.0001). They found that age, gender, and diuretic medications were not significant predictors of thirst in either the HF or control group in this specific population of elderly people admitted to the hospital. The same investigators conducted a descriptive prospective study in 2014 designed to assess the factors associated with persistent thirst in HF patients over an 18-month period following hospitalization for HF exacerbation. Persistent thirst was found in 121 (19%) of the total 649 patients, and this
subpopulation was significantly younger (mean age 64 years versus 70 years, p<0.01), more likely to be male (75%, p<0.01), more likely to be on diuretic medications (99% versus 95%, p=0.03), and had a greater number of HF symptoms at 1 month (four versus three, p<0.01), a higher mean BMI (29 kg/m² compared with 27 kg/m², p<0.01), and more depressive symptoms as assessed by the Center for Epidemiological Studies Depression Scale (median total score 14.5 versus 12.0, p=0.02). Ejection fraction, NYHA class, N-terminal pro-B-type natriuretic peptide, presence of diabetes or hypertension, and practice of fluid restriction were not significantly different among those who suffered from persistent thirst.

2.3b Fluid restriction

Holst et al. (2008)\textsuperscript{11} conducted a randomized crossover study of 74 patients who had improved from NYHA class III-IV HF to a stable condition in order to investigate the effects of a fluid restricted diet on thirst and other various outcomes. Fluid restriction and liberal fluid intake (control) interventions lasted for 16 weeks each. Median sense of thirst on VAS at the end of the intervention was 51 mm (interquartile range 16-69) in the fluid restricted group compared to 23 mm (6-53) for the liberal fluid intake group (p<0.001). Median VAS score for difficulties to adhere to fluid prescription was 23 mm (5-56) with fluid restriction, compared to 6 mm (1-24) with liberal fluid intake (p<0.001).

In 2013, Philipson et al. \textsuperscript{12} conducted a 12-week randomized controlled intervention trial of 97 stable HF patients on daily furosemide - a diuretic, comparing the effect of fluid restricted diet with no specific restrictions, on a number of outcomes including thirst. In this trial, difference in change between groups in regard to thirst, as measured by VAS 1-10mm, was not statistically significant (4.2 to 4.4 during the intervention
compared to 4.4 to 5.2 during the control, p=0.06). As stated previously, Waldreus et al. (2011)\textsuperscript{9} also found that the presence of persistent thirst was not correlated with fluid restriction. Inconclusive data such as these from the body of literature on the benefits and consequences of fluid restriction is why it remains a controversial, although often used, self-care measure in patients with HF as well as a possible confounder of thirst assessment.

2.3c Heart failure classification and severity

It is expected that the bothersome symptoms of thirst and dry mouth would increase in severity in a parallel fashion with disease severity, but this has yet to be clearly demonstrated in HF. Waldreus et al. (2011)\textsuperscript{9} demonstrated a trend in worsening thirst with increased NYHA functional classification in patients over 65 admitted to the hospital for ADHF. However, the same investigators later reported data\textsuperscript{10} suggesting that NYHA class, ejection fraction, and N-terminal pro-B-type natriuretic peptide were unchanged between those who suffered from persistent thirst and those who did not. A pilot study conducted by Reilly et al. (2010)\textsuperscript{13} on thirst and quality of life in HF found that thirst distress is moderately correlated to all subscales on the Heart Failure Symptom Survey. These consisted of frequency (r = .545, p = .005), severity (r = .538, p = .006), interference with physical activity (r = .605, p = .001), and interference with enjoyment of life (r = .552, p = .004). Some studies choose to stratify their data by NYHA class while others simply record this information in their baseline characteristics. Thus, all do include NYHA class in analyses, as it is a likely source of confounding despite a lack of clear evidence.
2.3d Preference

Preference for chewing gum or saliva substitute may have a confounding effect on the self-report scales used to quantify thirst and xerostomia. With these different interventions, it is impossible to blind participants to eliminate this effect. The question of preference is also closely related to compliance, another potential confounder. Therefore, reporting patient preference along with thirst outcomes is of utmost importance. The hypothesis of our proposed study is that irrespective of the results of the primary outcome, more patients will prefer chewing gum to artificial saliva based on similar findings throughout our literature review.2,3,8

2.4 Review of Relevant Methodology

Detailed methodology of the proposed study is outlined in Chapter 3. This section is designed to provide a review of relevant study methods. It is impossible to compare methodology used in studies on the effect of artificial saliva and chewing gum on thirst in heart failure patients, as none exist in the literature.

2.4a Design

In a 2011 Cochrane review by Furness et al.14 on topical therapies for dry mouth management, 29 out of the 36 included studies were crossover designs, with a washout period between interventions. Research on thirst lends itself to this study design as it is a stable, slowly changing condition, and the topical therapies designed to alleviate it have no known lasting effects and are considered reversible in a relatively short time frame, especially when a washout period is utilized. An added benefit of this design is that it decreases problems with confounding variables between groups, since each participant is
included in both arms of the trial, and thereby serves as their own control. This allows for statistical analyses that assume randomization, and gives participants the ability to directly compare preference. It also has unique characteristics for statistical analysis. The sample size needed to power a study and meet the same criteria in terms of type I and II errors is lower than studies with parallel groups, making it a statistically efficient design. There are some pitfalls of this type of study as well, some of which can be avoided with proper design. There can be unintended effects based on the order of intervention (treatment effect), and carry-over effects from one intervention period to another, for example, learning the study procedures over time (period effect). These can be avoided if the therapies being tested have short-term efficacy and a long enough washout period is used between interventions. Analysis can be performed after the fact to ensure the results are free from these unintended effects.\textsuperscript{15}

\textbf{2.4b Setting and selection criteria}

The proposed study will take place in outpatient HF clinics in Connecticut. Adults \(\geq 18\) years of age with evidence of structural underlying heart disease who fall into NHYA functional class II-IV will be eligible to participate. Patients included will be in a stable condition as determined by lack of symptoms or physical exam findings of fluid overload, and no medication adjustments in the preceding two weeks. Prior studies on thirst in this population had participants recruited at time of discharge from hospitalization for a HF exacerbation, but as our study aims to capture information from a more stable sample, hospitalization within the past month for any reason will be an exclusion criterion.\textsuperscript{11,12,16} Patients who are not able to chew gum, apply a salivary spray, or complete written surveys will be excluded.
2.4c Interventions

The most common interventions for thirst are topical and include either saliva substitutes (viscous material applied to the oral mucosa in the form of sprays, gels, oils, mouthwashes, or pills, also referred to as “palliative care”) or saliva stimulants (lozenges, chewing gum, or toothpaste which may contain medication). Less commonly, interventional studies have included acupuncture, electrostimulation, and systemic therapy such as oral pilocarpine.\textsuperscript{14}

Sugar free chewing gum and artificial saliva spray will comprise the two treatment arms in the proposed study. Sugar free chewing gum contains sugar substitutes, such as bulk sweeteners like xylitol, mannitol, and sorbitol, or intense sweeteners like aspartame; each of these have been shown to be non-cariogenic.\textsuperscript{17} A number of studies have demonstrated that chewing gum increases salivary flow for a limited time due to a number of stimuli it provides, including aroma, flavor, taste, and mastication.\textsuperscript{2} It has also been demonstrated that increased salivary flow enhances the buffering ability of saliva, so chewing gum can effectively neutralize the decrease in saliva and plaque pH that occurs after meals, thereby combating cariogenic acid production.\textsuperscript{17} As discussed previously, Bots et al. (2004)\textsuperscript{1} conducted a preliminary study on salivary stimulation and preference of eight different chewing gums, seven of which were Wm. Wrigley Jr. brand. Each gum, despite flavor and shape, stimulated salivary flow to the same extent and for the same time period, but patients had a variety of gum preferences. Based on these results, a number of studies that followed gave participants a choice of flavor in the hope of improving compliance, a practice that we will continue in the proposed study.\textsuperscript{2,3}
Different categories and brands of saliva substitutes have been compared and used in various trials, but data remain inconclusive regarding which is the most effective, or if there is any benefit to them over placebo.\textsuperscript{18} Xialine is a specific brand of saliva substitute that has been utilized most in the literature reviewed, and this will be used in the proposed study. Like all saliva substitutes, it provides a coating over the oral mucosa to help retain moisture. It contains 0.92\% polysaccharide xanthan gum as its active ingredient (giving it visco-elastic properties similar to human saliva), as well as sodium fluoride for tooth mineralization.\textsuperscript{3,6}

The intervention period of two weeks per treatment with a two-week washout period in-between was chosen, as it was the most common length of intervention and washout found in studies with positive results.\textsuperscript{3-5,7} Longer intervention periods such as three months in the case of Jagodzinska et al. (2011)\textsuperscript{2} and shorter time frames such as one week in Jellema et al. (2001)\textsuperscript{6} or five days in Davies (2000)\textsuperscript{8} showed no treatment effect of intervention versus placebo or between two interventions.

\textit{2.4d Outcome measurement}

The VAS is a scale commonly used to evaluate pain and breathlessness, and the one that has most commonly been used in HF to evaluate thirst intensity. A VAS is characterized by a continuous horizontal line from 0-10 or 0-100 mm with verbal descriptors on either end, and typically the left side of the line indicates lack of a symptom while the right indicates the greatest symptom level possible.\textsuperscript{7} Waldreus et al. (2013)\textsuperscript{19} and Allida et al. (2014)\textsuperscript{20} conducted similar reviews of original studies in patients with HF using thirst as an outcome measure. In total, five of the 11 studies included used the VAS, making it the most common scale utilized. It is commonly
employed in other populations suffering from thirst and dry mouth including HD, Sjögren’s Syndrome, and head and neck radiation. While it has not been specifically validated to evaluate thirst intensity in HF, its consistent use in research for purposes of assessing characteristics associated with thirst makes it the best tool to derive a treatment effect from in order to calculate sample size, and to assess our primary outcome in the proposed study.

The TDS is a scale that has been validated in HD patients to assess thirst distress, defined as the degree to which a person is bothered by thirst or its associated discomfort. It was developed in 2002 by Janet Welch and is a six-item tool, each with a five-point Likert scale where 1 corresponds to strongly disagree and 5 to strongly agree, for a total possible score ranging from 6-30. In the development of the TDS, Welch used a panel of experts to establish content validity and a convenience sample of 247 adults receiving outpatient HD to test the item pool. Cronbach’s alpha was 0.78, considered to be satisfactory in terms of reliability. Confirmatory and exploratory factor analysis, as well as observed associations between thirst distress, thirst intensity, and IWG supported construct validity. While it is not included as part of the TDS, Welch used a VAS for thirst intensity in conjunction with TDS for a more global assessment of the symptom. Jacob et al. performed a follow-up study in 2004 which again supported a correlation between TDS and IWG in HD patients. Due to this evidence of validity and reliability in HD, the TDS has been used commonly in this population but can also be found in recent articles on HF as this population lacks a specific validated scale. Reilly et al. used the TDS as the only measurement of thirst in a 2010 pilot study on thirst and quality of life in HF with mean of 15.6 (SD 7.7). They reported a moderate correlation between
all the symptoms of the Heart Failure Symptom Survey and the TDS: frequency (r = .545, p = .005), severity (r = .538, p = .006), interference with physical activity (r = .605, p = .001), and interference with enjoyment of life (r = .552, p = .004). This was the only study to use this scale in a 2014 comprehensive review of articles using subjective measures of thirst as a primary or secondary endpoint in HF patients conducted by Allida et al.\textsuperscript{20}, while four of the six studies included used the VAS. The discussion at the end of this review again suggested combining multiple scales for more thorough data.

XI is a tool composed of 11 questions relating to the symptom of dry mouth, each with a corresponding five-point Likert scale ranging from 1 (never) to 5 (very often). These scores are summed to total a final XI score between 11 and 55. It has since been validated in HD, but was originally developed and validated in the dental community by Thomson et al. (1999).\textsuperscript{5,24} Initially, 19 questions were compiled to evaluate xerostomia based on a combination of literature review, and interviews conducted in a convenience sample of four long-term sufferers of xerostomia. Further analysis divided these questions into two different scales, one being the 11-question XI score (Cronbach’s alpha of 0.84). The validity of the XI was then tested in a sample of subjects suffering from xerostomia who were part of a five-year South Australian Dental Longitudinal Study. XI questionnaires were completed and returned by 649 participants, and were compared with a standard single xerostomia question (“How often does your mouth feel dry?” Response options: “Never”, “Occasionally”, “Frequently”, “Always”), as well as salivary flow data. One-way ANOVA analysis determined that mean XI scores differed significantly between each of the four responses on the standard single xerostomia question (p<0.0001), with an overall correlation between the two data collection tools of 0.42
Correlation between XI score and resting whole salivary flow rates was low ($r = -0.05$) and not statistically significant.

This tool has since been widely utilized in a variety of populations, most commonly in populations with direct salivary gland involvement such as Sjögren’s Syndrome and those with head and neck cancer irradiation. However, it has also been used in research on thirst and dry mouth in HD patients, a population with a more complex cause of these symptoms. For example, Bots et al. (2005)$^3$ found a positive treatment effect of chewing gum on xerostomia based on the XI. Salivary flow was unaffected, consistent with initial data from Thomson et al.$^{24}$.

Salivary flow rates are commonly measured in studies on thirst as a form of objective data, in particular when saliva stimulants such as chewing gum are used. Salivary flow is diminished in autoimmune diseases such as Sjögren’s Syndrome and with radiation-induced damage to the salivary glands, or with certain medications, but is not known to be affected in HD or HF. Said et al. (2013)$^4$ utilized a sample of HD patients who demonstrated improved xerostomia, thirst, and salivary flow with the use of chewing gum. However, as stated previously, Thomson et al. (1999)$^{24}$, Bots et al. (2005)$^3$, and Fan et al. (2013)$^5$ found no correlation between XI and salivary flow, and a review on xerostomia management by Visvanathan et al. (2009)$^{25}$ concluded that salivary flow rates are highly variable and do not tend to correlate to subjective symptoms.

Each of the aforementioned scales (VAS for thirst intensity, TDS, and XI) evaluates a different part of the symptom in question. Since there is no clear gold standard and each measure contributes unique information, they will each be included in our proposed study. We will however, not include salivary flow as an outcome of thirst
since this is an inherently subjective symptom that has not been shown to correlate highly with salivary flow rates.

2.4e Follow-up

It has been demonstrated in prior research that the effect of saliva substitutes and stimulants occurs quickly, and common practice has been to collect relevant data at baseline as well as prior to and immediately following an intervention with no additional followup. \(^3,7,8\) Jagodzinska et al. (2011)\(^2\) was an exception to this practice, and found no change in thirst or xerostomia one month following the completion of a chewing gum intervention. Therefore, there will be no follow-up period in our proposed study.

2.5 Conclusion

Several studies have shown chewing gum to be effective at alleviating thirst and xerostomia due to a variety of causes in different populations. \(^2,5,7,8\) A more limited body of research has shown that saliva substitutes may alleviate these symptoms as well. \(^3,6-8\) There were two studies reviewed that provide a direct comparison of these interventions. Davies (2000)\(^8\) found that both Saliva Orthana salivary substitute and sugar-free chewing gum significantly alleviated thirst as measured by VAS in advanced cancer patients, with no between-treatment difference. There was an overall preference for chewing gum, but this was not a statistically significant finding. Bots et al. (2005)\(^3\) found that only chewing gum decreased xerostomia significantly, and there was a 50% greater treatment effect of chewing gum over Xialine on the XI. For thirst, both interventions significantly decreased the DTI score but there was still a significant 8% greater treatment effect of chewing gum over artificial saliva. In that study, preference for chewing gum was found
to be statistically significant. Due to the demonstrated lack of interventional studies at alleviating thirst in HF, our proposed study will integrate data from clinical trials in other populations with background information on the problem of thirst in HF in order to investigate the potential benefit that chewing gum and artificial saliva may have.
2.6 References


CHAPTER 3: Study Methods

3.1 Study Design

The proposed study will be a prospective, randomized, single-blinded crossover study comparing the efficacy of Freedent sugar-free chewing gum vs. Xialine salivary substitute spray in decreasing thirst and dry mouth in stable adult HF patients suffering from these symptoms.

3.2 Study Population and Sampling

A sample of 120 volunteers will be recruited from the outpatient HF clinics of Yale-New Haven Hospital, Bridgeport Hospital, Hartford Hospital, and the University of Connecticut Health Center. These clinics combined serve over 1,000 HF patients. Patients who report the symptom of thirst or xerostomia, meet the criteria listed below, and are willing to participate in the study will be enrolled.

Inclusion criteria include ≥18 years of age, previous diagnosis of HF documented in the electronic medical record, NYHA functional classification II-IV, and willing and able to complete survey instruments. Exclusion criteria include current signs or symptoms of volume overload, medication adjustment in the prior two weeks, hospitalization for any reason in the prior month, current use of methods besides water for thirst or xerostomia symptom management, Sjögren’s Syndrome or other salivary gland disorder, prior radiation for head or neck cancer, inability to chew gum or personally apply saliva spray, and non-English speaking or reading. Individuals who have had medication adjustments in the prior two weeks or been hospitalized in the prior month will be re-contacted after the requisite time period has passed.
3.3 Subject Protection and Confidentiality

Protocol application will be submitted to the Yale Human Investigation Committee (HIC) and the Yale Institutional Review Board (IRB) for study approval. Upon approval, letters will be sent to each collaborative site for study protocol approval via their own institution’s IRB. Approval letters will be returned and kept on file at the Yale HIC. All members of the research team and outside consultants involved in the study will complete the Health Insurance Portability and Accountability Act (HIPAA) privacy training and the Yale Human Subjects Protection Training prior to study initiation. Only after all of these requirements have been met will the study begin.

Identity and health information of participants will remain confidential. HIPAA policy will be strictly enforced, and each participant will be assigned a unique number with no personal identifiers, by which they are identified throughout the entire study. Written informed consent will be obtained, following standard IRB guidelines. (Appendix J).

3.4 Recruitment

In each participating center, flyers indicating the purpose of the study with contact information for a research associate responsible for telephone screening will be posted in the waiting area and examination rooms (Appendix A). Telephone screening will begin by confirming that the patient feels thirsty or feels their mouth is dry. A positive response to either of these questions will trigger application of the inclusion and exclusion criteria to determine eligibility. If eligible, potential candidates will be provided with the informed consent form. Given the combined numbers of patients seen
weekly in the designated practices, we anticipate that study recruitment will last for approximately 26 weeks.

3.5 Study Variables and Measures

3.5a Independent variables

Two interventions will be directly compared in this study: 1) Freedent (Wm Wrigley Jr Co., Chicago, IL, USA), a low-tack, sugar-free chewing gum, will be provided to patients with a choice of three flavors (Sweetmint, Winterfresh, and Peppermint) to optimize compliance, with instructions to use one to two pieces of gum at a time, at least four times daily (before each meal, before bedtime, and any other time they have symptoms), chewing at least 10 minutes each time; and 2) Xialine (Lommerse Pharma B.V., Oss, The Netherlands), a polysaccharide xanthan gum-based salivary substitute with visco-elastic properties similar to human saliva, will be provided in spray bottle (50mL) form, with instructions to apply the spray to coat the oral mucosa at least four times daily (before each meal, before bedtime, and any other time they have symptoms). The use of interventions for thirst other than those provided, or water, will be discouraged.

3.5b Dependent variables

The primary outcome of the proposed study will be change in thirst intensity, and the VAS will be the primary outcome measure to compare the effect of each treatment (Appendix D). The VAS is a horizontal line 100 mm in length with the left end indicating absence of thirst and the right end indicating the highest intensity of thirst. Patients will mark the line at the point that most accurately represents their perception of
the symptom in that moment, and the distance in mm from the left end of the scale will be used as the VAS score.

The TDS will be used to measure thirst distress (Appendix E), and the XI will measure xerostomia (Appendix F), both as secondary outcomes.

Each scale will be administered at baseline and before and after each treatment period, for a total of five assessments over time. Finally, preference for treatment will be assessed at the completion of the second intervention period with a series of two dichotomous questions; “Do you have a preference for either chewing gum or artificial saliva?” (yes/no), followed by “Which do you prefer?” (chewing gum/artificial saliva) if the initial response is “yes” (Appendix B).

3.5c Baseline variables

Additional variables to be collected at baseline will include age, gender, race, NHYA functional classification, alcohol/cigarette/denture use (yes/no), diuretic medication (yes/no), and fluid restriction (yes/no). (Appendix B)

3.6 Methodology Considerations

3.6a Assignment of Interventions

Assignment of participants to either chewing gum or artificial saliva for the initial intervention period will be accomplished via computer-generated random numbers, assigning participants in a 1:1 ratio to either order of interventions. An independent researcher who is not otherwise affiliated with the study will be responsible for this process. The initial intervention will last for a period of two weeks, followed by a washout period of two weeks in which participants do not use either intervention, and
finally each participant will complete another two-week period of the other intervention to which they were not originally randomized.

3.6b Blinding of Intervention

Due to the nature of the different treatment arms, blinding of participants to the order in which they receive interventions is not feasible. All data collectors will be blinded to condition. Participants will be instructed to not discuss treatment allocation with one another or members of the research team.

3.6c Blinding of Outcome

This study will utilize single blinding, as all researchers collecting and assessing data will be blinded to the order of intervention participants received.

3.6d Adherence

Adherence to treatment will be assessed at the end of each intervention period using a questionnaire, for a total of two adherence assessments (Appendix C). The questionnaire will also ask participants to record any tools, other than the gum or spray provided, that they used to treat thirst or xerostomia during the trial. Due to the benign nature of the proposed interventions, few adverse events are expected but any that occur will be recorded and monitored with the adherence checkpoints. These will be reported in list form in the final results.

3.7 Data Collection

Initial collection of baseline data at the beginning of the study will be accomplished by a combination of self-administered questionnaires, patient interviews, and medical record review to ensure accuracy of information obtained. Age, gender,
race, use of alcohol, use of cigarettes, use of dentures, and practice of fluid restriction will be obtained upon patient interview. Diuretic use will be assessed by a combination of medical record review and patient interview to ensure there is a prescription as well as adherence in taking the medication before answering “yes” to this question. To ensure consistency, one blinded researcher will be responsible for determining NYHA functional classification based on patient interview for all participants as this involves some subjectivity (Appendix G). Data regarding thirst and xerostomia will be collected by self-administered questionnaire at baseline and before and after each treatment period for a total of five data points over time. The two questions regarding preference will be administered once at the completion of the second intervention period.

3.8 Sample Size Calculation

The study will utilize a two-tailed test and alpha of 5%, beta of 20%, and power of 80%. Mean score on the VAS will be compared between the two treatments using values assessed at the end of the respective treatment conditions. Assuming a 10-point difference on the primary outcome between interventions, power analysis indicates the need for 200 participants. However, when a conversion is completed to account for the statistical efficiency of a crossover design, the result is a sample size of 50 participants per treatment arm, for a total of 100 participants. A dropout rate of 20% is expected based on previous research. When this is taken into account, the adjusted sample size requires 60 participants per treatment arm, for a total of 120 participants. Additional detail on sample size calculation is provided in Appendix I.
3.9 Analyses

We assume the absence of order effects given that, 1) each treatment is known to not have carryover effects on any of the dependent variables, and 2) we are utilizing a washout period between implementation of treatments. We will nonetheless test whether washout is successful by comparing values for each dependent variable at the end of baseline vs. the end of washout (Appendix H).¹

Assuming that washout is successful, a two sample t-test will be used to compare the values for each dependent variable (e.g., VAS thirst) at the end of the treatment conditions. If however we find that washout was not successful, we will utilize change scores as the dependent variable (e.g., change in VAS thirst from end of initial baseline to end of first treatment, end of washout to end of second treatment). These change scores will then be combined in t-test comparisons of the two treatments. Superiority of either treatment over the other will be demonstrated by a significant t-value. Chi-square analysis will be used in the same manner for the dichotomous dependent variable, treatment preference.

Additional, exploratory analyses will be conducted to determine whether subject level variables (e.g., gender, race, age (≤65 or >65), NHYA functional classification, alcohol/ cigarette/ denture use (yes/no), diuretic medication (yes/no), and fluid restriction (yes/no)) influence superiority of one treatment vs. the other. Given the categorical nature of these variables, chi-square tests will be used. In the case of missing data, the analysis will only include results from those participants who completed the entire study protocol in an effort to maintain equality in sequence groups, although all of the available data will be presented in the document.
3.10 Timeline and Resources

Recruitment will begin in January of 2017 and is expected to take about 26 weeks. The study will be initiated in a rolling manner, and analysis will be completed immediately after all 120 participants have completed the study.

The Principal Investigator of this study will be Matthew M. Burg, PhD and Co-Principal Investigator will be Alison Robb, PA-SII. One research associate will be needed to field telephone calls in order to screen and enroll participants. One independent researcher will be responsible for the computer-generated randomization and allocation process, and will not be involved in any other aspect of the study. One blinded assessor will collect all data and outcome measurements throughout the study. A statistician not affiliated with the study in any way will be consulted to assist with data input and analysis. Required equipment will include the chewing gum and artificial saliva, computer access for patient EMR review, and the paper flyers and data collection tools.
3.11 References

CHAPTER 4: Conclusion

4.1 Advantages and Disadvantages

The proposed prospective, randomized, single blinded crossover study comparing the effect of chewing gum vs. artificial saliva on thirst and xerostomia in HF patients would be the first of its kind and thus fill a gap in the literature. Since there is no tool validated to measure thirst or xerostomia in HF, three different self-report scales will quantify patient perception of different aspects of the complex problem of thirst, providing a more comprehensive look at the symptom than previous studies. We elected to forego objective measurements utilized in similar research with other populations as they did not specifically apply to the disease process of HF, have not been proven to correlate with symptoms, and distract focus from personal perception of thirst and its quality of life implications. A single, validated tool to comprehensively evaluate the symptom of thirst in HF would be a crucial step forward and should be addressed prior to conducting research subsequent to this study.

Frequency and length of interventions were estimated from previous studies that demonstrated a positive effect of chewing gum and/or artificial saliva, and tailored to maximize treatment effect while minimizing lapses in adherence and attrition rates. Since utilization of these interventions is intended to be long-term in stable HF patients, the short intervention period may be a limitation of the study. Besides unstable clinical condition and NYHA class I functional capacity (patients with cardiac disease but without resulting limitation of physical activity), everyone who reported thirst or xerostomia at initial screening and was able to utilize both interventions and complete the outcome measurement surveys was included in the study. The inclusive nature of our
criteria introduces multiple possible confounders, but allows excellent generalizability to
the general HF population. The multicenter nature of our study adds to external validity
as well. Diuretic therapy and fluid restricted diets are two examples of important
confounding variables specific to our population; these will be assessed at baseline and
not serve as exclusions in this first trial of its kind. Studies examining the effect of
interventions for thirst while stratifying by these variables should be a focus in future
trials.

Crossover study design is consistently utilized in the literature to compare efficacy
of saliva stimulants and substitutes with one another, or with placebo. Potential
limitations of this design include doubling the time frame, carryover effects between
treatments, and failure to use statistical analysis appropriate for the design, but these were
all accounted for in our initial design and analysis process. The numerous advantages of
this design include direct comparison of the chosen interventions, statistical efficiency,
and limiting of confounding variables by having each participant serve as his or her own
control. In addition, the short-term effect of our interventions makes it likely that the
order in which they are utilized will not affect results. These considerations make
crossover design the best option for our study.

A disadvantage of this study is the wide availability and use of one of the
interventions, namely chewing gum. While patients specifically utilizing a substance
other than water for thirst or xerostomia treatment will be excluded from study
participation, some patients will have used chewing gum to treat their thirst in the past.
This may introduce reporting bias and has the potential to skew preference towards
chewing gum, a trend found in previous studies, based on familiarity alone. Although
chewing gum is readily available to the public, explicit instructions to avoid using either intervention outside of its assigned two-week intervention period will be given, and verified with the adherence questionnaire.

4.2 Clinical and Public Health Significance

Over 5.1 million Americans have a diagnosis of HF, a number that is increasing as the population ages, and many of these patients experience the symptoms of thirst and dry mouth. Topical therapies such as saliva substitutes and stimulants have been shown to be effective and safe for treating thirst in other populations, and would be simple, cost-effective solutions to this problem in our target population. Willingness to utilize a therapy long-term is essential as the benefits of these interventions are short-lived, so assessment of preference is just as important, if not more important, than data determining which method decreases thirst to a greater extent. It is our hope that targeting this long-overlooked symptom in a stable HF population will improve their symptoms and quality of life. Further implications of these interventions on compliance with diuretic medications and fluid restricted diets, and ultimately on hospitalization rates, must be examined after a comprehensive, validated tool for thirst in HF has been formulated. As it stands, research on therapies designed to provide relief to HF patients suffering from thirst are long overdue, and our study aims to meet this need as well as provide a springboard for further investigation.
4.3 References


Many heart failure patients suffer from thirst or dry mouth...

...how about YOU?

If you are interested in participating in a short study to test simple approaches to treating these symptoms WITHOUT taking more pills, please call our research assistant at:

315-247-1566

Don’t wait! Availability in this study is limited and not guaranteed
Study Title: Chewing gum and saliva substitute for the treatment of thirst in heart failure: A crossover trial

Principal Investigators: Matthew M. Burg, PhD and Alison Robb, PA-SII

Participant Identification #: ______________________

Age: ______________________

Gender:  M  F  (Circle one response)

Race: ______________________

Use of alcohol:  Y  N

Use of cigarettes:  Y  N

Use of dentures:  Y  N

Fluid restricted diet:  Y  N

Diuretic therapy:  Y  N

NYHA functional classification:  II  III  IV

<table>
<thead>
<tr>
<th></th>
<th>VAS (0-100)</th>
<th>TDS (6-30)</th>
<th>XI (11-55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Start of intervention #1:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End of intervention #1:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Start of intervention #2:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End of intervention #2:</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Do you have a preference for one intervention over the other?  Y  N
If yes, which do you prefer?    Chewing gum    Artificial saliva

APPENDIX C: Adherence Assessment

Participant Identification #: _______________________

_In your responses, please do not include any information that would indicate which intervention you have been using for the past two weeks, or the order in which you received interventions._

**Intervention Period #1**

1. In the past two weeks, how many days did you fail to use the intervention as prescribed? __________________________________________________________

2. In the past two weeks, have you forgotten to take the intervention with you when you left the house? __________________________________________________________

3. Did you use the intervention as prescribed yesterday? _______________________

4. What other tools (besides water) have you used to treat your thirst and/or dry mouth in the past two weeks? ______________________________________________________

**Intervention Period #2**

1. In the past two weeks, how many days did you fail to use the intervention as prescribed? __________________________________________________________

2. In the past two weeks, have you forgotten to take the intervention with you when you left the house? __________________________________________________________

3. Did you use the intervention as prescribed yesterday? _________________________
4. What other tools (besides water) have you used to treat your thirst and/or dry mouth in the past two weeks? ____________________________________________________________

APPENDIX D: Visual Analogue Scale (VAS)

Visual Analog Scale (VAS):

How thirsty do you feel right now?

0 mm
not thirsty

100 mm
very thirsty

Image adapted from Millard-Stafford et al., 2012¹
APPENDIX E: Thirst Distress Scale (TDS)

My thirst causes me discomfort.
My thirst bothers me a lot.
I am very uncomfortable when I am thirsty.
My mouth feels like cotton when I am thirsty.
My saliva is very thick when I am thirsty.
When I drink less, my thirst gets worse.

Response options: Strongly disagree (1), moderately disagree (2), neutral (3), moderately agree (4), strongly agree (5)

from Welch, 2002
APPENDIX F: Xerostomia Inventory (XI) ³

- I sip liquids to help swallow food
- My mouth feels dry when eating a meal
- I get up at night to drink
- My mouth feels dry
- I have difficulty in eating dry foods
- I suck sweets or cough lozenges to relieve dry mouth
- I have difficulty swallowing certain foods
- The skin of my face feels dry
- My eyes feel dry
- My lips feel dry
- The inside of my nose feels dry

Response options: Never (scoring 1), hardly (2), occasionally (3), fairly often (4) and very often (5).
## APPENDIX G: New York Heart Association

### Functional Classification of Heart Failure

<table>
<thead>
<tr>
<th>Functional capacity</th>
<th>Objective assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.</td>
<td>A. No objective evidence of cardiovascular disease.</td>
</tr>
<tr>
<td>Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.</td>
<td>B. Objective evidence of minimal cardiovascular disease.</td>
</tr>
<tr>
<td>Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.</td>
<td>C. Objective evidence of moderately severe cardiovascular disease.</td>
</tr>
<tr>
<td>Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.</td>
<td>D. Objective evidence of severe cardiovascular disease.</td>
</tr>
</tbody>
</table>
APPENDIX H: Crossover Study Design Schematic

[Diagram of crossover study design with periods, treatments, and outcomes.]
APPENDIX I: Sample Size Calculation

Sample size calculation, unadjusted for study design

<table>
<thead>
<tr>
<th>Group</th>
<th>Population Mean</th>
<th>Standard Deviation</th>
<th>N Per Group</th>
<th>Standard Error</th>
<th>95% Lower</th>
<th>95% Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>estimates of effect from extrap</td>
<td>10.0</td>
<td>25.0</td>
<td>100</td>
<td>3.54</td>
<td>3.04</td>
</tr>
</tbody>
</table>

Alpha = 0.050, Tails = 2

Power = 0.804

Statistical considerations for a cross-over study where the outcome is a measurement

Note: The power calculation uses the non-central t function, pt(x, df, ncen), and its inverse qt
Power = pt(qt(0.025, n-1, 0), n-1, -(delta/sigma)*sqrt(n)), power is truncated rather than rounded. The parameter sigma is the standard deviation of the difference which is sqrt(2) times the within patient standard deviation. If power is specified the other parameters are found by searching.

Request

- 0.05 Significance Level (%) — 2-sided (default is 0.05, two-sided)
- 25 Within patient standard deviation (if known), or [ ] Standard deviation of the difference between the two value for the same patient (if known)

Enter two of the following three values and the remaining value will be calculated

1. Total number of patients
2. Power (usually 0.8 or 0.9)
3. Minimal detectable difference in means

Calculate

Response

Calculation performed at: June 6, 2016 at 10:39:16 AM EDT

The provided parameters were: significance level (adjusted for sidedness) = 0.025, standard deviation within patients = 25, standard deviation of the difference = undefined, number of patients = undefined, power = 0.8, difference in means = 10.

The variable calculated was the total number of patients.

A total of 101 patients will enter this two-treatment crossover study. The probability is 80 percent that the study will detect a treatment difference at a two-sided 0.05 significance level, if the true difference between treatments is 10.000 units. This is based on the assumption that the within-patient standard deviation of the response variable is 25.

This software developed by David Schoenfeld, Ph.D. (dschoenfeld@partners.org), with support from the MGH Mallinckrodt General Clinical Research Center. Javascript version developed by REMorse.

http://hedwig.mgh.harvard.edu/sample_size/js/js_crossover_quant.html
APPENDIX J: Informed Consent Form

COMPOUND AUTHORIZATION AND CONSENT FOR PARTICIPATION IN THE CHEWING GUM AND ARTIFICIAL SALIVA IN THE TREATMENT OF THIRST RESEARCH TRIAL

YALE UNIVERSITY SCHOOL OF MEDICINE

Study Title: Chewing gum and saliva substitute for the treatment of thirst in heart failure: A crossover trial
Principal Investigator: Matthew M. Burg, PhD; Alison Robb, PA-SII

Invitation to Participate and Description of Project

You are invited to take part in a research study designed to look at the effectiveness of chewing gum and artificial saliva on treating thirst in stable heart failure patients. You have been asked to take part because you have a diagnosis of heart failure, are clinically stable with a NYHA functional classification of II-IV, and reported the symptom of “thirst” or “dry mouth”. This study will be enrolling approximately 120 participants from four different heart failure clinics in the state of Connecticut.

In order to decide whether or not you wish to be a part of this research study you should know enough about its risks and benefits to make an informed decision. This consent form gives you detailed information about the study, which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, any risks of the procedures, possible benefits and possible alternative treatments. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this form.

Description of Procedures

If you are interested in participating, you will be asked questions about your health and habits to determine if you are eligible. Information collected will include your age, gender, race, functional capabilities and symptoms, other medical conditions current and prior, medications, fluid intake, and use of cigarettes, alcohol, and dentures. Before the study begins you will meet with a member of the research team who will instruct you to complete three different questionnaires to assess your level of thirst and dry mouth.

Everyone will have 2 weeks of each treatment, namely chewing gum and artificial saliva. The order in which you receive these interventions will be randomly assigned in order to have the same number of participants in either intervention group at a time. After the first intervention period, there will be a 2-week “washout” period during which you will not use any tool to help with dry mouth. The purpose of this is to ensure the effect of the first treatment you used does not carry over when you begin the next. During the two, 2-week intervention time periods you will utilize the gum or saliva spray before each meal and before bedtime, as well as any other time during the day when you need it. We will require that you complete the three aforementioned surveys a total of four more times during the trial: before and after each 2-week intervention period. You will also be asked
to complete a form describing how well you adhered to using the treatments at the end of each intervention time period.

The researcher collecting information from you via these surveys will not know which intervention you are currently using. We ask that you do not disclose this information to them, or to other participants. This is an important aspect of clinical research called “blinding”, which helps to ensure that the information we collect is free from any bias, whether intentional or unintentional. You should be aware that once the trial begins, you will only be identified by a specific number that holds no personal identifying information. Although you are agreeing to allow the primary research team access to your medical record for verification purposes, everyone involved will have been trained on The Health Insurance Portability and Accountability Act (HIPAA) laws and these will be strictly enforced to ensure your privacy.

A description of this clinical trial will be available on 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.

**Risks and Inconveniences**

It is important to know that you have the right to discontinue participating in this trial at any time. The risks and side effects associated with these interventions are minimal and include nausea, stomach upset, jaw tiring, and worsening or non-improvement of symptoms. None of these negative events are life threatening or permanent. Staff will be on hand to field any questions or concerns you may have and to document any side effects you wish to report.

As with all studies, there is a small risk of loss of confidentiality. The procedures in place to prevent this have been previously mentioned and every effort will be made to keep your information confidential, however this cannot be guaranteed.

Utilizing the interventions as instructed, and presenting for a total of five in-person meetings for data collection are the main inconveniences you will be faced with. The meetings will be a maximum of 30 minutes each, separated by the span of two weeks.

**Benefits**

Benefits of participating in this study may include improvement of the thirst and/or dry mouth symptoms you are experiencing.

**Economic Considerations**

The chewing gum and saliva spray will be provided at no cost to the participant. There is no direct compensation offered to those who agree to participate. You can expect a minimal expense to be incurred for traveling to your usual heart failure clinic a total of five times throughout six weeks.

**Treatment Alternatives/Alternatives**
There are no validated or well-studied options for thirst symptom management. Some home remedies used by other patients (besides drinking water) include drinking buttermilk or sucking on ice or hard candy. We are focusing this study on the chosen interventions because we believe they have the potential to be more effective than other options, without increasing the amount of water you take in daily, a common concern in patients with heart failure.

Confidentiality and Privacy

Under no circumstances will your information be released to outside parties without your explicit consent. Any identifiable information that is obtained from you during the course of this study will remain confidential and will only be disclosed without your explicit consent in the case of abuse or reportable diseases, as required by law. All data collection forms and questionnaires will be kept in a locked file cabinet in the locked office of the principle investigator. After all data has been analyzed, paper records will be shredded and destroyed in accordance with HIPAA requirements. When the results of this research are published or discussed in any forum, no information will be included that would reveal your identity unless you specifically consent to this. Representatives from Yale University, the Yale Human Research Protection Program and the Yale Human Investigation Committee (the committee that reviews, approves, and monitors research on human subjects), who are responsible for ensuring research compliance, may have access to your information during the course of the study. These individuals are required to keep all information confidential.

You have the right to review and copy your health information in your medical record in accordance with institutional medical records policies.

This authorization to use and disclose your health information collected during your participation in this study will never expire.

In Case of Injury

If you are injured while on study, seek treatment and contact the study doctor as soon as you are able. Yale School of Medicine and Yale New Haven Hospital do not provide funds for the treatment of research-related injury. If you are injured as a result of your participation in this study, treatment will be provided. You or your insurance carrier will be expected to pay the cost of this treatment. No additional financial compensation for injury or lost wages is available.

You do not give up any of your legal rights by signing this form.

Voluntary Participation and Withdrawal

Participating in this study is voluntary. You are free to choose not to take part in this study. Refusing to participate will involve no penalty or loss of benefits to which you are otherwise entitled (such as your health care outside the study, the payment for your health care, and your health care benefits). However, you will not be able to enroll
in this research study and will not receive study procedures as a study participant if you do not allow use of your information as part of this study.

If you do become a subject, you are free to stop and withdraw from this study at any time during its course. 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. This will cancel any future appointments. The researchers may withdraw you from participating in the research if necessary due to worsening medical condition, development of serious side effects, or subject non-compliance.

Withdrawing from the study will involve no penalty or loss of benefits to which you are otherwise entitled. It will not harm your relationship with your own doctors or with Yale School of Medicine or Yale-New Haven Hospital.

You may withdraw or take away your permission to use and disclose your health information at any time. You may withdraw your permission by telling the study staff or by writing to the principal investigator. If you withdraw your permission, you will not be able to stay in this study. When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others until the end of the research study, as necessary to ensure the integrity of the study and/or study oversight.

Questions

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the consent form carefully – as long as you feel is necessary – before you make a decision.
Authorization and Permission

I have read (or someone has read to me) this form and have decided to participate in the project described above. Its general purposes, the particulars of my involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

By signing this form, I give permission to the researchers to use information about me for the purposes described in this form. By refusing to give permission, I understand that I will not be able to be in this research.

Name of Subject:_____________________________

Signature:___________________________________

Date:______________________________________

___________________________________________
Signature of Principal Investigator

Date

or

___________________________________________
Signature of Person Obtaining Consent

Date

If after you have signed this form you have any questions about your privacy rights, please contact the Yale Privacy Officer at 203-432-5919.

If you have further questions about this project or if you have a research-related problem, you may contact the Principal Investigators Matthew M. Burg, PhD at 203-932-5711 or Alison Robb, PA-SII at 315-247-1566. If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at 203-785-4688.
References


30. Mirzaei-Dizgah I, Agha-Hosseini F. Unstimulated whole saliva parathyroid


