Randomis**E**d Contro**L**led trIal of ch**E**wing gum to relie**VE** thirst in **C**hronic **H**eart **F**ailure

(RELIEVE- CHF) Pilot Study

Chewing gum: a potential strategy to relieve thirst in chronic heart failure

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This thesis is presented in fulfilment of the Degree of Doctor of Philosophy

University of Technology Sydney

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CERTIFICATE OF ORIGINAL AUTHORSHIP

I certify that the work in this thesis has not previously been submitted for a degree nor has it been submitted as part of requirements for a degree except as part of the collaborative doctoral degree and/or fully acknowledged within the text.

I also certify that the thesis has been written by me. Any help that I have received in my research work and the preparation of the thesis itself has been acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis.

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LIST OF ACRONYMS AND ABBREVIATIONS IN THIS THESIS

Abbreviation	Full term
ACE	Angiotensin-Converting Enzyme
ACEIs	Angiotensin-Converting Enzyme Inhibitors
ACNC	Australian Cardiovascular Nursing College
AKPS	Australian-modified Karnofsky Performance Scale
ARBs	Angiontensin Receptor Blockers
CCI	Charlson Comorbidity Index
CCU	Coronary Care Unit
CHF	Chronic Heart Failure
CI	Confidence Interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CSANZ	Cardiac Society of Australia and New Zealand
DBP	Diastolic Blood Pressure
eGFR	Estimated Glomerular Filtration Rate
HF	Heart Failure
HRQoL	Health-related quality of life
KCCQ	Kansas City Cardiomyopathy Questionnaire
LVEF	Left Ventricular Ejection Fraction
NRS	Numeric Rating Scale
NYHA	New York Heart Association Classification
RCT	Randomised Controlled Trial
SBP	Systolic Blood Pressure
SD	Standard Deviation
SPSS	Statistical Package for the Social Sciences
TIA	Transient Ischaemic Attack
VAS	Visual Analogue Scale

ABSTRACT

Thirst is a common and burdensome symptom of chronic heart failure which adversely affects health related quality of life and compliance to self-care practices such as fluid restriction. Despite this, research on thirst remains scarce and there is no standard approach to identify patients with increased thirst and manage thirst in clinical practice. To date, previous studies have investigated various interventions to help alleviate thirst in chronic heart failure and other patient populations. While the other interventions such as artificial saliva showed differing results, chewing gum demonstrated promising outcomes in relieving thirst. Based on the comprehensive literature review and preliminary Bachelor Honours study, RELIEVE-CHF was developed. RELIEVE-CHF was a novel pilot intervention which sought to investigate the effect of chewing gum in the level of thirst of people with chronic heart failure in a single blind randomised controlled study.

A total of 71 individuals with chronic heart failure, aged ≥ 18 years, on oral loop diuretics from the inpatient and outpatient clinic were enrolled in a two-arm trial. Participants were randomised to receive either chewing gum or no chewing gum for two weeks. The primary outcome of the study is the change in the level of thirst at Day 4. Secondary outcomes included changes in the level of thirst at Day 14, weight and health related quality of life. Participants' level of thirst was measured using the Visual Analogue Scale (VAS) and the Numeric Rating Scale (NRS). The Kansas City Cardiomyopathy Questionnaire was used to assess health related quality of life. Participants were followed up at Day 28.

This thesis presents the clinical trial methodology and analysis of 71 participants who completed the trial. All participants' data were analysed based on the intention to treat

principle. The results showed statistical significant improvements in the level of thirst of those in the intervention group compared to the control group at Day 4 (VAS: *p=0.04* and NRS: *p*=0.019) and Day 14 (VAS: *p=0.02* and NRS: *p=0.021*). There was no statistically significant difference observed between the intervention and control group in weight over the study period and health related quality of life at Day 28. The findings indicate that chewing gum provided relief from thirst but did not influence weight or health related quality of life during the study period. Although promising, these findings must be interpreted in light of the limitations encountered in this trial. Nonetheless, RELIEVE-CHF have provided additional data to inform future clinical intervention studies and insights into the challenge of implementing a non-traditional approach in relieving thirst in people with chronic heart failure.

CHAPTER I- INTRODUCTION

1.1 BACKGROUND

Chronic heart failure (CHF) is a common, progressive and debilitating syndrome affecting the elderly. It is currently the leading cause of hospitalisations and deaths in developed countries. As demographic transitions result in an increased number of elderly individuals, the resources allocated to CHF care are likely to increase. Despite the range of innovative pharmacotherapy and non-pharmacotherapy strategies developed and evaluated to combat the increasing burden, individuals still experience a large number of symptoms which affects their daily functioning and quality of life. Among these symptoms, thirst is well-recognised, but rarely studied or addressed. This thesis presents the development and evaluation of an intervention designed to help alleviate thirst through the use of chewing gum. This chapter describes thirst, the burden of CHF, thirst in CHF and the scope of self-care and self-management strategies.

1.2 THIRST

1.2.1 Definition and descriptions of thirst

Thirst has been defined as a sensation and a symptom that is associated with a craving to drink (1). It is characterised by various sensations including dry mouth, lips and throat, light-headedness, tiredness, headache, loss of appetite and feeling of an “empty” stomach (2). To date there is no uniform definition of thirst. However, the various definitions suggest that

thirst is subjective and associated with a feeling of dryness in the mouth (3), and a desire or craving for water to drink (4).

To date, thirst has been previously measured and described in healthy persons (5), in patients with renal failure undergoing haemodialysis (6-9), terminal illness (10-12), diabetes (13, 14), in critically ill patients in intensive care unit (15, 16) and in patients with CHF (17, 18). In research, thirst has mostly been described with the sensation of intensity (strength of thirst) (9, 16, 18-24). It has also been described using the measurement of distress (the degree in which the patient is bothered by thirst) (16, 19, 25, 26), the frequency of thirst (16, 23, 27) and as the quality of thirst (28-30) (how thirst is described to feel like and its associated discomfort (23)).

1.2.2 Thirst as a symptom

The term "symptom" has been used as an indication of an individual's awareness of the manifestations of illness (31). A symptom indicates a change in normal functioning as experienced by the patient (32). It is observable only by the person and cannot be objectively measured (33). And as such is only known by the report of the person experiencing it. The definitions of thirst discussed previously shows that thirst is a symptom (1, 3, 4, 19, 32). It can only be known by the person experiencing it and is not detectable by others. Thirst is an indicator of change in normal functioning and reflects changes in physiological functioning (34).

1.2.3 Sensations related to thirst

As aforementioned, thirst is described by a number of sensations (2) but its relationship with thirst has not been established. When being thirsty, one can sometimes feel that their

stomach is “empty”, a sign of hunger (35). However, hunger is a different sensation which promotes accomplishment of minimal energy needs (36). While one can survive without eating for many weeks, not being able to quench thirst leads to dehydration, consequently reduced function within days and death within a week (35). Dry mouth is also often associated with thirst and is often thought of as synonymous with thirst (3).

1.2.4 Underlying mechanisms of thirst

Although it is not clear, thirst is influenced by many physiological factors such as changes in body fluids and increased sympathetic activity.

Changes in body fluids

The sensation of thirst is the regulator of body hydration and water intake. In healthy persons, thirst is mainly triggered by the thirst centre in the brain (subfornical organ located in the anterior portion of the brain causes excitation of magnocellular neurosecretory cells; releasing vasopressin) in response to changes in body fluid caused by dehydration or hypovolemia (37). Dehydration causing an increase in blood osmolality is the most common stimuli for thirst (37). Hypovolemia causes low blood pressure which the kidney detects (34, 37). The enzymatic cascade that follows involves renin which is released by the juxtaglomerular cells of the kidneys (37). This protease then cleaves a liver-derived angiotensinogen, converting it to angiotensin I. This is then further broken down to angiotensin II through an angiotensin converting enzyme (ACE) present in the lung capillaries. Angiotensin II also stimulates the release of aldosterone from the adrenal cortex (34, 38). In addition, angiotensin II is also a potent activator of the thirst centre (9, 37, 39).

Dehydration and hypovolaemia can also influence salivary flow in the mouth and be associated with dry mouth (2).

An increase of body fluids also stretches the walls of the heart and release natriuretic peptides such as N-terminal of the prohormone brain natriuretic peptide (NT-proBNP) causing the kidney to increase excretion of salt and water (37). Serum urea is also suggested to be a marker of body fluid status as well as neurohormonal activation (40-42). Several conditions that alter or disturb the body fluid balance may also potentially cause increased thirst, such as vomiting (43), bleeding (43), terminal illness (11, 12, 44), diabetes (13, 14), renal failure (6, 7, 9, 24) and heart failure (17, 45).

Sympathetic activity

The sympathetic response causes vasoconstriction of salivary glands and decreases salivary secretion, which is often experienced as dry mouth (37). Dry mouth can be sensed by specific receptors detecting osmotic changes or friction in the mucosa, and detected by the thirst centre in the brain (2). Receptors in the mouth can also sense changes of cold and signals the thirst centre in the brain (2).

1.3 HEART FAILURE

Heart failure is a complex clinical syndrome as a result of any structural or functional abnormality which impairs the ability of the ventricle to fill with or eject blood (46). While the cardinal manifestations of heart failure are dyspnoea and fatigue, decreased exercise tolerance and fluid retention leading to pulmonary congestion and peripheral oedema, this may or may not be present (47). Some people experience peripheral oedema with little change in exercise tolerance while others have exercise intolerance, but will not necessary

experience fluid retention (46, 47). The study presented in this thesis focuses on the syndrome of CHF as opposed to acute heart failure which is an acute decompensation of CHF, a common form of heart failure presentations in hospital.

1.3.1 Definition of 'chronic heart failure'

The definition of CHF has been very controversial. Over the past four decades, many definitions of CHF have emerged (46, 48). In 1968, it was described as *"a state in which the heart fails to maintain an adequate circulation for the needs of the body despite a satisfactory venous filling pressure."* (46 p. 6) The structural or functional abnormalities resulting in impaired cardiac filling and ejection have mostly been implicated in conjunction with neurohormonal regulation (49). While most clinicians use clinical criteria as a basis of their diagnosis, it is now largely accepted that both clinical features and objective measure of abnormal ventricular function is necessary in the diagnosis of CHF (46, 48). This lack of a universal definition along with difficulties in diagnosis remains the longstanding barrier in determining the incidence and prevalence of CHF in Australia and worldwide (46, 50). The definition of CHF that will be used in this thesis is derived from the National Heart Foundation and Cardiac Society of Australia and New Zealand which defines CHF as:

"a complex clinical syndrome with typical symptoms (e.g. dyspnoea, fatigue) that can occur at rest or on effort, and is characterised by objective evidence of an underlying structural abnormality or cardiac dysfunction that impairs the ability of the ventricle to fill with or eject blood (particularly during physical activity). A diagnosis of CHF may be further strengthened by improvement in symptoms in response to treatment." (46 p. 6)

Once the diagnosis of CHF is established, symptoms are often used to characterise the severity of the disease, and to quantify the degree of functional limitation imposed. The NYHA classification system is a method used to assess the effects of cardiac disease on the patients' physical limitation in clinical practice (51). The NYHA class was designed to assess patients by grading as class I, II, III, IV based on their limitation due to physical activity and severity of cardiac symptoms (46, 51). Table 1.1 shows the NYHA grading of symptoms in CHF.

Table 1.1 NYHA grading of symptoms in CHF (46).

NYHA class		`MET
Class I	No limitations. Ordinary physical activity does not cause undue fatigue, dyspnoea or palpitations (asymptomatic LV dysfunction)	>7
Class II	Slight limitation of physical activity. Ordinary physical activity results in fatigue, palpitation, dyspnoea or angina (mild CHF)	5
Class III	Marked limitation of physical activity. Less than ordinary physical activity leads to symptoms (moderate CHF)	2-3
Class IV	Unable to carry on any physical activity without discomfort. Symptoms of CHF present at rest (severe CHF)	1.6

NYHA, New York Heart Association; LV, left ventricular; CHF, chronic heart failure
`MET, Metabolic equivalent- defined as the resting VO_2 for a 40- year old 70 kg man, MET= 3.5 mL O_2/min/kg body weight

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1.4 AETIOLOGY

Chronic heart failure is now known as the final end-point of all progressive cardiac diseases. A variety of conditions such as ischemic heart disease can cause this clinical syndrome (52, 53). However regardless of the cause, ventricular dysfunction due to impaired myocardial contractility is the fundamental component of systolic heart failure (53). When myocardial

contractility is decreased, a cascade of events follows including depression of the left ventricular ejection fraction and cardiac output (52, 54). Compensatory mechanisms are then activated to maintain homeostasis. Activation of the sympathetic nervous system is one of the early compensatory responses (55). Its main purpose is to increase ventricular filling pressure, cardiac output and tissue perfusion (55). In the initial phase, these mechanisms are effective in increasing tissue perfusion. Conversely, as time progresses, other neurohormonal systems become activated and these mechanisms become counterproductive; contributing to further myocardial damage and progression of CHF (56, 57).

In response to decreased cardiac output, several haemodynamic alterations occur including vasoconstriction, fluid retention and increases in cardiac filling pressures (56-58). It is also important to note that in some cases CHF can present with normal ejection fraction (46). Although, systolic heart failure and CHF with preserved ejection fraction (formally known as diastolic heart failure) often coexist, they can be distinguished with relevance to the therapeutic approach (46, 48). As seen in Table 1.2, CHF has numerous causes. In addition, Table 1.2 also shows the aetiology of both systolic heart failure and diastolic heart failure.

Table 1.2 Aetiology of CHF (46).

Systolic heart failure	Diastolic heart failure/HPSF
Common causes	
- Coronary heart disease - Ischaemic heart disease - Prior myocardial infarction - Hypertension	- Hypertension - Coronary heart disease - Diabetes
Less common causes	
- Non- ischaemic idiopathic dilated cardiomyopathy	- Valvular heart disease
Uncommon causes	
- Valvular heart disease (mitral and aortic) - Long term alcohol misuse - Inflammatory cardiomyopathy or myocarditis (caused by viral infections) - Chronic arrhythmia - Thyroid dysfunction - Human Immunodeficiency virus- related cardiomyopathy - Drug- induced cardiomyopathy (anti-cancer therapy) - Peri-partum cardiomyopathy	- Hypertrophic cardiomyopathy - Restrictive cardiomyopathy, (idiopathic/ secondary to infiltrative disease e.g. amyloidosis

HPSF, Heart failure with preserved systolic function

Information source: National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand (Chronic Heart Failure Guidelines Expert Writing Panel). Guidelines for the prevention, detection and management of chronic heart failure in Australia. Updated October 2011. © 2011 Heart Foundation of Australia. Reproduced as a table.

1.5 THE BURDEN OF CHRONIC HEART FAILURE

1.5.1 Incidence and Prevalence

Epidemiological data and public health importance of CHF in Australia remains scarce (46, 48, 59). Currently, available data used to estimate incidence and prevalence of CHF rely mainly on large population studies from the United States and Europe (46, 48). Chronic heart failure is found to occur in 1.5-2.0% of Australians (46, 48). The point prevalence of CHF in Australia in people aged 50-59 years, aged ≥65 years and ≥ 85 years was about 1%,

10% and 50%, respectively (46, 48). Therefore, the overall pattern of incidence and prevalence of CHF increases significantly with age (46, 48, 59). This pattern is also seen in Europe and the United States where the reported prevalence of CHF in people aged 70-80 years is between 10 and 20% (50, 60). Chronic heart failure has become a growing epidemic worldwide. In Europe with a population of >900 million, at least 15 million people have CHF (50). Similarly, CHF has become a growing public health concern in the United States where approximately 550,000 people diagnosed with this syndrome each year while 5 million people are reported to already have CHF (60). In contrast to international prevalence of CHF, an estimated 300,000 Australians are believed to have CHF and 30,000 new cases are diagnosed each year (46, 48, 59). The overall incidence and prevalence of CHF is set to rise in the coming years due to the aging population and the ever growing medical breakthroughs; prolonging survival of patients suffering from previously fatal coronary events such as myocardial infarction and the success in postponing coronary events with effective prevention in those at high risk or those who are receiving secondary prevention (47, 50).

1.5.2 Morbidity

Chronic heart failure is one of the most common reasons for hospitalisation in people aged 70 years and older (46, 48). Based on extrapolated data, there were approximately 20,000 incidents of hospital admissions for CHF in the year 2000 in Australia (48). However this figure was found to increase to an estimated 49, 307 reported hospitalizations in the year 2007-2008 (59). Hospital admissions were particularly associated with the elderly (aged ≥ 70 years) with a total of 100, 000 hospital separations (See Figure 1.1); contributing to 1.4

million days of hospital stays (48). Similarly, in the United States, CHF is also the primary cause of hospital visits and longer hospital stays with a total of 12-15 million hospital visits and 6.5 million hospital days each year (60).

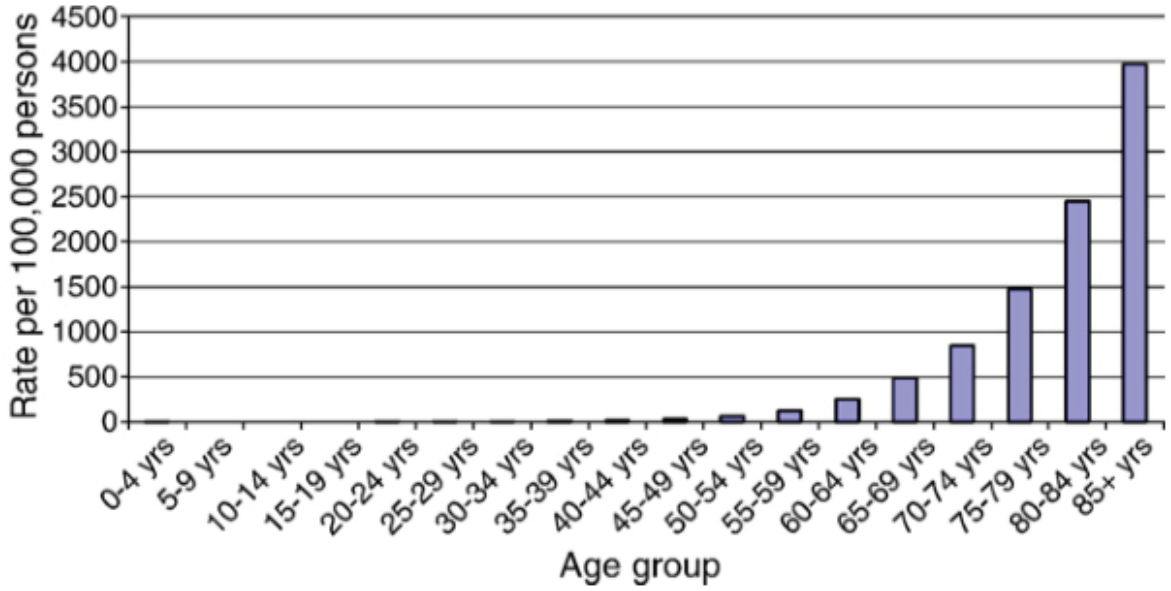

Figure 1.1 Chronic heart failure separations by age group, NSW, 1989-1990 to 2002-2003.

Hospital admissions were particularly associated with the elderly. The figure shows a massive increase in hospital separations from the age group 75-79 years to 85+ years.

In Europe and the United States, studies from national data sets have predicted the burden that CHF will impose on healthcare systems (61-64). The studies suggest that the overall numbers of admissions of CHF will continue to rise regardless of the slowing in the population rate of CHF-related admissions (46, 65). In addition, patients with CHF were also found to have worse survival rate compared to other common chronic diseases and terminal cancer except lung cancer (66). In comparison to terminal malignancy with a typical decline in illness trajectory, CHF is comprised of a cyclical and progressive clinical instability (46). Furthermore, CHF is also the most common reason for GP consultations due to difficulties associated with detection and optimal management (67). Overall, CHF is a

major contributor to the current burden of cardiovascular disease in Australia's healthcare system (46).

1.5.3 Mortality

Regardless of the improvement in population survival rates of CHF, it still remains associated with a worse prognosis compared to a variety of malignancies in both men and women (46). Five year survival in those with CHF is within a range of 50-75% but this depends on the timing and point of diagnosis (68). In the year 1996, the Australian Institute of Health and Welfare estimated there were approximately 3,000 deaths attributable to CHF (69). However, this figure increased to an estimated 4,055 deaths in 2007 (46, 47, 59). Nonetheless, due to the sudden cardiac deaths not directly related to CHF, statistical data on mortality is distorted (68, 70). International data suggests that the number of CHF-related deaths is more likely to be 10-fold of the official figures (68, 70).

1.5.4 Economic burden

In Australia alone, chronic cardiovascular disease accounts for > $5 billion per annum in health care costs (48). In the year 1993-1994, a reported $411 million of healthcare costs, (represents 0.4% of total healthcare costs), $140 million per year in hospitalisation costs and $135 million per year for nursing home costs were attributed to CHF (46). However, data from other developed countries suggest that this was an under-estimate (46). A more recent analysis estimates > $1 billion which represents 1.5-2% of the national health expenditure is contributed by CHF (48). The major reason for increases in CHF-related health care cost in Australia is hospital admissions; accounting for two-thirds of total health expenditure (48, 59). This is also seen in Europe with CHF as the cause of 5% of acute hospital admissions and

accounts for approximately 2% of national health expenditure (50). Frequent hospital re-admissions are the most preventable cost component (48). Common re-hospitalisation reasons include medication and dietary non- compliance, delays in symptom recognition and lack of knowledge and skills for competent self- care (46). There are major concerns that the increase in the prevalence of CHF will become the most significant burden not only in Australia's healthcare system but also worldwide (59).

1.5.5 Health- related quality of life

Despite the improved survival of people living with CHF, this often does not equate to an improvement in health-related quality of life (HRQoL). As previously mentioned, the syndrome of CHF is associated with debilitating symptoms, which have profound implications on an individual's HRQoL. In comparison to other chronic condition, CHF affects a person's HRQoL to a much greater degree in all aspects of the social determinants of health; physical, social and emotional functioning.

1.6 SYMPTOMS

The key to early detection of CHF are the signs and symptoms as this is what causes patients to seek medical attention (46, 50). Therefore, the main priorities of care for CHF patients involve early recognition and treatment of symptoms (71). It is now established that symptoms experienced play an important role in patient's deterioration (71-76). Symptoms greatly contribute to reduced quality of life, increased morbidity and mortality in CHF patients (71). Patients with left ventricular dysfunction often develop symptoms of CHF very late while some are asymptomatic due to their sedentary lifestyle (50). Breathlessness, fatigue and tiredness are the most common symptoms of CHF (46, 50). However, patients

also report a number of other symptoms such as thirst, sleeplessness, depression, memory loss and attention deficit (77).

1.7 THIRST IN CHRONIC HEART FAILURE

1.7.1 Descriptions of thirst

Thirst is a natural physiological function which serves to maintain fluid balance. Patients with worsening CHF and those at the end of life are known to frequently suffer from thirst. Over the last decade, there has been an increase in the number of studies reported about thirst in patients with CHF. The next chapter will thoroughly discuss these studies and the factors related to thirst in CHF.

1.7.2 Prevalence of thirst

To date, prevalence data of thirst in CHF remains lacking (78). Until recently, there was a lack of focus and attention on thirst as a symptom of CHF in scientific literature. However, a study of symptom prevalence and symptom burden have found that symptoms such as dry mouth (a characteristic of thirst) was much more prevalent compared to symptoms thought to be typical such as systemic oedema and lack of appetite (76). It was also reported as 'quite a bit' distressing in a third of patients. Similarly, a recent study also found that 20% of stable CHF patients had thirst (78). Information from medical records also showed a 9% frequency of persistent thirst at the end of life (79). However, as these were obtained from medical records, documentation is generally brief. Thus, the estimated prevalence of thirst may be underestimated.

1.7.3 Consequences of thirst

Thirst can affect the patient's ability to manage daily activities, including self-care especially with respect to compliance with fluid restriction. For some patients it becomes a struggle between following the restriction of fluid intake or their own desire to drink more than allowed (18). Non- compliance to fluid restriction may lead to increased weight resulting in fluid overload and hospitalisation. Further, there are associated feelings of guilt and self-blame for failing and gaining weight. Another common problem is preoccupation with thirst (18). Patients may spend a lot of time thinking about being thirsty, but not allowing themselves to drink, have a further negative impact on quality of life.

1.8 THEORETICAL FRAMEWORK

1.8.1 Theory of Unpleasant Symptoms

The purpose of the Theory of Unpleasant Symptoms is to improve understanding of symptom experience and to provide information for designing an intervention to prevent, improve or manage unpleasant symptoms (23, 32). The assumption for this theory is that there are sufficient commonalities between symptoms to warrant a theory that is not limited to one symptom (32). The commonalities are that symptom is a subjective sensation, present as acute or chronic, can occur under normal or illness conditions and can result from anxiety or depression (80). The Theory of Unpleasant Symptoms has been used in studies as the framework to explain fatigue in persons with chronic lung disease (81), and to explore the influence of dyspnoea duration, distress and intensity on decisions of patients with CHF to come to emergency department (82).

1.8.2 Components of the Theory of Unpleasant Symptoms

The Theory of Unpleasant Symptoms includes three components: (i) the factors that influence the symptom; (ii) the experience of the symptom; and (iii) the performance that is affected by the symptom (80).

The first component involves three factors; physiological, psychological and situational factors (Figure 1.2) (32). The physiological factors have an impact on the body's physiological functions (anatomical/structural, genetic and pharmacological variables) while psychological factors affect the individuals' cognition, mood or mental state (32). On the other hand, the situational factors are the external aspects, such as social and physical environment and lifestyle behaviours that can impact patient's experience and reporting of symptoms. These can be marital status, culture, temperature, light and availability and access to health care, social support, exercise, diet and fluid management (32, 80).

The second component is the symptom experience and comprises of four dimensions: duration, intensity, distress and quality (80). Duration describes the frequency with which a symptom occurs (23, 32). The intensity dimension refers to the strength of the symptom and can be measured by self-reporting on a Numeric Rating Scale or a Visual Analogue Scale. Distress is the degree to which the patient is bothered by the symptom and it can be measured qualitatively using interviews or quantitatively using scales (32). The quality of a symptom is what the symptom is described to feel like and its associated discomfort (32). It can include description of the location of the sensation and how the patient responds to an intervention. The quality description is often specific and portrays the symptom´s unique

nature and can be expressed in open-ended descriptions or checklists of descriptive characteristics (32).

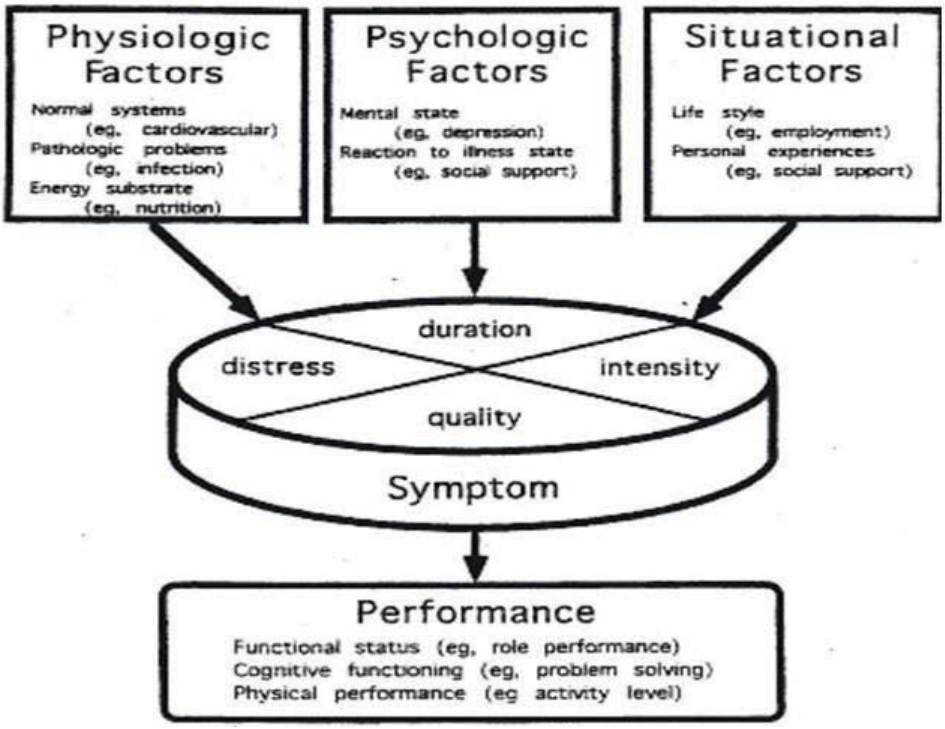

Figure 1.2 The original Theory of the Unpleasant Symptoms.

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The third component, the performance, is proposed to be influenced by the symptom experiences (32). The performance can include the functional performance, such as the activities of daily living, physical activity, and social interaction and the cognitive performance, such as thinking and concentrating.

1.9 THE RELIEVE-CHF STUDY

Within the context of increasing burden of CHF, increase prevalence of thirst among patients and lack of management strategies to alleviate thirst, the RELIEVE- CHF study was developed. This doctoral thesis builds upon the candidate's B Med Sci (Hons) thesis. The RELIEVE- CHF study adapted the trial protocol which tested the effectiveness of chewing gum in patients undergoing haemodialysis in the United States. The RELIEVE- CHF study is a novel approach and is the first interventional study which assesses the effect of chewing gum on thirst in patients with CHF.

1.10 RATIONALE OF THIS STUDY

As described in the background, patients with CHF are troubled by thirst (18). Patients struggle and are often preoccupied with being thirsty (30). To date, there is none, or little information about the prevalence of thirst and the factors that affect the thirst response (17, 18). Furthermore, there is no reliable and validated instruments to measure thirst subjectively (22). And lastly, little is known on the current strategies recommended to relieve thirst and there is no evidence-based approach to relieve thirst in clinical practice (83). Because of this lack of knowledge, healthcare professionals may fail to identify CHF patients suffering from thirst and help them alleviate this troublesome symptom. In order to support CHF patients with thirst, deeper understanding is needed on the factors that contribute to thirst. There is also a need for reliable validated tools to measure various thirst dimensions. Finally, research on the current thirst-relieving strategies advised to CHF patients in clinical setting and testing these innovative approach is necessary to combat the growing burden of thirst in CHF.

1.11 STUDY AIMS

The RELIEVE- CHF study is an approach to support people with CHF suffering from thirst. It has four discrete yet interrelated aims. ***Firstly***, it seeks to explore the factors related to thirst; ***secondly***, it identifies the current strategies recommended or used by health professionals to relieve thirst; ***thirdly***, it establishes the tools/instruments used to measure thirst, and ***fourthly*** it assess the effectiveness of chewing gum to alleviate thirst in CHF patients.

This randomised controlled trial sought to evaluate the impact of the RELIEVE-CHF study on the following aspects of health-related outcomes:

- Thirst
- Weight stability
- Self-reported health related quality of life

1.12 STRUCTURE OF THIS THESIS

This thesis is a series of discrete, yet interconnected studies which addresses the study questions. This thesis is presented in eight chapters. Three of these chapters are presented in the form of a peer-reviewed journal articles (published). Each chapter is presented as a stand-alone report in the style of the journal article. However, it is hoped this does not cause too much repetition for the reader. To meet journal requirements for manuscript submission, spelling may vary between US English and British English for Chapters 2-4. Chapters 1, 5, 6, 7 and 8 are written in Australian English. It is hoped this does not cause concern to the reader.

In ***Chapter One***, the significance of the growing burden of CHF, as well as the increasing prevalence of thirst in the CHF population has been highlighted. Due to our aging population and improvements in cardiovascular treatment, there is a growing number of CHF patients in society. These patients experience a large number of symptoms, consequently affecting their daily functioning and quality of life. Among these symptoms is thirst, which is rarely studied. Persistent thirst can affect the patient's ability to manage daily activities such as fluid restriction. The rationale, utility and significance of the RELIEVE-CHF study was to introduce an innovative approach of self-management to alleviate thirst (the use of chewing gum) and improve patient outcomes by eliminating one of the barriers to compliance to fluid restriction, better monitoring weight (fluid) stability and improving health related quality of life.

Chapter Two provides a review of the possible factors contributing to increased thirst in patients with CHF. In addition, it reviews randomised trials of various interventions used to relieve thirst in CHF or other population groups. It provides an assessment of their effectiveness in alleviating thirst to improve patient outcomes and paying close attention to the characteristics of the interventions, to inform future research. This paper was published in the *Journal of Clinical Nursing* in 2015.

Chapter Three presents the result of a survey which identified the current thirst-relieving strategies recommended by health professionals to their patients. It details their opinion on the usefulness of these interventions. This paper was published in *Contemporary Nurse* in 2016.

Chapter Four provides a review of the current tools used to measure thirst in CHF literature; highlighting the importance of valid and reliable tools in measuring patient reported outcomes. This paper was published in the *Contemporary Nurse* in 2014.

Chapter Five presents a critical description and justification of the study method. Study management and ethical issues are also discussed.

Chapter Six reports the study findings. Firstly, the primary analysis comparing the changes in primary outcome at Day 4 and secondary outcome at Day 14 is provided, followed by a sensitivity analysis of the completers at Day 4. And lastly, a repeated measures comparison of the intervention and control group from baseline to Day 28 is presented. Patient reported symptoms, usefulness of chewing gum and continued use of chewing gum after 2 weeks is also provided.

Chapter Seven discusses the findings, strengths and limitations of the study and the challenges experienced in implementing the use of chewing gum to alleviate thirst in the CHF population.

Chapter Eight provides a summary of the RELIEVE-CHF study and identifies implications for policy, practice and research.

References are provided at the end of each chapter. Copies of the data collection form, copies of ethics approval from University of Technology Sydney and St. Vincent's Hospital, Sydney, participants' information sheet and consent form are all provided in the appendix at the end of the thesis.

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CHAPTER II- THIRST IN CHRONIC HEART FAILURE: A REVIEW

2.1 CHAPTER PREFACE

Publication reference:

Allida SM, Inglis SC, Davidson PM, Lal S, Hayward CS, Newton PJ. Thirst in chronic heart failure: a review. J Clin Nurs. 2015; 24 (7-8): 916-926.

Chapter 1 provided a summary of chronic heart failure; its aetiology, epidemiology, symptoms and strategies patients develop to management to thirst. Further it provided an outline of this thesis, including the study aims, design, significance and innovation.

This chapter presents an article in its final accepted form, published in the Journal of Clinical Nursing (2015) Volume 24, Issue 7-8, Pages 916- 926. This article is provided in its published form as an appendix *(refer to* Appendix 10*)*.

Background

Thirst is a common and troublesome symptom of chronic heart failure. Despite the burden and prevalence of this symptom, there are limited strategies to assist in its management.

Aim of the study

This paper provides a review of factors related to thirst in chronic heart failure and interventions to alleviate thirst in chronic heart failure patients.

A review of the databases was conducted using the key words '*thirst', 'chronic heart failure', 'angiotensin II', 'fluid restriction'* and '*intervention'.* The following electronic databases were searched: Medline, Cumulative Index for Nursing and Allied Health, PubMed and Scopus.

Summary of results

Factors related to thirst in chronic heart failure were condition; prolonged neurohormonal activation, treatment; pharmacological interventions and fluid restriction and emotion. No intervention studies were found in chronic heart failure patients. Interventions such as artificial saliva and chewing gum have been investigated for their effectiveness as a thirst reliever in haemodialysis patients.

Implications

This paper emphasises that despite thirst being a common complaint in chronic heart failure patients, there is no systematic analysis of intervention in this group. Furthermore, this paper demonstrates that common chronic heart failure medications may promote thirst and an impairment in the inhibitory regulatory systems and prolonged neurohormonal activation are one of the many explanation of intense thirst in chronic heart failure. Lastly, this paper also shows that chewing gum may be a useful clinical tool in adhering to fluid restricted therapy through stimulation of saliva to eliminate thirst. This further highlights the need for evaluating this intervention in chronic heart failure patients.

2.2 INTRODUCTION

Thirst is a common and unpleasant symptom of chronic heart failure (CHF) (45). Despite this, there is very little scientific literature available to inform clinicians on how to best manage this troublesome symptom in daily practice (22). For healthy individuals thirst is a simple symptom of dehydration which plays a vital role in maintaining body fluid homeostasis through behavioural drinking (84). While individuals may feel the sensation of thirst differently, CHF patients experience unabated thirst regardless of their low serum osmolality (inhibits thirst) (45). The need to drink is so intense that it eventually causes distress (45).

A number of factors facilitate the sensation of thirst in CHF. Firstly, the pathophysiology of CHF involving prolonged activation of the renin-angiotensin-aldosterone system (RAAS) and other mechanisms of hormonal activation stimulates the thirst centre (2). Secondly, CHF patients are commonly on high doses of diuretic therapy to treat fluid retention (85-87). Xerostomia and loss of body water from this treatment also enhances the feeling of thirst. And lastly, fluid restriction prescribed to avoid fluid overload may also increase patient's perceived thirst (45). As a consequence patients are constantly immersed in the thought of being thirsty and struggle to follow their fluid restriction due to thirst (45) Non- compliance to their fluid restricted therapy can result to oedema, shortness of breath and fluid overload; leading to unnecessary hospitalisations. And in more life- threatening instances, pulmonary oedema may result (85).

In spite of the likely magnitude of this problem, there are limited data to inform interventions. And although, 'tricks of the trade' are used - for example sucking ice chips;

systematic evaluation of these methods are limited. To date intervention studies such as artificial saliva and chewing gum to alleviate thirst have been performed in end stage renal disease patients (6), whom like CHF patients are also prescribed with a fluid restricted therapy (7).

2.3 CONCEPTUAL FRAMEWORK

The Symptom Management Model states that in order to completely evaluate symptom experience, an assessment of distress, duration, frequency and intensity must be included (88). To date the only conceptual framework on thirst was developed based on the adaptation of the Symptom Management Model (19). And currently, there is no framework specifically addressing thirst in CHF. The framework proposes a positive relationship between thirst distress, duration, frequency and intensity (19). In addition, it also states a positive association between thirst distress, duration, frequency and intensity, and interdialytic weight gain seen in people undergoing haemodialysis (19). At present thirst has no conceptual definition however many definitions of thirst describe it as a symptom. Due to these definitions suggesting thirst is subjective, utilising self- reported methods of measurement is appropriate. There are four different dimensions of thirst which were conceptualised in this framework. Conceptual definitions for each were as follows: thirst intensity (severity, strength, or amount of thirst), thirst distress (degree to which a person is bothered by thirst, thirst duration (length of time that thirst is experienced by the person) and thirst frequency (how often during a day thirst is experienced by the person) (19).

2.4 AIMS AND OBJECTIVES

This review explored the factors related to thirst in CHF and described interventions to alleviate thirst in patients with CHF.

2.5 METHODS

In March 2013, a review of literature on the burden of thirst, contributors to thirst and potential management strategies of thirst in patients with chronic heart failure was conducted. A literature search was performed in Medline, Cumulative Index for Nursing and Allied Health (CINAHL), PubMed and Scopus using a combination of keywords and MeSH headings shown in Figure 2.1. The search terms had to be identified anywhere in the text. The search was restricted to humans and papers published in the English language. There were no limit to the years searched. One of the authors (S.M.A) reviewed the abstracts and included the papers that fulfilled any of the following criteria: (i) studies were included for data extraction if the participants were patients with a confirmed diagnosis of CHF (ii) if the study was a randomized controlled trial (RCT) of human participants with thirst as a primary or secondary outcome (iii) any study design involving human participants with thirst as a specific outcome and (iv) RCTs or any study design investigating interventions to alleviate thirst in participants with CHF. Intervention studies which included other patient populations' e.g. terminally ill cancer patients and patients with Sjogrens syndrome were excluded as thirst experienced by these patients are caused by impairment of their salivary glands leading to hyposalivation. Studies which investigated thirst related to exercise and dehydration were also excluded. Lastly, a manual search of the reference list of the included studies was also performed.

1.	Heart failure/
2.	Heart failure.mp.
3.	Cardiac failure.mp.
4.	Chronic heart failure.mp.
5.	Congestive heart failure.mp.
6.	Ventricular Dysfunction, Left/
7.	Ventricular Dysfunction, Left.mp.
8.	Thirst/
9.	Thirst.mp.
10.	Self-care/ OR Self-care.mp.
11.	Osmolality.mp.
12.	Sodium/ OR Sodium.mp.
13.	Angiotensin II/ OR Angiotensin II.mp.
14.	Intervention/ OR Intervention.mp.
15.	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7
16.	8 OR 9
17.	10 OR 11 OR 12 OR 13 OR 14
18.	15 AND 6
19.	17 AND 18
20.	Limit to ENGLISH language

Figure 2.1 Search strategy.

Data extraction was completed by author SMA using a data extraction form. The data extracted included the study objectives, participant information, intervention, and primary/secondary outcomes. The AMSTAR measurement tool was used to assess the quality of the included systematic review (89). The quality of evidence presented in the included studies were assessed using the Cochrane risk of bias tool (90). There were no quantitative analyses performed. The results are presented as a narrative summary description of the individual studies and outcomes. The studies are summarized in Table 2.1.

Table 2.1 Summary of studies on thirst in CHF.

Authors, year, country	Design	*n*	Participants	Intervention	Conclusion
Aliti (2014), Brazil	Randomized, blinded parallel- group study	75	ADHF and systolic dysfunction HF (60y ± 11), male 69%, NYHA class III/IV, EF 26%	*Intervention group:* Fluid restriction of 800mL/d and sodium restriction (800mg/d *Control group:* Liberal fluid intake (at least 2.5L) and sodium restriction (~ 3-5g) intake	The intervention showed no benefit on weight loss or clinical stability The intervention significantly increased perceived thirst
Albert (2013), USA	Randomized controlled pilot study	46	Hyponatraemic CHF (62.8y ± 12.8),male 51.3%, NYHA III/IV	*Intervention group:* Daily fluid allowance of 1,000 mL/d for 60 days and usual care discharge instructions and education *Control group:* Usual care discharge instructions and education	The strict allowance of 1,000 mL/d improved quality of life at 60 days post- discharge There were no significant difference in the level of thirst and difficulty in adhering to fluid restriction
Waldreus (2013), Sweden	Systematic review	4,375	Stable CHF, Severe CHF, Hyponatraemic CHF, (44-83y) NYHA I-III, III-IV, EF 32-45%,		Thirst is distressing in patients with CHF but there is limited knowledge on the causative factors Factors related to thirst are Treatment; fluid restriction, tolvaptan, emotion; anxiety and condition; NYHA class
Waldreus (2011),	Open controlled study	48	Worsening CHF (80y), male	Assessed VAS, HRQoL, EQ 5D,	Elderly patients perceive

Sweden			31%, NYHA III-IV, EF 32%, Group B (80y)	urine analyses, NYHA class	intensive thirst when admitted to hospital for worsening of HF
Reilly (2010), USA	Descriptive study	25	Stable CHF (44-83y), male 56%, NYHA II-IV, EF 34%	Assessed level of thirst (TDS) and QoL	Distress: 46% reported moderate to strong discomfort from thirst
Philipson (2010), Sweden	Randomized controlled study	30	Stable CHF (74y), male 73%, NYHA II-IV, EF 34%	*Intervention group:* Reduced daily sodium intake to 2-3 g and restricted fluid to 1.5 L/day *Control group:* Provided general diet information in accordance with ESC guidelines	Patients with moderate to severe HF were able to reduce their sodium and fluid intake without negative effects on thirst, appetite and QoL
Holst (2008), Sweden	Randomized cross over study	65	Stable CHF (70y), male 84%, NYHA I-III, EF <45%	*Intervention 1:* Maximum fluid intake of 1.5 L/day for six weeks *Intervention 2:* Fluid intake based on 30-35 mL/kg body weight/day for six weeks	Sense of thirst and difficulties to adhere to fluid restriction were reduced by less strict fluid restriction
Konstam (2007), USA	Randomized, double blind, placebo controlled study	4,133	CHF (65y), male 74%, NYHA III-IV, EF ≤40%	*Intervention 1:* Tolvaptan 30mg once per day. In addition to standard therapy *Intervention 2:* Placebo for a minimum of 60 days. In addition to standard therapy	Tolvaptan caused increased thirst and dry mouth
Van der Wal (2006),	Descriptive cross-sectional	501	Stable CHF patients (72y±11),	Assessed (CES-D), Revised Heart	More than a third of patients

Netherlands	design	male 60%, NYHA II-IV, EF 39%	failure Compliance Scale, Dutch HF knowledge scale, HF belief scale	(39%) had problems with it. The main problem was thirst (27%) 28% of patients answered they should drink more in case of thirst

ADHF, acute decompensated heart failure; HF, heart failure; CHF, chronic heart failure; EF, ejection fraction; LVEF, left ventricular ejection fraction; VAS, Visual Analogue Scale; HRQoL, health related quality of life; ESC, European Society of Cardiology; QoL, quality of life; EQ-5D, European Quality of life index in 5 dimensions; 6MWT, Six minute walk tests; NYHA, New York Heart Association; MLWHFQ, Minnesota living with HF questionnaire; NYHA, New York Heart Association; TDS, Thirst Distress Scale

From the search performed, there were 165 citations of which 157 were excluded (see Figure 2.2). Reasons for exclusion included intervention studies with other patient populations and studies that looked at thirst related to exercise and dehydration. A hand search of the reference lists of eligible studies yielded an additional study. Therefore, a total of nine studies were included in the review, one was a systematic review, three were descriptive, and five studies were randomized controlled trials. The sample sizes ranged from 15 to 4,375 participants. The total number of studied participants was 9,298. Studies included participants with symptomatic CHF with NYHA classes II-IV, ranging in age from 62 to 80 years. The mean ejection fraction ranged from 23% to 45%. Participants included were hospitalized and community-based patients. Percentage of males in the study ranged from 51% to 84%. The countries of study were from North America, Sweden, Brazil and the Netherlands. Based on the Cochrane risk of bias assessment, the overall evidence of data included in the studies was of high quality and presented a low risk of bias, shown in Table 2.2. The systematic review included in this study was of high quality according to the AMSTAR rating scale of 8/11 (Table 2.3).

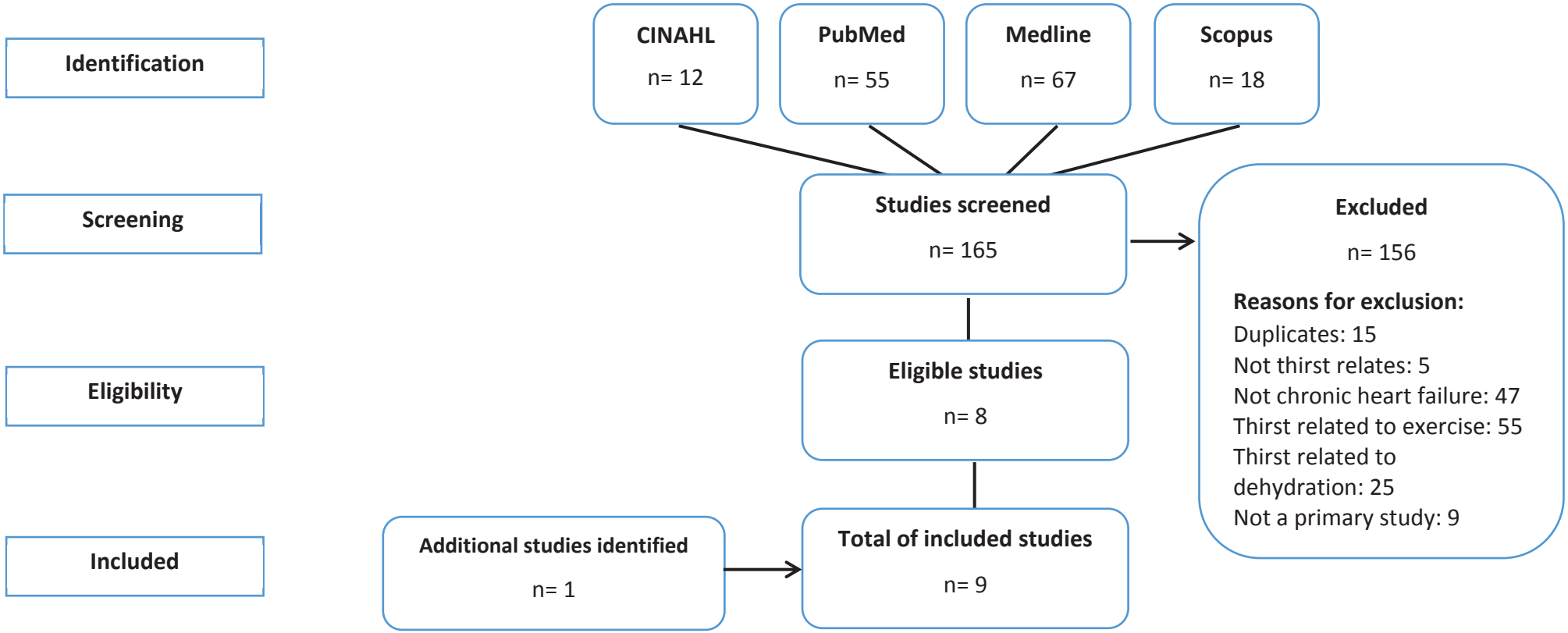

Figure 2.2 Flowchart of the article search on thirst in CHF.

Table 2.2 Risk of bias assessment.

Studies	Random sequence generation assessed	Allocation concealment assessed	Blinding of participants, personnel and outcome assessors assessed	Incomplete outcome data assessed	Selective outcome reporting assessed
Aliti (2013)	Low risk	Low risk	Low risk	Low risk	Low risk
Albert (2013)	Low risk	Low risk	Low risk	Low risk	Low risk
Waldreus (2011)				Low risk	Low risk
Reilly (2010)				Low risk	Low risk
Philipson (2010)	Low risk	Low risk	Low risk	Low risk	Low risk
Holst (2008)	Low risk	Low risk	High risk	Low risk	Low risk
Konstam (2007)	Low risk	Low risk	Low risk	Low risk	Low risk
Van der Wal (2006)				Low risk	Low risk

Table 2.3 AMSTAR rating for the systematic review.

	Waldreus et al (2013)
	Thirst in CHF- a systematic literature review
1. Was an 'a priori' design provided	No
2. Was there duplicate study selection and data extraction?	Yes
3. Was a comprehensive literature search performed?	Yes
4. Was the status of publication used as inclusion criteria?	Yes
5. Was a list of studies (included and excluded) provided?	No
6. Were the characteristics of the included studies provided?	Yes
7. Was the scientific quality of the included studies assessed and documented?	Yes
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes
9. Were the methods used to combine the findings of studies appropriate?	Yes
10. Was the likelihood of publication bias assessed?	No
11. Was the conflict of interest included?	Yes

CHF, chronic heart failure

2.6 RESULTS

1.5.1 Factors affecting thirst in CHF

There are many factors that contribute to the activation of the thirst response in CHF (18).

Condition

Chronic heart failure condition can also affect the thirst response. Despite their low serum osmolality (usually inhibits thirst); CHF patients still experience intense thirst (45). This unabated thirst is more likely due to the thirst-provoking effects of angiotensin II which activates peripheral and or central thirst stimulatory pathways (57). This central thirst stimulatory pathway is often primed in CHF which increases the expression of angiotensin 1 receptor in close proximity to the brain regions which controls water intake and vasopressin release (91).

Prolonged neurohormonal activation in CHF

Prolonged neurohormonal activation may influence the fluid balance in patients with CHF in many ways. Firstly, the central baroreceptors which inhibits the sympathetic nervous system and the release of vasopressin from the central nervous system (CNS) is impaired (57, 91). Due to the low cardiac output and blood pressure (clinical features of CHF), the central baroreceptors decrease the amount of inhibitory impulses to the brain; triggering the release of vasopressin from the CNS (57, 91). In addition, the normal feedback system which restores the inhibitory regulation of neurohormonal activity is impaired in persons with CHF (92). Secondly, renin secretion induced by a reduction in blood volume or hypovolemia evident in CHF dramatically increases the plasma concentration of angiotensin II to a level which can activate the cerebral thirst mechanism (84). Lastly, decreased arterial pressure

and volume can lead to elevated vasopressin levels often observed in patients with CHF (93). Nonetheless, no studies were found specifically addressing the role of these factors in thirst in CHF.

Treatment

Though pharmacological and non-pharmacological interventions are designed to manage symptom burden in CHF, many patients with CHF associate these interventions with troublesome thirst (18).

Pharmacological intervention

There were no studies investigating the effect of common pharmacotherapies used to manage symptoms in CHF on thirst (See Table 2.4). However, it is possible that pharmacological agents also stimulate the thirst response. Increased thirst may be associated with the loss of body water caused by diuretic use (94). Aldosterone antagonists, ACE inhibitors and angiotensin receptor blockers increases thirst by decreasing sodium and water concentration in the blood (95). However, the only drug reported to increase thirst in CHF was tolvaptan, a vasopressin receptor antagonists (27).

Table 2.4 Common CHF medications that stimulate the thirst response and its effect on the thirst pathway.

Pharmacological treatment	Examples	Effect on the thirst pathway
Loop diuretics	Frusemide	- Activates the RAAS; increasing the levels of angiotensin II - Activation of the thirst centre leads to vasopressin release - The end result is enhanced thirst
Aldosterone antagonists	Spironolactone	- Blocks the binding of aldosterone to its cytoplasmic receptor; increasing serum sodium concentration (a stimulus for thirst)
Angiotensin converting enzyme (ACE) inhibitors	Perindopril	- Reduces circulating levels of angiotensin II; decreasing aldosterone secretion - This leads to reduction in sodium reabsorption - The end result is thirst
Angiotensin receptor blockers (ARBs)	Losartan	- Competitively antagonizes angiotensin type I receptor; completely blocking angiotensin II action - The end result is similar to that of ACE inhibitors
Vasopressin receptor antagonist	Tolvaptan	- Inhibits vasopressin from binding to its receptor, promoting diuresis - The end result is thirst

ACE, angiotensin converting enzyme; ARBs, angiotensin receptor blockers

Fluid restriction

Patients also reported fluid restriction to be associated with burdensome thirst (20, 21, 86, 96). In the intervention study by Holst et al (2008), patients with stable CHF undergoing fluid restriction scored higher in the Visual Analogue Scale (VAS) (median 51, interquartile range [IQR] 16-89) in comparison to those on liberal fluid intake (23 (6-53); $p < 0.001$) (86). Similarly, another intervention study by Aliti et al (2013) also showed a greater perceived sense of thirst from an aggressive fluid restriction (800mL/d) compared to a liberal fluid intake (2.5L). The intervention group had a higher score in the VAS (5.1 ± 2.9) compared to the control group (3.44 ± 2.0) (P=0.01) (21). In contrast, Albert et al (2013) found no significant differences in the level of thirst between hyponatraemic CHF patients in the control group (50 (12.5-73.8)) and those on 1,000mL/day fluid therapy (40 (20-51.3); $p = 0.60$) at 60 day follow-up (20).

Emotion

Of all the psychological factors, anxiety was found to have a significant impact on the intensity of thirst. One study with anxious CHF patients (n=15) graded their thirst higher (median= 85mm) compared to eight patients without anxiety (median= 57mm; $p < 0.04$) (45).

1.5.2 Interventions to relieve thirst

There are no intervention studies with the purpose of relieving thirst in CHF. Ingestion of ice cubes, cold drinks and peppermint or buttermilk candies were among the following strategies advised to CHF patients experiencing thirst (30). Although no intervention studies were found in patients with CHF, three studies had thirst as a secondary outcome measure.

The first study compared the effects of fluid restricted therapy versus liberal fluid intake on quality of life and thirst, physical activity and hospitalisations. In comparison to the fluid restriction (17 ml/kg/day), liberal fluid intake (23 ml/kg) had a favourable effect on the level of thirst. Those on fluid restriction were found to have scored higher (median 51, interquartile range [IQR] 16-89) in comparison to those on liberal fluid intake (23 (6-53); $p < 0.001$) (86).

In contrast, another intervention study by Philipson et al (2010) examined if CHF patients can reduce their fluid intake without negative effects on thirst, appetite and quality of life. After 12 weeks of intervention, they found no significant changes to thirst between the baseline and follow up in both the fluid restriction and control group (54 ± 15 to 46 ± 17) versus from 50 ± 19 to 48 ± 26) (97). The last study investigated the effect of 1,000 ml per day fluid restriction on quality of life, thirst, all-cause death and hospitalisations in hyponatraemic CHF patients. The study also found no significant differences in the level of thirst between hyponatraemic CHF patients in the control group (50 (12.5-73.8)) and those on 1,000mL per day fluid therapy (40 (20-51.3); $p = 0.60$) at 60 day follow-up (20).

Two studies also explored the use of artificial saliva and chewing gum in patients with end-stage renal disease undergoing haemodialysis. The first one was a cross-over intervention study of comparing the effects of chewing gum versus artificial saliva on thirst and xerostomia for two weeks. Chewing gum was able to reduce the mean Xerostomia Inventory (XI) scores significantly from 33.2 ± 9.1 to 29.7 ± 8.4; $p < 0.05$ (6, 7). In both the treatment modalities, no overall treatment effect was found. The Dialysis Thirst Inventory (DTI) scores were comparable between artificial saliva spray (15.5 ± 5.0) and chewing gum (15.4 ± 4.8)

(6). However, both treatments were able to reduce the DTI scores from baseline 16.6 ± 5.1) (6, 7).

The other study examined whether a three-month use of chewing gum would relieve thirst and xerostomia in chronic haemodialysis patients. No significant changes were achieved in the patient's self-reported xerostomia. At baseline, 29% of the participants reported experiencing xerostomia frequently (8). After the 3 month chewing gum treatment, this figure increased to 35% and after 1 month of the intervention, it was reduced to 25% (8). On the other hand, there was a slight change in the frequency of self- reported thirst. Before starting the intervention, 41% of patients reported experiencing thirst frequently (8). After the chewing gum intervention, the frequency was reduced to 40% and at 1 month after the intervention, it was further reduced to 35% (8).

2.7 DISCUSSION

This review elucidated that thirst is a burdensome symptom commonly experienced by CHF patients. As presented, nine studies which investigated thirst in CHF were retrieved from the electronic search. Although the studies were difficult to compare due to their differences in aims and methods, the following studies are still evidence that thirst is a growing problem in CHF patients especially if they are following a fluid restriction which is not sufficient to relieve their thirst.

It is clear that prolonged neurohormonal activation such as the release of angiotensin II and vasopressin to increase cardiac output and tissue perfusion may explain the constant feelings of thirst in patients with CHF. However, there is lack of evidence to support this idea and identifying each of their physiological roles in the control of drinking still presents many

setbacks (98). Factors such as emotion may also influence the thirst response. Waldreus et al (2011) found that patients who were anxious scored the highest thirst intensity (45). The relationship between anxiety and thirst might be due to the activation of the sympathetic nervous system and worsening CHF (55). In addition, pharmacological agents administered to correct neurohormonal derangement in CHF may also influence the thirst response. One of the many examples is administration of diuretics to manage fluid retention (37). While it is efficient in relieving symptoms of fluid retention, diuretics interact with the renin angiotensin system increasing the circulating levels of angiotensin II (99, 100), a potent thirst activator.

In addition, other medications such as ACE inhibitors and angiotensin receptor blockers can also affect the thirst response. Several studies on ACE inhibitors and angiotensin receptor blockers have been undertaken to examine their ability to affect the processes controlled by angiotensin II. While an increase in dose of both drug classes will lead to greater central nervous system penetration and hence greater inhibition of the thirst mechanism (95), it is important to consider that the thirst mechanism is an integrated system. Therefore, another pathway of fluid regulation also becomes affected i.e. decreasing serum sodium and water concentration; causing an increase in sodium appetite followed by thirst. Tolvaptan therapy was the only drug reported to increase thirst in CHF (27). This may be explained by its ability to antagonize vasopressin from binding to its receptor; increasing excess fluid excretion; as a result a surge in thirst frequency is often observed (27). Although these are evident, confounding variables such as route of administration, dosage and duration of dose makes it difficult to assess the quantitative contribution of different drug classes to the levels of

angiotensin II/vasopressin to thirst (95). This emphasizes the need for further studies on classes of drugs as their specific effect on the thirst drive has been poorly studied.

Fluid restriction is an important part of non-pharmacological interventions, however thirst is an unpleasant consequence of this (96). A reported 23% and 73% of patients with CHF have difficulties with a fluid restricted diet due to thirst (30, 101, 102). Although it is poorly evaluated, fluid restriction is still widely used based on logical reasoning that it reduces burden on the heart. The studies showed conflicting results. Albert et al (2013) concluded that a strict allowance (1,000mL/day) in fluid therapy may be beneficial for hyponatraemic CHF patients (20). Their findings showed improvements in quality of life at 60 days post-discharge (20). Similarly, Philipson et al (2010) demonstrated that patients with moderate to severe CHF were able to undergo a fluid restricted therapy without negative effects on thirst (97). In contrast, Holst et al (2008) showed that a liberal fluid intake (30-35 mL/kg body weight/day) based on body weight alleviates thirst (96). Correspondingly, Aliti et al (2013) also support the findings of Holst and colleagues. They have found that a strict fluid restriction was associated with significantly greater perceived thirst.

Difference in research methodologies and populations enrolled in the studies may be accountable for the differences in findings. The population recruited in a study by Holst et al (2008) consisted of patients who were previously unstable with systolic dysfunction, Aliti et al (2013) recruited patients with acute decompensated heart failure/systolic dysfunction while Albert et al (2010) enrolled patients with both reduced or preserved ejection fraction and hyponatraemia. In addition, Holst et al (2008) used a cross-over design with 1,500ml/d then 30ml/kg/day interventions for 16 weeks and Aliti et al (2013) with a randomized

blinded trial of 800mL/d for 7 days compared to a fluid restriction of 1,000ml/d for an 8-week period by Albert et al (2013). A randomised controlled trial in a larger sample using a multicentre approach is needed in order to produce generalizable findings. As low compliance to fluid restriction is a common precipitant for readmission to hospital in CHF and adversely affects quality of life (87), systematically exploring therapeutic strategies to alleviate thirst in this cohort is warranted.

There were no intervention studies specifically addressing thirst in patients with CHF. However, there were several strategies recommended to patients to relieve thirst such as ingestion of ice cubes. The results presented on the effects of liberal fluid intake on thirst were inconclusive (20, 86, 96, 97). However, studies on interventions such as chewing gum and artificial saliva spray to alleviate thirst in end-stage renal disease are available (6, 8). Although the following studies were not conducted on CHF patients, thirst experienced by these patients is also caused by either an imbalance in fluid regulation due to their condition or a fluid restricted diet which is very similar to patients with CHF. Therefore, the following interventions may be considered a useful clinical tool in adhering to a fluid restricted therapy in CHF.

The first study found no overall treatment effect between artificial saliva and chewing gum (6). Artificial saliva was reported to reduce perceived thirst but had no effect on xerostomia (2). Although results of both treatment modalities were comparable, it is important to consider participants' opinion and preference from both interventions. Chewing gum was preferred by most of the participants in the study for several reasons. Firstly, chewing gum was found to be more effective in relieving thirst than artificial saliva (5.5 ± 2.7 vs. 3.3 ± 2.6;

p <0.001) (8). This effect is speculated to be due to the saliva stimulating capacity of gum. Secondly, the gum was easier to use than the artificial saliva (7.6 ± 2.3 vs. 6.7 ± 2.9; p<0.050). Participants also reported that the gum tastes better than artificial saliva spray (7.3 ± 2.2 vs. 6.0 ± 2.5; p<0.001). And lastly, majority of the participants were willing to use chewing gum longer than artificial saliva [46/65 (70%) vs. 25/65 (39%)]. The overall findings rated chewing gum as the better strategy in terms of its effectiveness, ease of use and taste.

In comparison to this, Jagodzinska and colleagues (2011) also explored the use of chewing gum in chronic haemodialysis patients. Although, participants were subjected to a three month use of chewing gum, no significant changes to either xerostomia or thirst were found (8). However, this may be explained by poor compliance to the intervention and the tool used to measure xerostomia and thirst. It is likely that a three-month period of treatment may result to poorer compliance compared to a two week intervention period. In addition, the tools used to measure thirst and xerostomia in this study involved a 19-multiple choice questionnaire as opposed to using a validated thirst and xerostomia tool.

Although the use of chewing gum or artificial saliva spray shows ambiguous results, participant's satisfaction response shows that the use of chewing gum may be promising. Therefore, the need to perform rigorous randomized controlled trials, where CHF patients are tested to see if chewing gum or artificial saliva can intervene with thirst is crucial. More studies which explore the prevalence and causes of thirst in CHF are also needed to raise awareness and stimulate research on interventions to help relieve chronic thirst in CHF patients.

2.8 CONCLUSION

In summary, the RAAS, vasopressin, plasma osmolality and the lower centres of the brain play a significant role in promoting fluid intake. Various factors elicit the thirst response. It is clear that neurohormonal activation associated with CHF also influences fluid regulation. However, its role in the context of thirst is still unknown. Although studies have speculated that elevated angiotensin II and vasopressin and disturbances in plasma osmolality may explain the feelings of thirst in CHF patients, this is insufficient to draw conclusions. Moreover, administration of drugs which should improve neurohormonal derangement in CHF also causes thirst. With the addition of recommended fluid restriction, a struggle between compliance to treatment and their own to desire to quench thirst, adversely affects their quality of life. Artificial saliva and chewing gum are the very few strategies tested to alleviate thirst in another patient population, with recommendations of use of lemon, ice chips and small sips of water in CHF. Among the two interventions, chewing gum was reported as the most effective and most preferred due to its ease of use and taste by most participants. More research is needed to understand how CHF and treatment affects the thirst mechanism. Lastly, interventions such as chewing gum to alleviate thirst in CHF patients warrant investigation through appropriately powered randomized controlled study designs.

2.9 RELEVANCE TO CLINICAL PRACTICE

Chronic heart failure is a progressive and burdensome syndrome with thirst as a major reason for non-compliance to self- care practices such as fluid restriction (45, 86, 87, 96). Due to the life threatening effects of non-compliance to fluid restricted therapy (46), increasing the awareness of thirst in clinical practice is pivotal to reduce unnecessary

hospitalisations. Systematic evaluation of available strategies such as chewing gum is essential in ensuring that the best possible management is provided to CHF patients in clinical care settings.

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CHAPTER III- A SURVEY OF HEALTH PROFESSIONALS MANAGING THIRST IN CHRONIC HEART FAILURE

3.1 CHAPTER PREFACE

Publication reference

Allida SM, Inglis SC, Davidson PM, Hayward CS, Shehab S, Newton PJ. A survey of health professionals managing thirst in chronic heart failure. Contemp Nurs. 2016; 1-16 Epub ahead of print.

Chapter 2 provided a summary of the current literature on thirst in chronic heart failure. The previous chapter also discussed the possible factors that contribute to thirst and describes various strategies used to help relieve thirst in chronic heart failure. This chapter discusses the current strategies recommended by health professionals managing thirst in chronic heart failure.

This chapter presents an article in its original form, submitted to the Contemporary Nurse Journal (2016) Epub ahead of print. This article is provided in its published form as an appendix *(refer to* Appendix 10*)*.

Background

Thirst is a common and burdensome symptom of chronic heart failure which affects compliance to self-care practices such as fluid restriction. Despite this, there is no standard clinical practice for managing the symptom of thirst.

Aims of the study

This study aimed to; 1) Identify the current strategies recommended by health professionals to relieve thirst in chronic heart failure; 2) Determine the opinion of health professionals of the following strategies: '*artificial saliva', 'ice chips', 'chewing gum', 'small sips of water', 'peppermint/buttermilk flavoured candies', 'cold water with a slice of lemon', 'lozenges'* and '*ice cold water'* in alleviating thirst.

A paper survey was distributed to attendees of the 8th Annual Scientific Meeting of the Australasian Cardiovascular Nursing College, February 2014.

Summary of results

There were 42/70 respondents to the survey. Majority of the respondents were registered nurses with primary specialty in coronary (19/40; 48%) and CHF care (18/40; 45%). The majority (33/40; 82.5%) had also recommended various strategies to alleviate thirst. The most recommended strategy was ice chips (36/38; 94.7%). Overall, the respondents reported 'some use' in all of the strategies. Other strategies specified by the health professionals were aligned with what CHF patients have reported using which suggests that CHF patients listen to the advises given by health professionals and include these strategies in their self-care. This highlights the need for enhancing communication between health professionals and CHF patients.

Implications

This paper demonstrates that there are various strategies recommended to CHF patients to help relieve thirst. Despite this, systematic evaluation of these methods is still limited. This emphasises the need for more research to investigate the efficacy of these interventions in relieving thirst. Information from this survey may help in the incorporation of thirst-relieving strategies into evidence based guidelines; further improving the quality of care of chronic heart failure patients.

3.2 INTRODUCTION

Chronic heart failure (CHF) is the syndrome describing the failure of the heart to maintain adequate circulation to meet the metabolic demands of the body (46). Structural and functional abnormalities resulting in impaired cardiac filling and ejection have mostly been implicated in conjunction with neurohormonal dysregulation (49). Despite recent developments in medical treatment many patients are still burdened with symptoms which affects their quality of life (18, 45). Patients with CHF experience a number of symptoms such as fatigue and shortness of breath. Among these symptoms, thirst is a common complaint in patients and the most rarely addressed.

Thirst is a subjective perception described by various sensations including dry mouth, lips and throat, light- headedness, tiredness, headache, loss of appetite and feeling of an "empty" stomach (2). It has been defined as a 'desire to drink caused by physiological and behavioural cues as a result of deficit in water' and is one of the most common and troublesome symptoms of CHF (18, 45). Several factors which promote thirst include the CHF condition, prescribed medications and self-care practices (18). Increased activation of neurohormonal systems often observed in CHF can stimulate the central thirst centre in the lateral hypothalamus (56, 57, 103, 104), xerostomia (dry mouth) and loss of body water from diuretic therapy to treat fluid retention also enhances thirst (18). Self-care practices such as weighing daily and fluid restriction is crucial in the management of CHF. Self- care involves cognitive decision making based on the recognition of signs and symptoms, and processing these within the context of existing knowledge and prior experiences (105). However, self-care practices such as fluid restriction may also increase patient's perception of thirst (86, 96, 97). Although thirst is vital in maintaining body homeostasis, in a chronic

state such as CHF, thirst is potentially detrimental and is one of the main reasons for non-compliance with fluid restricted therapy (86, 96, 104). Non-compliance with fluid restriction can lead to excessive fluid ingestion which can result in significant hyponatraemia manifesting clinically with lassitude and confusion in the most severe cases (106), as well as symptoms of fluid overload with symptoms of oedema, shortness of breath and fatigue (46, 48). In more serious instances, pulmonary oedema may result (46, 48).

To date, there is no prevalence data of thirst in CHF (78) however findings from a study of symptom prevalence and symptom burden demonstrates symptoms such as dry mouth as much more prevalent compared to symptoms thought to be typical such as systemic oedema and lack of appetite (76). Dry mouth was present in over 70% of patients in the study (76). It was reported to be frequent and severe and was quite a bit distressing in a third of patients (76). In addition, information from medical records also show a 9% frequency of persistent thirst in the last six months of life (79). Despite the enormity of this problem, there is very little scientific literature on thirst as a symptom (17) and there is no standard management of thirst in the clinical care setting. Thus, our aim was to (1) identify current strategies recommended by health professionals to their patients with CHF suffering from thirst and (2) identify their perceived usefulness of these strategies.

3.3 METHODS

3.3.1 Design, setting and sample

The study utilised a descriptive study design. The survey was a brief questionnaire developed by the investigators which sought to assess the effectiveness of various strategies recommended to patient with CHF to relieve their thirst. The paper survey was distributed to the attendees of the 8th Annual Scientific Meeting of the Australasian Cardiovascular

Nursing College, Gold Coast, Australia during one session on the first day of the conference in February 2014.

3.3.2 Measurements and item generation

Items were generated for the survey through a literature review (107) and piloting to minimise ambiguity and redundancies. This 3-item survey was adapted from another survey (108). Permission to reproduce these survey items was approved by the corresponding author. The survey was distributed in English. The survey ascertained basic demographics related to profession and primary area of specialty. Respondents were asked if they had recommended any strategies to help alleviate thirst to their patients suffering from CHF. For those who ticked 'yes' they had recommended any strategies, they were then asked if they had recommended to use the following; artificial saliva, ice chips, chewing gum, small sips of water, peppermint/buttermilk flavoured candies, cold water with a slice of lemon, lozenges and ice cold water. If they had recommended any of these strategies, they were asked what their perception is of the use of the following; some use, unsure or useful. In addition, they were also asked if they had recommended 'other' strategies not mentioned in the survey and specify what these strategies were. As this survey was adapted from a previously valid and reliable survey, the investigators did not feel the need to further validate this survey.

3.3.3 Data collection

The survey distribution was performed by two of the authors who also attended the conference. The paper survey was placed on all the delegates chair during the session and were invited by the convenor to participate. A participant information sheet detailing the purpose of the study and what was involved in participating was attached at the front of the survey. A participant consent statement was also included and respondents were asked if

they agree to participate in the survey. At the end of the session, the surveys were collected from the attendees.

3.3.4 Ethical considerations

Ethics approval was received from the University of Technology, Sydney Research Ethics Committee. Subsequently, the conference committee approved the circulation of the survey.

3.3.5 Data management and analysis

The responses from the paper survey were entered into the online-based survey in Survey Monkey™. Data generated from this were exported into an Excel spreadsheet. Descriptive analyses were used to describe the sample and the responses to study variables. Data are reported as number (percentage) unless otherwise stated.

3.4 RESULTS

Forty-two out of 70 (58%) attendees completed the survey. The majority of the respondents were registered nurses (14/39; 36%) (Figure 3.1); with a primary area of specialty in coronary (19/40; 48%) and CHF care (18/40; 45%). Figure 3.1 presents the full results; demonstrating the other healthcare professionals that responded to the survey. Responses were received from Australian and New Zealand-based conference attendees with the majority of responses from Australia (37/40; 93%).

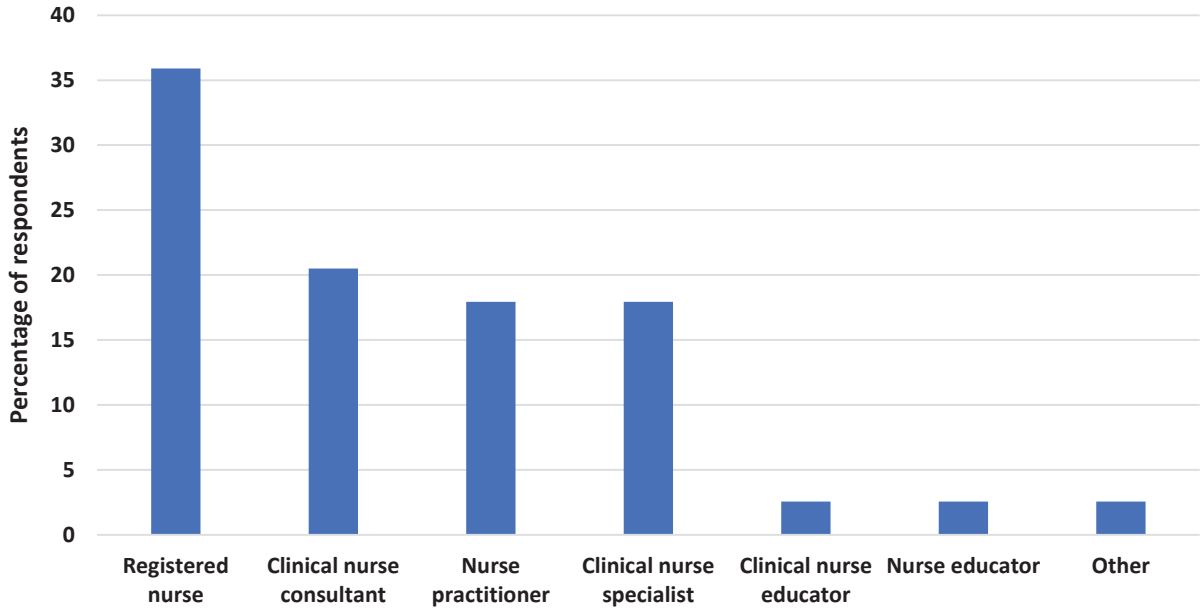

Figure 3.1 Professions of the respondents at the conference.

Strategies recommended to chronic heart failure patients

The majority of the respondents had recommended various strategies to alleviate thirst (33/40; 83%). The most recommended strategy to relieve thirst was ice chips (36/38; 95%). Peppermint/buttermilk flavoured candies were the least recommended strategy. The full result is presented in Figure 3.2.

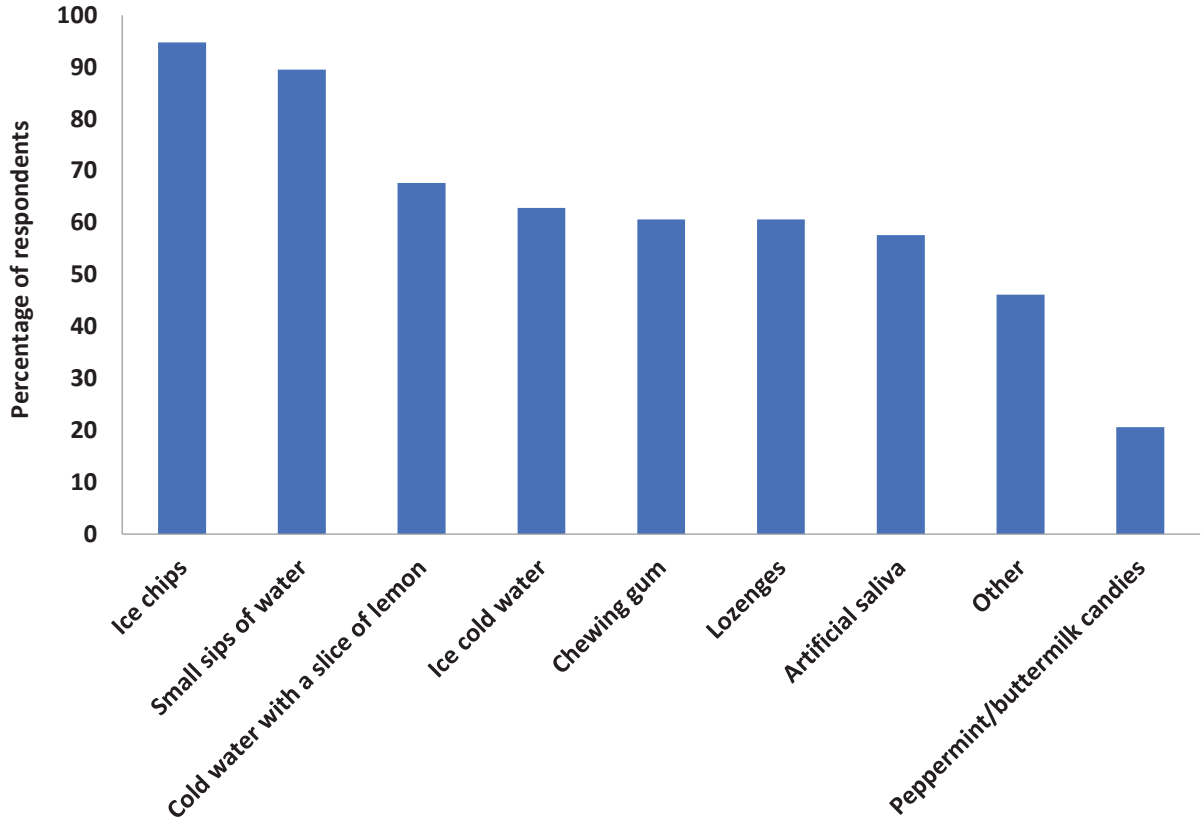

Figure 3.2 Percentage of health professionals recommending various strategies to relieve thirst.

Perceived efficacy of recommended strategies

The respondents reported 'some use' in all of the strategies. With ice chips as the most frequently recommended strategy, it was only reported to have 'some use' (18/36; 50%) in relieving patient's thirst by most of the respondents who had recommended this strategy. Some respondents have also reported ice chips useful in alleviating their patient's thirst (12/36; 33%). In terms of the least recommended strategy, peppermint/buttermilk flavoured candies were predominantly reported to have 'some use' (4/7; 57%) in managing patient's thirst. The full results are presented in Figure 3.3.

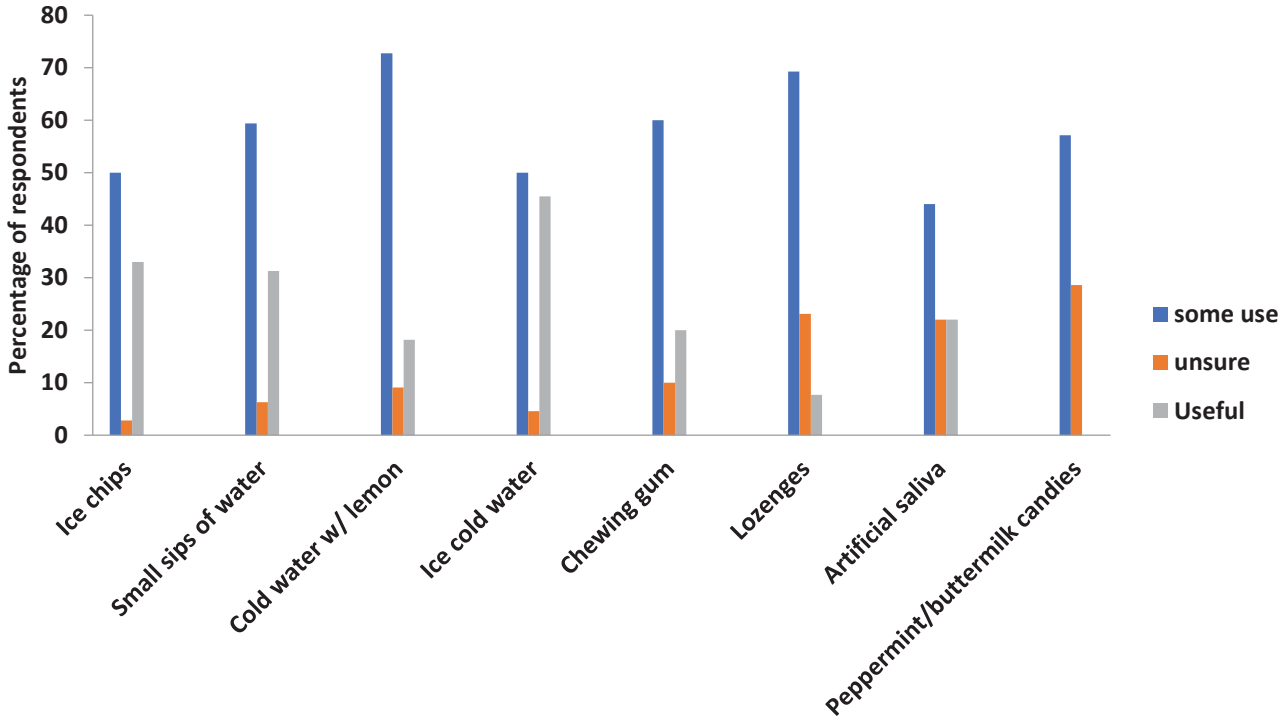

Figure 3.3 Perceived efficacies of various strategies.

Other strategies used to relieve thirst

Some respondents reported recommending 'other' (21/39; 54%) strategies apart from the list of strategies provided in the survey. The most common 'other' strategies included freezing fruits in ice cube trays or prepared ice blocks (Table 3.1). Some health professionals had also recommended developing a fluid plan to divide daily fluid intake and keeping a diary to remember it.

Table 3.1 Other strategy used to relieve thirst specified by health professionals.

'Other' strategies to relieve thirst
• Pacing out fluid across the day • Some food e.g. small amounts of watermelon • Freeze grapes, fruits etc. in ice cube trays • Drink small amounts often e.g. ½ a cup of tea • Don't drink sweet drinks (real or artificial sugar) • Avoid salty foods • Iced fruit jellies • Other commercially available liquids from pharmacy • Distraction • Mouthwash • Washing mouth out and spitting water out • Sipping from a bottle of ice water as it melts during the day • Ice cubes • Decanting fluid out of allowance into small bottle • Sugar- free lozenges • Spray atomizer water • Fluid plan- breakfast, lunch and dinner; measure and divide total day intake oral- no sugary drinks • Mints

3.5 **DISCUSSION**

Thirst is a common and troublesome symptom of CHF. To date there is no standard clinical practice to manage thirst. Most of the thirst literature and clinical trials were conducted in people with malignant disease and end- stage renal disease. However, the strategies investigated in these populations may potentially be useful in alleviating thirst in CHF. As clearly demonstrated by the survey, CHF health professionals have recommended similar strategies to help relieve patients' thirst. Useful thirst-relieving strategies includes artificial saliva, chewing gum, peppermints, lozenges and ice chips. Incorporation of these strategies into evidence- based guidelines may improve thirst management in CHF, consequently; improving compliance to fluid restriction. As demonstrated most clinicians are either unsure or not convinced of their usefulness. The results also showed variability in perceived usefulness of the interventions which is expected as patients' experience relief from thirst differently. While some may experience relief for many hours, others only remain thirst free for an hour. Health professionals are often told varying effects of the intervention by their patients, as a result they can only report what they have been told. Future studies should aim at identifying the views of the patients on the usefulness of various strategies to relieve thirst. In addition, systematic investigation of these strategies through appropriately powered randomised trials is crucial in implementing these strategies in clinical and community care settings. The results of this survey were used to inform the design and the intervention of a clinical trial aiming to help relieve thirst in people with CHF.

The results also show that some respondents also reported recommending 'other' strategies such as freezing fruits in ice cube trays or home- made/prepared ice blocks. Moreover, some health professionals had also recommended developing a fluid plan to

divide/distribute daily fluid intake and keeping a diary to remember it. Findings from a qualitative, descriptive study which examined compliance in CHF patients showed similar results. Patients reported using home-made “ice- lollies” or ice cubes to prevent thirst (30). In addition, 66% (10/15) of patients also stated that they measure and distribute the amount of fluid they used throughout the day (30). Other tips against thirst also included the advice to use less sugar (30) which is aligned with the recommendations of health professionals in this survey.

This survey has also identified that nurses play an important role in the management of thirst. The patient/nurse relationship constitutes trust which enables discussion of problems related to fluid restriction, thirst and compliance. This then allows for advice to be given to patients on how to manage thirst and fluid restriction. Findings from the study by van der Wal (2010) show that patients do adapt some of the strategies they are advised (30). Therefore, patient-nurse communication should be further encouraged in clinical practice.

3.6 LIMITATIONS

Our response rate of 58% (42/70) is better compared to other surveys of professional practice (108-113). However, it is still likely that the response rate of our survey would have been further improved had we been able to distribute our survey on both days of the conference or to another conference. Due to these respondents were limited to ACNC members who attended the conference. Secondly, as there were no similar studies to our survey, comparisons of our findings were difficult.

Another limitation in this study was the descriptive nature of the study design. Descriptive studies present the possibility for lack of objectivity as the questions in this survey were

predetermined and prescriptive. The use of a Likert scale also poses a disadvantage which involves its uni-dimensionality. Attitudes of the population for one particular item is vast and multi-dimensional. Therefore, providing 3-5 options of choice fails to measure the true attitudes of respondents. In addition, it is likely that respondents' answers to the previous questions will influence the next. Although these limitations are evident, Likert scale was chosen as it is easily understood and very easy to code when accumulating data. It is also unrestrictive in terms of how participants can respond to questions as opposed to yes/no. Convenience sampling used in this study is also another limitation. While this is efficient, it poses risk of bias which can lead to inaccuracy of our study findings. And lastly, in order to reduce respondent burden and improve the response rate of the survey, the investigators only collected information based on country of residence as opposed to states. As CHF management, may vary between states in Australia, it may have been useful to obtain information of the states the respondents were from.

3.7 CONCLUSION

This survey shows that various strategies to relieve thirst are recommended to CHF patients. However, most healthcare professionals are unsure of their efficacy. Therefore, systematic evaluation of these methods is warranted. Although, strategies such as ice chips and chewing gum was reported useful in alleviating thirst by most healthcare professionals, identifying patients' perception of these strategies is crucial to provide useful insight on patient preferences. More research is needed to investigate the efficacy of these strategies in relieving thirst.

3.8 RELEVANCE TO CLINICAL PRACTICE

Thirst greatly affects compliance to self-care practices such as fluid restriction. As demonstrated in this survey, there are many thirst- relieving strategies that clinicians can recommend or have recommended to patients. Systematic evaluation of these strategies is essential in incorporating these strategies into evidence- based guidelines to improve patient's quality of care.

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CHAPTER IV- MEASUREMENTS OF THIRST IN CHRONIC HEART FAILURE: A REVIEW

4.1 CHAPTER PREFACE

Publication reference:

Allida SM, Inglis SC, Davidson PM, Hayward CS, Newton PJ. Measurement of thirst in chronic heart failure- a review. Contemp Nurse. 2014; 5 134-152.

Chapter 3 provided the results of a survey identifying current strategies recommended by health professionals to help relieve thirst. This chapter reports on the tools used to measure thirst in chronic heart failure.

This chapter presents an article in its final accepted form, published in the Contemporary Nurse Journal (2014) Volume 5, Pages 134-152. This article is provided in its published form as an appendix *(refer to* Appendix 10*)*.

Background

Thirst is a bothersome symptom of chronic heart failure (CHF) which impacts adversely on quality of life. Despite this, limited work has been done to investigate thirst as a symptom or to develop reliable and valid measures of thirst in CHF.

Aim of the study

The purpose of this manuscript is to establish which tools have been used in research to measure thirst in CHF.

A review of key databases was conducted using the following key words: '*thirst', 'heart failure', 'measure', 'scale', 'randomised controlled trials'* and '*multicentre studies'*. The following electronic databases were searched: Medline, PubMed, CINAHL, and Scopus.

Summary of results

To date, there are only three measurement tools utilised in studies examining thirst in CHF patients (Visual Analogue Scale, Numeric Rating Scale and Thirst Distress Scale). In recent studies, the VAS has been used to measure thirst intensity. While this measurement tool is very easy and quick to administer, using a uni-dimensional tool in conjunction with a multi-dimensional tool may be beneficial to capture all dimensions of thirst.

Implications

This paper shows that thirst in CHF is measured in a non- systematic way. In order to further understand the symptom of thirst, identify its causes, its prognostic significance in chronic heart failure and manage thirst efficiently, consistent measurement of thirst in CHF is vital. This highlights the need for a valid and reliable instrument to measure thirst.

4.2 INTRODUCTION

Chronic heart failure (CHF) is a common, progressive, and debilitating syndrome. It is the leading cause of hospitalization and deaths (114, 115). Although the treatment of CHF continues to advance, most patients still suffer from symptoms and consequences of treatment, which affects quality of life (18, 45). While breathlessness is the main focus of scientific literature on symptoms, thirst, on the other hand is rarely discussed (18). Unlike breathlessness, to date there is no standardised definition of thirst. However, it has been defined as 'the desire to drink caused by physiological and behavioural cues as a result of deficit in water' (116). There are several factors which promotes thirst in CHF. Increased activation of neurohormonal systems can activate the thirst centre, dry mouth and loss of body water from diuretic therapy also enhances thirst and fluid restriction may also increase patient's perceived thirst (18, 86, 96).

Research into alleviating thirst has largely been conducted in patients with end-stage renal disease undergoing haemodialysis (6, 7). Attention has been focused on reducing thirst to help patient's compliance with fluid restriction, in order to avoid excessive interdialytic weight gain and associated complications (6, 7, 19). In clinical practice, a growing number of CHF patients also complain of troublesome thirst (79). Thirst is also the main reason for non-compliance with fluid restricted therapy (86, 96). Similar to patients on haemodialysis, excessive fluid ingestion can result in oedema, shortness of breath and fluid overload (46, 48). In more serious instances, pulmonary oedema or hospitalization may result (46, 48). Assessment and management of symptoms are imperative to monitor progress and the impact of symptoms on outcomes. Symptom experience is multidimensional which means it includes not only the presence or absence of symptoms, but also its frequency, severity and

distress. To date, symptom assessment remains challenging as standardised symptom measures are still lacking or CHF patients. At present, limited work has been done to investigate the symptom of thirst or to develop reliable and valid measures of thirst in CHF. The purpose of this manuscript is to establish which tools have been used in research to measure thirst in CHF.

4.3 METHODS

In November 2013, a literature search was performed in Medline, Cumulative Index for Nursing and Allied Health (CINAHL), and Scopus using all the following key words; thirst, heart failure, cardiac failure, left ventricular dysfunction, measure, rating, scale, clinical trials, randomised controlled trials and multicentre studies. The search was restricted to humans and papers published in the English language. There was no limit to the years searched. One of the authors reviewed the abstracts and retrieved studies which met the following inclusion criteria: (i) studies had to include participants with a confirmed diagnosis of CHF (ii) the study had to be either a randomised controlled trial or any study design involving human participants using a subjective measure of thirst as either a primary or secondary endpoint. Studies in other patient populations and not thirst related were excluded. The studies are summarised in Table 4.1.

One of the authors used a data extraction form to extract the following data; study objectives, participant information, measurement tool to measure thirst and the outcomes. The Cochrane risk of bias tool was used to assess the quality of the included studies (90). Quantitative analyses were not performed. A narrative description of the individual studies results is presented.

Table 4.1 Studies using specific uni-dimensional scale and multi- dimensional questionnaires to assess thirst frequency, intensity and distress in CHF patients.

Author, year, country	Study design	Sample size, *n*	Participants	Thirst measurement	Study finding
Aliti (2013), Brazil (21)	Randomised, blinded parallel- group study	75	ADHF and systolic dysfunction HF (60y ± 11), 69% male, NYHA III/IV, EF 26%	VAS (0-100mm)	Thirst intensity: 5.1 ± 2.9 in the intervention group (800ml/day) and 3.44 ± 2.0 in the control group (at least 2.5L); *P*= 0.01
Albert (2013), USA (20)	Randomised controlled pilot study	46	Hyponatraemic CHF (62.8y ± 12.8), 51.3% male, NYHA III/IV	NRS (0-10)	Thirst intensity: thirst was scored 50mm with usual care and the intervention (1,000mL/d); *P* = 0.77
Waldreus (2011), Sweden (45)	Descriptive controlled cross-sectional study	23 (A) CHF + 25 (B) without CHF	A: Worsening HF (80y), 31% male, NYHA III-IV, EF 32% B: (80y)	VAS (0-100mm)	Thirst intensity: Group A scored 75mm and 25mm in group B (*P* < 0.0001)
Philipson (2010), Sweden (97)	Randomised prospective study with an intervention and control group	30	Stable CHF (74y), 73% male NYHA II-IV, EF 34%	VAS (0-100mm)	Thirst intensity: at baseline groups A and B scored 54 and 50mm, respectively. After 12 weeks group A scored 46mm and group B with 48mm
Reilly (2010), USA (26)	Descriptive study	25	Stable HF (44-83y), NYHA II-IV, EF 23%	TDS 6- item scale	Distress from thirst: 46% reported moderate to strong discomfort from thirst
Holst (2008), Sweden (96)	Randomised crossover study	65	Stable HF (70y), 84% male, NYHA I-III, EF <45%	VAS (0-100mm)	Thirst intensity: 51mm with strict fluid restriction (1.5ml/day) and 23mm in liberal fluid intake (30ml/kg/day); *P* < 0.001 Thirst intensity: a change of -6% in thirst from strict fluid restriction (1.5ml/day) and -24% in those on liberal fluid intake (30ml/kg/day); *P* < 0.05

CHF, chronic heart failure; HF, heart failure; ADHF, acute decompensated heart failure; EF, ejection fraction; NYHA, New York Heart Association; VAS, Visual Analogue Scale; TDS, Thirst Distress Scale; NRS, Numeric Rating Scale

4.4 RESULTS

4.4.1 Study selection

The search discovered 37 studies of which 31 were excluded. Reasons for exclusion included studies which examined other patient populations (n=11) and were not thirst related (n=8). Therefore, six studies met the inclusion criteria (Figure 4.1) (20, 26, 45, 86, 96, 97). Of all the studies included, two were descriptive (26, 45) and four were randomised controlled studies (20, 86, 96, 97). One study was a research abstract (26) and five were full- text studies (20, 45, 86, 96, 97). Sample sizes ranged from 25 to 75 participants, yielding a combined sample size of 286 participants. Studies included participants with symptomatic CHF with NYHA Class I-IV, ranging in age from 44-83 years. The mean ejection fraction ranged from 23% to 45%. Participants included were hospitalised and community- based patients. The majority were male [n= 215 (31%-84%)] in the study. The overall evidence of data included in the studies was of high quality and presented a low risk of bias based on the Cochrane risk of bias assessment (see Table 4.2).

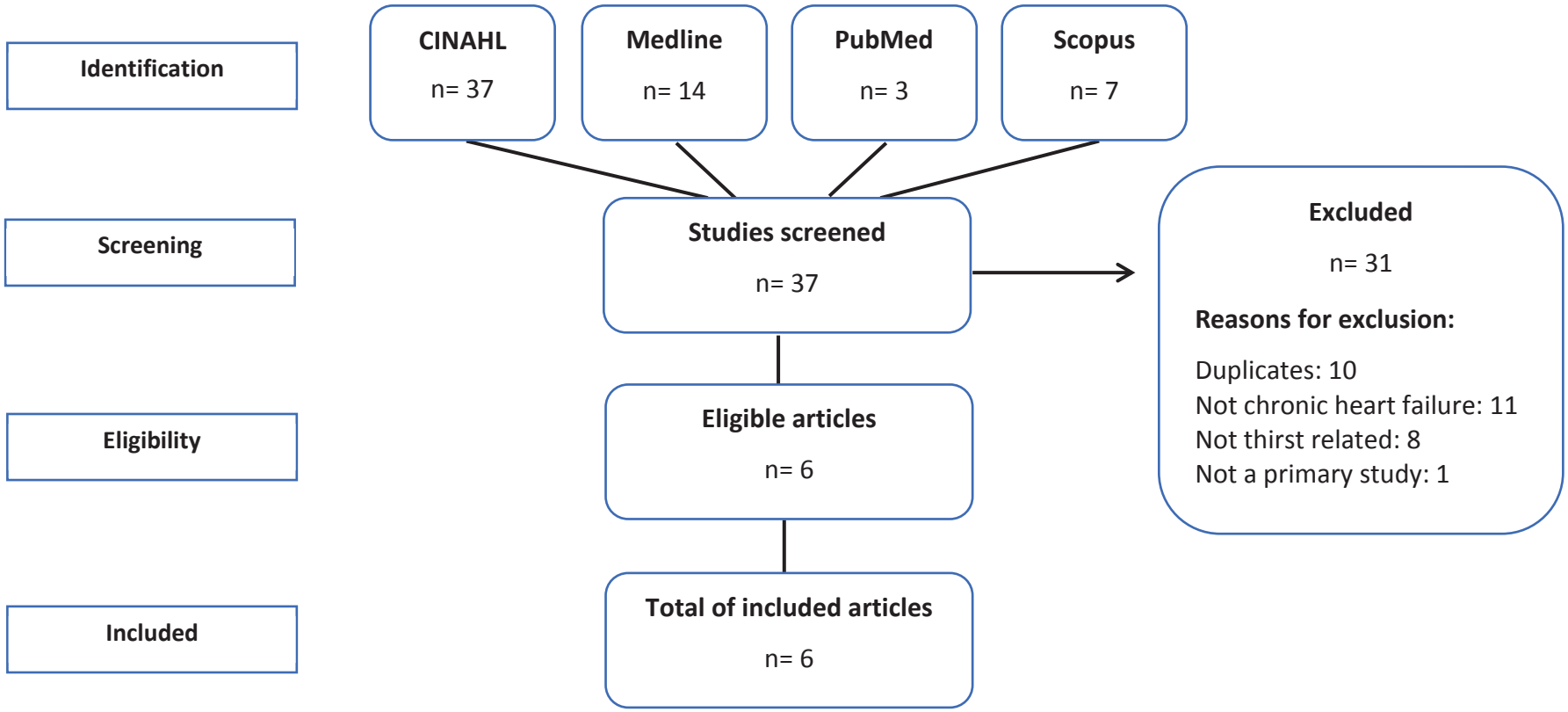

Figure 4.1 Prisma flowchart for selecting the included studies.

Table 4.2 Risk of bias assessment.

Studies	Random sequence generation assessed	Allocation concealment assessed	Blinding of participants, personnel and outcome assessors assessed	Incomplete outcome data assessed	Selective outcome reporting assessed
Aliti (2013)	Low risk	Low risk	Low risk	Low risk	Low risk
Albert (2013)	Low risk	Low risk	Low risk	Low risk	Low risk
Waldreus (2011)				Low risk	Low risk
Reilly (2010)				Low risk	Low risk
Philipson (2010)	Low risk	Low risk	Low risk	Low risk	Low risk
Holst (2008)	Low risk	Low risk	High risk	Low risk	Low risk

4.5 MEASUREMENT TOOLS IN CHRONIC HEART FAILURE

There were three different types of tools used to measure thirst. Most of the studies (5) used a uni-dimensional tool (20, 21, 45, 96, 97). These were the Visual Analogue Scale (VAS) (4) (21, 45, 96, 97) and a numeric rating scale (NRS) (1) (20). (See Table 4.3) Only one study used a multi-dimensional tool (26). This study used the Thirst Distress Scale (TDS) to measure thirst frequency, duration and distress. Thirst was the primary endpoint in three studies (26, 45, 96) and secondary endpoint in three (20, 21, 97).

None of the studies looked at all the dimensions of thirst. Only one study had any data on the frequency and distress of thirst (26) while the remaining five studies only measured thirst intensity (20, 45, 86, 96, 97).

Table 4.3 Uni-dimensional and multi-dimensional tools of thirst.

Uni-dimensional tool	
Name of tool	**Commentary**
Numeric rating scale	- A horizontal scale ranging from 0 to 10 with a statement (0= no thirst at all; 10= extreme thirst) anchored at either end. Patients are asked to circle the number that best describes thirst. - A widely used and validated scale in pain and breathlessness.
Visual Analogue Scale	- A horizontal line of 100mm with a statement (0mm= no thirst at all; 100mm= extreme thirst) anchored at each end. Patients are asked to mark a line at the position that best represents how thirsty they are. This mark is then measured in mm from the zero mark by the researcher. - A widely used and validated scale in pain and breathlessness.
Multi- dimensional tool	
Thirst Distress Scale	- A six-item scale scored based on a four- point likert scale assessing thirst distress (0= no distress; 4= very distress). - A widely used and validated scale for assessing thirst distress in patients undergoing haemodialysis - Reliable and: • Good item correlation, all items scored within the range (≥

	0.30 but < 0.70). • Achieved standard deviations ranging from 0.95- 1.04 suggesting good variability. • All items scored 0.94 in the goodness-of-fit index suggesting a good fit. • Chi-square of 40.70 and 9 degrees of freedom was achieved indicating a good data model fit. - Valid: • All items in the scale scored a factor loading between 0.59-0.81 which indicates validity of each item.

4.6 DISCUSSION

Optimal and complete evaluation of any symptom such as thirst must include measuring frequency, intensity, quality and distress (80, 117). These dimensions of thirst are important as they represent the patient's overall symptom experience (perception, evaluation and response to symptoms) (88, 117). This is crucial in understanding the barriers to effective symptom management strategies and improvement in symptom outcomes. Despite this, there seems to be no consensus among researchers on which tool should be used to measure all of the dimensions of thirst (frequency, quality, intensity, distress). As exemplified, none of the studies included in this review looked at all the dimensions of thirst (20, 21, 26, 45, 96, 97). Only one study measured the frequency and distress of thirst (26). Intensity was the most measured dimension of thirst among the studies (20, 21, 45, 86, 96, 97). This is also evident in past research, however reasons for this remains unknown. Measurement of thirst intensity is a major disadvantage as thirst cannot be accurately described and measured on the basis of intensity alone. Therefore, it may be beneficial to use both uni-dimensional and multi-dimensional tool in order to capture all aspects of thirst to more accurately reflect the patient symptom experience. For instance, the TDS only measures the frequency, duration and distress of thirst (19, 26) and so, the VAS can then measure the other dimension of thirst (intensity) (45, 118).

While this may also suggests a lack of weighting placed on thirst dimensions in current research, it is important to note that there is very limited number of studies which investigate thirst (20, 26, 45, 86, 96, 97). Moreover, there are only three different tools recently used to measure thirst with none of them specifically designed to measure thirst in

CHF (20, 26, 45). Further research into measurement and perhaps management of thirst in this patient population is needed.

The review has also found very little methodological research to develop a tool to assess thirst and there is still a lack of focus on thirst as a symptom of CHF. Patients often use a characteristic language to describe a particular symptom dimension and it is necessary to assess what these words mean to the population. For example, some patients may not describe their thirst as thirst, but as dry mouth or a nuisance. Therefore, it is important to understand the use and meaning of language for the patient. At present, using a validated tool for pain/breathlessness to measure thirst is invalid and inappropriate as these tools were specifically designed to assess the following symptoms in a particular patient population.

There was also limited research on thirst distress as the primary endpoint. This may yet again be explained by the recent emergence of research in this area. Overall, some of the studies reported thirst as the primary endpoint (45, 86, 96, 97), particularly those involving fluid restriction. However, most of these studies are underpowered and used either a uni-dimensional or a multi-dimensional tool only. Thirst was most often self- assessed using a uni-dimensional tool such as the VAS (20, 21, 45, 86, 96, 97). Only one study utilised a multi-dimensional tool i.e. TDS (26). However, findings from this study are very limited as only the abstract of the trial was published (26).

4.6.1 Uni- dimensional tools

Uni- dimensional tools measure a single dimension of the patient's symptom experience such as intensity. While this eliminates responder burden, uni- dimensional tools can

oversimplify patient symptom experience. Uni- dimensional tools most often used are the Visual Analogue Scale and the Numeric Rating Scale.

Visual Analogue Scale/ Numeric rating scale

The Visual Analogue Scale and the Numeric Rating scale have been widely used and validated in pain and breathlessness research (118, 119). Both have the advantage of being administered to patients' quickly, easily and subjectively. It avoids imprecise descriptive terms seen in the categorical scales (119). However, depending on the patient's interpretation, the anchoring text can influence the scores. At present, the VAS and the NRS have not been validated specifically for thirst.

There are certain disadvantages to the VAS which must be considered. While it can be quickly administered, the VAS is more demanding and requires greater cognitive skills (concentration, understanding and language skills) compared to the NRS. In fact, up to 26% of patients find it confusing. In addition, it is often difficult for some patients to convert a very subjective sensation such as thirst to a straight line (119). Mistakenly placing an x or a circle across the line may result in invalid results (79). Teaching patients how to use the scale or detailed instructions at the top of the scale was often provided to overcome this disadvantage (119, 120). Nonetheless, this may be inadequate to overcome difficulties associated with accurately recalling previous sensations such as the amount of change experienced since the last measurement (121). This is often observed in patients with difficulties remembering previous experiences such as the elderly (121).

Moreover, problems in recording change in scores after repeated measurements may also arise (122). However, success in recording change may be dependent on the patient

population being studied (121). For instance, it is more likely to obtain stable measurements from patients with chronic diseases compared to patients with continuous changing sensations (116). Patient expectations may also influence their scores (19). Patients are more likely to report a decrease in pain after receiving an intervention. However, this can be easily solved by using absolute values rather than change scores (122). Lastly, VAS was found to be less reproducible in comparison to NRS (123). However, the NRS is not necessarily linear. In comparison to a change from 1 to 2, a single point change from 7 to 8 may represent a greater subjective increase (118).

There are many benefits in using the VAS. It can be applied to measure different aspects or dimensions of thirst such as intensity (severity of thirst), distress (how much distress does thirst causes) and the timeframe (did the patient experience thirst now, over the past 24 hours and over the past 2 weeks) (119, 124). Therefore, it can also be applied as a multi-dimensional measure to assess thirst. In terms of its ability to measure thirst, the VAS is relatively similar to the TDS i.e. one dimension remains unassessed. For example, the VAS may measure thirst intensity, distress and timeframe but not the frequency dimension. The choice to use one of either tool is still largely dependent on the researcher's familiarity and preference.

4.6.2 Multi- dimensional tool

Multi-dimensional tools assess multiple dimensions or component of symptoms experienced by the patient. It gives a broader understanding of not just the intensity of the symptom but also the frequency of the symptom and its impact on the patient (distress).

Thirst Distress Scale

The Thirst Distress Scale (TDS) is a validated 6 item scale based on a conceptual framework encompassing thirst distress, thirst duration and frequency (125). It was developed to provide a multi- dimensional measurement of thirst in patients undergoing haemodialysis. Similar to the VAS and the NRS, the TDS is also relatively easy to administer. Each item was scored based on a 4 point Likert scale which assessed the relevance of thirst ranging from 1 (not relevant) to 4 (extremely relevant) (125). The patient can circle the number that best represents their subjective rating. The scores are summed which provided an overall individual score of 6 (no abnormal thirst) to 24 (thirst almost always present) (125). Thirst intensity is not measured in this scale; therefore it can be used alongside a uni- dimensional tool such as the VAS or the NRS to provide better overall representation of the patient's thirst experience.

4.7 CONCLUSION AND RECOMMENDATION

This review has shown that in order to better understand thirst, identify the causes of thirst, its prognostic significance in CHF and devise an effective management plan, there is a need for valid and reliable tools to measure thirst. At present, there are only three measurement tools utilised in studies examining thirst in patients with CHF. However, the following tools have not been validated for use in CHF patients. The VAS has been used primarily to measure thirst intensity in recent studies. This measurement tool is very easy and quick to administer to patients. It also has the advantage of being applied to measure various aspects of thirst i.e. distress and timeframe (frequency and duration). However, using a uni-dimensional tool in conjunction with a multi-dimensional tool may be beneficial to capture all dimensions of thirst. The use of qualitative methodology combined with a quantitative

study design will add more depth to our understanding of the patient's thirst experience. A consistent approach of measuring thirst in patients with CHF may help collate prevalence data needed to understand thirst in CHF. Consequently, developing management strategies to combat this bothersome symptom and improve patient's quality of life.

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CHAPTER V- THE DESIGN OF A SINGLE BLIND, RANDOMISED PILOT STUDY OF CHEWING GUM TO RELIEVE THIRST

5.1 INTRODUCTION

The previous chapter has provided a summary of the tools used to measure thirst in CHF. The findings from the literature review highlighted the importance of valid and reliable tools to measure thirst. Chapters 3 and 4 complements this chapter as it informed the design of this study, suitability of the questionnaires and provided the justification to investigate chewing gum in a randomised trial. This chapter will provide the rationale for the study designs; study aims and present a detailed description of all major study elements, including the study setting, participant recruitment, randomisation and the required sample size. Primary and secondary outcome measures will be defined, and a description of the study instruments and their scoring presented. Finally, the statistical methods undertaken will be provided.

5.2 RATIONALE FOR THE STUDY DESIGN

A randomized pilot design was chosen, as it minimises bias in treatment allocation, particularly selection bias and confounding factors. However, the main reason for the choice of this design was to address the issue of lack of blinding. As the RELIEVE-CHF was a self-administered intervention involving an intervention group which received chewing gum and a control group with no chewing gum, blinding the participant was not possible. Although

this is evident, the researcher who undertook the assessment of 2 week and 4 week outcomes was blinded to treatment allocation. Thus, a prospective, randomised, open label, blinded endpoint study was undertaken, as is commonly used in heart failure trials (126).

5.3 STUDY HYPOTHESIS

The RELIEVE-CHF study sought to alleviate thirst in people living with CHF. The study null hypothesis of this study was:

- There will be no observed improvement in the level of thirst of participants in the intervention group, at Day 4 compared to participants in the control group.

5.4 AIMS

The primary aim of this study was to assess the effectiveness of chewing gum to reduce the level of perceived thirst in people with CHF in the short term (Day 4). The secondary aims included assessing the effectiveness of chewing gum to reduce the level of perceived thirst in people with CHF in the longer term (Days 7, 14 weeks and 28 weeks), improvements in health-related quality of life (HRQoL) and investigating the effect of chewing gum on weight stability over the study period. And lastly, to determine the views and perception of CHF patients on the use of chewing gum.

5.5 STUDY DESIGN AND SETTING

The study was a single- blind, randomised pilot study with two arms (chewing gum and no chewing gum) conducted at St. Vincent's Hospital, Sydney. Ethics approval was received from St. Vincent's Hospital Human Research Ethics Committee (14/136) and ratification of the approval from the University of Technology Sydney Human Research Ethics Committee

(UTS HREC 2014000458). This trial was also registered under the Australian New Zealand Clinical Trials Registry (ACTRN12614000943640).

5.6 SELECTION CRITERIA

The inclusion criteria included those aged ≥ 18 years, with a primary or secondary diagnosis of heart failure a per NHFA and ESC guidelines (46, 127). At the time of inclusion, the participants were on oral loop diuretics, able to safely chew and swallow, able to provide informed consent and read, speak and understand English. Ineligible were participants who met the exclusion criteria shown in Table 5.1. Regular gum chewers was defined based on how often they chewed gum i.e. more than once a day. Participants on intravenous inotropes, were eligible once they were weaned off the drug.

Table 5.1 Inclusion and exclusion criteria.

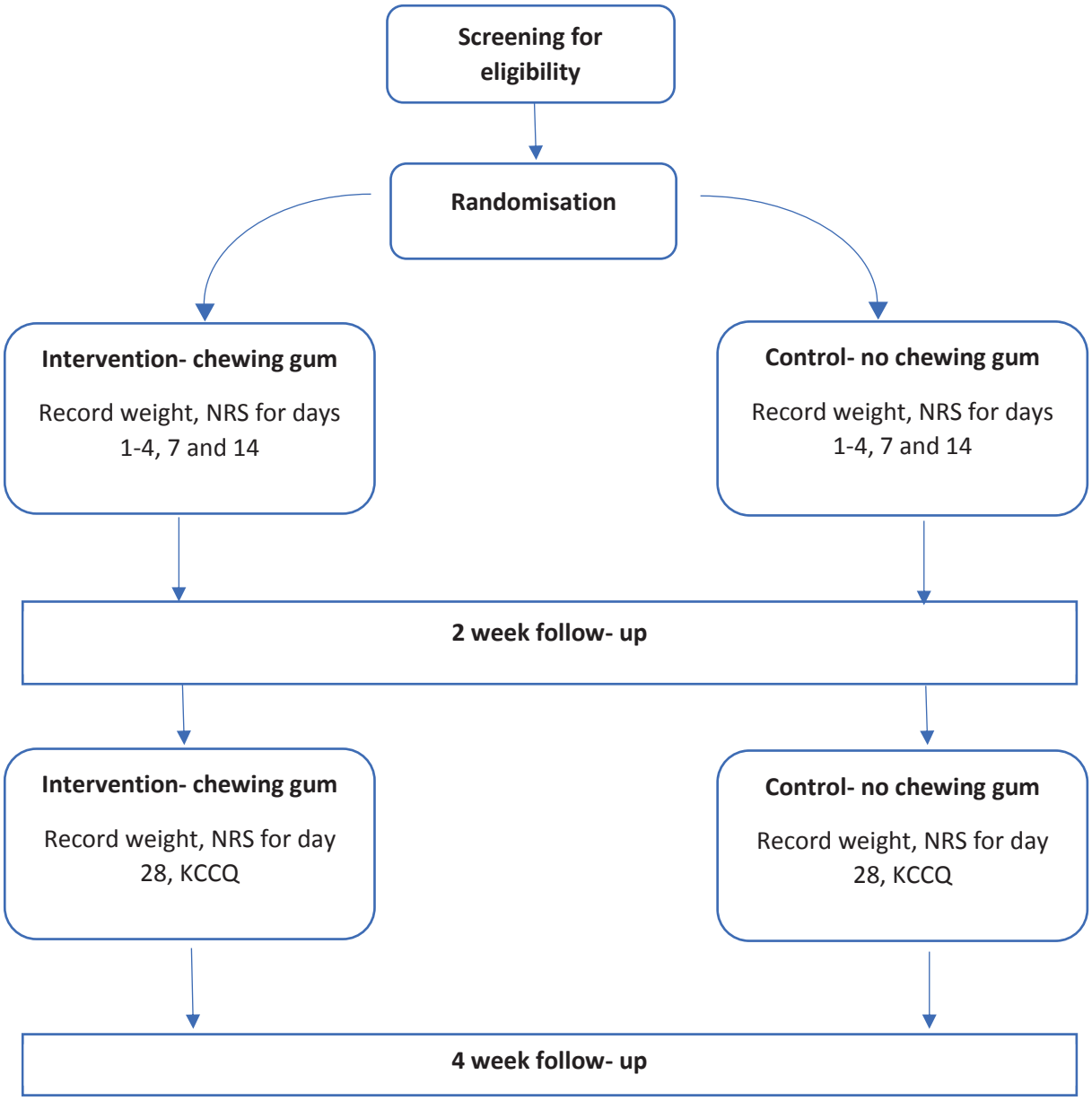
Inclusion criteria	Exclusion criteria
- Aged ≥ 18 years - With a primary or secondary of heart failure - On oral loop diuretics - Able to safely chew and swallow	- On intravenous inotropes - Regular gum chewers - With restricted chewing and/or swallowing due to dysphagia or other impairment

5.7 SAMPLE SIZE CALCULATION

Based on previous assessment of thirst by Philipson et al (2010) (97), the estimated baseline level of thirst was five and the standard deviation was two. To detect a one-point difference in the level of thirst with a standard deviation of two points, an estimated sample size of 65 per group is needed with a two-sided 5% significance level and 81% power. When taking into account a loss to follow-up of 10% per group, 144 participants (72 per group) were required to be enrolled in the study.

5.8 RECRUITMENT

Potential participants were identified through cardiac inpatient lists and outpatient clinic lists at St. Vincent's Hospital. The trial co-ordinator approached the patients and invited them to participate in the study. Participants underwent a screening phase which included review of their medication chart. Once consented, baseline data (included demographic profile, clinical status, comorbidities, results of their physical examination, level of thirst and health-related quality of life) for each participant were collected and recorded. A study log recorded all screened potential participants and the reason for not enrolling in the study was recorded. This enabled an overall breakdown of the pool of patients accessed for the duration of the trial. The study design allowed for a period of 4 weeks' follow- up per patient. A summary of the study schemata is presented in Figure 5.1.



NRS; Numeric Rating Scale, **KCCQ**; Kansas City Cardiomyopathy Questionnaire

Figure 5.1 RELIEVE- CHF study schemata.

5.9 CONSENT FORM

Participants were asked to sign an informed consent form to participate in this study after thoroughly reading and understanding the Information sheet provided *(refer to* Appendix 7*)*. A statement was also made to potential participants as well as in the Participant Information Sheet, that refusal to participate in this study would not alter the caring relationship between them and the hospital staff at St. Vincent's Hospital. Participants were also advised during the study that they had the option to withdraw from the study at any time without fear of penalty, and data collected would only be used as specified in the approved ethics documents, and any dissemination of research study outcomes would not identify any individual participant. Any questions participants had were answered appropriately.

5.10 RANDOMISATION

After informed consent was obtained participants were randomised 1:1 into either the intervention group (chewing gum) or control group (no chewing gum group) using a block randomization and computer generated random numbers.

5.11 BLINDING

This study was a self- administered intervention, blinding of the participants and the researcher responsible for the 4-week telephone follow-up was not possible. However, the investigators did not have access to the randomization schedule and were blinded to the group allocation prior to randomization and during data analysis.

5.12 PROCEDURE

All participants were provided with the questionnaires to record their weight, thirst and quality of life measurements. Participants in the intervention group were given 14 packets of Xylitol Epic Dental LLC peppermint flavour chewing gum (Figure 5.2) over the 2-week study period. They were instructed to chew the gum gently, for at least 10 minutes, six times a day and as desired throughout the day when the mouth feels dry or when they are thirsty (6, 7). There were several reasons for choosing Xylitol peppermint flavour in this study. Xylitol chewing gum is sugar-free (128) which is suitable in this study as some CHF patients may have comorbidities such as diabetes. Xylitol also protects the teeth from acid producing bacteria and it naturally stimulates saliva flow which helps in re-mineralisation of the enamel and cleans the teeth to avoid plaques (128), and is recommended by the Australian Dental Association.

Participants in the control group were not provided with any chewing gum. They were instructed to continue with what they normal use to relieve their thirst. During the 2-week intervention, all participants were asked to weigh themselves each morning after passing urine and before breakfast and record these measurements in the questionnaire provided. All participants also completed a Visual Analogue Scale and a Numeric Rating Scale to rate their level of thirst each day for 4 days (days 1-4), at day 7, 14 and 28. The study investigator collected the completed questionnaires from the participants' in hospital at 2 weeks and 4 weeks. If participants were discharged before conclusion of the 2-week intervention, they were asked to continue on with the intervention at home. They then received a phone call to collect these measurements. On the other hand, participants from the outpatient clinic

received a phone call at 2 weeks and 4 weeks. During this phone call they were asked to report their weight and level of thirst.

Figure 5.2 Xylitol Peppermint gum from Epic Dental LLC.

After the 2-week intervention, if participants perceived there had been any benefit in the use of chewing gum and they wished to continue using the gum, they were allowed to do so. However, after the intervention period, participants were not provided with any chewing gum. At 4 weeks (day 28) after the intervention, participants were also instructed to complete the Kansas City Cardiomyopathy Questionnaire to measure their health-related quality of life. The study investigators were concerned that measuring health-related quality of life at 2 weeks is a short duration to observe change, thus it was measured at 4 weeks. Four weeks is the minimum duration of follow-up for KCCQ in the literature (129). Participants were also asked if they were continuing to use the chewing gum to relieve their thirst and their perceived usefulness of the intervention in alleviating thirst.

5.13 STUDY MEASUREMENTS

5.13.1 Demographic information and physical assessment

Demographic information, clinical status, comorbidities, physical measures (height; weight; heart rate and blood pressure), thirst status and quality of life as shown in Table 5.2 were collected for participants in both the intervention and control group. No physical examination was carried out on any participants. Height, weight, heart rate and blood pressure were measurements obtained from the patient's medical file.

Table 5.2 **Study measurements for both intervention and control group.**

Demographic profile	Age, sex and date of birth
Clinical status	Comorbidities (Charlson Comorbidity Index (130)), previous medical history, existing most recent blood test results, current medications, New York Heart Association Class, existing height, weight (collected to calculate body mass index (BMI) and baseline weight for change), heart rate and blood pressure results
Thirst status	Visual Analogue Scale and Numeric Rating Scale
Health-related quality of life	Kansas City Cardiomyopathy Questionnaire

5.14 STUDY OUTCOME MEASUREMENTS

5.14.1 Rationale for using the following outcome measures

As mentioned in the previous chapters to achieve optimal and complete evaluation of thirst, measuring frequency, intensity, quality and distress are recommended when measuring symptoms. In this study the intensity of thirst were the only dimensions measured. There were several reasons for this which included avoiding responder burden. Considering that the cohort recruited in this study were very sick patients, it is likely that a long- detailed questionnaire such as an addition of the Thirst Distress Scale would have further

discouraged them from partaking in the study. While none of these measures are validated in CHF, the VAS and NRS are brief and can be easily administered compared to the Thirst Distress Scale. Secondly, the Thirst Distress Scale is only validated for use in patients with chronic kidney disease. And lastly, based on the study undertaken for the Bachelor of Medical Science (Hons) in a different population group (healthy individuals), the study investigators were not convinced of its suitability for this study. The following are the instruments used in this study to measure thirst and health-related quality of life:

Visual Analogue Scale

Visual Analogue Scale was used to measure the intensity of thirst in the cohort. The VAS consists of a 100 mm line with two end-points representing 'no thirst at all' and 'worst thirst imaginable'. Patients were asked to rate their thirst by placing a mark on the line corresponding to their current level of thirst. The distance along the line from the 'no thirst at all' marker is then measured with a ruler giving a score out of 100.

The VAS has been used in studies to measure pain and thirst intensity in different populations. Its validity and reliability of the VAS has previously been established through the use of various techniques such as the test-retest method (119). The study have found that participants were able to reproduce the previous mark of their subjective sensations (119). The results have also demonstrated that reliability coefficients tend to be higher when repeated after an hour compared to after 2 weeks (119).

Numeric Rating Scale

To measure the intensity of thirst, a numeric rating scale was also used. The participants' rated their sense of thirst by circling a number on a horizontal scale from 1 to 10 anchored at either end with a statement ('no thirst at all'= 1; 'the worst thirst imaginable'= 10) (118).

The NRS has been widely used and validated in pain and breathlessness research in CHF (118). It has the advantage of being administered quickly, easily and subjectively. It avoids imprecise terms seen in categorical scales (118).

Kansas City Cardiomyopathy Questionnaire

Health related quality of life was measured using the Kansas City Cardiomyopathy Questionnaire (KCCQ). The KCCQ is a validated instrument which assesses the following five domains (physical limitation, self-efficacy, social limitation and quality of life (131). The instrument is completed by the patient and scores range from 0 (worst) to 100 (best).

The validity of the individual domains of the KCCQ has been established (132). All components are considered valid representations of their intended domains. When compared with the NYHA, the mean KCCQ summary scores decreased as NYHA classes increased (*p<0.001)* which shows a strong association between the two (133). In terms of its reliability, a multicentre study of 548 patients have determined an internal consistency reliability, assessed with Cronbach's α, ranging 0.66−0.95 and an intraclass correlation coefficient of 0.88 which is considered stable (132). Another study also found that the KCCQ's responsiveness statistic was >2.4 times higher than the Minnesota Living with Heart Failure Questionnaire or the SF-12, suggesting greater sensitivity to clinical change compared to these other measures (131).

Table 5.3 presents the timeline of when the study measurements were administered to each participants.

Table 5.3 Timeline of study measurements.

Measures	Baseline	Days 1-4	Day 7	Day 14	Day 28
Socio-demographic data	**X**				
Clinical history, physical assessment	**X**				
Numeric rating scale	**X**	**X**	**X**	**X**	**X**
Visual Analogue Scale	**X**	**X**	**X**	**X**	**X**
Kansas City Cardiomyopathy	**X**	**X**	**X**	**X**	**X**

5.15 STUDY ENDPOINTS

5.15.1 Primary endpoint

The primary endpoint for this study was to compare the level of perceived thirst between the two study arms at Day 4.

5.15.2 Secondary endpoint

The secondary endpoints for this study included level of thirst in the longer term (Days 7, 14 and 28), improvements in quality of life and changes in weight (kg) over the study period. It also included the views and perception about the usefulness of chewing gum in reducing perceived thirst and whether participants are continuing to use chewing gum to relieve their thirst.

5.16 ADVERSE- EVENT MONITORING

In this study any serious adverse event was defined as any untoward medical occurrence which resulted in hospitalisation or prolonged hospitalisation, or was life- threatening, or resulted in death or disability.

5.17 DATA ANALYSIS

5.17.1 Baseline demographics and clinical characteristics

Data from this study was analysed based on the intention to treat principle in order to provide unbiased assessment of treatment effect (134). Before analysis was performed, all data was checked and cleaned for inconsistency. Descriptive statistics summarised the baseline demographics and clinical characteristics of the overall sample and groups (chewing gum vs. no chewing gum). All continuous data were summarised using mean and standard deviation while non-normal distributed data were presented as median. Continuous data with normal distribution was analysed using the Independent t-test (135) and non- normally distributed data were analysed using the Mann-Whitney U test (136). Categorical data were summarised in terms of percentages. Associations between categorical data was analysed using the Chi-square test (137). A *p- value* of <0.05 was considered statistically significant. All continuous variables were inspected visually through frequency histograms and box plots for normality. Data analysis was supervised by a statistician who was not involved in screening, recruitment and follow-up of the study participants.

5.17.2 Intention to treat

Data were analysed according to intention to treat. All participants who were allocated to their groups (chewing gum vs. no chewing gum) were included in the analysis and were analysed in their respective groups. The 'multiple imputation' method in IBM SPSS Statistics version 19 (IBM Corporation, Somers, NY) was used to analyse patterns of missing values in the dataset. There were 25% of incomplete data on individual cases in the dataset. After the patterns of missing values were analysed, the same method was utilised in generating

possible values for the missing values (138). Thus, creating several "complete" sets of data and a pooled output which estimates the results of the original dataset if it had no missing values (138). The pooled results are generally more accurate compared to results provided by single imputation methods (138). As such, a default of five imputation methods were used. A pooled output of the five imputations was used to obtain the outcome scores at baseline (Day 0) to Day 28.

Using the pooled output, change in the mean scores of the VAS and NRS were calculated by groups at Days 4 and 14 whilst change in weight and mean scores of the KCCQ (all domains) were calculated at Day 1-4, 7, 14 and 28. When comparing the scores over time in the overall sample and within groups; and between baseline and each follow-up point, an independent sample t-test was used. All analyses were two tailed and a *p-value* of <0.05 was considered statistically significant. To ensure an accurate picture of the effect of our two treatments, the analysis of covariance was also performed on the primary endpoint (level of thirst at Day 4) to "statistically control" for any confounding variable (covariate) in this study. This method is often used to determine whether there are any significant differences between the means of two or more independent groups that could potentially negatively affect the results (139). Similarly, a *p-value* of <0.05 was considered significant.

In spite of the use of intention to treat analysis, it is possible that bias estimates of treatment effects can still occur. To aid in the interpretation of our study results and evaluate the effect of using intention to treat analysis, a sensitivity analysis was recommended to compare findings based on the intention to treat against those who completed the primary endpoint ('completers') (140). This is to prevent misleading conclusions and inappropriate recommendations (140). As such, a sensitivity analysis was

performed on the 'completers' without imputation of missing data, as a comparison to the intention to treat primary analysis.

5.17.3 Repeated measures

To demonstrate that the results for the primary endpoint are consistent throughout the analyses, two-way repeated measures analysis of variance was also performed. This statistical method compares the mean differences between groups (intervention or control) divided by two independent variables i.e. 'type of treatment' [chewing gum or no chewing gum] and 'at various 'days' (Day 1-4, 7, 14 and 28) (141). Its primary purpose is to determine if there is an interaction between these two factors on the dependent variable (VAS and NRS scores) (141).

5.18 ETHICAL ISSUES

The study was conducted according to the National Health and Medical Research Council Guidelines for the ethical conduct of clinical research (142) and adhered to the principals of Good Clinical Practice for conducting clinical trials (143). Ethical approval was obtained from the University of Technology Sydney and St. Vincent's Hospital, Sydney. Copies of relevant approval letters can be found in the Appendices *(refer to* Appendix 3*)*. The RELIEVE-CHF study is registered on the Australian New Zealand Clinical Trial Registry (ACTRN12614000943640).

5.18.1 Data management

Data collected as part of the RELIEVE-CHF study was identified by a unique record number. All data collected in this study was filed and stored in a locked cabinet at St. Vincent's Hospital and will be stored for a period of fifteen years in accordance with national guidelines (NHMRC) (142). Data will be destroyed by means of shredding at the end of the

fifteen-year period. Only authorised study personnel have access to the study database which is password protected and the stored study files stored data. Data collected in this study will only be used for this current study. Only de-identified, aggregated data will be published. Participant's identity will be concealed to protect their confidentiality in the case of disseminating results in refereed scientific journals, professional forums and conferences.

5.19 CONCLUSION

This chapter has detailed the methods of this study. RELIEVE-CHF is a novel approach to thirst management in CHF. Thirst is one of the main reasons for non-compliance to fluid restricted therapy. Low compliance to fluid restriction may often result in frequent re-hospitalisations and life threatening complications. Highlighting the need to explore innovative ways to manage people with CHF suffering from thirst in community settings. If the use of chewing gum is evaluated as successful in relieving thirst, it can be easily implemented into the community based management of CHF. Chewing gum is a simple management strategy; one that is low cost, easily accessible and can accommodate for those with dentures (non- stick gums). The next chapter will present the results of this study.

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CHAPTER VI- RESULT OF A SINGLE BLIND, RANDOMISED PILOT STUDY OF CHEWING GUM

6.1 INTRODUCTION

RELIEVE- CHF is a randomised pilot study of chewing gum to relieve thirst in people with chronic heart failure. This trial sought to investigate the effectiveness of chewing gum in relieving thirst. Chapter 5 presented the study design and methodology of this trial. Both the intervention and control group were assessed at baseline, at Days 1-4, 7, 14 and 28 follow-up.

As described in the previous chapter, data were analysed using intention to treat analysis. In this chapter, the recruitment of participants through each stage of the trial is presented first. This is followed by the baseline demographic and clinical characteristics of all participants to establish comparability between study groups. Outcome measures are all presented comparing the changes over time and between groups.

6.2 PARTICIPANTS

Between November 2014 and September 2015, 366 individuals were screened for eligibility, and 107 were identified as eligible to participate in the trial. Of the 295 who were excluded, 249 did not meet the inclusion criteria after reviewing their medication chart. Thirty-six refused to participate and 10 were participating in other studies at time of recruitment. Therefore, a total of 71 participants were enrolled in the trial (Figure 6.1). After providing written informed consent, each individual completed a thirst questionnaire which measured

the presence and intensity of thirst using a numeric rating scale and the Kansas City Cardiomyopathy Questionnaire which measured health-related quality of life (*refer to* Appendix 8). In addition, participants' general demographics, previous medical history, clinical status and existing physical measurements were obtained from their records (*refer to* Appendix 8). A total of 35 participants were randomised into the 'control group' (no chewing gum) and the other 36 participants in the 'intervention group' (chewing gum).

Nine participants (3 in the intervention group and 6 in the control group) were lost to follow-up. There were 5 participants (2 in the intervention group and 3 in the control group) who withdrew from the study after randomisation due to personal reasons and dislike of the intervention. However, using intention to treat principles their results were imputed using multiple imputation. Two participants died during the study period. One participant received an urgent heart transplant and another had a ventricular assist device implanted and therefore were unable to complete the study.

6.2.1 Reasons for refusing participation

The recruitment rate in this study was 66% (71/107). Reasons for refusing participation in RELIEVE- CHF included personal circumstances relating to health, dislike of and attitude towards chewing gum. Some patients reported not liking chewing gum because it causes hunger, bloating and dry mouth. Reasons for refusing participation in the elderly involves chewing gum sticking to their dentures and lack of social acceptance of chewing gum in public.

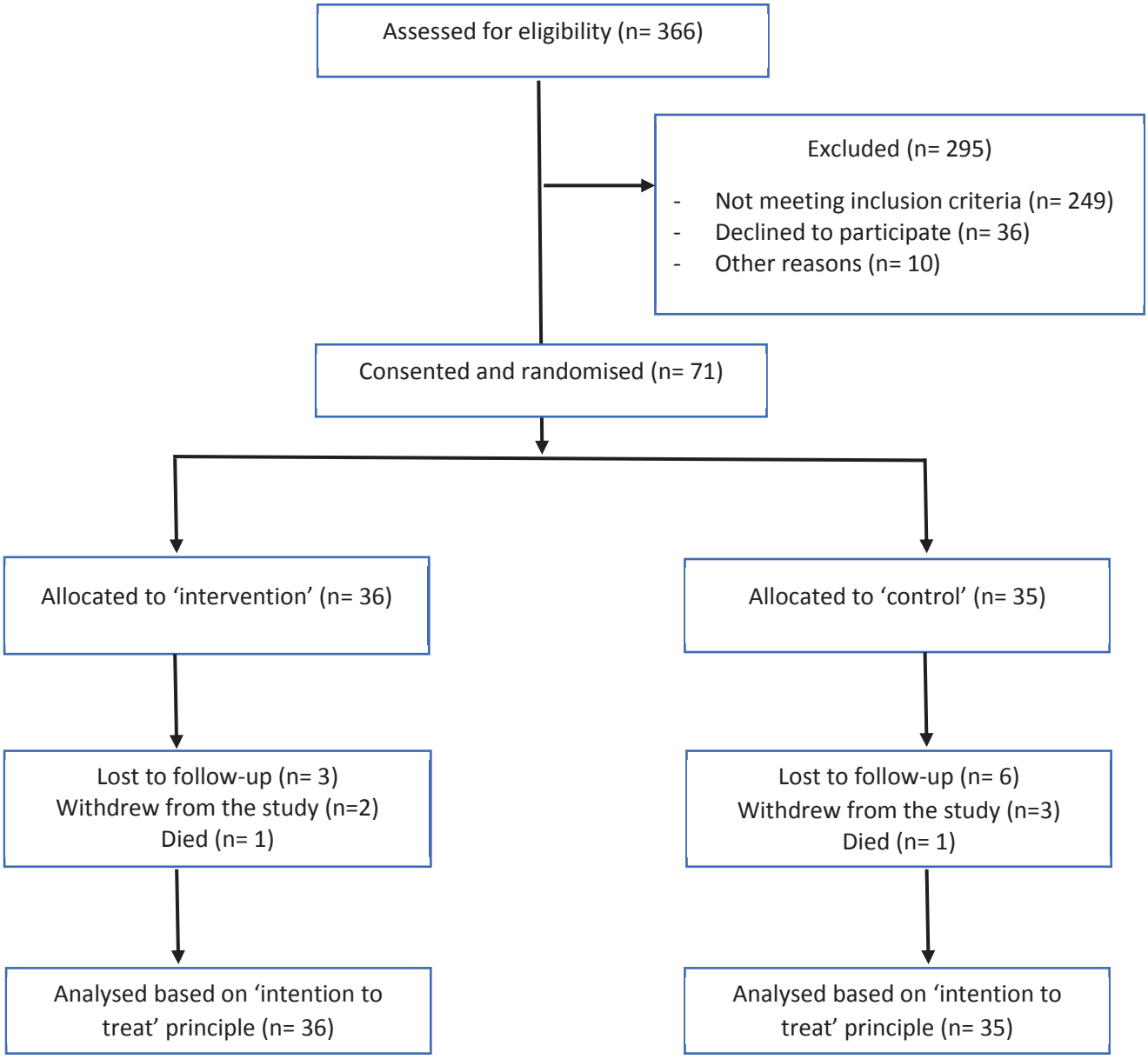

Figure 6.1 Consort flow diagram of RELIEVE-CHF.

6.3 BASELINE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF OVERALL STUDY COHORT

Table 6.1 presents the baseline demographic and clinical characteristics of the 71 participants who were enrolled into the study by the end of September 2015. All data gathered from participants were included for analysis. The mean age of the overall cohort (n= 71) was 53.5 ± 13.8 years, ranging from 19 to 84 years. The majority of the participants were male (n= 45, 63%). The majority of the patients were NYHA class I/II (52%). The mean ejection fraction was 33% ± 15%. Thirty-five participants with a mean age of 53.5 ± 15.1 years were randomised to the 'control group' (no chewing gum). In contrast, 36 participants with the mean age of 53.5 ± 12.7 years were randomised to the 'intervention group' (chewing gum). The *p-value* shows no significant difference in baseline and clinical characteristics between the two groups, except for the body mass index, BMI (28±6 vs. 26±4; *p= 0.028*. All values are reported as mean and standard deviation, unless otherwise stated.

Table 6.1 Baseline demographic and clinical characteristics of participants.

Characteristics	Total (n= 71)	Intervention group (n=36)	Control group (n= 35)	*p*-value
Age, mean (SD) years	53.5 (13.8)	53.5 (12.7)	53.5 (15.1)	0.899
Sex (Male/Female) %	(63%/37%)	(61%/39%)	(66%/34%)	0.687
Weight, mean (SD)	82 (18)	87 (20)	77 (14)	0.300
Body Mass Index, mean (SD)	27 (5)	28 (6)	26 (4)	0.028*
Ejection fraction, mean (SD)	33 (15)	37 (17)	29 (12)	
Systolic pressure, mean (SD) (mm/Hg)	134 (20)	117 (22)	111 (17)	0.299
Diastolic pressure, mean (SD) (mm/Hg)	68 (10)	70 (11)	66 (8)	0.099
NYHA class %				1.000
Class I/II	52 (74%)	27 (75%)	25 (71%)	
Class III/IV	18 (26%)	9 (25%)	9 (26%)	
Length of stay (LoS), days	15 (15)	17 (21)	13 (8)	0.556
Admission status %				0.778
Inpatient	20%	19%	23%	
Outpatient	80%	81%	77%	
Past admission history, mean (SD)				
Emergency	0.6 (1.1)	0.4 (0.8)	0.8 (1.4)	
Elective	0.2 (0.5)	0.3 (0.6)	0.1 (0.3)	
All previous hospitalisations	0.7 (1.2)	0.5 (0.8)	0.8 (1.5)	
Comorbidities, n (%)				
Hypertension	14 (20%)	9 (25%)	5 (14%)	0.371
Myocardial infarction	13 (18%)	5 (14%)	8 (23%)	0.540
Diabetes Mellitus	22 (31%)	11 (31%)	11 (31%)	1.000
Coronary artery disease	15 (21%)	6 (17%)	9 (26%)	0.561
Lung Disease	10 (14%)	3 (8%)	7 (20%)	0.306
Stroke/Mini stroke	9 (13%)	4 (11%)	5 (14%)	1.000
Charlson Index, mean (SD)	2.0 (1.5)	2.1 (1.6)	2.0 (1.4)	0.715
AKPS, mean (SD)	8.3 (1.2)	8.2 (1.0)	8.4 (1.3)	0.379
Prescribed medications %				
ACE Inhibitor	25 (35%)	10 (29%)	15 (43%)	0.314
ARBs	9 (13%)	7 (19%)	2 (9%)	0.305
Beta- blockers	46 (65%)	23 (64%)	23 (66%)	1.000
Diuretic dose %				0.078
Low diuretic dose (<40mg/day)	3 (5%)	0 (0%)	3 (9%)	
High diuretic dose (≥40mg/day)	61 (95%)	32 (89%)	29 (91%)	

Fluid restriction %	60 (84%)	32 (89%)	28 (80%)	0.309
Sodium, mean (SD)	139 (3)	139 (3)	139 (4)	0.429
Potassium, mean (SD)	4.3 (0.5)	4.3 (0.4)	4.3 (0.5)	0.948
Plasma urea (SD)	9.9 (4.5)	9.4 (4.5)	9.1 (4.5)	0.423
Creatinine, mean (SD)	119 (45)	114 (36)	124 (53)	0.492
eGFR, mean (SD)	59 (19)	61(20)	57 (19)	0.621

* statistically significant; NYHA, New York Heart Association; AKPS, Australia- modified Karnofsky Performance Scale; ACE, Angiotensin Converting Enzyme; ARBs, Angiotensin Receptor Blockers; SD, Standard deviation

6.3.1 Medication use in participants

Figure 6.2 shows the baseline medication used in the intervention and control group. Beta blockers were the most commonly used medication in both groups, followed by anticoagulant, ACEIs/ARBs and other vasodilators. As part of the inclusion criteria, all participants were on oral loop diuretics. There were no statistically significant difference between the intervention and control group in all the medications.

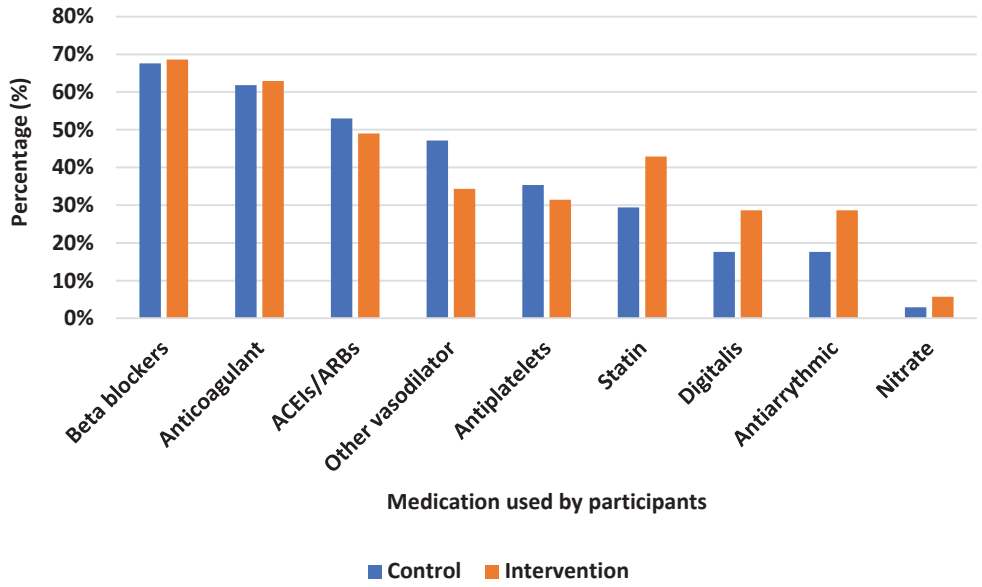

Figure 6.2 Baseline medication use.

6.4 BASELINE OUTCOME MEASURES

Table 6.2 presents the baseline HRQoL and thirst measurements of the overall study participants. Health related quality of life was measured by the Kansas City Cardiomyopathy

Questionnaire (KCCQ). The mean overall summary and clinical summary score of the KCCQ among this cohort was 52.8 ± 22.7 and 57.8 ± 23.2, respectively.

The level of thirst was measured by the Visual Analogue Scale (VAS) and the Numeric Rating Scale (NRS). The mean VAS score of all participants was 43.9 ± 19.8. Participants scored 4.7 ± 1.8 in the Numeric Rating Scale. The majority of study participants were mildly thirsty (48%). The level of thirst between the intervention group and the control group were not statistically different (*p*= 0.341).

Table 6.2 Baseline outcome measures (n=71).

Outcome measures	Scores at Day 0
Visual Analogue Scale	43.9 ± 19.8
Numeric Rating Scale	
How is your thirst now?	4.2 ± 2.1
How has your thirst been in the last 24 hours?	4.7 ± 1.8
What is the worst your thirst has been in the last 24 hours?	
▪ None	4 (5.7%)
▪ Mild	29 (41%)
▪ Moderate	30 (43%)
▪ Severe	7 (10%)
Kansas City Cardiomyopathy Questionnaire	
Physical limitation	53.6 ± 25
Symptom stability	49.3 ± 27.6
Symptom frequency	58.2 ± 24.3
Symptom burden	66.1 ± 28.4
Total symptom	62.1 ± 25.4
Self-efficacy	83 ± 17.7
Quality of life	44 ± 26
Social limitations	52 ± 34
Overall summary score	52.8 ± 22.7
Clinical summary score	57.8 ± 23.2

6.5 OUTCOME MEASURES

6.5.1 Primary endpoint: Change in the level of thirst at Day 4

Visual Analogue Scale

Figure 6.3 demonstrates the change in the mean VAS scores of participant's in the intervention vs. the control group from Day 0 to Day 4. The VAS scores at Days 4 of those in the intervention group significantly decreased by 11.0 ± 14.6 mm. In comparison participant's scores in the control group increased by 0.5 ± 16.0 mm. This was a statistically significant difference between the intervention and control group (*p= 0.04).* Based on the analysis of covariance performed, there was no statistically significant differences between the groups when adjusted for the BMI (*p= 0.165)*.

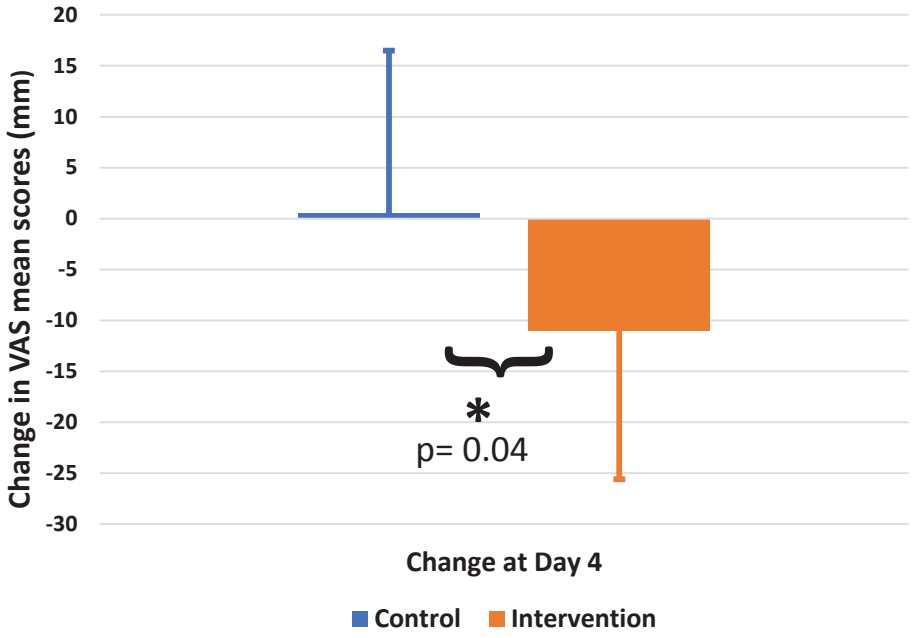

Figure 6.3 Change in the mean VAS scores between the control and intervention group from Day 0 to Day 4.

Numeric Rating Scale

a. How is your thirst now?

Figure 6.4 presents the change in the mean NRS: How is your thirst now scores of the intervention vs. the control group from Day 0 to Day 4. The NRS scores at Day 4 of the intervention group significantly decreased by 0.8 ± 1.8 mm. In contrast, participant's scores in the control group also increased by 0.3 ± 2.0 mm. This was a statistically significant difference between the intervention and control group (*p= 0.0019).* There was no statistically significant differences between the groups when adjusted for the BMI (*p= 0.165)*.

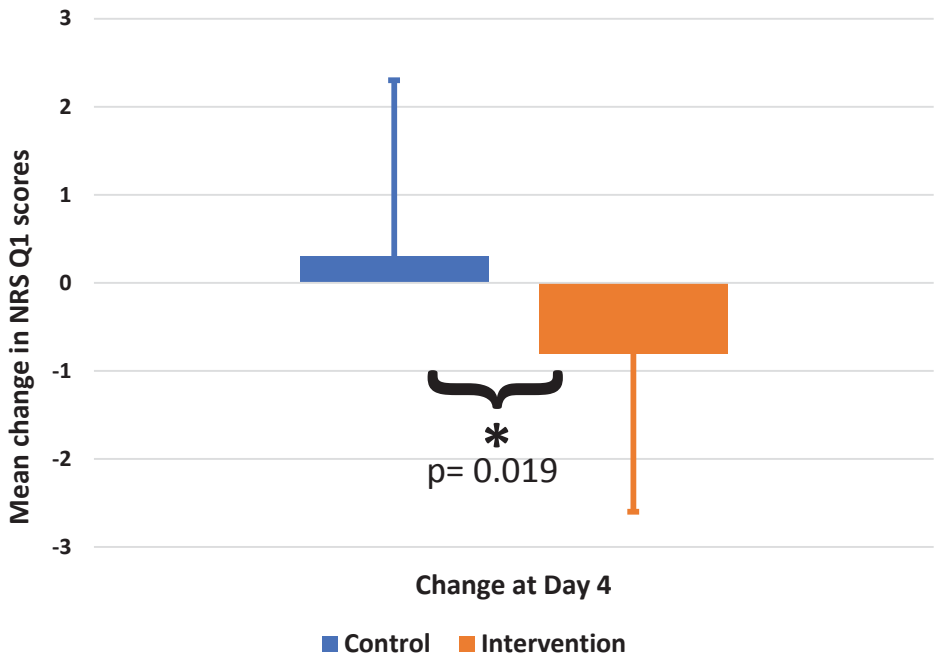

Figure 6.4 Change in the mean NRS Q1: How is your thirst now scores between the control and intervention group from Day 0 to Day 4.

b. How has your thirst been in the last 24 hours?

Figure 6.5 also presents the change in the mean NRS: How has your thirst been in the last 24 hours scores of the intervention vs. the control group from Day 0 to Day 4. The NRS scores at Day 4 of the intervention group also decreased by 0.6 ± 1.4 mm. Similarly, participant's

scores in the control group also decreased by 0.1 ± 1.2 mm. However, there was no statistically significant difference between the two groups. *T*he analysis of covariance performed showed no statistically significant differences between the groups when adjusted for the BMI (*p= 0.165)*.

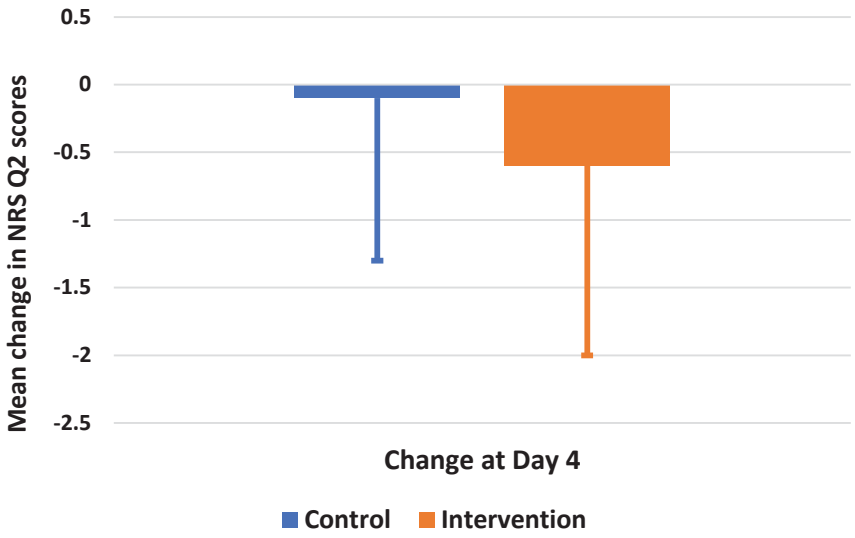

Figure 6.5 Change in the mean NRS Q2: How has your thirst been in the last 24 hours scores between the control and intervention group from Day 0 to Day 4.

6.5.2 Secondary endpoint: Change in the level of thirst at Day 14

Visual Analogue Scale

Figure 6.6 demonstrates the change in the mean VAS scores of participants in the intervention vs. the control group from Day 0 to Day 14. The VAS scores at Day 14 of those in the intervention group significantly decreased by 13.5 ± 15.2 mm. In comparison participant's scores in the control group also decreased by 2.0 ± 20.3 mm. This was a statistically significant difference between the intervention and control group (*p= 0.02).*

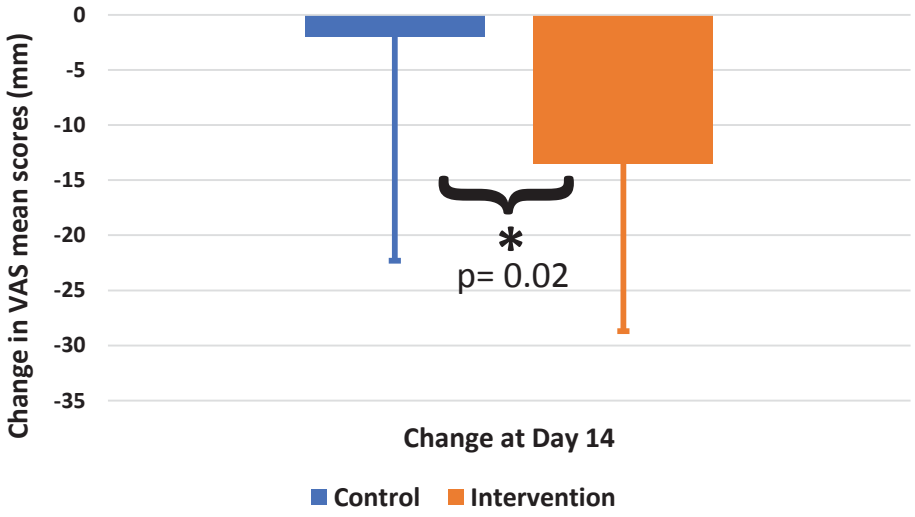

Figure 6.6 Change in the mean VAS scores between the control and intervention group from Day 0 to Day 14.

Numeric Rating Scale

a. How is your thirst now?

Figure 6.7 presents the change in the mean NRS: How is your thirst now scores of the intervention vs. the control group from Day 0 to Day 14. The NRS Q1 scores at Day 14 of the intervention group significantly decreased by 0.7 ± 1.5 mm. In contrast, participant's scores in the control group also increased by 0.2 ± 1.8 mm. This was a statistically significant difference between the intervention and control group (*p= 0.021).*

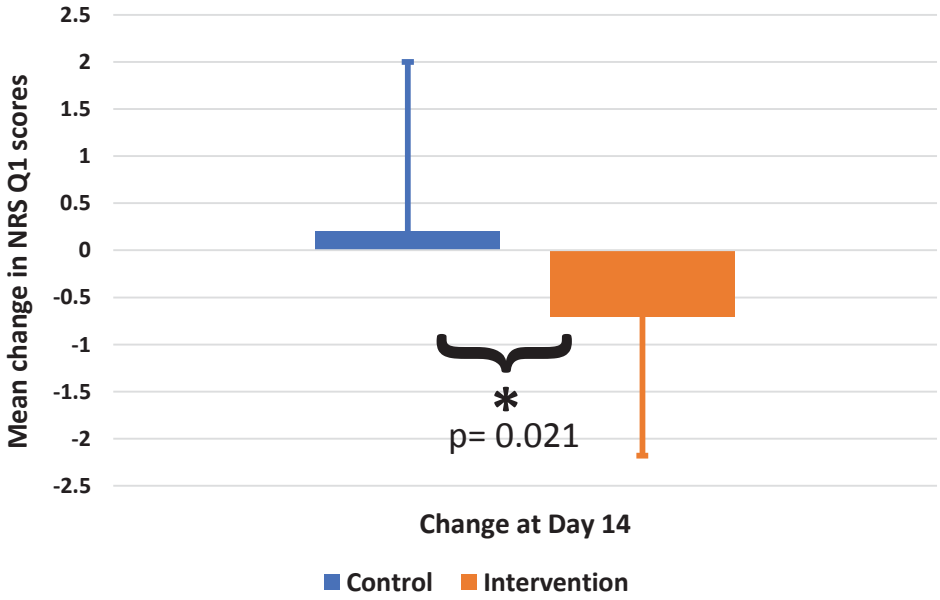

Figure 6.7 Change in the mean NRS Q1: How is your thirst now scores between the control and intervention group from Day 0 to Day 14.

b. How has your thirst been in the last 24 hours?

Figure 6.8 also presents the change in the mean NRS: How has your thirst been in the last 24 hours scores of the intervention vs. the control group from Day 0 to Day 14. The NRS Q2 scores at Day 14 of the intervention group also decreased by 0.9 ± 1.4 mm. Similarly, participant's scores in the control group also decreased by 0.5 ± 1.2 mm. However, there was no statistically significant difference between the two groups.

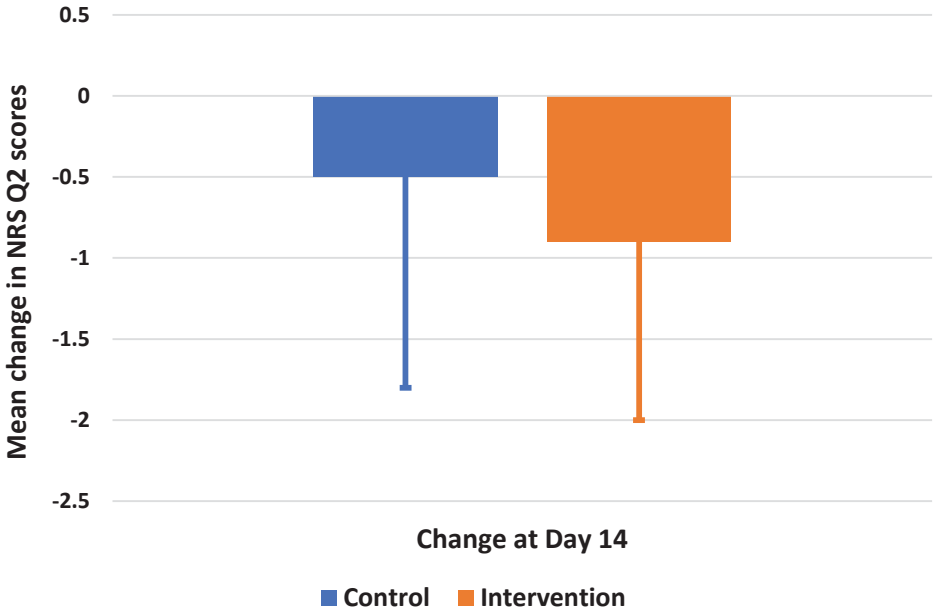

Figure 6.8 Change in the mean NRS Q2: How has your thirst been in the last 24 hours scores between the control and intervention group from Day 0 to Day 14.

6.5.3 Secondary endpoint: Weight stability

Figure 6.9 presents the change in weight of the intervention group vs. control group from baseline (Day 0) to Day 28. Overall the study participants showed fluctuation in the mean weight from baseline to Day 28 follow-up for both the intervention (77.3kg to 77.1kg) and control group (86.7kg to 87.2kg). These changes were not statistically significant.

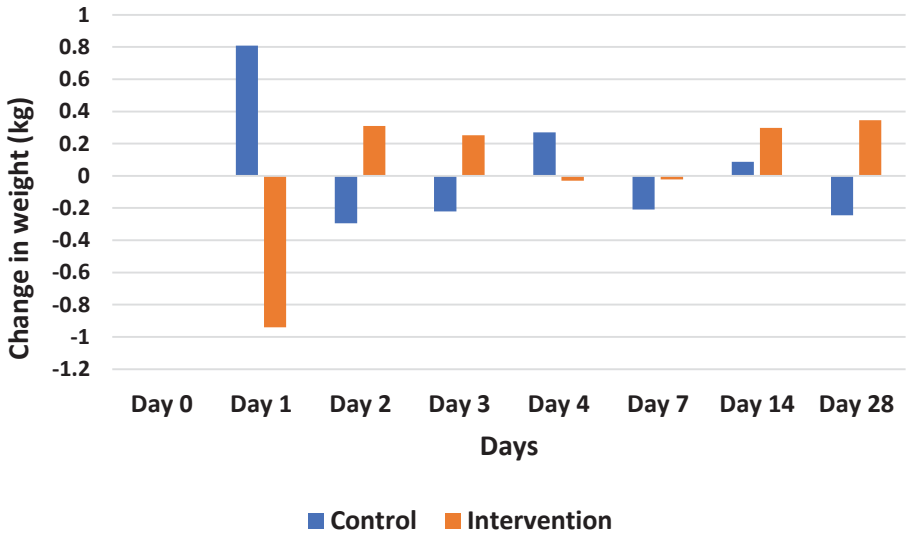

Figure 6.9 Change in weight between the intervention and control group over the study period (Day 0- 28).

6.5.4 Secondary endpoints: Health-related quality of life

In KCCQ, an overall summary score is derived from the physical function, symptom (frequency and severity), and social function and quality of life domains. Scores are transformed to a range of 0-100, a higher score reflects better health status. In contrast the clinical summary score is derived from the physical limitation and total number of symptoms domains.

Figure 6.10 demonstrates the mean KCCQ overall summary scores of the intervention group against the control group from baseline (Day 0) to follow-up (Day 28). There was no statistically significant difference in the mean change of KCCQ (8 domains, overall and clinical summary) scores between the intervention and control group at baseline (Day 0) and Day 28.

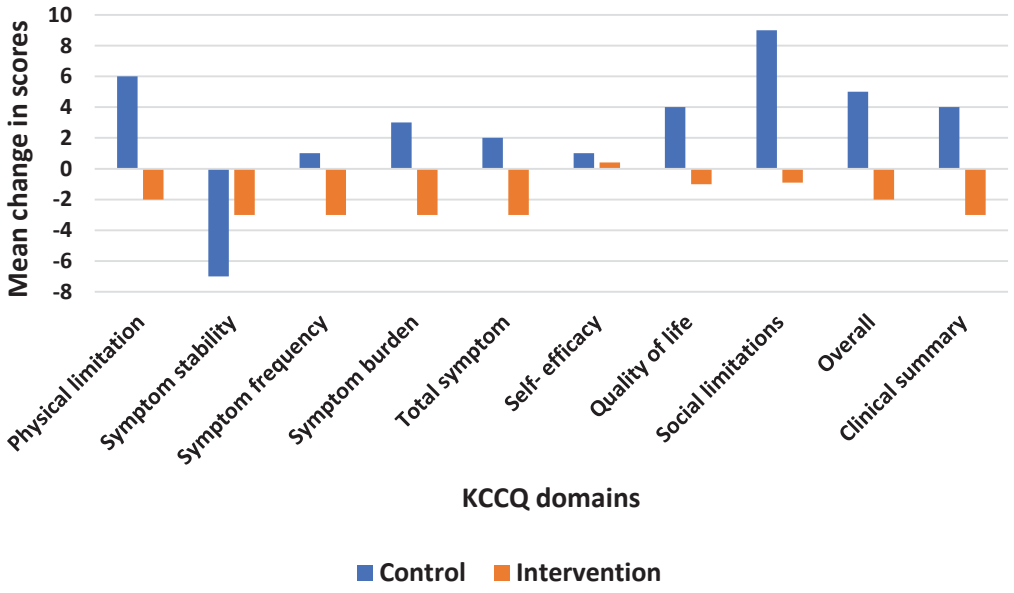

Figure 6.10 Change in the mean KCCQ scores (8 domains, overall and clinical summary) between groups from baseline (Day 0) to Day 28.

6.6 SENSITIVITY ANALYSIS OF THE PRIMARY ENDPOINT

6.6.1 Intention to treat vs. completers of primary outcome at Day 4

Table 6.3 presents the baseline demographic and clinical characteristics of 54 participants who completed the primary outcome; 'completers' at Day 4. The mean age of this cohort (n= 54) was 53.2 ± 13.6 years which is similar to the overall ('intention to treat') cohort of 71 participants. The majority of the participants were also male (61%). Similarly the majority of the patients were NYHA class I/II (80%). The mean ejection fraction was also 33% ± 15. Twenty-five participants were allocated to the 'control group' (no chewing gum). In contrast, 29 participants were allocated to the 'intervention group' (chewing gum). The *p-value* shows that there was no significant difference in baseline and clinical characteristics between the two groups, except for the ejection fraction *(p= 0.019)*. This suggests that the demographics and clinical characteristics of the 'completers' are similar to the overall ('intention to treat') study cohort.

Table 6.3 Baseline demographic and clinical characteristics of participants' who completed the primary outcome at Day 4.

Characteristics	Completers (n=54)	Intervention (n=29/54)	Control (n=25/54)	*p-value*
Age, mean (SD) years	53.2 (13.6)	54.0 (13.5)	52.4 (14.0)	0.521
Sex (Male/Female) %	(61/39)	(59/41)	(64/36)	0.432
Body Mass Index, mean (SD)	27 (5)	28 (6)	26 (4)	0.426
Ejection fraction, mean (SD)	33 (15)	37 (17)	28 (11)	0.019*
Charlson Index, mean (SD)	1.8 (1.3)	2.1 (1.6)	1.5 (1.0)	0.047
NYHA class %				0.902
Class I/II	43 (80%)	23 (79%)	20 (80%)	
Class III/IV	11 (20%)	6 (21%)	5 (20%)	
Prescribed medications %				
ACE/ARBs	30 (56%)	14 (50%)	16 (67%)	0.073
Beta- blockers	39 (72%)	21 (75%)	18 (75%)	1.000

*statistically significant, SD; standard deviation, NYHA; New York Heart Association, ACE; Angiotensin converting enzyme, ARBs; Angiotensin receptor blockers

Visual Analogue Scale

Figure 6.11 demonstrates the change in the mean VAS scores of the 'intention to treat' in the intervention vs. the control group and the mean change in VAS scores of the 'completers' from Day 0 to Day 4. The VAS scores at Day 4 of those in the intervention group significantly decreased by -11.0 ± 14.6 mm for the 'completers' and 'intention to treat' cohort. In comparison scores of those in the control group gained a slight increase of 0.5 ± 17.0 mm and 0.7 ± 16.0 mm, respectively. These were statistically significant difference between the intervention and control group (*p= 0.007* and *0.008)* in both cohorts ('intention to treat' vs. 'completers'). Based on the analysis of covariance performed, there was no statistically significant differences between the groups when adjusted for the ejection fraction (*p= 0.175)*.

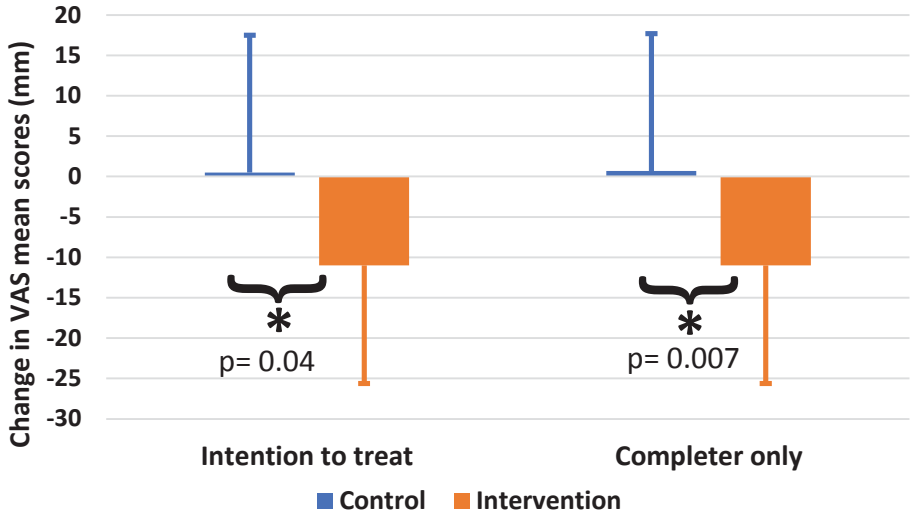

Figure 6.11 Change in the mean VAS scores of participants of the overall ('intention to treat') vs. the 'completers' of Day 4 (n=54).

Numeric Rating Scale

a. How is your thirst now?

Figure 6.12 presents the change in the mean NRS Q1: How is your thirst now scores of the 'intention to treat' for the intervention vs. those in the control group and the mean change in NRS Q1 scores of the 'completers' from Day 0 to Day 4. The NRS Q1 scores at Day 4 of the intervention group significantly decreased by 0.8 ± 1.8 mm for both the 'intention to treat' and 'completers' cohort. In contrast, NRS scores in the control group increased by 0.3 ± 2.1 mm and 0.4 ± 2.0 mm in both cohorts, respectively. These were statistically significant difference between the intervention and control group (*p= 0.018 and 0.027)* in both cohorts ('intention to treat' vs. completers'). There was no statistically significant differences between the groups when adjusted for the ejection fraction (*p= 0.175)*.

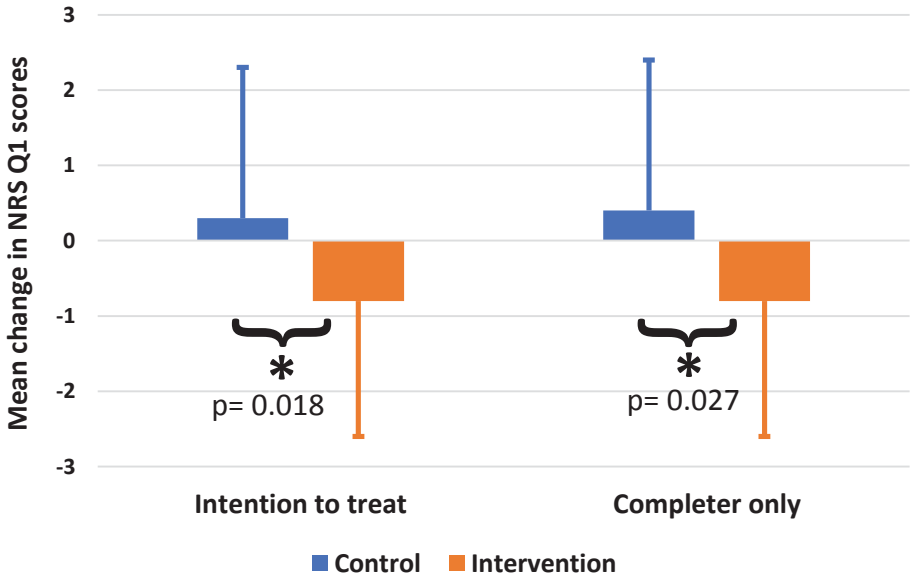

Figure 6.12 Change in the mean NRS Q1: How is your thirst now scores of participants of the overall ('intention to treat') vs. the 'completers' of Day 4 (n=54).

b. How has your thirst been in the last 24 hours?

Figure 6.13 also presents the change in the mean NRS Q2: How has your thirst been in the last 24 hours scores of the 'intention to treat' in the intervention vs. the control group and the mean change in NRS scores of the 'completers' from Day 0 to Day 4. The NRS scores at Day 4 of the intervention group in the 'intention to treat' decreased by 0.6 ± 1.6 mm and the 'completers' by 0.8 ± 1.4 mm, respectively. Similarly, participant's scores in the control group also decreased by 0.1 ± 1.0 mm and 0.04 ± 1.2 mm in both cohorts ('intention to treat' vs. 'completers'). These were not statistically significant difference between the two groups at Day 4. The analysis of covariance performed showed no statistically significant differences between the groups when adjusted for the ejection fraction (*p= 0.175)*.

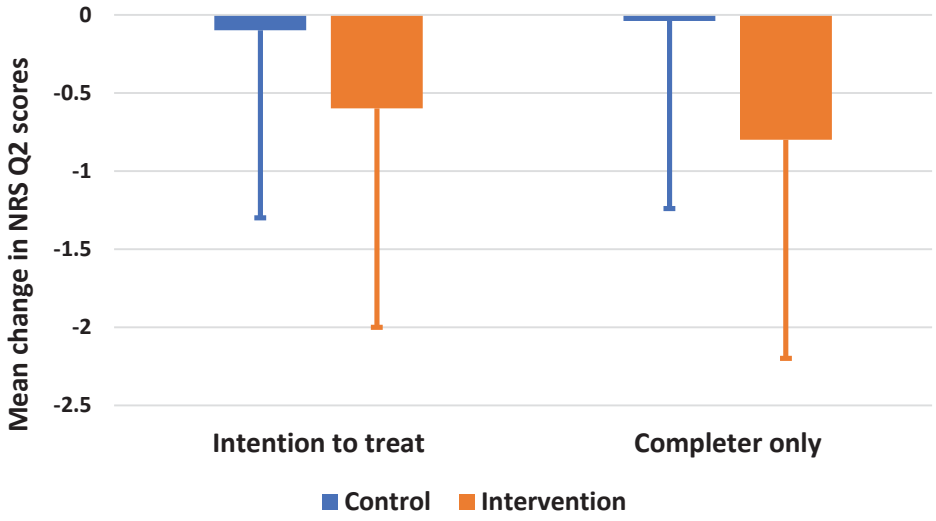

Figure 6.13 Change in the mean NRS Q2: How has thirst been in the last 24 hours scores of participants of the overall ('intention to treat') vs. the 'completers' of Day 4 (n=54).

6.7 REPEATED MEASURES

6.7.1 Primary endpoint

Visual Analogue Scale: level of thirst (short term level of thirst at Days 1-4)

Figure 6.14 demonstrates the mean scores of each group over the 4- day period. There was a statistical significant decrease in the intervention group's mean score from baseline (46.4 ± 17.5) to Day 4 (39.2 ± 18.0) follow- up compared to the control group (*p= 0.04)*.

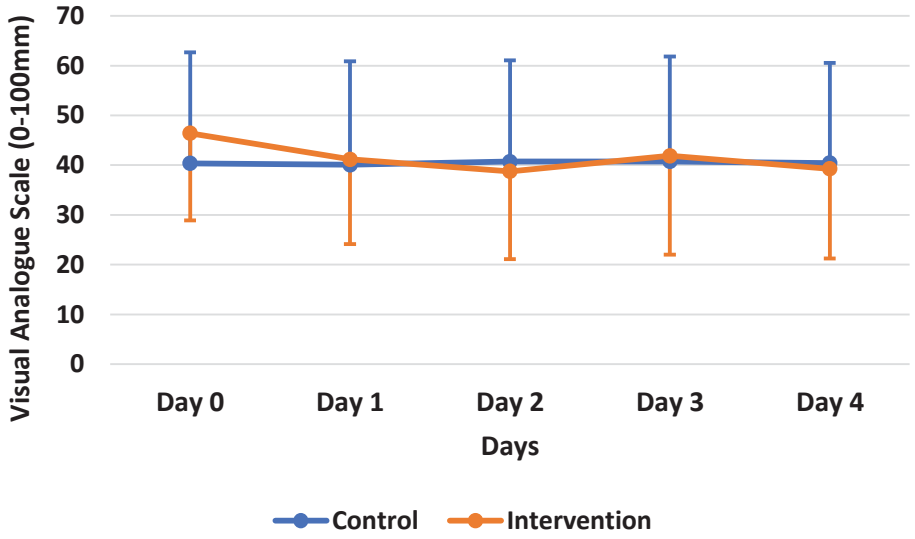

Figure 6.14 Visual Analogue Scale (0-100mm) for Days 0-4 between the control and intervention group.

Numeric rating scale: level of thirst (short term level of thirst at Days 1-4)

a. How is your thirst now?

Figure 6.15 shows the mean scores of each group over the 4- day period in the first question of the NRS. There was a statistical significant decrease in the intervention group's mean score from baseline (4.5 ± 1.9) to Day 4 (3.7 ± 1.8) follow- up compared to the control group (*p= 0.018)*.

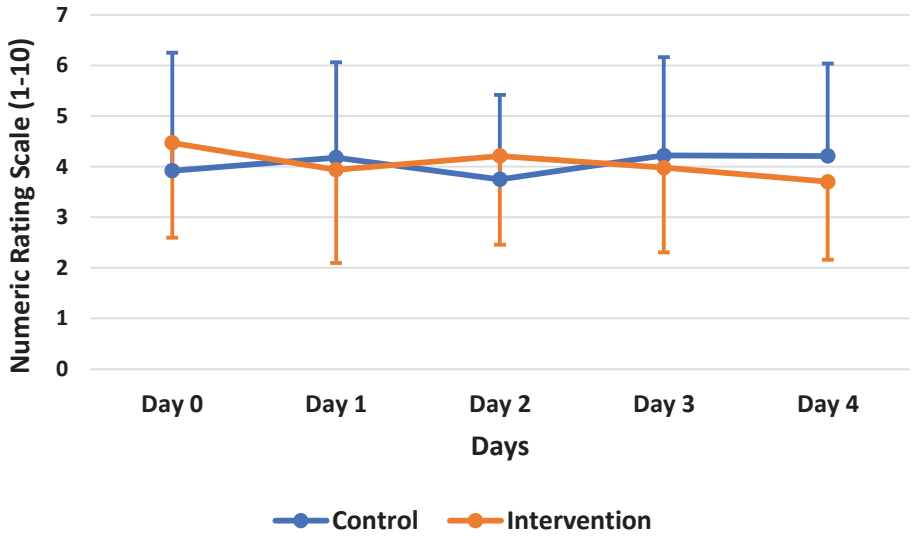

Figure 6.15 Numeric Rating Scale: How is your thirst now? (1; no thirst at all- 10 worst thirst imaginable) for Days 0-4 between the control and intervention group.

b. How has your thirst been in the last 24 hours on average?

Figure 6.16 presents the mean scores of each group over the 4- day period in the second question of the NRS. There was no statistical significant difference in the intervention group's mean score from baseline (4.5 ± 1.9) to Day 4 (3.7 ± 1.8) follow- up compared to the control group (*p= 0.116)*.

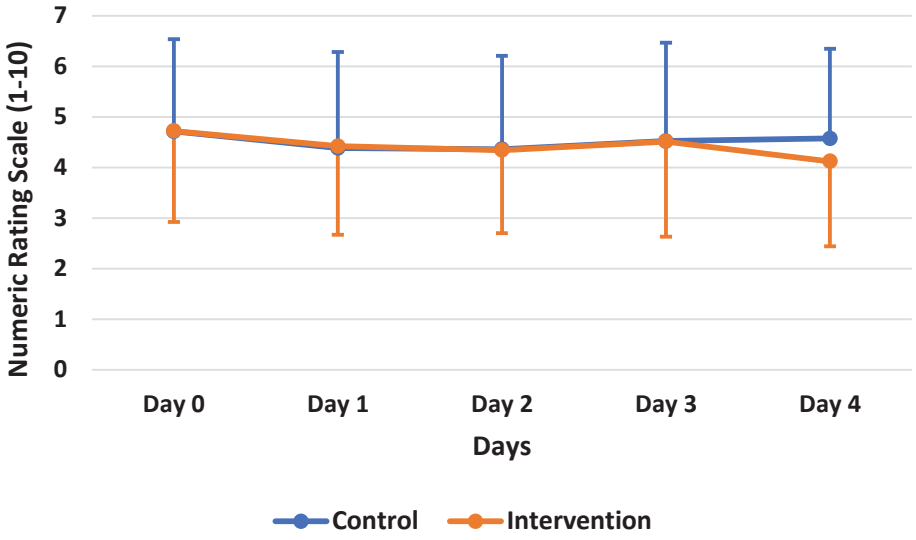

Figure 6.16 Numeric Rating Scale: How has your thirst been in the last 24 hours? (1; no thirst at all- 10; worst thirst imaginable) for Days 0-4 between the control and intervention group.

c. What is the worse your thirst has been in the last 24 hours on average?

Figure 6.17 presents the mean score of the overall study cohort from baseline (Day 0) to Day 1-4 in the Numeric Rating Scale measuring the intensity of thirst in a stacked column graph. Overall the majority of the study participants were moderately thirsty (42.3%) at baseline but improved to mildly thirsty (50.6%) at Day 4 follow-up.

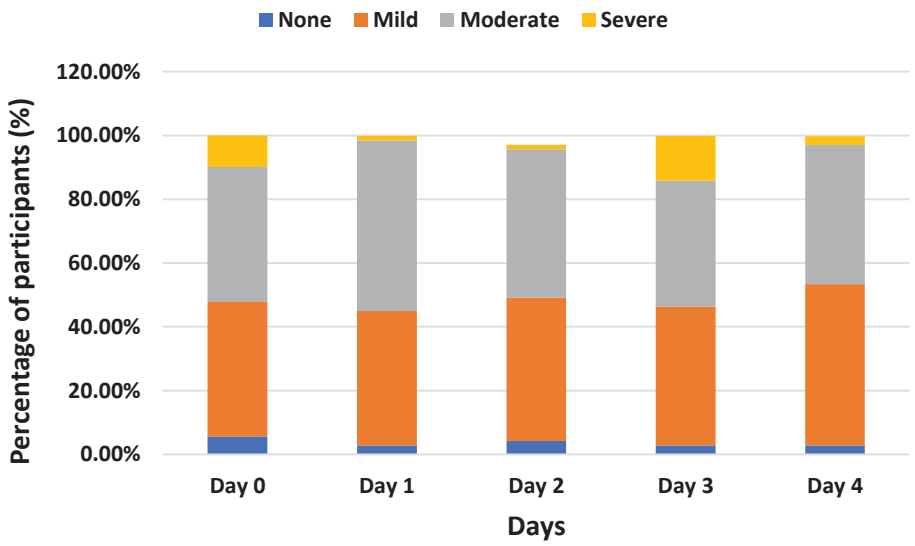

Figure 6.17 Numeric Rating Scale: What is the worst your thirst has been in the last 24 hours? (None, Mild, Moderate or Severe) for Days 0-4.

6.7.2 Secondary outcome measures

Visual Analogue Scale: level of thirst (longer term Days 7, 14 and 28)

Figure 6.18 demonstrates the mean scores of each group over the 28- day period in the VAS. There was statistical significant difference in the intervention group's mean score from baseline (46.4 ± 17.5) to Day 7 (36.0 ± 17.0; *p= 0.001*), Day 14 (38.0 ± 18.5; *p= 0.02*) and Day 28 (37.4 ± 18.2; *p= 0.001*) follow- up compared to the control group.

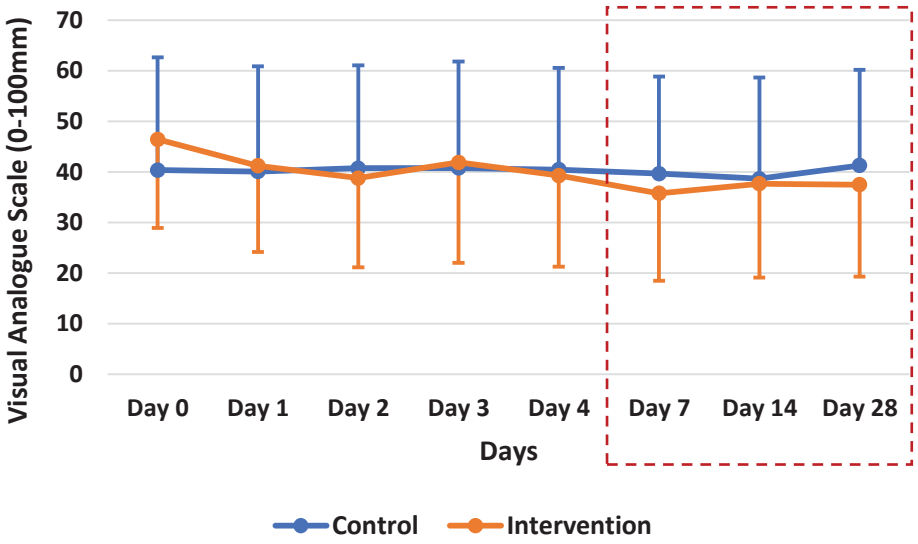

Figure 6.18 Visual Analogue Scale (0-100mm) from Day 0 to Day 28 between the control and intervention group.

Numeric rating scale: level of thirst (longer term Days 7, 14 and 28)

a. How is your thirst now?

Figure 6.19 demonstrates the mean scores of each group over the 28- day period in the NRS: How is your thirst. There was no statistical significant difference in the intervention group's mean score from baseline (4.5 ± 1.9) to Day 7 (3.9 ± 1.5; *p= 0.199*) in comparison to the control group. However, Day 14 (3.8 ± 1.4; *p= 0.021*) and Day 28 (3.7 ± 1.6; *p= 0.08*) follow-up showed statistical significant difference compared to the control group.

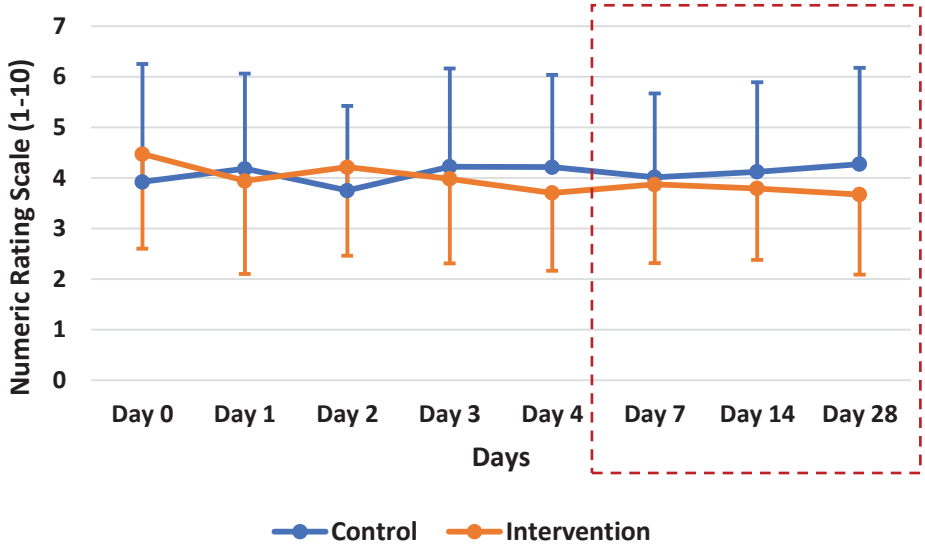

Figure 6.19 Numeric Rating Scale: How is your thirst now? (1; no thirst at all- 10 worst thirst imaginable) for Days 7, 14 and 28.

b. How has your thirst been in the last 24 hours on average?

Figure 6.20 shows the mean scores of each group over the 28- day period in the NRS: How has your thirst been in the last 24 hours. There was no statistically significant difference in the intervention group's mean score from baseline (4.7 ± 1.8) to Day 7 (3.9 ± 1.5; *p= 0.05*) and Day 14 (3.8 ± 1.4; *p= 0.09*) follow- up compared to the control group. However, Day 28 (3.7 ± 1.6; *p= 0.02*) follow-up showed statistical significant difference in comparison to the control group.

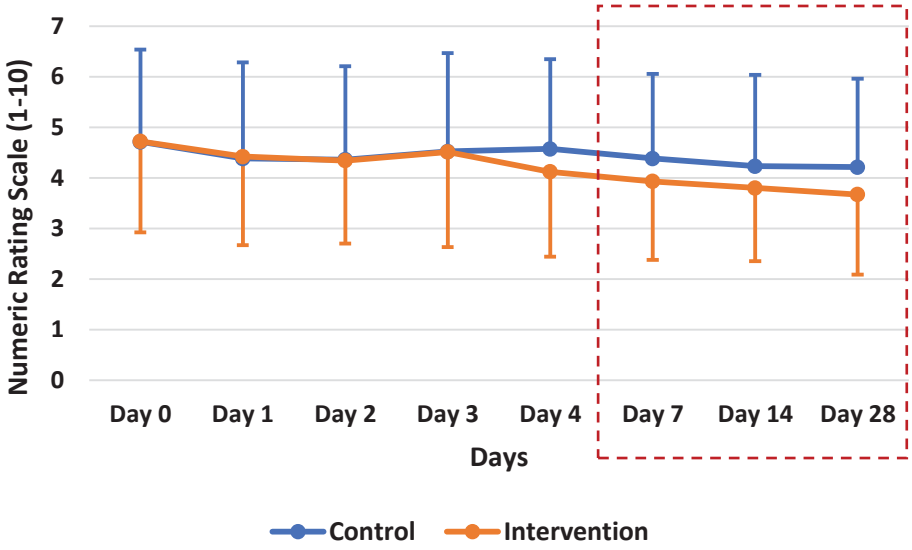

Figure 6.20 Numeric Rating Scale: How has your thirst been in the last 24 hours? (1; no thirst at all-10; worst thirst imaginable) for Days 7, 14 and 28.

c. What is the worst your thirst has been in the last 24 hours on average?

Figure 6.21 presents the mean score of the overall study cohort at Days 7, 14 and 28 in the Numeric Rating Scale. Overall the study participants were mildly thirsty at Days 7 (47.8%), 14 (54.8%) to Day 28 (56.2%) compared to baseline (moderately thirsty; 42.3%).

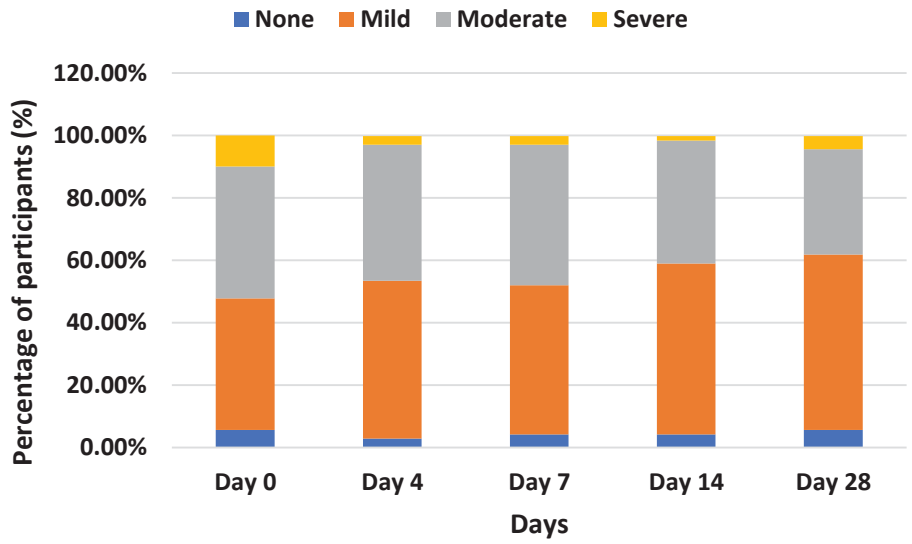

Figure 6.21 Numeric Rating Scale: What is the worst your thirst has been in the last 24 hours? (None, Mild, Moderate or Severe) for Days 7, 14 and 28.

6.8 USEFULNESS OF CHEWING GUM

Figure 6.22 illustrates the study participant's perception of the usefulness of chewing gum in alleviating thirst during the intervention period of 2 weeks. At least 31% of the participants (11/36) found chewing gum useful in relieving thirst while others found no use (9/36; 25%).

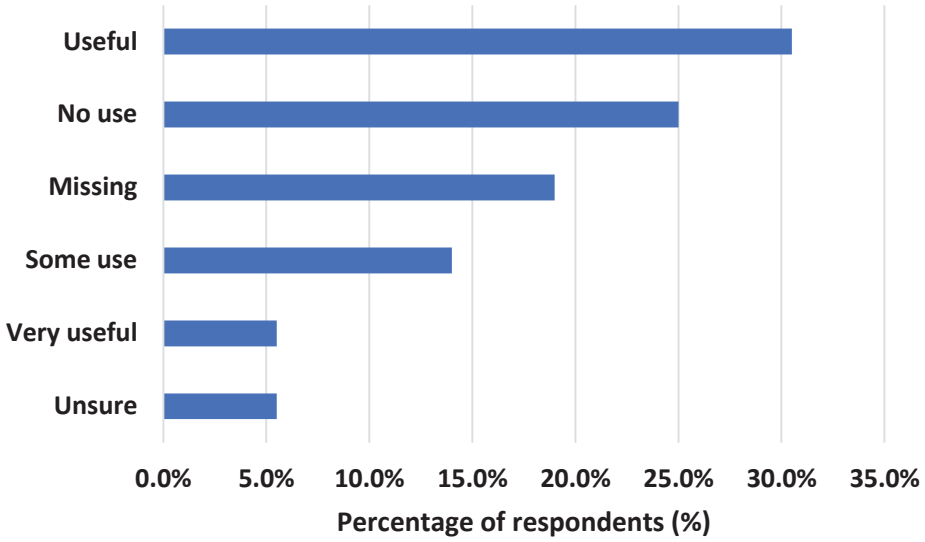

Figure 6.22 Participant's perception of the usefulness of chewing gum in relieving thirst.

6.9 CONTINUED USE OF CHEWING GUM AFTER 2 WEEKS

Figure 6.23 presents the study participant's continued use of chewing gum to help relieve thirst. Fifty-three percent of the participants continued chewing gum (19/36) after the 2-week intervention period while others did not continue using chewing gum (9/36; 25%). Less than a quarter of participants did not complete the question. Reasons for continued use included relief from thirst and the distracting effect it provided from drinking water. On the other hand, some of the reasons for not continuing to use chewing gum were lack of thirst as they were not on fluid restriction, so they could drink water freely and haemodynamic improvements after ventricular assist device implantation.

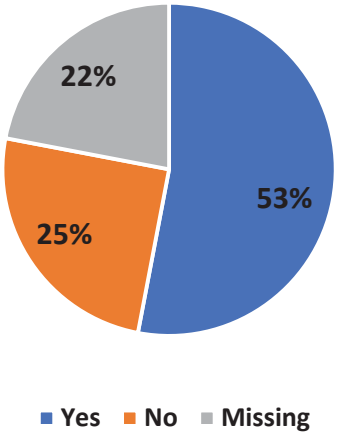

Figure 6.23 Participant's continued use of chewing gum after the 2-week study period.

6.10 REPORTED SYMPTOMS

In this study one participant reported experiencing jaw discomfort while on the chewing gum intervention. This was considered minor and did not require any additional action to be taken.

6.11 ADVERSE EVENT

There were 2 deaths and 10 re-hospitalisations (n=6 from the intervention group and n=4 from the control group) among the 71 participants. None of these were attributed to the RELIEVE-CHF trial. These data were collected for safety monitoring only. The RELIEVE-CHF trial is not powered to detect differences in mortality or hospitalisations.

6.12 CONCLUSION

This chapter has presented the results of the 71 participants in a randomised controlled pilot study with 28-days follow-up. Participants who received chewing gum to relieve thirst (intervention group) were compared to those who did not receive chewing gum (control group). Besides from the significant decrease in the Visual Analogue Scale scores in the intervention group, both groups had no significant change in any of the outcome measures (KCCQ, weight and NRS). The following Chapter will interpret and discuss the results presented in this chapter.

CHAPTER VII- DISCUSSION

7.1 INTRODUCTION

The previous chapter has reported the findings of the RELIEVE-CHF study evaluating the effect of chewing gum on thirst, weight stability and health-related quality of life in CHF patients. The study aims were achieved via a single blind, randomised controlled trial with two parallel groups. Individuals in the intervention group completed a 14- day chewing gum regime and those in the control group continued without chewing gum. All participants were followed up at Days 1-4, 7, 14 and 28. The Visual Analogue Scale, Numeric Rating Scale and weight were assessed at baseline and Day 1-4, 7, 14 and 28. The Kansas City Cardiomyopathy Questionnaire was assessed at baseline and Day 28 follow- up.

In this chapter, the study findings will be discussed in the context of existing literature, specifically addressing the RELIEVE-CHF aims. While this trial did not achieve its target sample size, the study results have elucidated some useful consideration for intervention development. The study strengths, limitations and challenges associated with promoting chewing gum in the management of people with CHF will also be discussed.

7.2 RELIEVE-CHF STUDY

Chapter Two and Three highlighted the lack of awareness of thirst as a symptom of CHF amongst health professionals and the limited approaches to assist in its management. Thirst is a common and burdensome symptom of people living with CHF which can greatly affect

self-care practices such as fluid restriction. Non-compliance to fluid restriction frequently leads to worsening symptoms of CHF, reduced quality of life and hospitalisations (18). Creative and innovative interventions to relieve thirst are critical in eliminating it as a barrier to compliance with fluid restriction. The purpose of this present study was to evaluate a self-administered intervention (chewing gum) in its ability to relieve thirst.

7.3 PARTICIPANT CHARACTERISTICS

The study participants were recruited from one hospital in metropolitan Sydney; St. Vincent's Hospital. Most participants (80%) were recruited from the CHF outpatient clinic. The mean age of all participants was 53.5 years, significantly younger than the average age of 67 years of other CHF intervention studies investigating thirst (20, 21, 96, 97). There was also a high proportion (63%) of male participants compared to female participants in this study. These differences likely reflect the transplant population at St. Vincent's Hospital Outpatient Clinic. The mean BMI of all participants was 27 kg/m^2 ± 5 which is classified as overweight. The mean ejection fraction was 33% ± 15 is slightly lower than the average of other CHF studies (21, 26, 96, 97). Demographic and clinical characteristics between the intervention and control groups showed no significant differences except for BMI (*p=0.028*). Due to a recent study showing correlation between BMI and thirst, BMI was treated as a potential confounder. However, the analysis of covariance performed revealed that BMI did not affect the primary endpoint. Despite the limitations of convenience sampling and small sample size, it is considered that our sample reflects the sociodemographic and clinical characteristics of the broader sample from which they were recruited from. Nonetheless, these limitations must still be considered when interpreting the results.

7.4 RATIONALE FOR CHOICE OF PRIMARY OUTCOME MEASURE

The burden of thirst in patients with CHF have been discussed in detail in Chapter Two. In summary, patients with CHF frequently suffer from thirst due to factors related to CHF and its treatment. Many patients have reported that complying with fluid restriction is often challenging because of preoccupation with thirst (30). Thirst is a strong sensation which is difficult to ignore and when patients are not successful in complying with fluid restriction, they are plagued with feelings of guilt which adversely affects their quality of life (28). Moreover, non-compliance may result in increased fluid retention leading to increased symptoms (86, 96, 97) and consequently, hospitalisation. Hence interventions which relieve thirst are likely to be useful.

As thirst is a subjective sensation, it was measured subjectively through self-reported questionnaires in this study. However, there are objective measurements of thirst such as obtaining patient's blood samples to detect hormones linked with thirst (angiotensin II and vasopressin). The reason thirst was not measured objectively was that these hormone levels are confounded by the neurohormonal pharmacological management in CHF patients and repeated blood tests were felt to be a barrier to study participation. Thirst was measured using both the Visual Analogue Scale (119) and the Numeric Rating Scale (118). Both tools were utilised to measure the intensity of thirst. The level of thirst in the first 4 days was chosen as the primary outcome. The reason for this is purely based on the likelihood that if the intervention (chewing gum) does alleviate thirst, the effect will be seen within the first 4 days.

7.5 IMPACT OF THE RELIEVE- CHF STUDY

The aims of the RELIEVE- CHF study was to assess the impact of chewing gum on the following aspects: 1) level of thirst; 2) weight stability; and 3) health- related quality of life. The goal was to contribute to the improvement in care by raising awareness of thirst and identifying possible approaches to relieve thirst in patients with CHF. Overall, there was a statistically significant change observed in the Visual Analogue Scale and the Numeric Rating Scale from baseline (Day 0) to Day 4 (primary endpoint) in the intervention (chewing gum) group.

7.5.1 Effect of chewing gum on the level of thirst

Fluid restriction is a traditional approach in dealing with electrolyte imbalances such as hyponatraemia, avoidance of CHF symptoms and congestion (95). However, an increase in serum sodium concentration causes severe thirst (144, 145). In clinical practice, patients experience numerous problems e.g. dry mouth, altered sense of taste and impaired dental health connected to fluid restriction. Due to these nuisances, patient compliance is often not optimal. The guilt and agony of non-compliance can cause patients to experience resignation towards fluid restriction. With the recent advancement in supportive care, a range of strategies to relieve thirst have been increasingly investigated in various patient populations (6, 10, 146). However, these results were ambiguous. To date, the only intervention studies performed in CHF patients are those investigating the effect of strict/liberal fluid restriction with conflicting findings (96, 97). Although artificial saliva were comparable with chewing gum in reducing the feelings of thirst in patients undergoing haemodialysis, patients preferred using chewing gum (6). Based on these results, chewing

gum may offer the potential to also address thirst in patients with CHF; undergoing similar fluid imbalance as those on haemodialysis.

This study is the first to investigate the effect of chewing gum as an intervention to alleviate thirst in patients with CHF. Participants' level of thirst at Day 4 was measured as the primary outcome by the Visual Analogue Scale and the Numeric Rating Scale. At baseline, participants in this study showed moderate levels of thirst intensity in the VAS (43.9 ± 19.8 mm) and NRS (n=30; 43%) which is comparable with other CHF studies investigating the effect of fluid restriction on thirst (52 ± 17 mm)(96, 97) and investigating the effect of chewing gum in other patient population (Dialysis Thirst Inventory scores [5; never thirsty-25; very often thirsty] of 16.5 ± 5.1) (6). This is expected as most of the participants enrolled in this study were from the outpatient clinic (80%) and were predominantly NYHA class I/II (n=52; 74%). Patients hospitalised for CHF deterioration and higher NYHA class (III-IV) often have greater thirst intensity compared to those at an outpatient clinic or lower NYHA class (I-II) (45, 78).

Thirst intensity is the strength of thirst and is the dimension of thirst that is most commonly measured in both research and clinical practice (22, 45, 78, 96, 97). It is the sensation that arises as a result of dehydration and is vital for survival (35). The difference in intensity levels among our cohort may be explained by many factors such as cerebral blood flow and sensitivity receptors responding to changes in central blood volume (147, 148) as well as individual perceptions of thirst intensity (18, 117). Previous research shows the perception of symptoms can be influenced by personality, cognitive capacity, culture and impaired symptom recognition (18, 149, 150).

At baseline group comparisons, participants in the intervention group (chewing gum) were thirstier compared to those in the control group (no chewing gum) demonstrated by their VAS (46.4 ± 17.5 mm vs. 40 ± 18.0 mm) and NRS scores (4.5 ± 1.9 vs. 3.9 ± 1.8). This may be due to several factors. Firstly, majority of the participants enrolled in this study were on fluid restriction (60/71; 84.5%) but no significant differences were observed between groups. There is a significant link between fluid restriction and high thirst intensity in research (30, 86, 96, 97). Those on fluid restriction on top of an oral loop diuretic are more likely to feel thirstier (86, 96, 97). Guidelines often recommend fluid restriction in patients with advanced CHF and are in need of relief from symptoms and congestion (46). However, some patients continue to be on fluid restriction, even when they no longer require it. This highlights the importance of evaluating the need for fluid restriction in CHF patients. For CHF patients who truly need a fluid restricted diet, clinicians should consider the patient's ability to succeed in restricting fluid especially when they have increased thirst as this may be dependent on factors such as motivation, habits and support from family.

Secondly, most participants were on high doses (≥ 40 mg/day) of oral loop diuretics (61/71; 95.3%) which can promote a heightened sensation of thirst (78). Diuretics are used to relieve symptoms of fluid retention in patients with CHF. It works by increasing the excretion of body water (46) and might therefore cause dehydration, which is known to cause thirst (37). Serum osmolality is often used to detect dehydration. A recent study has found that those with higher thirst intensity was observed to have increased serum osmolality (301.0 ± 6.0 mOsmol/kg) (78). Although serum osmolality was not measured in this study, participants' plasma urea was collected from their most recent existing blood test results. Plasma urea has been found to be associated with high thirst intensity (78) and has

been described as a marker of dehydration and neurohormonal activation, as it increases in blood when body water is in short supply (37) in patients with CHF. The neurohormonal activation leads to vasoconstriction of arteriole causing a reduction in renal perfusion (37). This action increases water and urea absorption, resulting in an increased concentration of urea (37). Previous research has shown that even mild to moderate elevations of plasma urea can predict hospitalisations, adverse effects of diuretics and mortality (40, 151, 152). However, correlation between plasma urea and high thirst intensity was not observed in our study which again can be explained by the high proportion of participants with NYHA class I/II enrolled from the outpatient clinic.

And lastly, participants in this study were predominantly male and younger which reflects the transplant population at St. Vincent's Hospital Outpatient Clinic. In a previous study, men were found to have higher thirst intensity than females (78). This is consistent with studies on healthy persons demonstrating that men are usually slightly more dehydrated, which can initiate increased thirst (153). Younger age was also associated with higher thirst intensity, which concurs with studies showing diminished thirst awareness in aging (148, 154, 155). The elderly often undergo changes in physiology precipitated by aging such as decreased cerebral blood flow, attenuated sensitivity of receptors responding to changes in central blood flow (148, 155), decrease effectiveness of vasopressin (156), changes in the oral mucosa (157), salivary chemical composition (158) and thinning of the oral epithelium (159) that results in the blunting of their thirst response.

The current study has identified that participants who received chewing gum showed significant improvements in their level of thirst in the VAS at Day 4 (a decrease of 11 ± 14.6

mm in overall VAS scores; *p= 0.04*) compared to the control group (an increase of 0.5 ± 16.0 mm). This significant change is also observed when those in the intervention group were asked 'How is your thirst now?' in the NRS compared to their control group counterparts (decrease of 0.8 ± 1.8 mm vs. increase of 0.3 ± 2.0 mm; *p= 0.0019*). However, this was not the case with the second question in the NRS 'How has your thirst been in the last 24 hours?', which also showed a decrease of 0.6 ± 1.4 mm in the intervention and 0.1 ± 1.2 mm in the control group scores but was not statistically significant (*p=0.165*). This difference may be attributed to the difficulties associated with accurate recollection of the amount of change in participants' thirst from when they have started chewing gum. Participants are more likely to quantify their sense of thirst now as opposed to averaging the change in sensation in the last 24 hours which can be influenced by their daily activities and the number of other symptoms that have occurred during that day. Short-term memory loss due to a reduction in cerebral blood flow caused by their condition plays a major role (74). A similar downward trend in thirst intensity can also be seen at Day 14 and Day 28 of the study in those who received chewing gum (38.0 ± 18.5; *p= 0.02* and 37.4 ± 18.2; *p= 0.001,* respectively) compared to the control.

When compared with other studies investigating chewing gum in other patient populations, our results also demonstrate a significant improvement in the level of thirst (a decrease of 11 ± 14.6 mm in overall VAS scores; *p= 0.04* vs. a decrease of 1.2 in Dialysis Thirst Inventory scores [from 16.6 ± 5.1 to 15.4 ± 4.8; *p <0.05*] (6) vs. 6% reduction in the frequency of thirst (8), respectively). Furthermore, our results are also comparable with artificial saliva (15.5 ± 5.0; *p <0.05*) (6). While promising, several aspects must be considered when comparing the results of these studies. Firstly, the dimension of thirst measured in this study is thirst

intensity compared to the other two studies which measured the frequency of thirst (6, 8). Thirst intensity and frequency differ from each other where one dimension quantifies the strength of thirst while the other on how often thirst occurs (22). And lastly, the differences in the instruments used to measure thirst; our study utilised the VAS and NRS as opposed to a Dialysis Thirst Inventory (6) or a non-validated 19 multiple choice tool (8) used by the other two. Scoring and measurement of thirst in both scales are completely different to the VAS and the NRS. Thus, these make comparisons between studies troublesome.

In comparison to other studies in patients with CHF investigating the effect of liberal vs. strict fluid restriction on thirst, the use of chewing gum also showed a significant reduction in the level of thirst intensity in the VAS (a decrease of 0.8 mm on strict fluid restriction (20, 97) vs. a decrease of 24 mm on liberal fluid restriction (21, 96) vs. decrease 11 ± 14.6 mm on chewing gum). As previously discussed in Chapter 2, research methodologies utilised and the type of CHF population enrolled may be attributed to the conflicting results on fluid restriction (17). As observed, liberal fluid restriction demonstrated better reduction in the level of thirst compared to chewing gum. Nonetheless, in those severely decompensated CHF patients, a strict fluid restriction may still be necessary. In that case, chewing gum can be utilised to combat increased thirst. Despite not achieving the target sample size, the intention to treat analysis and sensitivity analysis shows a significant impact of chewing gum on participants' level of thirst. While chewing gum shows promising results in relieving thirst, there is still a need in coaching patients through exchange of ideas on distributing fluid intake evenly throughout the day and using other alternatives of relief such as ice chips or peppermints (30). Future studies should aim to test other thirst-relieving strategies in a rigorous randomised controlled study.

7.5.2 Effect of the RELIEVE-CHF study on weight stability

As previously mentioned, most patients with CHF have to maintain a fluid-restricted diet to help prevent fluid overload (18). High fluid intake through beverages and food leads to increased weight (30, 87). Long term non-compliance to fluid restriction can induce complications such as increased CHF symptoms e.g. shortness of breath, systemic and pulmonary oedema (78) resulting in unnecessary hospitalisations. Several strategies have been advocated to reduce fluid retention such as the administration of diuretics and dietary measures (46). While these measures work in decreasing fluid retention, patients often suffer from thirst and dry mouth which nevertheless increases water consumption (30, 87).

As a secondary endpoint, participants' weight was observed for any changes while on chewing gum or not on chewing gum. The results demonstrate fluctuations in the mean weight (kg) from Day 0 to Day 28 in both groups. Thus, weight was not affected by chewing gum during the study period. This finding is in agreement with studies investigating fluid restriction (96, 97) and chewing gum in patients with end-stage renal disease (6). The body's water composition and thus weight varies according to numerous daily activities such as eating, drinking, urinating, bowel movement and exercise (160). As such, simply recording participants' weight measurements was not enough to show changes in fluid loss/gain for the duration of the study period. While measuring fluid intake with body weight may give a better indication of changes in hydration, a food/fluid diary, raises the risk of responder burden. Based on our experience from the Bachelor of Medical Science (Honours) pilot study, the greatest amount of missing data encountered were from the food diary. Future studies can incorporate a simplified version food/fluid diary to better detect changes in body fluid level as well as avoid missing data due to responder burden.

7.5.3 Effect of the RELIEVE-CHF study on health- related quality

Traditionally, the major aim of treatment in patients with CHF are to relieve symptoms and to improve prognosis. Recently, another major goal of care is to maximise function in everyday life and achieve the highest level of quality of life (66). Measuring quality of life is relatively new and often used to evaluate effectiveness of treatment strategies and the course of disease (161). It is often that changes in an individual's own perceptions of their quality of life may not be readily apparent to the clinician or may not be reflected by these assessments (161). As such, these measures are being commonly used to provide complimentary and additional insight into the person's quality of life.

Although the secondary outcome was the change in overall and clinical summary scores from baseline to Day 28, all domains were analysed. At baseline the total cohort of 71 participants had above average scores in physical limitation (53.6 ± 25), symptom stability (49.3 ± 27.6), symptom frequency (58.2 ± 24.3), symptom burden (66.1 ± 28.4), total symptom (62.1 ± 25.4), self-efficacy (83 ± 17.7), social limitations (52 ± 34), overall summary score (52.8 ± 22.7) and clinical summary score (57.8 ± 23.2), with the exception of quality of life (44 ± 26). This is similar to the study by Holst et al (2008) (96) and Bots et al (2005) (6), in terms of overall quality of life score [median 13 (interquartile range 10 to 42)] and symptom problem (77.6 ± 13.7), respectively. However, this was not the case with physical (37.1 ± 11.4) and mental well-being (47.0 ± 9.6) in Bots et al (2005) study (6). These conflicting results are likely due to differences in the questionnaires used to measure health-related quality of life, mode of intervention and patient population. Bots et al (2005) was a crossover trial which administered the Kidney Disease Quality of Life, a 36 item questionnaire which focuses on health-related concerns of individual with kidney disease on

haemodialysis (6). On the other hand, Holst et al (2008) was also a crossover study comparing strict vs. liberal fluid restriction and utilised the Minnesota Living with Heart Failure Questionnaire (96) while our study was a single blind randomised study with two arms which used the KCCQ to measure health-related quality of life.

Comparing the change in mean KCCQ scores (all domains) from baseline to Day 28 in the intervention and control group, there were no significant differences between groups. Similarly, this is also seen in other CHF (96) and non-CHF intervention studies (6). Although the minimum duration of follow-up for KCCQ is 28 days, this may still not be sufficient to show change in health-related quality of life. The intervention group experienced a small decline in most of the KCCQ domains compared to the control group. Two domains and the overall summary score had clinical meaningful changes from baseline to day 28 follow-up in the control group. These two domains were physical limitation (6 ± 3), social limitations (9 ± 6) and the overall summary score (5 ± 2.5) (minimum of 5 points change). This was surprising as the control group had higher proportion of participants as inpatients compared to the intervention group. Hospitalised patients are generally sicker and bed-ridden which can affect most domains of physical limitation, symptom burden, total symptom, quality of life and social limitations.

Despite these conflicting findings, it is important to highlight that self- efficacy (83 ± 17.7) was particularly higher compared to the rest of the domains. After 28 days, scores in self-efficacy further improved in both groups. Although this was not a clinical meaningful difference, it is still an indicator of their performance of self- care. Self-care is part of successful CHF treatment and can significantly impact on symptoms, functional capacity,

well-being and prognosis (102). As such, achieving slight improvements in self-efficacy is promising. However, patients' success in self-care is still dependent on motivation and support from others (162). This highlights the need for further support of patients with CHF to recognise, interpret and monitor symptoms and to use appropriate self-care management strategies.

7.6 USEFULNESS OF CHEWING GUM

As with any intervention, patient perception of the intervention is the key to compliance. Thirty one percent of participants found chewing gum useful in relieving thirst (11/36) which agrees with Bots et al (2005) findings in dialysis patients (7). Seventy-two percent (47/65; $p<0.001$) of their participants found chewing gum a beneficial therapy in relieving thirst (7).

7.7 CONTINUED USE OF CHEWING GUM AFTER THE STUDY

At the end of the study period, participants were asked if they continued using chewing gum as a way to relieve thirst. Most of the participants continued to use chewing gum (19/36; 53%) which is similar to Bots et al (2005) whereby majority of their participants were willing to use chewing gum after the study (46/65; 70%) compared to artificial saliva (7). Although their participants were willing to use chewing gum, they did not follow-up on whether they continued chewing gum after the study.

Aside from relief from thirst, participants found that chewing gum provided a distraction from drinking water; it tasted pleasant and freshened their breath. This also reflects the findings of Bots et al (2005). When chewing gum was compared with artificial saliva, participants preferred its use over the saliva substitute as they found it effective in relieving thirst (5.5 ± 2.7; $p<0.001$), easy to use (7.6 ± 2.3; $p<0.05$) and tasted delicious (7.3 ± 2.0;

p<0.001) (7). On the other hand, a quarter of participants did not continue chewing gum (9/36; 25%) as they were not as thirsty and could drink water more freely than the rest.

7.8 SIDE- EFFECTS OF CHEWING GUM

The use of chewing gum to alleviate thirst has been widely investigated in numerous patient groups. In this study, participants were asked of any side- effects while on chewing gum but very little reported experiencing any. Only one patient reported experiencing a side-effect from chewing gum i.e. jaw discomfort. This may be attributed to either prolonged gum chewing (163). Although, aging contributes to decreased density of the jaw muscles, thinning of the oral epithelium and decreased collagen synthesis which can make chewing gum less tolerable, this was not the case as this participant was relatively younger. Therefore, the more likely explanation is that this participant chewed the gum longer than 10 minutes. It is also likely that the chosen duration of 10 minutes to chew the gum in this study is still quite extensive that it caused some jaw discomfort. Similar to other studies, jaw discomfort was also one of the side-effects experienced by their participants (6, 10). This similarity is expected as the duration and procedure of gum chewing utilised in this study are based on these previous studies (6, 10).

In comparison to previous studies of chewing gum, our participants only experienced one minor symptom (6, 10). Other studies which investigated the use of chewing gum to relieve thirst in other patient populations have reported numerous side-effects including irritation of the mouth, nausea, unpleasant taste, jaw discomfort, biting mouth, sensitive teeth and flatulence (6, 10). Several reasons could explain the differences in findings. Participants recruited in this study are much younger compared to other studies. Therefore, they are

likely to be more tolerant to the effect of chewing gum. Furthermore, it is also probable that the following reported side-effects are caused by their condition and its treatment. People with advanced cancer or undergoing haemodialysis are often plagued with numerous symptoms which can be mistaken as a side-effect of chewing gum. For example, people undergoing chemotherapy or haemodialysis are reported to experience nausea.

7.9 ADVERSE EVENTS

Although 2 deaths and 10 re-hospitalisations occurred among our study cohort, these were not caused by our study. The majority of hospitalisations were due to urgent heart transplantation, ventricular assist device implantation, other procedures or CHF decompensation. The study was not powered to detect differences in mortality and rehospitalisation so further analyses of these data were not undertaken.

7.10 POSITIVE EFFECTS OF CHEWING GUM

While there were negative effects from chewing gum, participants also reported some benefits from it. Most participants reported great relief from thirst which can be explained by the saliva stimulating capacity of the gum. Whereas others only found some relief from thirst. This variability in thirst relief is expected as patients' experience relief from a symptom differently. While some may experience relief from thirst for hours, others only remain thirst free for an hour. Other participants also found that chewing gum freshened their breath; potentially influencing thirst relief. This can be attributed to the flavour of the gum. Mint based gums such as peppermint used in this study often invoke a feeling of freshness in the mouth.

7.11 TRIAL RELATED FACTORS FOR CONSIDERATION

7.11.1 Missing data

Despite all effort in ensuring complete data is obtained from the participants, there were still missing data present in our study data set. Missing data poses several problems including reduction in the study power and introduction of bias in the study results. Deleting cases is a default method used for dealing with missing data in most statistical software packages. However, in this study with an already small sample size, deleting cases would have further reduce our study power.

Thus, missing values were replaced using multiple imputation, previously mentioned in Chapter 6. Missing data at Days 1-4, 7, 14 and 28 were due to participants not returning follow-up calls or urgent heart transplantation or ventricular assist device implantation; resulting in the inability to complete the trial. Missing values at baseline were minimal and caused by missing information in medical records. Therefore, these were not imputed.

7.11.2 Follow-up and regime compliance

The RELIEVE-CHF study was designed to have a 28-day follow-up. Sixteen participants (six in the intervention group and ten in the control group) were unable to be followed-up, resulting in a dropout rate of 23%. Nine did not return follow-up calls, two died and five withdrew from the study due to personal reasons or dislike of the chewing gum. Therefore, the follow-up and regime compliance of this study was 78%. With the use of the 'intention to treat' principle, all participants were analysed in their groups and missing data were imputed as previously described.

7.12 Study strengths

7.12.1 Study design

This study has utilised a randomised controlled trial design, which is generally considered to produce the most robust evidence for the effectiveness of health interventions. The design presents several strengths. Firstly, it was prospective which increases precision compared to retrospective/observational data. Secondly, it also allows specific allocation and administration of an intervention to a chosen population i.e. CHF, thus decreasing allocation bias. Thirdly, the process of randomisation also lowers the likelihood of selection bias and enable groups to be evenly matched; decreasing the effect of confounders. And lastly, blinding participants and investigators can be easily achieved. However, in this case blinding the participants was impossible.

7.12.2 Other study strengths

This study is a novel approach well-informed by literature. It used specific, measurable, relevant elements. It was conducted observing methodological rigour and compliance to ethical guidelines. The study design also played close attention to the attitudes and preferences of study participants. Further, the sample was derived using formal sample size calculations to estimate the desired effect.

7.13 Study limitations

7.13.1 Sampling

Convenience sampling involves the use of the most conveniently accessible people as study participants. While this is efficient, there are possibilities that these people may not be representative of the CHF population being studied. Convenience sampling also poses risk of

bias which can lead to inaccuracy of the study findings. In spite of this, the socio-demographic and clinical characteristics presented in the previous chapter are typical of the CHF population from which our sample was derived. However, it is still important to interpret the study results with sampling bias in consideration.

7.13.2 Sample size

In Chapter 5, the sample size calculation showed 144 participants were required to detect a one-point difference in the level of thirst at Day 4 (primary endpoint). However, this study encountered numerous difficulties during recruitment. Firstly, many elderly CHF patients did not want to partake in the study as they found chewing gum a disgusting habit. Secondly, although the study investigator explained that xylitol chewing gum does not stick to dentures, most elderly patients were still reluctant to try. Thirdly, most patients were hesitant to commit to the study as they were already overwhelmed with other commitments (weekly doctor's appointments, CHF treatment and lifestyle changes). And lastly, some patients were uninterested in the study as they were very sick either waiting for heart transplantation or ventricular assist device implantation. As such, only 71 participants were enrolled in the study. Nonetheless, this pilot study is the largest trial of chewing gum to date with 71 participants (6, 8). Furthermore, despite not achieving the calculated sample size, our study results consistently demonstrate significant difference in participants' level of thirst between groups based on our primary endpoint 'intention to treat' analysis (imputed missing data) and sensitivity analysis (completers only).

7.13.3 Issue with self- reporting

Another potential limitation of this study is the use of self-reported instruments. Utilising self-reported measurements carry the risk of over reporting or under reporting from the participants. However, this is likely to be evenly distributed between the randomised groups. While the self-directed RELIEVE-CHF program appeared simple to follow, there is also the risk of following the protocol incorrectly due to misperception of when to record their level of thirst. Inappropriate reporting may produce inaccurate results. Unfortunately, there were no procedures implemented to avoid this. The study protocol was explained to participants as a clearly as possible. Participants were also given the information sheet which contained the instructions of the study. Future studies should implement an efficient, non-bothersome approach to remind participants of the study schedules.

7.13.4 Blinding

RELIEVE-CHF was a single-blind study thus, only the study investigators were blinded to treatment allocation prior to randomisation and during follow-up. Blinding is often used to avoid bias particularly when measuring subjective outcomes. Lack of blinding could potentially introduce bias to the study through knowledge of treatment allocation. Bias can influence participants' responses to the treatment, for instance, they may respond favourably to the chewing gum intervention as opposed to the no chewing gum intervention. Nonetheless, this was unavoidable as blinding the participants to an intervention like chewing gum is impossible. Participants would know if they are chewing gum or not chewing gum.

7.13.5 Contamination

To the best of our knowledge no participants in either group (intervention or control) crossed over, but it is possible that participants may have discussed the study with a fellow CHF participants attending the same heart failure clinic. Similarly, the staff at the study sites were also provided with information about the study to assist in recruitment. However, it is probable that staff may have also undertaken their own exploration of ways to alleviate thirst while providing care and information to individuals attending the clinic.

7.13.6 Flavour and size of the chewing gum

The choice of peppermint flavoured chewing gum is a potential limitation in this study. A recent study on the effect of five different flavoured gums demonstrate varying effect on salivary flow rate and pH which affects the degree of relief it provides from thirst (164). Peppermint flavour has been shown to produce lower salivary flow rates compared to cinnamon or spearmint flavoured gums (164). Increase in salivary flow rate corresponds to increase in saliva secretion and ability to alleviate thirst.

Another potential limitation of this study is the size of chewing gum. As previously described, we used the pellet size chewing gum from Epic Dental LLC. Compared to the normal strip size chewing gum, pellet size losses flavour and softens more quickly further reducing the size of the gum (165). This then leads to a reduced stimulation of periodontal mechanoreceptors; contributing to decrease in salivary flow rate (165).

Despite these limitations, there were several reasons for choosing Xylitol Epic Dental LLC peppermint flavour and pellet size. Firstly, xylitol is sugar-free (128) which is suitable for many CHF patients who also have diabetes. Secondly, this chewing gum contains more

amounts of xylitol, unlike other types of chewing gum (128). This means more protection from acid producing bacteria, helps with re-mineralisation of the enamel and avoids plaque development (128). Thirdly, based on the preliminary study from Bachelor of Medical Science (Honours) and previous study on chewing gum, peppermint flavour is the most preferred flavour by participants (166). And lastly, the pellet size is easier for elderly patients to chew and does not stick to dentures or metal appliances (128).

7.14 CHALLENGES IN PROMOTING CHEWING GUM

As the prevalence of thirst in CHF increases, there is a need for innovative approaches and interventions to help those suffering from severe thirst. New approaches need to seek appropriateness, feasibility and effectiveness. Although this study has shown that chewing gum relieves thirst in patients with CHF, our study has also highlighted major challenges in advocating the use of chewing gum in clinical practice based on our experiences during recruitment. Firstly, people with CHF are predominantly elderly thus high proportions are wearing dentures. Chewing gum often sticks to the denture base which can promote dislike towards it. However, low-tack gum which does not stick to dentures has been recently introduced and may therefore be better accepted by patients with dentures or metal appliances. Secondly, there is a negative social stigma attached to chewing gum. The aged generation often see someone chewing gum as disgusting, disrespectful and rude. In addition, bad gum disposal habits also contribute to the negativity attached to it. Some gum chewers would spit their gum out on the pavement, slyly stick it under a desk or foist it under a chair which is unhygienic, costly in terms of clean-up and promotes the spread of diseases. And lastly, chewing gum habits in Australia differ to the United States where chewing gum is often used recreationally and better accepted socially. This explains the

slow recruitment of participants in this study. Nonetheless, with the recent rise in the promotion of chewing gum to improve oral health, these obstacles may be overcome in the future.

7.15 CONCLUSION

Innovative strategies such as the use of chewing gum are important within the growing prevalence of thirst in CHF. This chapter has provided a discussion of the results of the RELIEVE-CHF trial in the context of understanding of thirst and therapeutic approaches. Our findings show significant improvements in participants' level of thirst after chewing gum, comparable to another study in literature. Although we have shown that chewing gum relieves thirst in CHF patients, social stigma and attitudes towards chewing gum are important aspect for consideration in its implementation in clinical practice. The implications of the RELIEVE-CHF trial on policy, practice and research will be discussed in the next chapter.

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CHAPTER VIII- CONCLUSION: IMPLICATIONS FOR PRACTICE, POLICY AND RESEARCH

8.1 INTRODUCTION

The previous chapters have provided a discussion of the growing burden of thirst in CHF patients and the importance of testing innovative approach to help relieve thirst. This thesis has provided the rationale of a randomised controlled trial to evaluate the effect of chewing gum on the level of thirst, weight stability and health-related quality of life of patients with CHF. The findings of the trial have also been presented. Although, there were significant improvements in the level of thirst in participants who received chewing gum compared to the control group, caution must be taken when interpreting these findings as the target sample size of 144 was not achieved. Despite this, RELIEVE-CHF is still a novel approach to alleviate thirst in CHF. This chapter provides a summary of this research and identifies the implications for practice, policy and research.

8.2 REVIEW AND DISCUSSION

This thesis has described the barriers of advocating the use of chewing gum in patients with CHF. This work emphasises the need for evidence-based and patient-centred approach to relieve thirst. With the growing number of patients diagnosed with CHF, the numbers of individuals with thirst and the burden associated with it is only set to rise exponentially.

The findings in this thesis are summarised into four parts. Chapter two has carefully elucidated the factors contributing to thirst in CHF (17) and identified potential therapeutic approaches to relieve thirst. This paper emphasised the need to recognise what begets thirst and consider novel approaches in the context of the best available evidence.

8.2.1 Greater understanding of thirst in CHF

Chapter two described the factors related to thirst in CHF. Our comprehensive review of electronic databases and search engines revealed that complex integration of prolonged neurohormonal activation in CHF, diuretic therapy to reduce fluid retention and fluid restriction prescribed to avoid fluid overload, all play a vital role in generating the sensation of thirst (17). Each factors are multifaceted and requires further investigation. For instance, prolonged neurohormonal activation affects many pathways such as the sympathetic nervous system, renin-angiotensin system and vasopressin which influences thirst (57, 91, 93). This is also the case with various CHF medications. While it is established that these medications affect the thirst response, their quantitative contribution to thirst is difficult to assess due to confounders such as dosage. Further testing may identify the specific role of these factors in thirst and establish these as biomarkers of thirst. Hence, facilitating identification of patients who are suffering from thirst and allowing clinicians to be better informed of thirst as a symptom of CHF and its consequences. By doing so, patients can be educated about thirst, be monitored over time and advised appropriate interventions to help cope with thirst, promoting patient centred care.

Recommendation 1:

- There is need for deeper understanding of the specific role of various factors related to thirst.
- Raising awareness of thirst as a symptom of CHF is vital.
- Improving clinicians' knowledge of thirst will likely enhance identification of CHF patients with thirst and provide a more tailored, patient-centred treatment.

Chapter three demonstrated that many clinicians provide advice to their patients on what strategies may be helpful in relieving thirst. This paper also highlighted the similarities in the strategies recommended to patients in this study and in the literature. This paper provided a framework for RELIEVE-CHF.

8.2.2 Evidence-based strategies to relieve thirst

The literature review in Chapter two identified that there were several oral interventions examined in CHF patients and other patient populations which may potentially be useful in alleviating thirst. Non- traditional interventions such as artificial saliva spray and chewing gum have been examined in patients on haemodialysis; showing favourable results in effectiveness, taste and patients preference for chewing gum (6). The effect of strict or liberal fluid restriction in reducing thirst in CHF has also been widely explored (20, 21, 96, 97). However, findings from these studies were ambiguous. Ingestion of ice cubes, cold drinks and peppermint or buttermilk candies have also been advised to CHF patients as reported in literature (87) which aligns with the results of our survey of health professionals in clinical settings in Australia and New Zealand. Nonetheless, however there is little to no

evidence to support these recommendations. In order to provide evidence-based treatment, future studies are vital to assess the effectiveness of these interventions.

Recommendation 2:

- Testing various thirst-relieving strategies in a rigorous randomised controlled study will ensure patients are provided with the treatment based on the best available evidence.

Chapter four provided a timely review of the current tools used to measure thirst in CHF. This provided valuable insight into the difficulties in measuring thirst in clinical settings. This paper highlighted the importance of valid and reliable tools to assess thirst.

8.2.3 Development of thirst assessment scale in CHF

Optimal evaluation involves assessment of all thirst dimensions (frequency, intensity, distress and quality) (22). While validated uni-dimensional tools are available such as the Numeric Rating Scale and the Visual Analogue Scale, the addition of a multidimensional enhances the assessment of thirst. Furthermore, using qualitative approach in conjunction with a quantitative methodology will add more depth to the understanding of patients' thirst experience. Thus, development of a multidimensional thirst assessment scale validated in CHF and encompasses all dimensions of thirst is essential.

Recommendation 3:

- Development of a valid, reliable, multidimensional thirst assessment scale will ensure better monitoring of thirst.

8.2.4 Addressing trial barriers and limitations

The trial highlighted the challenges with implementing a non-traditional intervention of relieving thirst. Despite willingness of some individuals to participate in the study, there was evidence of dislike and hesitation related to the chewing gum. Many individuals who refused to participate, expressed dislike towards chewing gum as the reason. Although chewing gum is not socially acceptable for everyone, our study has shown that it is an inexpensive, safe and effective intervention to alleviate thirst in patients with CHF experiencing thirst. The trial has also provided insights on its limitations which must be addressed to improve future intervention studies. Nevertheless, this study has provided informative data, highlighted the challenges with promoting chewing gum and suggested a trend of improved level of thirst in the intervention group.

Recommendation 4:

- Addressing the barriers and limitations encountered in RELIEVE-CHF will likely improve future intervention studies.
- Chewing gum is an inexpensive, safe and effective intervention to relieve thirst in CHF patients suffering from thirst.

8.2.5 Potential predictors of thirst

This thesis has summarised the factors that contribute to thirst in CHF. Based on the review of the literature, thirst is influenced by the prolonged neurohormonal activation in CHF, medications to treat fluid retention such as diuretics and fluid restriction. Findings from the RELIEVE-CHF trial have underlined potential predictors such as age, sex, serum osmolality and plasma urea which warrant further exploration.

Recommendation 5:

- Further investigation on possible predictors of thirst will ensure CHF patients suffering from thirst are identified quickly, monitored closely and provided with a more tailored treatment.

8.3 SUMMARY OF RECOMMENDATIONS GENERATED FROM THIS THESIS

Recommendation 1: Greater understanding of thirst in CHF
• *There is need for deeper understanding of the specific role of various factors related to thirst* • *Raising awareness of thirst as a symptom of CHF is vital* • *Improving clinicians' knowledge of thirst will likely enhance identification of CHF patients with thirst and provide a more tailored, patient-centred treatment*
Recommendation 2: Evidence-based strategies to relieve thirst
• *Testing various thirst-relieving strategies in a rigorous randomised controlled study will ensure patients are provided with the treatment based on the best available evidence*
Recommendation 3: Development of thirst assessment scale in CHF
• *Development of a valid, reliable, multidimensional thirst assessment scale is will ensure better monitoring of thirst in clinical setting*
Recommendation 4: Addressing trial barriers and limitations
• *Addressing the barriers and limitations encountered in RELIEVE-CHF will likely improve future intervention studies* • *Chewing gum is an inexpensive, safe and effective intervention to relieve thirst in CHF patients suffering from thirst*
Recommendation 5: Potential predictors of thirst
• *Further investigation on possible predictors of thirst will ensure CHF patients suffering from thirst are identified quickly, monitored closely and provided with a more tailored treatment*

8.4 CONCLUSION

The literature reviews, survey of health professionals and the RELIEVE-CHF trial undertaken as part of this thesis is highly significant as it addresses thirst, a symptom that is frequent and common across many conditions and addressed by an innovative therapeutic approach i.e. chewing gum. The question raised in this thesis is whether the improvement in thirst provided by chewing gum exceeds the hassle of having a further management item. The data presented in this thesis have provided methodological rigour and pragmatic considerations for future clinical trials on other strategies to relieve thirst.

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APPENDICES

Appendix 1 Survey Ethics Approval Letter

FW: UTS HREC Letter of Noting

Phillip Newton <Phillip.Newton@uts.edu.au>
Wed 19/02/2014 1:58 PM
To: Sabine Allida <Sabine.Allida@student.uts.edu.au>;

-----Original Message-----
From: Research.Ethics@uts.edu.au [Research.Ethics@uts.edu.au]
Received: Wednesday, 19 Feb 2014, 13:41
To: Research Ethics [research.ethics@uts.edu.au]; Phillip Newton [Phillip.Newton@uts.edu.au]
Subject: UTS HREC Letter of Noting

Dear Applicant,

The Faculty has considered your Nil/Negligible Risk Declaration Form for your project titled, "Thirst management in chronic heart failure", and agree your research does not require review from the UTS Human Research Ethics Committee. Please keep a copy of your Declaration form on file to show you have considered risk.

For tracking purposes, you have been provided with an ethics application number, which is UTS HREC 2014000014.

I also refer you to the AVCC guidelines relating to the storage of data, which require that data be kept for a minimum of 5 years after publication of research. However, in NSW, longer retention requirements are required for research on human subjects with potential long-term effects, research with long-term environmental effects, or research considered of national or international significance, importance, or controversy. If the data from this research project falls into one of these categories, contact University Records for advice on long-term retention.

You should consider this your official letter of noting.

Instructions for saving the declaration form can be downloaded from:
http://www.research.uts.edu.au/policies/restricted/human/forms.html#instructions
To access this application, please follow the URLs below:
* if accessing within the UTS network: http://rmprod.itd.uts.edu.au/RMENet/HOM0001N.aspx
* if accessing outside of UTS network: https://remote.uts.edu.au , and click on "RMENet - ResearchMaster Enterprise" after logging in.

If you or anyone connected with this research have any queries please do not hesitate to contact Research.Ethics@uts.edu.au

Yours sincerely,

Professor Marion Haas
Chairperson
UTS Human Research Ethics Committee
C/- Research & Innovation Office
University of Technology, Sydney
T: (02) 9514 9772
F: (02) 9514 1244
E: Research.Ethics@uts.edu.au
I: http://www.research.uts.edu.au/policies/restricted/ethics.html
P: PO Box 123, BROADWAY NSW 2007
[Level 14, Building 1, Broadway Campus]
CB01.14.08.04

REF: E28

Appendix 2 Survey of various strategies to relieve thirst

1. Participant Information Sheet

Thank you for taking the time to complete this survey. This page will provide you some background information about the survey.

Who is doing the research?
- My name is Sabine Allida, a PhD candidate receiving funding from the University of Technology, Sydney. My supervisors are Dr Phillip Newton, RN (University of Technology, Sydney), Dr Sally Inglis, RN (University of Technology, Sydney), Professor Patricia Davidson, RN (St. Vincent's Hospital & University of Technology, Sydney), and Associate Professor Christopher Hayward, Senior Cardiologist (St. Vincent's Hospital). This study is being conducted as part of a PhD degree.

What is the research about?
- To date there are various strategies used to alleviate thirst in chronic heart failure, however, there is very little evidence to support or refute these practices.

The purpose of this study is to:
1. Identify current strategies used in the management of thirst in chronic heart failure
2. Identify views and perceptions on the use of various strategies to relieve thirst in Australian care setting

What will it involve?
- Completing a survey which should take approximately 5-10 minutes to complete.

Participation in this research is voluntary. If you do not wish to participate, you do not have to. You can change your mind at any time and you don't have to say why. If you wish to withdraw from this study please advise the study team. Results of this research may be published in peer reviewed journals. All information collected will be unidentifiable.

Information from this survey will assist us in planning future clinical trials.

Sabine Allida (PhD candidate)
Dr Phillip Newton
Dr Sally Inglis
Professor Patricia Davidson
Associate Professor Christopher Hayward

Participant Consent Statement

Ethics approval No:

I am making a decision to voluntarily participate in the research project named above. By ticking the box below I indicate that I have read and understood the 'Participant Information Sheet' provided.

I understand that:

- Participation involves completing a paper questionnaire which will take approximately 5-10 minutes to complete

- If you have any concerns about the way in which this research is being conducted you may contact Yordanka Krastev the Ethics Manager at the University of Technology Sydney on (02)9514 1279 quoting the ethics approval number.

- The research study is strictly confidential and no information about me will be used in any way that reveals my identity.

***1. Do you agree to participate in this research study?**

- ○ I hereby agree to participate in this research study
- ○ I do not wish to participate in this study

Some information about you

2. What is your profession/job title?

- Registered Nurse
- Clinical Nurse Specialist
- Clinical Nurse Consultant
- Enrolled Nurse
- Nurse Practitioner
- Practice Nurse
- Nurse educator
- Clinical nurse educator
- Endorsed enrolled nurse
- Aboriginal Health Worker
- Multicultural Community Health Care Worker
- Dietitician
- Cardiologist
- Palliative Care Consultant
- Palliative Care Registrar
- Physician
- General Practitioner
- Social Worker
- Community Pharmacist
- Hospital Based Pharmacist
- Speech therapist
- Other (please specify)

3. Where do you work?

- Australia
- New Zealand
- Other (please specify)

4. What is your primary area of specialty? Please tick all the areas that have been the primary focus of your care in the past until now

- ☐ Chronic heart failure (CHF)
- ☐ Acute Coronary Syndrome (ACS)
- ☐ Coronary Care Unit (CCU)
- ☐ Cardiac rehabilitation
- ☐ Cardiac step- down
- ☐ Cath lab
- ☐ Research
- ☐ Education
- ☐ Primary care
- ☐ Community
- ☐ General medicine
- ☐ Aged care
- ☐ Transplant
- ☐ Paediatric
- ☐ Other (please specify)

Use of various strategies to alleviate thirst

5. Have you recommended any strategies to relieve thirst in people with CHF?

- ○ Yes
- ○ No

Use of various strategies to alleviate thirst

6. Have you recommended artificial saliva to relieve thirst in people with CHF?

- ○ Yes
- ○ No (Go to Question 7)

If you have recommended strategies to alleviate thirst

7. What is your perception of the use of artificial saliva in relieving thirst?

- no use
- some use
- unsure
- useful
- very useful

Use of various strategies to alleviate thirst

8. Have you recommended ice chips to relieve thirst in people with CHF?

- ○ Yes
- ○ No (Go to Question Question 9)

If you have recommended strategies to alleviate thirst

9. What is your perception of the use of ice chips in relieving thirst?

- no use
- some use
- unsure
- useful
- very useful

Use of various strategies to alleviate thirst

10. Have you recommended chewing gum to relieve thirst in people with CHF?

- ○ Yes
- ○ No (Go to Question 11)

If you have recommended strategies to alleviate thirst

11. What is your perception of the use chewing gum in relieving thirst?

- ○ no use
- ○ some use
- ○ unsure
- ○ useful
- ○ very useful

Use of various strategies to alleviate thirst

12. Have you recommended 'small sips of water' to relieve thirst in people with CHF?

- ○ Yes
- ○ No (Go to Question 13)

If you have recommended strategies to alleviate thirst

13. What is your perception of the use of 'small sips of water' in relieving thirst?

- ○ no use
- ○ some use
- ○ unsure
- ○ useful
- ○ very useful

Use of various strategies to alleviate thirst

14. Have you recommended peppermint/buttermilk flavoured candies to relieve thirst in people with CHF?

- ○ Yes
- ○ No (Go to Question 15)

If you have recommended strategies to alleviate thirst

15. What is your perception of the use of peppermint/buttermilk flavoured candies in relieving thirst?

- no use
- some use
- unsure
- useful
- very useful

Use of various strategies to alleviate thirst

16. Have you recommended cold water with a slice of lemon to relieve thirst in people with CHF?

- ○ Yes
- ○ No (Go to Question 17)

If you have recommended strategies to alleviate thirst

17. What is your perception of the use of cold water with a slice of lemon in relieving thirst?

- no use
- some use
- unsure
- useful
- very useful

Use of various strategies to alleviate thirst

18. Have you recommended lozenges to relieve thirst in people with CHF?

- ○ Yes
- ○ No (Go to Question 19)

If you have recommended strategies to alleviate thirst

19. What is your perception of the use of lozenges in relieving thirst?

- no use
- some use
- unsure
- useful
- very useful

Use of various strategies to alleviate thirst

20. Have you recommended ice cold water to relieve thirst in people with CHF??

- ○ Yes
- ○ No (Go to Question 21)

If you have recommended strategies to alleviate thirst

21. What is your perception of the use of ice cold water in relieving thirst?

- no use
- some use
- unsure
- useful
- very useful

Use of various strategies to alleviate thirst

22. Have you recommended 'other' strategies to relieve thirst in people with CHF?

- ○ Yes
- ○ No

If you have recommended strategies to alleviate thirst

23. If you have recommended 'other' strategies for thirst relief, what was it?

End of survey

Thank you for taking the time to participate in our survey.

Appendix 3 RELIEVE-CHF St. Vincent's Hospital and UTS Ethics Approval Letter

St Vincent's Hospital

A facility of St Vincent's & Mater Health Sydney

St Vincent's Hospital Sydney Ltd
ABN 77 054 338 872
390 Victoria Street
Darlinghurst NSW 2010
Australia

T + 61 2 9382 1111
F + 61 2 9332 4142
www.stvincents.com.au

22 July 2014

A/Prof. Christopher Hayward
Cardiology Department
St Vincent's Hospital
390 Victoria Street
Darlinghurst NSW 2010

Dear Christopher,

SVH File Number: 14/136
Project Title: RandomisEd controLled trial of chEwing gum to relieVE thirst in chronic heart failure (RELIEVE- CHF)
HREC Reference Number: HREC/14/SVH/171

Thank you for Dr Phillip Newton's letter, dated **8 July 2014**, responding to issues raised regarding the above project, which was first considered by the St Vincent's Hospital HREC at its meeting held on **12 June 2014.** This HREC has been accredited by NSW Ministry of Health as a Lead HREC under the model for sing e ethical and scientific review and Certified by the NHMRC under the National model for Harmonisation of Multicentre Ethical Review (HoMER). This lead HREC is constituted and operates in accordance with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research* and the *CPMP/ICH Note for Guidance on Good Clinical Practice*. No HREC members with a conflict of interest were present for review of this project.

I am pleased to advise that the Committee at an Executive meeting on **21 July 2014** has granted ethical and scientific approval of the above single centre project.

You are reminded that this letter constitutes *ETHICAL* and *SCIENTIFIC* approval only. You must not commence this research project at a site until a completed Site Specific Assessment Form/Access Request and associated documentation have been submitted to the site Research Governance Officer and authorised. A copy of this letter must be forwarded to all site investigators for submission to the relevant Research Governance Officer.

The project is approved to be conducted at **St Vincent's Hospital (Sydney).**

If a new site(s) is to be added please inform the HREC in writing and submit a Site Specific Assessment Form (SSA) to the Research Governance Officer at the new site.

The following documentation has been reviewed and approved by the HREC:

- Participant Information Sheet & Consent Form Interventional Study – *Adult providing own consent* Version 1.1 dated 1 March 2014
- Withdrawal of Participation Form – *Adult providing own consent* Version 1.1 dated 1 March 2014
- Study Protocol Version 1.1 dated 1 March 2014
- Case Report Form 1 Version 1 dated 1 March 2014
- Case Report Form 2 Version 1 dated 1 March 2014
- Case Report Form 3 Version 1 dated 1 March 2014

The National Ethics Application Form (NEAF) document reviewed by the HREC was NEAF **AU/1/1CA815**

Please note the following conditions of approval:

- HREC approval is valid for 5 years from the date of the HREC Executive Committee meeting and expires on **21 July 2019**. The Co-ordinating Investigator is required to notify the HREC 6 months prior to this date if the project is expected to extend beyond the original approval date at which time the HREC will advise of the requirements for ongoing approval of the study.
- The Co-ordinating Investigator will provide an annual progress report beginning in **July 2015**, to the HREC as well as a final study report at the completion of the project in the specified format.
- The Co-ordinating Investigator will immediately report anything which might warrant review of ethical approval of the project in the specified format, including unforeseen events that might affect continued ethical acceptability of the project and any complaints made by study participants regarding the conduct of the study.
- Proposed changes to the research protocol, conduct of the research, or length of HREC approval will be provided to the HREC for review, in the specified format.
- The HREC will be notified, giving reasons, if the project is discontinued before the expected date of completion.
- Investigators holding an academic appointment (including conjoint appointments) and students undertaking a project as part of a University course may also be required to notify the relevant University HREC of the project. Investigators and students are advised to contact the relevant HREC to seek advice regarding their requirements.

Please note it is the responsibility of the sponsor or the co-ordinating investigator of the project to register this study on a publicly available online registry (eg. Australian Clinical Trial Registry www.actr.org.au).

Please note that only an electronic copy of this letter will be provided. If you require the original signed letter please contact the Research Office and we will be happy to provide this.

Should you have any queries about your project please contact the Research Office, Tel: 8382-2075, email SVHS.Research@svha.org.au. The HREC Terms of Reference, Standard Operating Procedures, *National Statement on Ethical Conduct in Human Research* (2007) and the *CPMP/ICH Note for Guidance on Good Clinical Practice* and standard forms are available on the Research Office website: www.stvincents.com.au/researchoffice or internal: http://cxwwwsvh.stvincents.com.au/researchoffice.

Please quote **SVH File Number: 14/136** in all correspondence.

The HREC wishes you every success in your research.

Yours sincerely,

Sarah Charlton
HREC Executive Officer
St Vincent's Research Office
Level 6, de Lacy Building

Cc: Dr Phillip Newton
TRIM REF: D/2014/34125

Dear Applicant

[External Ratification: St Vincent's Hospital HREC - HREC/14/SVH/171 - 21/07/14 to 21/07/19]

The UTS Human Research Ethics Expedited Review Committee reviewed your application titled, "RandomisEd controLled trial of chEwing gum to relieVE thirst in chronic heart failure (RELIEVE- CHF)", and agreed that the application meets the requirements of the NHMRC National Statement on Ethical Conduct in Human Research (2007). I am pleased to inform you that your external ethics approval has been ratified.

Your approval number is UTS HREC REF NO. 2014000458

Please note that the ethical conduct of research is an on-going process. The National Statement on Ethical Conduct in Research Involving Humans requires us to obtain a report about the progress of the research, and in particular about any changes to the research which may have ethical implications. This report form must be completed at least annually, and at the end of the project (if it takes more than a year). The Ethics Secretariat will contact you when it is time to complete your first report.

I also refer you to the AVCC guidelines relating to the storage of data, which require that data be kept for a minimum of 5 years after publication of research. However, in NSW, longer retention requirements are required for research on human subjects with potential long-term effects, research with long-term environmental effects, or research considered of national or international significance, importance, or controversy. If the data from this research project falls into one of these categories, contact University Records for advice on long-term retention.

You should consider this your official letter of approval. If you require a hardcopy please contact Research.Ethics@uts.edu.au.

To access this application, please follow the URLs below:
* if accessing within the UTS network: http://rmprod.itd.uts.edu.au/RMENet/HOM001N.aspx
* if accessing outside of UTS network: https://remote.uts.edu.au , and click on "RMENet - ResearchMaster Enterprise" after logging in.

We value your feedback on the online ethics process. If you would like to provide feedback please go to:http://surveys.uts.edu.au/surveys/onlineethics/index.cfm

If you have any queries about your ethics approval, or require any amendments to your research in the future, please do not hesitate to contact Research.Ethics@uts.edu.au.

Yours sincerely,

Professor Marion Haas
Chairperson
UTS Human Research Ethics Committee
C/- Research & Innovation Office
University of Technology, Sydney
T: (02) 9514 9772
F: (02) 9514 1244
E: Research.Ethics@uts.edu.au
I: http://www.research.uts.edu.au/policies/restricted/ethics.html

Appendix 4 Site Specific Authorisation Approval Letter

St Vincent's Hospital

A facility of St Vincent's & Mater Health Sydney

St Vincent's Hospital Sydney Ltd
ABN 77 064 038 872
390 Victoria Street
Darlinghurst NSW 2010
Australia

T + 61 2 8382 1111
F + 61 2 9332 4142
www.stvincents.com.au

22 August 2014

A/Prof. Christopher Hayward
Cardiology Department
St Vincent's Hospital
390 Victoria Street
Darlinghurst NSW 2010

Dear Christopher,

SVH File Number: 14/136
Project Title: RandomisEd controLled trial of chEwing gum to relieVE thirst in chronic heart failure (RELIEVE- CHF)
HREC Reference Number: HREC/14/SVH/171
SSA Reference Number: SSA/14/SVH/214

Thank you for submitting an application for authorisation of this project. I am pleased to advise that the Director of Research, on **20 August 2014**, has granted authorisation for the above project to commence at **St Vincent's Hospital, Sydney.**

Documents to be used at this site are:

- Participant Information Sheet & Consent Form Interventional Study – *Adult providing own consent* Version 1.1 dated 1 March 2014
- Withdrawal of Participation Form – *Adult providing own consent* Version 1.1 dated 1 March 2014
- Study Protocol Version 1.1 dated 1 March 2014
- Case Report Form 1 Version 1 dated 1 March 2014
- Case Report Form 2 Version 1 dated 1 March 2014
- Case Report Form 3 Version 1 dated 1 March 2014

The SSA form reviewed was **AU/2/EFA816.**

Site authorisation will cease on the date of HREC expiry (21 July 2019).

Please Note: Sabine Allida and Phillip Newton cannot commence study related responsibilities until all SVH Human Resources Department requirements have been met. St Vincent's Hospital Senior Medical Workforce Unit will be in contact with you shortly to facilitate the Honorary Research Appointment/s.

The following conditions apply to this research project. These are additional to those conditions imposed by the Human Research Ethics Committee that granted ethical approval:

1. An annual progress report will be provided to the Research Governance Officer acknowledged by the LEAD HREC beginning in **August 2015.**
2. Proposed amendments to the research protocol or conduct of the research which may affect the ethical acceptability of the project, and are submitted to the lead HREC for review, are copied to the Research Governance Officer prior to implementation of the amendment on site.
3. Proposed amendments to the research protocol or conduct of the research which may affect the ongoing site acceptability of the project are to be submitted to the Research Governance Officer.

4. The relevant University HREC may require notification for projects that are undertaken by investigators holding an academic appointment (including conjoint appointments) or by students as part of a University course. This is the responsibility of the investigators.

Please note that only an electronic copy of this letter will be provided, if you require the original signed letter please contact the Research Office and we will be happy to provide this.

Should you have any queries about your project please contact the Research Office, Ph 8382 2075, email SVHS.Research@svha.org.au. The HREC Terms of Reference, Standard Operating Procedures, *National Statement on Ethical Conduct in Human Research* (2007) and the *CPMP/ICH Note for Guidance on Good Clinical Practice* and standard forms are available on the Research Office website to be found at: www.stvincents.com.au/researchoffice or at http://exwwwsvh.stvincents.com.au/researchoffice (internally)

Please quote **SVH file reference SVH 14/136** and **HREC reference HREC/14/SVH/171** in any correspondence.

Yours sincerely,

Sabine Giesebrecht
Research Governance Officer
St Vincent's Hospital Research Office
Level 6, de Lacy Building

TRIM REF: D/2014/39929

Appendix 5 Australian New Zealand Clinical Trials Registration Letter

Your ACTRN (registration number): ACTRN12614000943640

info@actr.org.au

Wed 3/09/2014 3:33 PM
To: Sabine Allida <Sabine.Allida@student.uts.edu.au>;
Dear Sabine Allida,

Re: Chewing gum to relieve thirst in chronic heart failure

Thank you for submitting the above trial for inclusion in the Australian New Zealand Clinical Trials Registry (ANZCTR).

Your trial has now been successfully registered and allocated the ACTRN: ACTRN12614000943640

Web address of your trial: http://www.ANZCTR.org.au/ACTRN12614000943640.aspx
Date submitted: 27/08/2014 12:03:14 PM
Date registered: 3/09/2014 3:33:13 PM
Registered by: Sabine Allida

If you have already obtained Ethics approval for your trial, could you please send the ANZCTR a copy of at least one Ethics Committee approval letter? A copy of the letter can be sent to info@actr.org.au (by email) OR (61 2) 9565 1863, attention to ANZCTR (by fax).

Please be reminded that the quality and accuracy of the trial information submitted for registration is the responsibility of the trial's Primary Sponsor or their representative (the Registrant).
The ANZCTR allows you to update trial data, but please note that the original data lodged at the time of trial registration and the tracked history of any changes made will remain publicly available.

The ANZCTR is recognised as an ICMJE acceptable registry (http://www.icmje.org/faq.pdf) and a Primary Registry in the WHO registry network (http://www.who.int/ictrp/network/primary/en/index.html).

If you have any enquiries please send a message to info@actr.org.au or telephone +61 2 9562 5333.

Kind regards,
ANZCTR Staff
T: +61 2 9562 5333
F: +61 2 9565 1863
E: info@actr.org.au
W: www.ANZCTR.org.au

1

Appendix 6 Agreement and Licensing for the KCCQ

OUTCOMES
Instruments, LLC

LICENSE AGREEMENT

THIS LICENSE AGREEMENT is made as of this 27 August 2014, by and between Outcomes Instruments, LLC, a for-profit organization in Missouri, whose address is 18 W. 52nd Street, Kansas City, Missouri, 64112, United States ("Licensor") and University of Technology, Sydney, Centre for Cardiovascular and Chronic Care, a not-for-profit organization in , whose address is Level 6, 235 Jones St, (Po Box 123)., Ultimo, 2007, Australia ("Licensee").

RECITALS

A. Licensor has rights in certain research methodologies, technical developments, know-how, discoveries, works of authorship, questionnaires, registries, study protocols, processes, datasets and other useful art, whether or not protected by patents, copyrights, trademarks, trade secrets or other laws protecting intellectual property rights, as more particularly described on Schedule A attached hereto and incorporated herein by this reference (the "Licensed Properties").

B. Licensee is engaged in that certain study more particularly described on Schedule B attached hereto and incorporated herein by this reference (the "Subject Study").

C. Licensor desires to grant Licensee the right to use the Licensed Properties solely in connection with the Subject Study, and Licensee desires to use the Licensed Properties in connection therewith, subject to all of the terms and conditions hereof.

NOW, THEREFORE, in consideration of the promises and the mutual promises and undertakings contained herein, the parties hereto agree as follows:

1. Grant of Limited License. Subject to the terms and conditions hereof, Licensor grants to Licensee a non-exclusive, non-transferable, non-assignable limited license to use the Licensed Properties solely in connection with the conduct of the Subject Study.
2. Ownership of Licensed Properties. As between Licensor and Licensee, Licensee acknowledges that Licensor retains all ownership rights in and to the Licensed Properties, and any improvements, modifications and derivatives thereof (whether prepared by Licensor or Licensee or otherwise), and that except for the rights granted hereunder, Licensee has no right, title or interest in and to the Licensed Properties. Licensee agrees to reproduce the appropriate copyright legends and/or trademark symbols on all written or displayed versions of the Licensed Properties and/or the results attributed to the use thereof. Licensee further acknowledges and understands that Licensor reserves the right to (i) grant others the license to use the Licensed Properties and (ii) use the Licensed Properties in its own research and investigations, without the need to account to Licensee in connection with such activities.
3. Fees. In consideration for the license granted hereunder, Licensee shall pay Licensor the license fees set forth on Schedule C attached hereto and incorporated herein by this reference, at the times, and in the manner, set forth on such Schedule.
4. Licensor's Representations and Covenants. Licensor represents and warrants to Licensee that Licensor has the full power and authority to execute and deliver this

Agreement and to perform its obligations hereunder without need to obtain the consent of any third party.

5. Site Visits. Licensor shall have the right to inspect and observe from time to time through such agents or representatives as Licensor may designate, on Licensee's site, the activities conducted by or for Licensee with respect to the Licensed Properties to determine whether Licensee is using the Licensed Properties in a proper fashion as provided hereunder. To the extent Licensor is granted access to a patient's "protected health information" ("PHI"), as such term is defined in the Health Insurance Portability and Accountability Act of 1996 and the regulations promulgated thereunder, the parties agree to negotiate and execute a Business Associates Agreement containing customary covenants regarding the confidentiality and limited use of such PHI.
6. Reports. Licensee shall keep and maintain comprehensive and accurate records pertaining to its use of the Licensed Properties, and the status and progress of the Subject Study. Such reports shall be available for examination by Licensor and its agents or representatives at any time upon reasonable advance notice.
7. Licensee's Conduct. Licensee agrees that it shall use the Licensed Properties only as permitted hereunder and further agrees to refrain from modifying, altering or amending the Licensed Properties or taking any action which could adversely affect the validity, goodwill and reputation thereof. Upon the termination or expiration of this Agreement, Licensee shall immediately discontinue all use of the Licensed Properties.
8. Litigation. As between Licensor and Licensee, only the Licensor shall have the right to commence or prosecute any claims or litigation to protect or enforce its rights in and to the Licensed Properties. Licensee agrees that it will immediately provide notice to Licensor upon learning of any litigation, whether actual or threatened, against Licensee in connection with Licensee's use of the Licensed Properties. Licensee further agrees that it will cooperate fully with Licensor by providing any information requested by Licensor in any litigation arising in connection with Licensee's use of the Licensed Properties.
9. Disclaimers; Limitations of Liability. LICENSEE ACKNOWLEDGES THAT THE LICENSED PROPERTIES ARE LICENSED "AS IS", WITH ALL FAULTS. LICENSOR HAS MADE NO REPRESENTATION OR WARRANTY THAT THE LICENSED PROPERTIES ARE SUITABLE FOR LICENSEE'S USE IN CONNECTION WITH THE SUBJECT STUDY. LICENSEE SHALL RELY ON ITS OWN JUDGMENT IN EVALUATING ITS USE OF THE LICENSED PROPERTIES AND ANY OUTCOMES ATTRIBUTABLE THERETO, WITHOUT RELYING ON ANY MATERIAL OR INFORMATION PROVIDED BY LICENSOR. LICENSOR DISCLAIMS ANY REPRESENTATIONS OR WARRANTIES, EXPRESS OR IMPLIED, INCLUDING WITHOUT LIMITATION ANY REPRESENTATIONS OR WARRANTIES AS TO THE LICENSED PROPERTIES' MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE. IN NO EVENT SHALL LICENSOR BE LIABLE FOR SPECIAL, CONSEQUENTIAL, EXEMPLARY OR PUNITIVE DAMAGES. LICENSOR'S LIABILITY HEREUNDER SHALL BE LIMITED TO LICENSEE'S DIRECT DAMAGES RESULTING FROM LICENSOR'S BREACH OF ANY OF ITS OBLIGATIONS HEREUNDER WHICH CONTINUES UNREMEDIED FOR THIRTY DAYS AFTER WRITTEN NOTICE BUT SHALL IN NO EVENT EXCEED THE AMOUNT OF THE FEES ACTUALLY PAID BY LICENSEE TO LICENSOR HEREUNDER.
10. Indemnification of Licensor. Licensee hereby agrees to hold Licensor harmless at and from and indemnifies it against any and all losses, liabilities, claims, damages and expenses (including attorneys' fees and expenses) which Licensor may incur or be obligated to pay, or for which it may become liable or be compelled to pay in any action, claim or proceeding for or by reason of any acts, whether of omission or commission, that may be claimed to be or are actually committed or suffered by Licensee arising out of Licensee's use of the Licensed Properties. The provisions of this paragraph and Licensee's obligations hereunder shall survive the expiration or termination of this Agreement.

11. Indemnification of Licensee. Subject to Section 9 hereof, Licensor hereby agrees to hold Licensee harmless of and from and indemnifies it against any and all losses, liabilities, claims, damages and expenses (including attorneys' fees and expenses) which Licensee may incur or be obligated to pay, or for which it may become liable or compelled to pay in any action, claim or proceeding for or by reason of any breach of any representation, warranty or agreement on the part of Licensor under this Agreement.
12. Nondisclosure. During the term of this Agreement, the parties may have access to trade secrets, proprietary information, or other sensitive materials belonging to the other which are not generally known to the public ("Confidential Information"). During the term of this Agreement and for a period of five (5) years after termination or expiration hereof, the receiving party ("Recipient") agrees to maintain in trust and confidence all Confidential Information of the other party (the "Disclosing Party"). The Recipient agrees to safeguard the Confidential Information using the same standard of care it uses to protect its own Confidential Information. The Recipient will not disclose any Confidential Information to any third party, or make any use thereof other than as expressly permitted hereby, without the prior written consent of the Disclosing Party. As used herein, Confidential Information does not include any information which the Recipient can demonstrate (i) was known to the Recipient or to the general public at the time of disclosure; (ii) was independently developed by the Recipient without the use of any of the Confidential Information; or (iii) was disclosed by a third party without violating any restriction or duty to the Disclosing Party.
13. Publications. Notwithstanding the general restrictions set forth in Section 12 above, the parties agree that publication of the results of research activities serves their mutual interests in improving the quality of health care. Accordingly, Licensee shall be free to publish the results of its research and development activities carried out with respect to the Licensed Properties and the Subject Study. Licensee agrees to refer to Licensor and the Licensed Properties in the bibliography section of the publication.
14. Term. Subject to the provisions of Section 15 hereof, this Agreement shall remain in effect from 09/01/2014 to 08/31/2015. Subsequent renewal of this Agreement shall be optionally available through application through the web site.
15. Licensor's Right to Terminate. Licensor shall have the right to immediately terminate this Agreement by giving written notice to Licensee in the event Licensee: (i) fails to perform any of its duties and obligations set forth herein, and the continuation thereof for thirty (30) days after notice; (ii) files a petition in bankruptcy or is adjudicated a bankrupt or insolvent, or makes an assignment for the benefit of creditors; (iii) makes any use of the Licensed Properties not otherwise expressly permitted here in or (iv) the Subject Study is cancelled, abandoned, withdrawn or suspended. In such event, Licensee shall immediately cease and terminate its use of any of the rights granted hereby and shall, upon the request of Licensor, return to Licensor all records, copies, documents, media and files making use of the Licensed Properties, or furnish evidence, satisfactory to Licensor, of the destruction thereof.
16. Equitable Remedies. The parties further acknowledge that the breach, whether threatened or actual, of any of the terms hereof by Licensee shall result in immediate, irreparable injury to Licensor and its goodwill and that accordingly, Licensor shall be entitled to apply for a preliminary and/or permanent injunction to restrain the threatened or actual violation of the terms hereof by the Licensee or to compel specific performance of the terms and conditions of this License Agreement. Nothing set forth herein shall be construed as prohibiting the Licensor from pursuing any other remedies available for such breach or threatened breach, including the recovery of damages and costs incurred, together with attorneys' fees.
17. Miscellaneous.

e. This Agreement together with the exhibits hereto constitutes the entire understanding between the parties with respect to this Agreement. No change or modification of any of the provisions of this Agreement shall be effective unless memorialized by an instrument in writing signed by the parties hereto. All notices required or permitted to be given hereunder shall be given in writing, to the parties at their addresses set forth herein, or to such other address with respect to which notice has been given in accordance herewith. Whenever possible, each provision of this License Agreement shall be interpreted in such a manner as to be effective and valid under applicable law. If any covenant or other provision of this Agreement, or portion thereof, under circumstances not now contemplated by the parties, is invalid, illegal or incapable of being enforced, by reason of any rule of law, administrative order, judicial decision or public policy, all other conditions and provisions of this Agreement shall, nevertheless, remain in full force and effect, and no covenant or provision shall be deemed dependent upon any other covenant or provision unless so expressed herein. The parties desire and consent that the court or other body making such determination shall, to the extent necessary to avoid any unenforceability, so reform such covenant, term, condition or other provision or portion of this Agreement to the minimum extent necessary so as to render the same enforceable in accordance with the intent herein expressed.

b. This Agreement shall inure to the benefit of Licensor, its successors and assigns. Licensee shall not have the right to assign this Agreement, or delegate its duties, by operation of law or otherwise, without first obtaining the written consent of Licensor.

c. This Agreement shall be governed by and construed in accordance with the laws of the State of Missouri.

IN WITNESS WHEREOF, the parties hereto have caused this Agreement to be duly executed as of the day and year first above mentioned.

Outcomes Instruments, LLC	**University of Technology, Sydney, Centre for Cardiovascular and Chronic Care**
By: John Spertus	By: Professor David Robson
Title: President	Title: Director, Research and Innovation Office
"Licensor"	"Licensee"

SCHEDULE A: LICENSED PROPERTIES

KCCQ – English (Australia)
This version of the KCCQ has been designed for English-speaking patients in Australia. This zip file includes two PDF files: the KCCQ itself and scoring instructions.

SCHEDULE B: DESCRIPTION OF STUDY

Project Name
A RandomisEd controLled triAl of chEwing gum to relieVE thirst in chronic heart failure (RELIEVE- CHF)

Project Type

Clinical Trial

Project Dates

Start: 09/01/2014

End: 08/31/2015

Duration: 364 days

Enrollment

Sites: 1

Average subjects per site: 150

Total enrollment: 150

Schedule of Use

Administer to subjects thus: Before the start of the intervention (baseline) and at the end of the intervention (4 week follow-up)

Total uses per subject: 2

Total uses: 300

Sponsor Name

University of Technology, Sydney

Sponsor Type

Other

SCHEDULE C: LICENSE FEES & PAYMENT TERMS

Payment Terms
Payable on Receipt

Total Instrument Fees

$ 345.00

Total License Fee

$ 345.00

Appendix 7 Participant Information and Consent Form

ST VINCENT'S HOSPITAL

Participant Information Sheet/Consent Form

Interventional Study - *Adult providing own consent*

St Vincent's Hospital, Sydney

Title	Randomised controlled trial of chewing gum to relieve thirst in chronic heart failure
Short Title	RELIEVE- CHF study
Protocol Number	Version 1.1
Project Sponsor	University of Technology Sydney
Coordinating Principal Investigator/ Principal Investigator	A/Professor Chris Hayward
Associate Investigator(s)	Dr Phillip Newton, Sabine Allida, Dr Sally Inglis

Part 1 What does my participation involve?

1 Introduction

You are invited to take part in this research project. This is because you have a condition known as chronic heart failure. The research project is testing the use of chewing gum to relieve thirst for sufferers of chronic heart failure.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether or not you take part.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:
- Understand what you have read
- Consent to take part in the research project
- Consent to have the tests and treatments that are described
- Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

2 What is the purpose of this research?

The aim of this study is to find out if chewing gum can relieve thirst in people with chronic heart failure. Thirst is a common and burdensome symptom of chronic heart failure. The nature of this syndrome, medications, and dietary/fluid restrictions used to treat it causes thirst. Studies have shown chewing gum as an effective strategy in the management of thirst and dry mouth in people with other conditions. However, there is no evidence to support or refute the use of chewing gum in people with CHF. This project will provide important information in regards to the prevalence of thirst in chronic heart failure and the effectiveness/usefulness of chewing gum as a strategy to relieve thirst.

This research has been initiated by the study investigator, Associate Professor Christopher Hayward (St. Vincent's Hospital) and associate investigators Dr Phillip Newton (University of Technology, Sydney), Dr Sally Inglis (University of Technology, Sydney) and Professor Patricia Davidson (St. Vincent's Hospital). The results of this research will be used by the study investigator Sabine Allida to obtain a Doctor of Philosophy degree through the University of Technology, Sydney.

3 What does participation in this research involve?

You will be participating in a randomised controlled research project. Sometimes we do not know which treatment is best for treating a condition. To find out we need to compare different treatments. We put people into groups and give each group a different treatment. The results are compared to see if one is better. To try to make sure the groups are the same, each participant is put into a group by chance (random).

This research project has been designed to make sure the researchers interpret the results in a fair and appropriate way and avoids study doctors or participants jumping to conclusions.

There are no additional costs associated with participating in this research project, nor will you be paid. If you are randomised to the chewing gum group, the study Investigators will provide the chewing gum to you free of charge for the duration of the study. If you wish to continue chewing gum at the end of the study, you are allowed to do so at your own expense. The study investigator will not provide the chewing gum after the study.

4 What do I have to do?

There are no lifestyle or dietary restrictions involved in this study. You will continue to take your regular medication as prescribed by your doctor during this study. The study will be conducted over 2 weeks.

Each day for the first four days, at 7days and at 2 weeks, we will ask you to:

- Weigh yourself each morning after you first wake up but before you have had breakfast and record these measurements
- Complete questionnaires that measure the sensation of thirst at the end of each day and we will contact you over the phone at days 4, 7, and 14 to collect these measurements

a. If you have been allocated to chew gum, we will ask you to:
   - Chew one or two pieces of sugar free gum provided for at least 10 minutes, six times a day or as desired throughout the day when your mouth feels dry or when you are thirsty

b. If you have not been allocated to chew gum, you will not be given/asked to chew the gum provided at the time frame mentioned above. You can continue on with what you normally use/do to relieve your thirst.

If you feel that there has been benefit in the use of chewing gum at the end of 2 weeks and you wish to continue using it, you are allowed to do so. However, this will not be provided to you by us. We will continue to follow you up until 4 weeks.

Follow- up is at 4 weeks. During this we will ask you to:

- Complete questionnaires that measure the sensation of thirst and quality of life and we will contact you over the phone to collect these measurements

5 Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish the participant to take part, the participant does not have to. If you decide that the participant can take part and later change your mind, you are free to withdraw the participant from the project at any stage.

If you do decide that the participant can take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Your decision whether you can take part or not take part, or take part and then be withdrawn, will not affect your routine treatment, relationship with those treating you, or your relationship with St. Vincent's Hospital.

7 What are the alternatives to participation?

You do not have to take part in this research project to receive treatment at this hospital. Other options are available. Your study doctor will discuss these options with you before you decide whether or not to take part in this research project. You can also discuss the options with your local doctor.

8 What are the possible benefits of taking part?

We cannot guarantee or promise that you will receive any benefits from this research; however, possible benefits may include relief from thirst.

9 What are the possible risks and disadvantages of taking part?

This study will pose low risks to participants. This study does not involve invasive procedures. You may have none, some or all of the effects listed below, and they may be mild, moderate or severe. If you have any of these side effects, or are worried about them, talk with your study doctor. Your study doctor will also be looking out for side effects.

There may be side effects that the researchers do not expect or do not know about and that may be serious. Tell your study doctor immediately about any new or unusual symptoms that you get.

Many side effects go away shortly after treatment ends

Side Effect	How often is it likely to occur?	How severe might it be?	How long might it last?
Jaw pain	Occasionally	Not severe	Minutes to an hour

If you become upset or distressed as a result of your participation in the research, the study doctor will be able to arrange for counselling or other appropriate support. Any counselling or support will be provided by qualified staffs who are not members of the research project team. This counselling will be provided free of charge.

10 What if new information arises during this research project?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your study doctor will tell you about it and

discuss with you whether you want to continue in the research project. If you decide to withdraw, your study doctor will make arrangements for your regular health care to continue. If you decide to continue in the research project you will be asked to sign an updated consent form.

Also, on receiving new information, your study doctor might consider it to be in your best interests to withdraw you from the research project. If this happens, he/ she will explain the reasons and arrange for your regular health care to continue.

11 Can I have other treatments during this research project?

Whilst you are participating in this research project, you may be able to take some or all of the medications or treatments you have been taking for your condition or for other reasons. It is important to tell your study doctor and the study staff about any treatments or medications you may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments. You should also tell your study doctor about any changes to these during your participation in the research project. Your study doctor should also explain to you which treatments or medications need to be stopped for the time you are involved in the research project.

12 What if I withdraw from this research project?

If you decide to withdraw from the project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to discuss any health risks or special requirements linked to withdrawing.

If you do withdraw your consent during the research project, the study doctor and relevant study staff will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected by the sponsor up to the time you withdraw will form part of the research project results. If you do not want them to do this, you must tell them before you join the research project.

Part 2 How is the research project being conducted?

13 What will happen to information about me?

By signing the consent form you consent to the study doctor and relevant research staff collecting and using personal information about the participant for the research project. Any information obtained in connection with this research project that can identify the participant will remain confidential. Data collected as part of this study will be identified by the unique record number. All data collected will be filed and stored in a locked cabinet level 10 South St. Vincent's Hospital, Sydney for a period of 7 years. Only authorised study personnel will have access to study database which is password protected and stored study files stored data. Your information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law.

Information about you may be obtained from your health records held at this and other health services for the purpose of this research. By signing the consent form you agree to the study team accessing health records if they are relevant to participation in this research project.

It is anticipated that the results of this research project will be published and or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your permission. Only de-identified, aggregated data will be published.

Information about participation in this research project may be recorded in your health records.

In accordance with relevant Australian and/or New South Wales privacy and other relevant laws, you have the right to request access to the participant's information collected and stored by the study team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access the participant's information.

Any information obtained for the purpose of this research project that can identify you will be treated as confidential and securely stored. It will be disclosed only with your permission, or as required by law.

14 Complaints and compensation

If you suffer any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

15 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of St Vincent's Hospital, Sydney.

This project will be carried out according to the National Statement on Ethical Conduct in Human Research (2007). This statement has been developed to protect the interests of people who agree to participate in human research studies.

16 Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the principal study doctor on 8382 1111 or any of the following people:

Clinical contact person

Name	Julee McDonagh
Position	Heart failure clinical trial co-ordinator
Telephone	8382 3569
Email	Julee.mcdonagh@svha.org.au

For matters relating to research at the site at which you are participating, the details of the local site complaints person are:

Complaints contact person

Telephone	02 8382 2075
Email	SVHS.Research@svha.org.au

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Reviewing HREC approving this research and HREC Executive Officer details

Telephone	02 8382 2075
Email	SVHS.Research@svha.org.au

ST VINCENT'S HOSPITAL

Consent Form - *Adult providing own consent*

Title	Randomised controlled trial of chewing gum to relieve thirst in chronic heart failure
Short Title	RELIEVE- CHF study
Protocol Number	Version 1.1
Project Sponsor	University of Technology Sydney
Coordinating Principal Investigator/ Principal Investigator	A/Professor Christopher Hayward

Declaration by Participant

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to St Vincent's Hospital, Sydney concerning my disease and treatment for the purposes of this project. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the study without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

Name of Participant (please print) _____

Signature _____ Date _____

Name of Witness* to Participant's Signature (please print) _____

Signature _____ Date _____

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

ST VINCENT'S HOSPITAL SYDNEY

Form for Withdrawal of Participation - *Adult providing own consent*

Title	Randomised controlled trial of chewing gum to relieve thirst in chronic heart failure
Short Title	RELIEVE- CHF study
Protocol Number	Version 1.1
Project Sponsor	University of Technology Sydney
Coordinating Principal Investigator/ Principal Investigator	A/Professor Chris Hayward
Associate Investigator(s)	Dr Phillip Newton, Sabine Allida, Dr Sally Inglis

Declaration by Participant

I wish to withdraw from participation in the above research project and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me or my relationship with St. Vincent's Hospital.

Name of Participant (please print) _____

Signature _____ Date _____

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of and information concerning withdrawal from the research project.

Note: All parties signing the consent section must date their own signature.

RELIEVE-CHF Study

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Office use only

Subject ID | Subject Initials

Form 1

Instructions: Shade circles like this: ● Not like this: ⊘ Please print in BLOCK STYLE in the boxes

Section 1 Patient Profile

Date of birth D D / M M / Y Y Y Y Age ◯Female ◯Male

Admission status ◯ Emergency ◯ No ◯Outpatient

Date of Admission D D / M M / Y Y Y Y Length of stay days

Date of Discharge D D / M M / Y Y Y Y

Cause of Admission ◯ CV ◯ Non-CV ◯ Not applicable

If CV related, is it HF? ◯Yes ◯No ◯Not applicable

Precipitating factors

1 _____

2 _____

3 _____

4 _____

5 _____

Smoking status ◯Never smoked ◯Ex-smoker ◯Current smoker

Number of cigarettes smoked / day ☐ Number of years smoking /ed for ☐

Section 2 Charlson Index

◯ Myocardial infarction
◯ Congestive heart failure
◯ Peripheral vascular disease
◯ Cerebrovascular disease
◯ Dementia
◯ Chronic pulmonary disease
◯ Connective tissue disease
◯ Ulcer disease
◯ Mild liver disease
◯ Diabetes
◯ Hemiplegia
◯ Moderate or severe renal disease
◯ Diabetes with end organ damage
◯ Any tumor
◯ Leukemia
◯ Moderate or severe liver disease
◯ Metatastic tumor
◯ AIDS

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Form 1

Section 3 Previous Medical History

	Has the patient had any of the following conditions? No	Yes
Myocardial Infarction	○	○
Hypertension	○	○
High blood cholesterol	○	○
Type I Diabetes	○	○
Type II Diabetes	○	○
Heart Failure	○	○
Stroke/Mini Stroke	○	○
Mental Illness ○ Depression	○	○
Mental Illness ○ Other (eg Bi-polar, schizophrenia	○	○
Irregular Heart Beat / Atrial Fibrillation / Palpitations	○	○
Angina	○	○
Coronary Artery Disease	○	○
Vascular disease ○ Peripheral arterial disease	○	○
Vascular disease ○ Other - *Please specify*_____	○	○
Aneurysm *(Abdominal, thoracic)*	○	○
Heart Valve Condition	○	○
Pacemaker	○	○
Implanted Defibrillator	○	○
Renal Disease	○	○
Sleep Apnoea	○	○
Asthma / Lung Disease *(eg. Emphysema, COPD)*	○	○
Arthritis ○ Rheumatoid	○	○
Arthritis ○ Osteoarthritis	○	○
Eye disease / retinopathy	○	○
Migraine	○	○
Stomach ulcer	○	○
Cancer	○	○
Other serious condition Please specify _____	○	○

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Subject ID ☐☐☐☐ Subject Initials ☐☐☐

Form 1

Section 4 Blood test results

Blood chemistries

Date of test D D / M M / Y Y Y Y

Sodium	☐☐☐ mmol/L	ALT	☐☐☐ mmol/L
Potassium	☐.☐ mmol/L	AST	☐☐☐ mmol/L
Urea	☐☐.☐ mmol/L	GGT	☐☐☐ mmol/L
Creatinine	☐☐☐ umol/L	Alkaline Phosphate Level	☐☐☐ mmol/L
eGFR	☐☐☐	Calcium Level	☐.☐☐ mmol/L
Total Bilirubin	☐☐☐ umol/L	Corrected Calcium Level	☐.☐☐ mmol/L
Albumin	☐☐☐ g/L	Magnesium	☐.☐☐ mmol/L
Total Protein	☐☐☐ g/L	Phosphate	☐.☐☐ mmol/L
HbA1c	☐.☐☐ %	C-Reactive protein	☐☐.☐☐ mg/L
Homocysteine	☐☐☐ umol/L		

Haematology results

Red blood cells	☐.☐ $x10^{12}$/L	Haemoglobin	☐☐☐ g/L
Haematocrit	☐.☐☐	White blood cells	☐.☐☐ $x10^{9}$/L
Platelets	☐☐☐ $x10^{9}$/L	Fibrinogen	☐.☐ g/L

Coagulation studies

PT	☐☐ sec	INR	☐.☐
APTT	☐☐☐ sec		

Endocrinology

TSH	☐.☐ mIU/L	ft 3	☐☐.☐ pmol/L

Lipids

Fasting ◯Yes ◯No

Total cholesterol	☐.☐ mmol/L	HDL	☐.☐ mmol/L
LDL	☐.☐ mmol/L	Triglycerides	☐.☐ mmol/L

Were these bloods taken at time of admission? ◯Yes ◯No ◯Outpatient bloods

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Section 5 Current medications

	Generic name	Route	Dose	Unit	Frequency
1.					
2.					
3.					
4.					
5.					
6.					
7.					
8.					
9.					
10.					
11.					
12.					
13.					
14.					
15.					
16.					
17.					

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Section 6 Current medications

- ACE inhibitor
- Angiotensin Receptor Blocker
- Beta blocker
- Diuretic
- Anticoagulant
- Antiplatelet
- Digitalis
- Lipid lowering agent
- Nitrate
- Other vasodilator
- Antiarrhythmic

Section 7 Past Admission History

	Number of admission (s) in the past 12 months:		Total length of stay	
Emergency		times		days
Elective		times		days
Emergency room presentations only		times		

Section 8 Physical examination

Date of assessment D D / M M / Y Y Y Y

NYHA Class ○ I ○ II ○ III ○ IV

AKPS ○ 0 ○ 10 ○ 20 ○ 30 ○ 40 ○ 50 ○ 60 ○ 70 ○ 80 ○ 90 ○ 100

Heart rate beats/min

Respiratory rate breaths/min

SaO2 (Room air) %

Height cm

Weight . Kg

Blood pressure

$Lying_1$ / mm/Hg

$Sitting_1$ / mm/Hg

$Lying_2$ / mm/Hg

$Sitting_2$ / mm/Hg

RELIEVE-CHF Study

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Form 2

Instructions: Shade circles like this: ● Not like this: ⊘

Kansas City Cardiomyopathy Questionnaire

The following questions refer to your **heart failure** and how it may affect your life. Please read and complete the following questions. There are no right or wrong answers. Please mark the answer that best applies to you.

1. **Heart failure** affects different people in different ways. Some may mainly feel shortness of breath while others mainly feel fatigue. Please indicate how much you have been limited by **heart failure** (for example, shortness of breath or fatigue) in your ability to do the following activities over the past 2 weeks.

	Extremely limited	**Quite a bit** limited	**Moderately** limited	**Slightly** limited	**Not at all** limited	**Limited for other reasons or did not do the activity**
Dressing yourself	○	○	○	○	○	○
Showering / Bathing	○	○	○	○	○	○
Walking 1 block on level ground	○	○	○	○	○	○
Doing gardening, housework or carrying groceries	○	○	○	○	○	○
Climbing a flight of stairs without stopping	○	○	○	○	○	○
Jogging or hurrying (as if to catch a bus)	○	○	○	○	○	○

2. Compared with 2 weeks ago, have your symptoms of **heart failure** (for example, shortness of breath, fatigue, or ankle swelling) changed?

My symptoms of **heart failure** are now ...

Much worse	Slightly worse	Not changed	Slightly better	Much better	I've had no symptoms over the last 2 weeks
○	○	○	○	○	○

3. Over the past 2 weeks, how many times did you have **swelling** in your feet, ankles or legs when you woke up in the morning?

Every morning	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
○	○	○	○	○

4. Over the past 2 weeks, how much has **swelling** in your feet, ankles or legs troubled you?
It has been ...

Extremely troublesome	**Quite a bit** troublesome	**Moderately** troublesome	**Slightly** troublesome	**Not at all** troublesome	I've had **no swelling**
○	○	○	○	○	○

5. Over the past 2 weeks, on average, how many times has **fatigue** limited your ability to do what you wanted?

All of the time	Several times a day	At least once a day	3 or more times a week but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
○	○	○	○	○	○	○

6. Over the past 2 weeks, how much has your **fatigue** troubled you?
It has been ...

Extremely troublesome	**Quite a bit** troublesome	**Moderately** troublesome	**Slightly** troublesome	**Not at all** troublesome	I've had **no fatigue**
○	○	○	○	○	○

7. Over the past 2 weeks, on average, how many times has **shortness of breath** limited your ability to do what you wanted?

All of the time	Several times a day	At least once a day	3 or more times a week but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
○	○	○	○	○	○	○

8. Over the past 2 weeks, how much has your **shortness of breath** troubled you?
It has been ...

Extremely troublesome	**Quite a bit** troublesome	**Moderately** troublesome	**Slightly** troublesome	**Not at all** troublesome	I've had **no shortness of breath**
○	○	○	○	○	○

9. Over the past 2 weeks, on average, how many times have you been forced to sleep sitting up in a chair or with at least 3 pillows to prop you up becuase of **shortness of breath**?

Every night	3 or more times a week, but not every night	1-2 times a week	Less than once a week	Never over the past 2 weeks
○	○	○	○	○

10. **Heart failure** symptoms can worsen for a number of reasons. How sure are you that you know what to do, or whom to call, if your **heart failure** gets worse?

Not at all sure	**Not very** sure	**Fairly** sure	**Mostly** sure	**Completely** sure
○	○	○	○	○

11. How well do you understand what things you are able to do to keep you **heart failure** symptoms from getting worse (for example, weighing yourself regularly, eating a low salt diet etc.)?

Do not understand at all	Do not understand very well	Somewhat understand	Mostly understand	Completely understand
○	○	○	○	○

12. Over the past 2 weeks, how much has your **heart failure** limited your enjoyment in life?

It has **extremely** limited my enjoyment of life	It has limited my enjoyment of life **quite a bit**	It has **moderately** limited my enjoyment of life	It has **slightly** limited my enjoyment of life	It has **not limited** my enjoyment of life at all
○	○	○	○	○

13. If you had to spend the rest of your life with your **heart failure** the way it is right now, how would you feel about this?

Completely dissatisfied	Mostly dissatisfied	Fairly satisfied	Mostly satisfied	Completely satisfied
○	○	○	○	○

14. Over the past 2 weeks, how often have you felt discouraged or down in the dumps because of your **heart failure?**

I felt that way **all of the time**	I felt that way **most of the time**	I **occassionaly** felt that way	I **rarely** felt that way	I **never** felt that way
○	○	○	○	○

15. How much does your **heart failure** afffect your lifestyle? Please indicate how your **heart failure** may have limited your participation in the following activities over the past 2 weeks.

Please fill in one circle on each line

Activity	Extremely limited	Quite a bit limited	Moderately limited	Slightly limited	Not at all limited	Limited for other reasons or did not do the activity
Hobbies, recreational activities	○	○	○	○	○	○
Working or doing household chores	○	○	○	○	○	○
Visiting family or friends out of your home	○	○	○	○	○	○
Intimate or sexual relationships	○	○	○	○	○	○

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Form 2

Day 0

Visual Scale Analogue

Mark the line at the point that best describes how thirsty you have been in the last 24 hours.

not at all _____ *extremely*

Office use only ☐ mm

Numeric rating scale

Instructions: Shade circles like this: ● Not like this: ⊘

How is your thirst now?

No thirst at all									Worst thirst imaginable
1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○

How has your thirst been in the last ***24 hours*** on average?

No thirst at all									Worst thirst imaginable
1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○

What is the worst your thirst has been in the last ***24 hours***?

No thirst at all			Worst thirst imgainable
None	Mild	Moderate	Severe
○	○	○	☐

Note: The VAS line is not to scale

RELIEVE-CHF Study

Office use only

Subject ID ☐☐☐☐ Subject Initials ☐☐☐

Form 3

Day 1

Today's weight: ☐☐☐.☐ Kg

Visual Scale Analogue

Mark the line at the point that best describes how thirsty you have been in the last 24 hours.

not at all ——————————————— *extremely*

Office use only ☐ mm

Numeric rating scale

Instructions: Shade circles like this: ● Not like this: ⊘

How is your thirst now?

No thirst at all									Worst thirst imaginable
1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○

How has your thirst been in the last ***24 hours*** on average?

No thirst at all									Worst thirst imaginable
1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○

What is the worst your thirst has been in the last ***24 hours***?

No thirst at all			Worst thirst imgainable
None	Mild	Moderate	Severe
○	○	○	○

Note: The VAS line is not to scale

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Form 3

Day 2

Today's weight: ☐☐☐ . ☐ Kg

Visual Scale Analogue

Mark the line at the point that best describes how thirsty you have been in the last 24 hours.

not at all _____ *extremely*

Office use only ☐ mm

Numeric rating scale

Instructions: Shade circles like this: ● Not like this: ⊘

How is your thirst now?

No thirst at all									Worst thirst imaginable
1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○

How has your thirst been in the last ***24 hours*** on average?

No thirst at all									Worst thirst imaginable
1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○

What is the worst your thirst has been in the last ***24 hours***?

No thirst at all			Worst thirst imgainable
None	Mild	Moderate	Severe
○	○	○	☐

Note: The VAS line is not to scale

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Form 3

Day 3

Today's weight: ☐☐☐ . ☐ Kg

Visual Scale Analogue

Mark the line at the point that best describes how thirsty you have been in the last 24 hours.

not at all ——————————————— *extremely*

Office use only ☐ mm

Numeric rating scale

Instructions: Shade circles like this: ● Not like this: ⊘

How is your thirst now?

No thirst at all									Worst thirst imaginable
1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○

How has your thirst been in the last ***24 hours*** on average?

No thirst at all									Worst thirst imaginable
1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○

What is the worst your thirst has been in the last ***24 hours***?

No thirst at all			Worst thirst imgainable
None	Mild	Moderate	Severe
○	○	○	☐

Note: The VAS line is not to scale

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Form 3

Day 4

Today's weight: ☐☐☐ . ☐ Kg

Visual Scale Analogue

Mark the line at the point that best describes how thirsty you have been in the last 24 hours.

not at all ——————————————— *extremely*

Office use only ☐ mm

Numeric rating scale

Instructions: Shade circles like this: ● Not like this: ⊘

How is your thirst now?

No thirst at all									Worst thirst imaginable
1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○

How has your thirst been in the last ***24 hours*** on average?

No thirst at all									Worst thirst imaginable
1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○

What is the worst your thirst has been in the last ***24 hours***?

No thirst at all			Worst thirst imgainable
None	Mild	Moderate	Severe
○	○	○	○

Note: The VAS line is not to scale

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Form 3

Day 7

Today's weight: ☐☐☐ . ☐ Kg

Visual Scale Analogue

Mark the line at the point that best describes how thirsty you have been in the last 24 hours.

not at all ——————————————— *extremely*

Office use only ☐ mm

Numeric rating scale

Instructions: Shade circles like this: ● Not like this: ⊘

How is your thirst now?

No thirst at all									Worst thirst imaginable
1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○

How has your thirst been in the last ***24 hours*** on average?

No thirst at all									Worst thirst imaginable
1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○

What is the worst your thirst has been in the last ***24 hours***?

No thirst at all			Worst thirst imgainable
None	Mild	Moderate	Severe
○	○	○	☐

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Form 3

Day 14

Today's weight: ☐☐☐ . ☐ Kg

Visual Scale Analogue

Mark the line at the point that best describes how thirsty you have been in the last 24 hours.

not at all _____ *extremely*

Office use only ☐ mm

Numeric rating scale

Instructions: Shade circles like this: ● Not like this: ⊘

How is your thirst now?

No thirst at all									Worst thirst imaginable
1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○

How has your thirst been in the last ***24 hours*** on average?

No thirst at all									Worst thirst imaginable
1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○

What is the worst your thirst has been in the last ***24 hours***?

No thirst at all			Worst thirst imgainable
None	Mild	Moderate	Severe
○	○	○	☐

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Form 3

Day 28

Today's weight: ___ . ___ Kg

Visual Scale Analogue

Mark the line at the point that best describes how thirsty you have been in the last 24 hours.

not at all _____ *extremely*

Office use only ___ mm

Numeric rating scale

Instructions: Shade circles like this: ● Not like this: ⊘

How is your thirst now?

No thirst at all									Worst thirst imaginable
1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○

How has your thirst been in the last ***24 hours*** on average?

No thirst at all									Worst thirst imaginable
1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○

What is the worst your thirst has been in the last ***24 hours***?

No thirst at all			Worst thirst imgainable
None	Mild	Moderate	Severe
○	○	○	○

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Form 3

Instructions: Shade circles like this: ● Not like this: ⊘

Kansas City Cardiomyopathy Questionnaire

The following questions refer to your **heart failure** and how it may affect your life. Please read and complete the following questions. There are no right or wrong answers. Please mark the answer that best applies to you.

1. **Heart failure** affects different people in different ways. Some may mainly feel shortness of breath while others mainly feel fatigue. Please indicate how much you have been limited by **heart failure** (for example, shortness of breath or fatigue) in your ability to do the following activities over the past 2 weeks.

	Extremely limited	**Quite a bit** limited	**Moderately** limited	**Slightly** limited	**Not at all** limited	**Limited for other reasons or did not do the activity**
Dressing yourself	○	○	○	○	○	○
Showering / Bathing	○	○	○	○	○	○
Walking 1 block on level ground	○	○	○	○	○	○
Doing gardening, housework or carrying groceries	○	○	○	○	○	○
Climbing a flight of stairs without stopping	○	○	○	○	○	○
Jogging or hurrying (as if to catch a bus)	○	○	○	○	○	○

2. Compared with 2 weeks ago, have your symptoms of **heart failure** (for example, shortness of breath, fatigue, or ankle swelling) changed?

My symptoms of **heart failure** are now ...

Much worse	Slightly worse	Not changed	Slightly better	Much better	I've had no symptoms over the last 2 weeks
○	○	○	○	○	○

3. Over the past 2 weeks, how many times did you have **swelling** in your feet, ankles or legs when you woke up in the morning?

Every morning	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
○	○	○	○	○

4. Over the past 2 weeks, how much has **swelling** in your feet, ankles or legs troubled you?
It has been ...

Extremely troublesome	**Quite a bit** troublesome	**Moderately** troublesome	**Slightly** troublesome	**Not at all** troublesome	I've had **no swelling**
○	○	○	○	○	○

5. Over the past 2 weeks, on average, how many times has **fatigue** limited your ability to do what you wanted?

All of the time	Several times a day	At least once a day	3 or more times a week but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
○	○	○	○	○	○	○

6. Over the past 2 weeks, how much has your **fatigue** troubled you?
It has been ...

Extremely troublesome	**Quite a bit** troublesome	**Moderately** troublesome	**Slightly** troublesome	**Not at all** troublesome	I've had **no fatigue**
○	○	○	○	○	○

7. Over the past 2 weeks, on average, how many times has **shortness of breath** limited your ability to do what you wanted?

All of the time	Several times a day	At least once a day	3 or more times a week but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
○	○	○	○	○	○	○

8. Over the past 2 weeks, how much has your **shortness of breath** troubled you?
It has been ...

Extremely troublesome	**Quite a bit** troublesome	**Moderately** troublesome	**Slightly** troublesome	**Not at all** troublesome	I've had **no shortness of breath**
○	○	○	○	○	○

9. Over the past 2 weeks, on average, how many times have you been forced to sleep sitting up in a chair or with at least 3 pillows to prop you up becuase of **shortness of breath**?

Every night	3 or more times a week, but not every night	1-2 times a week	Less than once a week	Never over the past 2 weeks
○	○	○	○	○

10. **Heart failure** symptoms can worsen for a number of reasons. How sure are you that you know what to do, or whom to call, if your **heart failure** gets worse?

Not at all sure	**Not very** sure	**Fairly** sure	**Mostly** sure	**Completely** sure
○	○	○	○	○

11. How well do you understand what things you are able to do to keep you **heart failure** symptoms from getting worse (for example, weighing yourself regularly, eating a low salt diet etc.)?

Do not understand at all	Do not understand very well	Somewhat understand	Mostly understand	Completely understand
○	○	○	○	○

12. Over the past 2 weeks, how much has your **heart failure** limited your enjoyment in life?

It has **extremely** limited my enjoyment of life	It has limited my enjoyment of life **quite a bit**	It has **moderately** limited my enjoyment of life	It has **slightly** limited my enjoyment of life	It has **not limited** my enjoyment of life at all
○	○	○	○	○

13. If you had to spend the rest of your life with your **heart failure** the way it is right now, how would you feel about this?

Completely dissatisfied	Mostly dissatisfied	Fairly satisfied	Mostly satisfied	Completely satisfied
○	○	○	○	○

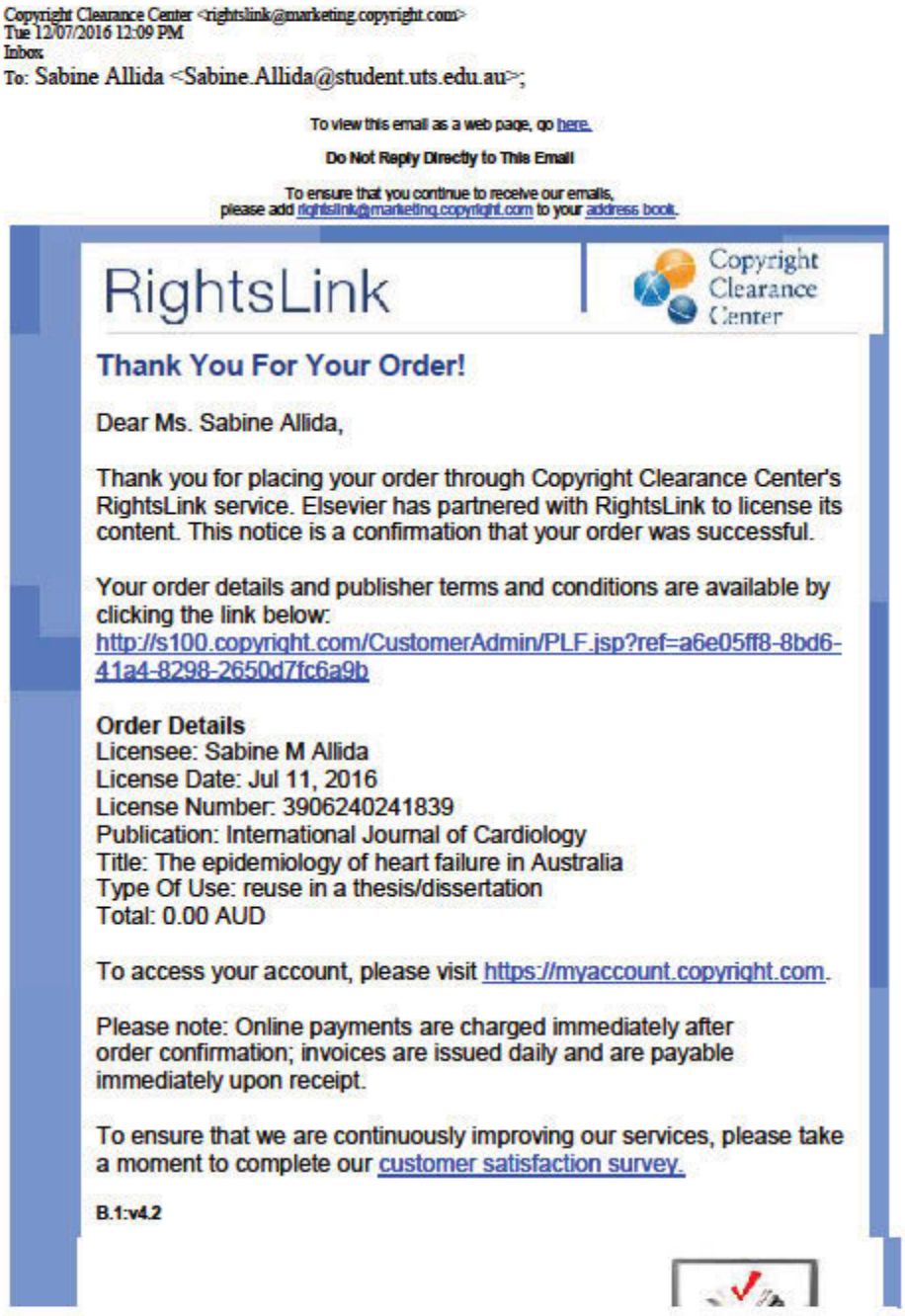
14. Over the past 2 weeks, how often have you felt discouraged or down in the dumps because of your **heart failure?**

I felt that way **all of the time**	I felt that way **most of the time**	I **occassionaly** felt that way	I **rarely** felt that way	I **never** felt that way
○	○	○	○	○

15. How much does your **heart failure** afffect your lifestyle? Please indicate how your **heart failure** may have limited your participation in the following activities over the past 2 weeks.

Please fill in one circle on each line

Activity	Extremely limited	Quite a bit limited	Moderately limited	Slightly limited	Not at all limited	Limited for other reasons or did not do the activity
Hobbies, recreational activities	○	○	○	○	○	○
Working or doing household chores	○	○	○	○	○	○
Visiting family or friends out of your home	○	○	○	○	○	○
Intimate or sexual relationships	○	○	○	○	○	○



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REVIEW

Thirst in chronic heart failure: a review

Sabine M Allida, Sally C Inglis, Patricia M Davidson, Sara Lal, Christopher S Hayward and Phillip J Newton

Aims and objectives. This review will (1) explore factors related to thirst in chronic heart failure and (2) describe interventions to alleviate thirst in chronic heart failure patients.

Background. Thirst is a common and troublesome symptom of chronic heart failure. Despite the burden and prevalence of this symptom, there are limited strategies to assist in its management.

Design. This is a review of literature on the burden of thirst, contributors to thirst and potential management strategies of thirst in patients with chronic heart failure.

Methods. Medline, Cumulative Index for Nursing and Allied Health, PubMed and Scopus were searched using the key words thirst, chronic heart failure, angiotensin II, fluid restriction and intervention. Of the 165 citations yielded, nine studies ($n = 9$) were included. The eligibility criteria included participants with confirmed diagnosis of chronic heart failure, randomised controlled studies or any studies with thirst as primary or secondary outcome, in humans and in English. There was no limit to the years searched.

Results. Factors related to thirst in chronic heart failure were condition; prolonged neurohormonal activation, treatment; pharmacological interventions and fluid restriction and emotion. No intervention studies were found in chronic heart failure patients. Interventions such as artificial saliva and chewing gum have been investigated for their effectiveness as a thirst reliever in haemodialysis patients.

Conclusion. Thirst is a frequent and troublesome symptom for individuals with chronic heart failure. It is highly likely that this contributes to poor adherence with fluid restrictions. Chewing gum can help alleviate thirst, but investigation in people with heart failure is needed.

Relevance to clinical practice. Increasing awareness of thirst and interventions to relieve it in clinical practice is likely to improve the quality of care for people with chronic heart failure.

What does this paper contribute to the wider global clinical community?

- Despite thirst being a common complaint in chronic heart failure patients, there is no systematic analysis of intervention in this group.
- This review shows that common chronic heart failure medications promote thirst.
- This review shows that impairment in inhibitory regulatory systems and prolonged neurohormonal activation are few of the many explanations of intense thirst in chronic heart failure.
- This review demonstrates that chewing gum may be a useful clinical tool in adhering to fluid-restricted therapy through elimination of thirst.

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Introduction

Thirst is a common and unpleasant symptom of chronic heart failure (CHF) (Waldréus *et al*. 2011). Despite this, there is very little scientific literature available to inform clinicians on how to best manage this troublesome symptom in daily practice (Allida *et al*. 2014). For healthy individuals, thirst is a simple symptom of dehydration which plays a vital role in maintaining body fluid homoeostasis through behavioural drinking (Fitzsimons 1992). While individuals may feel the sensation of thirst differently, CHF patients experience unabated thirst regardless of their low serum osmolality (inhibits thirst) (Waldréus *et al*. 2011). The need to drink is so intense that it eventually causes distress (Waldréus *et al*. 2011).

A number of factors facilitate the sensation of thirst in CHF. First, the pathophysiology of CHF involving prolonged activation of the renin–angiotensin–aldosterone system (RAAS) and other mechanisms of hormonal activation stimulates the thirst centre (Kenney & Chiu 2001). Second, CHF patients are commonly on high doses of diuretic therapy to treat fluid retention (Holst *et al*. 2003, 2008a, van der Wal *et al*. 2006). Xerostomia and loss of body water from this treatment also enhances the feeling of thirst. And lastly, fluid restriction prescribed to avoid fluid overload may also increase patient's perceived thirst (Waldréus *et al*. 2011). As a consequence, patients are constantly immersed in the thought of being thirsty and struggle to follow their fluid restriction due to thirst (Waldréus *et al*. 2011) Nonadherence to their fluid-restricted therapy can result to oedema, shortness of breath and fluid overload; leading to unnecessary hospitalisations. And in more life-threatening instances, pulmonary oedema may result (Holst *et al*. 2003).

In spite of the likely magnitude of this problem, there are limited data to inform interventions. And although, 'tricks of the trade' are used, for example, sucking ice chips, systematic evaluation of these methods is limited. To date, intervention studies such as artificial saliva and chewing gum to alleviate thirst has been performed in end-stage renal disease patients (Bots *et al*. 2005a), whom like CHF patients are also prescribed with a fluid-restricted therapy (Bots *et al*. 2005b). This review article seeks to: (1) explore factors related to thirst in CHF and (2) describe interventions to alleviate thirst in patients with CHF.

Conceptual framework

The Symptom Management Model states that to completely evaluate symptom experience, an assessment of distress, duration, frequency and intensity must be included (University of California San Francisco 1994). To date, the only conceptual framework on thirst was developed based on the adaptation of the Symptom Management Model (Welch 2002). And currently, there is no framework specifically addressing thirst in CHF. The framework proposes a positive relationship between thirst distress, duration, frequency and intensity (Welch 2002). In addition, it also states a positive association between thirst distress, duration, frequency and intensity, and interdialytic weight gain seen in people undergoing haemodialysis (Welch 2002). At present, thirst has no conceptual definition; however, many definitions of thirst describe it as a symptom. Due to these definitions suggesting thirst is subjective, using self-reported methods of measurement is appropriate. There are four different dimensions of thirst which were conceptualised in this framework. Conceptual definitions for each were as follows: thirst intensity (severity, strength or amount of thirst), thirst distress (degree to which a person is bothered by thirst), thirst duration (length of time that thirst is experienced by the person) and thirst frequency (how often during a day thirst is experienced by the person) (Welch 2002).

Methods

In March 2013, a review of literature on the burden of thirst, contributors to thirst and potential management strategies of thirst in patients with chronic heart failure was conducted. A literature search was performed in Medline, Cumulative Index for Nursing and Allied Health (CINAHL), PubMed and Scopus using a combination of keywords and MeSH headings shown in Table 1. The search terms had to be identified anywhere in the text. The search was restricted to humans and papers published in the English language. There were no limit to the years searched. One of the authors (S.M.A) reviewed the

Table 1 Search strategy

1	Heart failure/
2	Heart failure.mp.
3	Cardiac failure.mp.
4	Chronic heart failure.mp.
5	Congestive heart failure.mp.
6	Ventricular Dysfunction, Left/
7	Ventricular Dysfunction, Left.mp.
8	Thirst/
9	Thirst.mp.
10	Self-care/OR Self-care.mp.
11	Osmolality.mp.
12	Sodium/OR Sodium.mp.
13	Angiotensin II/OR Angiotensin II.mp.
14	Intervention/OR Intervention.mp.
15	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7
16	8 OR 9
17	10 OR 11 OR 12 OR 13 OR 14
18	15 AND 6
19	17 AND 18
20	Limit to ENGLISH language

abstracts and included the papers that fulfilled any of the following criteria: (1) studies were included for data extraction if the participants were patients with a confirmed diagnosis of CHF, (2) if the study was a randomised controlled trial (RCT) of human participants with thirst as a primary or secondary outcome, (3) any study design involving human participants with thirst as a specific outcome and (4) RCTs or any study design investigating interventions to alleviate thirst in participants with CHF. Intervention studies which included other patient populations, for example, terminally ill cancer patients and patients with Sjogren's syndrome were excluded as thirst experienced by these patients are caused by impairment of their salivary glands leading to hyposalivation. Studies which investigated thirst related to exercise and dehydration were also excluded. Lastly, a manual search of the reference list of the included studies was also performed.

Data extraction was completed by author SMA using a data extraction form. The data extracted included the study objectives, participant information, intervention and primary/secondary outcomes. The AMSTAR measurement tool was used to assess the quality of the included systematic review (Shea *et al.* 2009). The quality of evidence presented in the included studies was assessed using the Cochrane risk of bias tool (Higgins & Green 2011). There were no quantitative analyses performed. The results are presented as a narrative summary description of the individual studies and outcomes. The studies are summarised in Table 2.

From the search performed, there were 165 citations of which 157 were excluded (see Fig. 1). Reasons for exclusion included intervention studies with other patient populations and studies that looked at thirst related to exercise and dehydration. A hand search of the reference lists of eligible studies yielded an additional study. Therefore, a total of nine studies were included in the review; one was a systematic review, three were descriptive, and five studies were randomised controlled trials. The sample sizes ranged from 15–4375 participants. The total number of studied participants was 9298. Studies included participants with symptomatic CHF with NYHA classes II–IV, ranging in age from 62–80 years. The mean ejection fraction ranged from 23–45%. Participants included were hospitalised and community-based patients. Percentage of males in the study ranged from 51·3–84%. The countries of study were from North America, Sweden, Brazil and the Netherlands. Based on the Cochrane risk of bias assessment, the overall evidence of data included in the studies was of high quality and presented a low risk of bias, shown in Table 3. The systematic review included in this study was of high quality according to the AMSTAR rating scale of 8/11 (Table 4).

Results

Factors affecting thirst in CHF

There are many factors that contribute to the activation of the thirst response in CHF (Waldréus *et al.* 2013).

Condition

Chronic heart failure condition can also affect the thirst response. Despite their low serum osmolality (usually inhibits thirst), CHF patients still experience intense thirst (Waldréus *et al.* 2011). This unabated thirst is more likely due to the thirst-provoking effects of angiotensin II which activates peripheral and/or central thirst stimulatory pathways (Packer 1988). This central thirst stimulatory pathway is often primed in CHF which increases the expression of angiotensin 1 receptor in close proximity to the brain regions which controls water intake and vasopressin release (Packer 1992).

Prolonged neurohormonal activation in CHF

Prolonged neurohormonal activation may influence the fluid balance in patients with CHF in many ways. First, the central baroreceptors which inhibits the sympathetic nervous system and the release of vasopressin from the central nervous system (CNS) is impaired (Packer 1988, 1992). Due to the low cardiac output and blood pressure (clinical features of CHF), the central baroreceptors decrease the amount of inhibitory impulses to the brain; triggering the

Table 2 Summary of studies on thirst in CHF

Authors, year, country	Design	*n*	Participants	Intervention	Conclusion
Alici *et al.* (2013), Brazil	Randomised, blinded parallel-group study	75	ADHF and systolic dysfunction HF (60 year ± 11), male 69%, NYHA class III/IV, EF 26%	*Intervention group:* Fluid restriction of 800 ml/day and sodium restriction 800 mg/day *Control group:* Liberal fluid intake (at least 2.5 l) and sodium restriction (~ 3–5 g) intake	The intervention showed no benefit on weight loss or clinical stability The intervention significantly increased perceived thirst
Albert *et al.* (2013), USA	Randomised controlled pilot study	46	Hyponatraemic CHF (62·8 year ± 12·8), male 51·3%, NYHA III/IV	*Intervention group:* Daily fluid allowance of 1000 ml/day for 60 days and usual care discharge instructions and education *Control group:* Usual care discharge instructions and education	The strict allowance of 1000 ml/day improved quality of life at 60 days postdischarge There were no significant difference in the level of thirst and difficulty in adhering to fluid restriction
Waldréus *et al.* (2013), Sweden	Systematic review	4375	Stable CHF, Severe CHF, Hyponatraemic CHF, (44–83 year) NYHA I–III, III–IV, EF 32–45%		Thirst is distressing in patients with CHF, but there is limited knowledge on the causative factors Factors related to thirst are Treatment; fluid restriction, tolvaptan, emotion; anxiety and condition; NYHA class
Waldréus *et al.* (2011), Sweden	Open controlled study	48	Worsening CHF (80 years), male 31%, NYHA III–IV, EF 32%, Group B (80 years)	Assessed VAS, HRQoL, EQ 5D, urine analyses, NYHA class	Older patients perceive intensive thirst when admitted to hospital for worsening of HF
Reilly (2010), USA	Descriptive study	25	Stable CHF (44–83 years), male 56%, NYHA II–IV, EF 34%	Assessed level of thirst (TDS) and QoL	Distress: 46% reported moderate to strong discomfort from thirst
Philipson *et al.* (2010), Sweden	Randomised controlled study	30	Stable CHF (74 years), male 73%, NYHA II–IV, EF 34%	*Intervention group:* Reduced daily sodium intake to 2–3 g and restricted fluid to 1.5 l/day *Control group:* Provided general diet information in accordance with ESC guidelines.	Patients with moderate to severe HF were able to reduce their sodium and fluid intake without negative effects on thirst, appetite and QoL
Holst *et al.* (2008a,b), Sweden	Randomised cross-over study	65	Stable CHF (70 years), male 84%, NYHA I–III, EF < 45%	*Intervention 1:* Maximum fluid intake of 1.5 l/day for six weeks *Intervention 2:* Fluid intake based on 30–35 ml/kg body weight/day for six weeks	Sense of thirst and difficulties to adhere to fluid restriction were reduced by less strict fluid restriction
Konstam *et al.* (2007), USA	Randomised, double blind, placebo controlled study	4133	CHF (65 years), male 74%, NYHA III–IV, EF ≤ 40%	*Intervention 1:* Tolvaptan 30 mg once per day. In addition to standard therapy *Intervention 2:* Placebo for a minimum of 60 days. In addition to standard therapy	Tolvaptan caused increased thirst and dry mouth

Table 2 (Continued)

Authors, year, country	Design	n	Participants	Intervention	Conclusion
van der Wal *et al.* (2006), Netherlands	Descriptive cross-sectional design	501	Stable CHF patients (72 years ± 11, male 60%, NYHA II-IV, EF 39%	Assessed (CES-D), Revised Heart failure Compliance Scale, Dutch HF knowledge scale, HF belief scale	More than a third of patients (39%) had problems with it. The main problem was thirst (27%) 28% of patients answered they should drink more in case of thirst

ADHF, acute decompensated heart failure; HF, heart failure; CHF, chronic heart failure; EF, ejection fraction; LVEF, left ventricular ejection fraction; VAS, Visual Analogue Scale; HRQoL, health-related quality of life; ESC, European Society of Cardiology; QoL, quality of life; EQ-5D, European Quality of life index in five dimensions; 6MWT, Six-minute walk tests; NYHA, New York Heart Association; MLWHFQ, Minnesota living with HF questionnaire; NYHA, New York Heart Association; TDS, Thirst Distress Scale.

release of vasopressin from the CNS (Packer 1988, 1992). In addition, the normal feedback system which restores the inhibitory regulation of neurohormonal activity is impaired in persons with CHF (Johnson & Thunhorst 1997). Second, renin secretion induced by a reduction in blood volume or hypovolaemia evident in CHF dramatically increases the plasma concentration of angiotensin II to a level which can activate the cerebral thirst mechanism (Fitzsimons 1992). Lastly, decreased arterial pressure and volume can lead to elevated vasopressin levels often observed in patients with CHF (Johnston *et al.* 1987). Nonetheless, no studies were found specifically addressing the role of these factors in thirst in CHF.

Treatment

Though pharmacological and nonpharmacological interventions are designed to manage symptom burden in CHF, many patients with CHF associate these interventions with troublesome thirst (Waldréus *et al.* 2013).

Pharmacological intervention

There were no studies investigating the effect of common pharmacotherapies used to manage symptoms in CHF on thirst (See Table 5). However, it is possible that pharmacological agents also stimulate the thirst response. Increased thirst may be associated with the loss of body water caused by diuretic use (Szady & Hill 2009). Aldosterone antagonists, ACE inhibitors and angiotensin receptor blockers increases thirst by decreasing sodium and water concentration in the blood (Sica & Prakash 2001). However, the only drug reported to increase thirst in CHF was tolvaptan, a vasopressin receptor antagonists (Konstam *et al.* 2007).

Fluid restriction

Patients also reported fluid restriction to be associated with burdensome thirst (Holst *et al.* 2008a,b, Albert *et al.* 2013, Aliti *et al.* 2013). In the intervention study by Holst *et al.* (2008a,b), patients with stable CHF undergoing fluid restriction scored higher in the Visual Analogue Scale (VAS) (median 51, interquartile range [IQR] 16–89) in comparison to those on liberal fluid intake (23 (6–53); $p < 0{\cdot}001$) (Holst *et al.* 2008a). Similarly, another intervention study by Aliti *et al.* (2013) also showed a greater perceived sense of thirst from an aggressive fluid restriction (800 ml/day) compared to a liberal fluid intake (2·5 l). The intervention group had a higher score in the VAS (5·1 ± 2·9) compared to the control group (3·44 ± 2·0) ($p = 0{\cdot}01$) (Aliti *et al.* 2013). In contrast, Albert *et al.* (2013) found no significant differences in the level of thirst

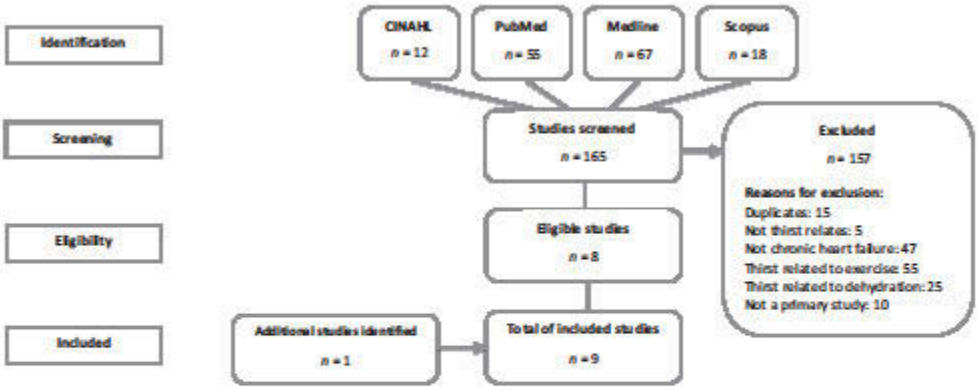

Figure 1 Flow chart of the article search on thirst in chronic heart failure.

Table 3 Risk of bias assessment

Studies	Random sequence generation assessed	Allocation concealment assessed	Blinding of participants, personnel and outcome assessors assessed	Incomplete outcome data assessed	Selective outcome reporting assessed
Aliti *et al.* (2013)	Low risk	Low risk	Low risk	Low risk	Low risk
Albert *et al.* (2013)	Low risk	Low risk	Low risk	Low risk	Low risk
Waldréus *et al.* (2011)				Low risk	Low risk
Reilly (2010)				Low risk	Low risk
Philipson *et al.* (2010)	Low risk	Low risk	Low risk	Low risk	Low risk
Holst *et al.* (2008a,b)	Low risk	Low risk	High risk	Low risk	Low risk
Konstam *et al.* (2007)	Low risk	Low risk	Low risk	Low risk	Low risk
van der Wal *et al.* (2006)				Low risk	Low risk

between hyponatraemic CHF patients in the control group (50 (12·5–73·8)) and those on 1000 ml/day fluid therapy (40 (20–51·3); $p = 0·60$) at 60-day follow-up (Albert *et al.* 2013).

Emotion

Of all the psychological factors, anxiety was found to have a significant impact on the intensity of thirst. One study with anxious CHF patients ($n = 15$) graded their thirst higher (median = 85 mm) compared to eight patients without anxiety (median = 57; $p < 0·04$) (Waldréus *et al.* 2011).

Interventions to relieve thirst

There were no intervention studies with the purpose of relieving thirst in CHF. Ingestion of ice cubes, cold drinks and peppermint or buttermilk candies were among the following strategies advised to CHF patients experiencing thirst (van der Wal *et al.* 2010). Although no intervention studies were found in patients with CHF, three studies had thirst as a secondary outcome measure. The first study compared the effects of fluid-restricted therapy vs. liberal fluid intake on quality of life and thirst, physical activity and hospitalisations. In comparison to the fluid restriction (17 ml/kg/day), liberal fluid intake (23 ml/kg) had a favourable effect on the level of thirst. Those on fluid restriction were found to have scored higher (median 51, interquartile range [IQR] 16–89) in comparison to those on liberal fluid intake (23 (6–53); $p < 0·001$) (Holst *et al.* 2008a).

In contrast, another intervention study by Philipson *et al.* (2010) examined if CHF patients can reduce their fluid intake without negative effects on thirst, appetite and quality of life. After 12 weeks of intervention, they found no significant changes to thirst between baseline and follow-up in both the fluid restriction and control group (54 ± 15–46 ± 17 vs. 50 ± 19–48 ± 26) (Philipson *et al.* 2010). The last study investigated the effect of 1000 ml/day fluid restriction on quality of life, thirst, all-cause death and

Table 4 AMSTAR rating for the systematic review

	Waldréus *et al.* (2013) Thirst in chronic heart failure – a systematic literature review
1 Was an '*a priori*' design provided	No
2 Was there duplicate study selection and data extraction?	Yes
3 Was a comprehensive literature search performed?	Yes
4 Was the status of publication used as an inclusion criteria	Yes
5 Was a list of studies (included and excluded) provided?	No
6 Were the characteristics of the included studies provided?	Yes
7 Was the scientific quality of the included studies assessed and documented?	Yes
8 Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes
9 Were the methods used to combine the findings of studies appropriate?	Yes
10 Was the likelihood of publication bias assessed?	No
11 Was the conflict of interest included?	Yes

Table 5 Common chronic heart failure medications that stimulate the thirst response and its effect on the thirst pathway

Pharmacological treatment	Examples	Effect on the thirst pathway
Loop diuretics	Frusemide	• Activates the RAAS; increasing the levels of angiotensin II • Activation of the thirst centre leads to vasopressin release • The end result is enhanced thirst
Aldosterone antagonists	Spironolactone	• Blocks the binding of aldosterone to its cytoplasmic receptor; increasing serum sodium concentration (a stimulus for thirst)
Angiotensin-converting enzyme (ACE) inhibitors	Perindopril	• Reduces circulating levels of angiotensin II; decreasing aldosterone secretion • This leads to reduction in sodium reabsorption • The end result is thirst
Angiotensin receptor blockers (ARBs)	Losartan	• Competitively antagonises angiotensin type I receptor; completely blocking angiotensin II action • The end result is similar to that of ACE inhibitors
Vasopressin receptor antagonist	Tolvaptan	• Inhibits vasopressin from binding to its receptor, promoting diuresis • The end result is thirst

hospitalisations in hyponatraemic CHF patients. The study also found no significant differences in the level of thirst between hyponatraemic CHF patients in the control group (50 (12·5–73·8)) and those on 1000 ml/day fluid therapy (40 (20–51·3)); $p = 0·60$) at 60-day follow-up (Albert *et al.* 2013).

Two studies also explored the use of artificial saliva and chewing gum in patients with end-stage renal disease undergoing haemodialysis. The first one was a cross-over intervention study of comparing the effects of chewing gum vs. artificial saliva on thirst and xerostomia for two weeks. Chewing gum was able to reduce the mean Xerostomia Inventory (XI) scores significantly from 33·2 ± 9·1–29·7 ± 8·4; $p < 0·05$ (Bots *et al.* 2005a,b). In both the treatment modalities, no overall treatment effect was found. The Dialysis Thirst Inventory (DTI) scores were comparable between artificial saliva spray (15·5 ± 5·0) and chewing gum (15·4 ± 4·8) (Bots *et al.* 2005a). However, both treatments were able to reduce the DTI scores from baseline 16·6 ± 5·1) (Bots *et al.* 2005a,b).

The other study examined whether a three-month use of chewing gum would relieve thirst and xerostomia in chronic haemodialysis patients. No significant changes were achieved in the patient's self-reported xerostomia. At baseline, 29% of the participants reported experiencing xerostomia frequently (Jagodzińska *et al.* 2011). After the three-month chewing gum treatment, this figure increased to 35% and after one month of the intervention, it was reduced to 25% (Jagodzińska *et al.* 2011). On the other hand, there was a slight change in the frequency of self-reported thirst. Before starting the intervention, 41% of patients reported experiencing thirst frequently (Jagodzińska *et al.* 2011). After the chewing gum intervention, the frequency was reduced to 40% and at one month after the intervention, it was further reduced to 35% (Jagodzińska *et al.* 2011).

Discussion

This review elucidated that thirst is a burdensome symptom commonly experienced by CHF patients. As presented, nine studies which investigated thirst in CHF were retrieved from the electronic search. Although the studies were difficult to compare due to their differences in aims and methods, the following studies are still evidence that thirst is a growing problem in CHF patients especially if they are following a fluid restriction which is not sufficient to relieve their thirst.

It is clear that prolonged neurohormonal activation such as the release of angiotensin II and vasopressin to increase cardiac output and tissue perfusion may explain the constant feelings of thirst in patients with CHF. However, there is lack of evidence to support this idea and identifying each of their physiological roles in the control of drinking still presents many setbacks (Ramsay 1989). Factors such as emotion may also influence the thirst response. Waldréus *et al.* (2011) found that patients who were anxious scored the highest thirst intensity (Waldréus *et al.* 2011). The relationship between anxiety and thirst might be due to the activation of the sympathetic nervous system and worsening CHF (Levine *et al.* 1982). In addition, pharmacological agents administered to correct neurohormonal derangement in CHF may also influence the thirst response. One of the many examples is administration of diuretics to manage fluid retention (Finkel *et al.* 2009). While it is efficient in relieving symptoms of fluid retention, diuretics interact with the renin–angiotensin system increasing the circulating levels of angiotensin II (Goldsmith *et al.* 1983, Grönhagen-Riska 1986), a potent thirst activator.

In addition, other medications such as ACE inhibitors and angiotensin receptor blockers can also affect the thirst response. Several studies on ACE inhibitors and angiotensin receptor blockers have been undertaken to examine their ability to affect the processes controlled by angiotensin II. While an increase in dose of both drug classes will lead to greater central nervous system penetration and hence greater inhibition of the thirst mechanism (Sica & Prakash 2001), it is important to consider that the thirst mechanism is an integrated system. Therefore, another pathway of fluid regulation also becomes affected, that is, decreasing serum sodium and water concentration; causing an increase in sodium appetite followed by thirst. Tolvaptan therapy was the only drug reported to increase thirst in CHF (Konstam *et al.* 2007). This may be explained by its ability to antagonise vasopressin from binding to its receptor; increasing excess fluid excretion; as a result a surge in thirst frequency is often observed (Konstam *et al.* 2007). Although these are evident, confounding variables such as route of administration, dosage and duration of dose make it difficult to assess the quantitative contribution of different drug classes to the levels of angiotensin II/vasopressin to thirst (Sica & Prakash 2001). This emphasises the need for further studies on classes of drugs as their specific effect on the thirst drive has been poorly studied.

Fluid restriction is an important part of nonpharmacological interventions, however thirst is an unpleasant consequence of this (Holst *et al.* 2008b). A reported 23% and 73% of patients with CHF have difficulties with a fluid-restricted diet due to thirst (Jaarsma *et al.* 2000, de Geest *et al.* 2003, van der Wal *et al.* 2010). Although it is poorly evaluated, fluid restriction is still widely used based on logical reasoning that it reduces burden on the heart. The studies showed conflicting results. Albert *et al.* (2013) concluded that a strict allowance (1000 ml/day) in fluid therapy may be beneficial for hyponatraemic CHF patients (Albert *et al.* 2013). Their findings showed improvements in quality of life at 60 days postdischarge (Albert *et al.* 2013). Similarly, Philipson *et al.* (2010) demonstrated that patients with moderate to severe CHF were able to undergo a fluid-restricted therapy without negative effects on thirst (Philipson *et al.* 2010). In contrast, Holst *et al.* (2008a,b) showed that a liberal fluid intake (30–35 ml/kg body weight/day) based on body weight alleviates thirst (Holst *et al.* 2008b). Correspondingly, Aliti *et al.* (2013) also support the findings of Holst and colleagues. They have found that a strict fluid restriction was associated with significantly greater perceived thirst.

Difference in research methodologies and populations enrolled in the studies may be accountable for the differences in findings. The population recruited in a study by Holst *et al.* (2008a,b) consisted of patients who were previously unstable with systolic dysfunction, Aliti *et al.* (2013) recruited patients with acute decompensated heart failure/systolic dysfunction, while Albert *et al.* (2013) enrolled patients with both reduced or preserved ejection fraction and hyponatraemia. In addition, Holst *et al.* (2008a,b) used a cross-over design with 1500 ml/day, then 30 ml/kg/day interventions for 16 weeks, and Aliti *et al.* (2013) with a randomised blinded trial of 800 ml/day for seven days compared to a fluid restriction of 1000 ml/d for an eight-week period by Albert *et al.* (2013). A randomised controlled trial in a larger sample using a multicentre approach is needed to produce generalisable findings. As low adherence to fluid restriction is a common precipitant for readmission to hospital in CHF and adversely affects quality of life (van der Wal *et al.* 2006), systematically exploring therapeutic strategies to alleviate thirst in this cohort is warranted.

There were no intervention studies specifically addressing thirst in patients with CHF. However, there were several strategies recommended to patients to relieve thirst such as ingestion of ice cubes. The results presented on the effects of liberal fluid intake on thirst were inconclusive (Holst *et al.* 2008a,b, Philipson *et al.* 2010, Albert *et al.* 2013). However, studies on interventions such as chewing gum and artificial saliva spray to alleviate thirst in end-stage renal disease are available (Bots *et al.* 2005a, Jagodzińska *et al.* 2011). Although the following studies were not conducted on CHF patients, thirst experienced by these patients is also caused by either an imbalance in fluid regulation due to their condition or a fluid-restricted diet which is very similar to patients with CHF. Therefore, the following interventions may be considered a useful clinical tool in adhering to a fluid-restricted therapy in CHF.

The first study found no overall treatment effect between artificial saliva and chewing gum (Bots *et al.* 2005a). Artificial saliva was reported to reduce perceived thirst, but had no effect on xerostomia (Kenney & Chiu 2001). Although results of both treatment modalities were comparable, it is important to consider participants opinion and preference from both interventions. Chewing gum was preferred by most of the participants in the study for several reasons. First, chewing gum was found to be more effective in relieving thirst than artificial saliva ($5{\cdot}5 \pm 2{\cdot}7$ vs. $3{\cdot}3 \pm 2{\cdot}6$; $p < 0{\cdot}001$) (Jagodzińska *et al.* 2011). This effect is speculated to be due to the saliva stimulating capacity of gum. Second, the gum was easier to use than the artificial saliva ($7{\cdot}6 \pm 2{\cdot}3$ vs. $6{\cdot}7 \pm 2{\cdot}9$; $p < 0{\cdot}050$). Participants also reported that the gum tastes better than artificial saliva spray ($7{\cdot}3 \pm 2{\cdot}2$ vs. $6{\cdot}0 \pm 2{\cdot}5$; $p < 0{\cdot}001$). And lastly, majority of the participants was willing to use chewing gum longer than artificial saliva [46/65 (70%) vs. 25/65 (39%)]. The overall findings rated chewing gum as the better strategy in terms of its effectiveness, ease of use and taste.

In comparison to this, Jagodzińska *et al.* (2011) also explored the use of chewing gum in chronic haemodialysis patients. Although, participants were subjected to a three-month use of chewing gum, no significant changes to either xerostomia or thirst were found (Jagodzińska *et al.* 2011). However, this may be explained by poor compliance to the intervention and the tool used to measure xerostomia and thirst. It is likely that a three-month period of treatment may result to poorer compliance compared to a two-week intervention period. In addition, the tools used to measure thirst and xerostomia in this study involved a 19 multiple choice questionnaire as opposed to using a validated thirst and xerostomia tool.

Although the use of chewing gum or artificial saliva spray shows ambiguous results, participant's satisfaction response shows that the use of chewing gum may be promising. Therefore, the need to perform rigorous randomised controlled trials, where CHF patients are tested to see if chewing gum or artificial saliva can intervene with thirst is crucial. More studies which explore the incidence and causes of thirst in CHF are also needed to raise awareness and stimulate research on interventions to help relieve chronic thirst in CHF patients.

Conclusion

In summary, the RAAS, vasopressin, plasma osmolality and the lower centres of the brain play a significant role in promoting fluid intake. Various factors elicit the thirst response. It is clear that neurohormonal activation associated with CHF also influences fluid regulation. However, its role in the context of thirst still remains unknown. Although studies have speculated that elevated angiotensin II and vasopressin and disturbances in plasma osmolality may explain the feelings of thirst in CHF patients, this is insufficient to draw conclusions. Moreover, administration of drugs which should improve neurohormonal derangement in CHF also causes thirst. With the addition of recommended fluid restriction, a struggle between adherence to treatment and their own to desire to quench thirst, adversely affects their QoL. Artificial saliva and chewing gum are the very few strategies trialled to alleviate thirst in another patient population, with recommendations of use of lemon, ice chips and small sips of water in CHF. Among the two interventions, chewing gum was reported as the most effective and most preferred due to its ease of use and taste by most participants. More research is needed to understand how the CHF condition and treatment affects the thirst mechanism. Lastly, interventions such as chewing gum to alleviate thirst in CHF patients warrant investigation through appropriately powered randomised controlled study designs.

Relevance to clinical practice

Chronic heart failure is a progressive and burdensome syndrome with thirst as a major reason for noncompliance to self-care practices such as fluid restriction (van der Wal *et al.* 2006, Holst *et al.* 2008a,b, Waldréus *et al.* 2011). Due to the life threatening effects of nonadherence to fluid-restricted therapy (National Heart Foundation of Australia & the Cardiac Society of Australia & New Zealand 2011), increasing the awareness of thirst in clinical

practice is pivotal to reduce unnecessary hospitalisations. Systematic evaluation of available strategies such as chewing gum is essential in ensuring that the best possible management is provided to CHF patients in clinical care settings.

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The authors have confirmed that all authors meet the ICMJE criteria for authorship credit (www.icmje.org/ethical_1author.html), as follows: (1) substantial contributions to conception and design of, or acquisition of data or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content and (3) final approval of the version to be published.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Measurement of thirst in chronic heart failure – A review

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ABSTRACT: *Background: Thirst is a bothersome symptom of chronic heart failure (CHF) which impacts adversely on quality of life. Despite this, limited work has been done to investigate thirst as a symptom or to develop reliable and valid measures of thirst in CHF. The purpose of this manuscripts is to establish which tools have been used in research to measure thirst in CHF. Methods: Medline, PubMed, Cumulative Index for Nursing and Allied Health, and Scopus were searched using following key words thirst, heart failure, measure, scale, randomised controlled trials and multicentre studies. Results: The search discovered 37 studies of which 6 studies met the inclusion criteria. One study was a research abstract and five were full-text studies. To date, there are only three measurement tools utilised in studies examining thirst in CHF patients [Visual Analogue Scale (VAS), Numeric Rating Scale and Thirst Distress Scale]. Conclusion: Thirst in CHF is measured in a non-systematic way. In recent studies, the VAS has been used to measure thirst intensity. While this measurement tool is very easy and quick to administer, using a uni-dimensional tool in conjunction with a multi-dimensional tool may be beneficial to capture all dimensions of thirst. In order to manage thirst efficiently, consistent measurement of thirst in CHF is vital.*

KEYWORDS: thirst, heart failure, measures, Visual Analogue Scale

Chronic heart failure (CHF) is a common, progressive, and debilitating syndrome. It is the leading cause of hospitalisation and deaths (Stewart, Ekman, Ekman, Odén, & Rosengren, 2010; Teng, Finn, Hobbs, & Hung, 2010). Although the treatment of CHF continues to advance, most patients still suffer from symptoms and consequences of treatment, which affects quality of life (Waldréus, Hahn, & Jaarsma, 2013; Waldréus, Sjöstrand, & Hahn, 2011). While breathlessness is the main focus of scientific literature on symptoms, thirst, on the other hand is rarely discussed (Waldréus et al., 2013). Unlike breathlessness, to date there is no standardised definition of thirst. However, it has been defined as 'the desire to drink caused by physiological and behavioural cues as a result of deficit in water' (Greenleaf, 1992). There are several factors which promotes thirst in CHF. Increased activation of neurohormonal systems can activate the thirst centre, dry mouth and loss of body water from diuretic therapy also enhances thirst and fluid restriction may also increase patient's perceived thirst (Holst, Strömberg, Lindholm, & Willenheimer, 2008a, 2008b; Waldréus et al., 2013).

Research into alleviating thirst has largely been conducted in patients with end-stage renal disease undergoing haemodialysis (Bots, Brand, Veerman, Korevaar, et al., 2005; Bots, Brand, Veerman, Valentijn-Benz, et al., 2005). Attention has been focussed on reducing thirst to help patient's compliance with fluid restriction, in order to avoid excessive interdialytic weight gain and associated complications (Bots, Brand, Veerman, Korevaar, et al., 2005; Bots, Brand, Veerman, Valentijn-Benz, et al., 2005; Welch, 2002). In clinical practice, a growing number of CHF patients also complain of troublesome thirst (Nordgren & Sörensen, 2003). Thirst is also the main reason for non-compliance with fluid restricted therapy (Holst et al., 2008a, 2008b). Similar to patients on haemodialysis, excessive fluid ingestion can result in oedema, shortness of breath and fluid overload (Krum et al., 2006; National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand, 2011). In more serious instances, pulmonary oedema or hospitalisation may result (Krum et al., 2006; National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand, 2011). Assessment and management

of symptoms are imperative to monitor progress and the impact of symptoms on outcomes. Symptom experience is multi-dimensional which means it includes not only the presence or absence of symptoms, but also its frequency, severity and distress. To date, symptom assessment remains challenging as standardised symptom measures are still lacking for CHF patients. At present, limited work has been done to investigate the symptom of thirst or to develop reliable and valid measures of thirst in CHF. The purpose of this manuscript is to establish which tools have been used in research to measure thirst in CHF.

Methods

In November 2013, a literature search was performed in Medline, Cumulative Index for Nursing and Allied Health Literature (CINAHL), and Scopus using all of the following key words: thirst, heart failure, cardiac failure, left ventricular dysfunction, measure, rating, scale, clinical trials, randomised controlled trials and multicentre studies. The search was restricted to humans and papers published in the English language. There were no limit to the years searched. One of the authors reviewed the abstracts and retrieved studies which met the following inclusion criteria: (i) studies had to include participants with a confirmed diagnosis of CHF and (ii) the study had to be either a randomised controlled trial or any study design involving human participants using a subjective measure of thirst as either a primary or secondary endpoint. Studies in other patient populations and not thirst related were excluded. The studies are summarised in Table 1.

One of the authors used a data extraction form to extract the following data; study objectives, participant information, measurement tool to measure thirst and the outcomes. The Cochrane risk of bias tool was used to assess the quality of the included studies (Higgins & Green, 2011). Quantitative analyses were not performed. A narrative description of the individual studies results is presented.

Results

Study selection

The search discovered 37 studies of which 31 were excluded. Reasons for exclusion included studies which examined other patient populations ($N = 11$) and were not thirst related ($N = 8$). Therefore, six studies met the inclusion criteria (Figure 1) (Albert, Nutter, Forney, Slifcak, & Tang, 2013; Holst et al., 2008a, 2008b; Philipson, Ekman, Swedberg, & Schaufelberger, 2010; Reilly, Meadows, Dunbar, Culler, & Smith, 2010; Waldréus et al., 2011). Of all the studies included, two were descriptive (Reilly et al., 2010; Waldréus et al., 2011) and four were randomised controlled studies (Albert et al., 2013; Holst et al., 2008a, 2008b; Philipson et al., 2010). One study was a research abstract (Reilly et al., 2010) and five were full-text studies (Albert et al., 2013; Holst et al., 2008a, 2008b; Philipson et al., 2010; Waldréus et al., 2011). Sample sizes ranged from 25 to 75 participants, yielding a combined sample size of 286 participants. Studies included participants with symptomatic CHF with NYHA Class I–IV, ranging in age from 44 to 83 years. The mean ejection fraction ranged from 23 to 45%. Participants included were hospitalised and community-based patients. The majority were male [$N = 215$ (31–84%)] in the study. The overall evidence of data included in the studies was of high quality and presented a low risk of bias based on the Cochrane risk of bias assessment (see Table 2).

Measurement tools used in CHF

There were three different types of tools used to measure thirst. Most of the studies (5) used a unidimensional tool (Albert et al., 2013; Aliti et al., 2013; Holst et al., 2008b; Philipson et al., 2010; Waldréus et al., 2011). These were the Visual Analogue Scale (VAS) (4) (Aliti et al., 2013; Holst et al., 2008b; Philipson et al., 2010; Waldréus et al., 2011) and a Numeric Rating Scale (NRS) (1) (Albert et al., 2013) (see Table 3). Only one study used a multi-dimensional tool (Reilly et al., 2010). This study used the Thirst Distress Scale (TDS) to measure thirst frequency, duration and distress. Thirst was the primary endpoint in three studies (Holst et al., 2008b; Reilly et al., 2010; Waldréus et al., 2011) and secondary endpoint in three (Albert et al., 2013; Aliti et al., 2013; Philipson et al., 2010).

None of the studies looked at all the dimensions of thirst. Only one study had any data on the

TABLE 1: STUDIES USING SPECIFIC UNI-DIMENSIONAL SCALE AND MULTI-DIMENSIONAL QUESTIONNAIRES TO ASSESS THIRST FREQUENCY, INTENSITY AND DISTRESS IN C HF PATIENTS

Author, year, country	Study design	Sample size, N	Participants	Thirst measurement	Study finding
Aliti et al. (2013), Brazil (Aliti et al., 2013)	Randomised, blinded parallel-group study	75	ADHF and systolic dysfunction HF (60 ± 11 years), 69% male, NYHA III/IV, EF 26%	VAS (0–100 mm)	Thirst intensity: 5.1 ±2.9 in the intervention group (800 ml/day) and 3.44 ± 2.0 in the control group (at least 2.5 l); $P = 0.01$
Albert et al. (2013), USA (Albert et al., 2013)	Randomised controlled pilot study	46	Hyponatraemic CHF (62.8 ± 12.8 years), 51.3% male, NYHA III/IV	NRS (0–10)	Thirst intensity: Thirst was scored 50 mm with usual care and the intervention (1000 ml/day); $P = 0.77$
Waldréus et al. (2011), Sweden (Waldréus et al., 2011)	Descriptive controlled cross-sectional study	23 (A) CHF + 25 (B) without CHF	A: Worsening HF (80 years), 31% male, NYHA III/IV, EF 32%; B: (80 years)	VAS (0–100 mm)	Thirst intensity: Group A scored 75 and 25 mm in group B ($P < 0.0001$)
Philipson et al. (2010), Sweden (Philipson et al., 2010)	Randomised prospective study with an intervention and control group	30	Stable CHF (74 years), 73% male NYHA II–IV, EF 34%	VAS (0–100 mm)	Thirst intensity: At baseline groups A and B scored 54 and 50 mm, respectively. After 12 weeks group A scored 45 mm and group B with 48 mm
Reilly et al. (2010), USA (Reilly et al., 2010)	Descriptive study	25	Stable HF (44–83 years), NYHA II–IV, EF 23%	TDS 6-item scale	Distress from thirst: 46% reported moderate to strong discomfort from thirst
Holst et al. (2008a), Sweden (Holst et al., 2008b)	Randomised crossover study	65	Stable HF (70 years), 84% male, NYHA I–III, EF <45%	VAS (0–100 mm)	Thirst intensity: 51 mm with strict fluid restriction (1.5 ml/day) and 23 mm in liberal fluid intake (30 ml/kg/day); $P < 0.001$ Thirst intensity: A change of –6% in thirst from strict fluid restriction (1.5 ml/day) and –24% in those on liberal fluid intake (30 ml/kg/day); $P < 0.05$

CHF, chronic heart failure; HF, heart failure; ADHF, acute decompensated heart failure; EF, ejection fraction; NYHA, New York Heart Association; VAS, Visual Analogue Scale; TDS, Thirst Distress Scale; NRS, Numeric Rating Scale.

FIGURE 1: PRISMA FLOWCHART FOR SELECTING THE INCLUDED STUDIES

TABLE 2: RISK OF BIAS ASSESSMENT

Studies	Random sequence generation assessed	Allocation concealment assessed	Blinding of participants, personnel and outcome assessors assessed	Incomplete outcome data assessed	Selective outcome reporting assessed
Aliti et al. (2013)	Low risk	Low risk	Low risk	Low risk	Low risk
Albert et al. (2013)	Low risk	Low risk	Low risk	Low risk	Low risk
Waldréus et al. (2011)				Low risk	Low risk
Reilly et al. (2010)				Low risk	Low risk
Philipson et al. (2010)	Low risk	Low risk	Low risk	Low risk	Low risk
Holst et al. (2008a)	Low risk	Low risk	High risk	Low risk	Low risk

frequency and distress of thirst (Reilly et al., 2010) while the remaining five studies only measured thirst intensity (Albert et al., 2013; Holst et al., 2008a, 2008b; Philipson et al., 2010; Waldréus et al., 2011).

DISCUSSION

Optimal and complete evaluation of any symptom such as thirst must include measuring frequency, intensity, quality and distress (Dodd et al., 2001; Lenz, Suppe, Gift, Pugh, & Miligan, 1995). These dimensions of thirst are important as they represent the patient's overall symptom experience (perception, evaluation and response to symptoms) (Dodd et al., 2001; University of California, San Francisco School of Nursing Symptom Management Faculty Group, 1994). This is crucial in understanding the barriers to effective symptom management strategies and improvement in symptom outcomes. Despite this, there seems to be no consensus among researchers on which tool should be used to measure all of the dimensions of thirst (frequency, quality, intensity, distress). As exemplified, none of the studies included in this review looked at all the dimensions of thirst (Albert et al., 2013; Aliti et al., 2013; Holst et al., 2008b; Philipson et al., 2010; Reilly et al., 2010; Waldréus et al., 2011). Only one study measured the frequency and distress of thirst (Reilly et al., 2010). Intensity was the most measured dimension of thirst among the studies (Albert et al., 2013; Aliti et al., 2013; Holst et al., 2008a, 2008b; Philipson et al., 2010; Waldréus et al., 2011). This is also evident in past research, however reasons for this remains unknown. Measurement of thirst intensity is a major disadvantage as thirst cannot be accurately described and measured on the basis of intensity

TABLE 3: UNI-DIMENSIONAL AND MULTI-DIMENSIONAL TOOLS OF THIRST

Name of tool	Commentary
Uni-dimensional tool	
Numeric Rating Scale	– A horizontal scale ranging from 0 to 10 with a statement (0 = no thirst at all; 10 = extreme thirst) anchored at either end. Patients are asked to circle the number that best describes thirst – A widely used and validated scale in pain and breathlessness
Visual Analogue Scale	– A horizontal line of 100 mm with a statement (0 mm = no thirst at all; 100 mm = extreme thirst) anchored at each end. Patients are asked to mark a line at the position that best represents how thirsty they are. This mark is then measured in mm from the zero mark by the researcher – A widely used and validated scale in pain and breathlessness
Multi-dimensional tool	
Thirst Distress Scale	– A six-item scale scored based on a four-point Likert scale assessing thirst distress (0 = no distress; 4 = very distress) – A widely used and validated scale for assessing thirst distress in patients undergoing haemodialysis – Reliable and • Good item correlation, all items scored within the range (≥0.30 but <0.70) • Achieved standard deviations ranging from 0.95 to 1.04 suggesting good variability • All items scored 0.94 in the goodness-of-fit index suggesting a good fit • Chi-square of 40.70 and 9 degrees of freedom was achieved indicating a good data model fit – Valid • All items in the scale scored a factor loading between 0.59 and 0.81 which indicates validity of each item

alone. Therefore, it may be beneficial to use both uni-dimensional and multi-dimensional tool in order to capture all aspects of thirst to more accurately reflect the patient symptom experience. For instance, the TDS only measures the frequency, duration and distress of thirst (Reilly et al., 2010; Welch, 2002) and so, the VAS can then measure the other dimension of thirst (intensity) (Gift & Narsavage, 1998; Waldréus et al., 2011).

While this may also suggests a lack of weighting placed on thirst dimensions in current research, it is important to note that there is very limited number of studies which investigate thirst (Albert et al., 2013; Holst et al., 2008a, 2008b; Philipson et al., 2010; Reilly et al., 2010; Waldréus et al., 2011). Moreover, there are only three different tools recently used to measure thirst with none of them specifically designed to measure thirst in CHF (Albert et al., 2013; Reilly et al., 2010; Waldréus et al., 2011). Further research into measurement and perhaps management of thirst in this patient population is needed.

The review has also found very little methodological research to develop a tool to assess thirst and there is still a lack of focus on thirst as a symptom of CHF. Patients often use a characteristic language to describe a particular symptom dimension and it is necessary to assess what these words mean to the population. For example, some patients may not describe their thirst as thirst, but as dry mouth or a nuisance. Therefore, it is important to understand the use and meaning of language for the patient. At present, using a validated tool for pain/breathlessness to measure thirst is invalid and inappropriate as these tools were specifically designed to assess the following symptoms in a particular patient population.

There were also limited research on thirst distress as the primary endpoint. This may yet again be explained by the recent emergence of research in

this area. Overall, some of the studies reported thirst as the primary endpoint (Holst et al., 2008a, 2008b; Philipson et al., 2010; Waldréus et al., 2011), particularly those involving fluid restriction. However, most of these studies are underpowered and used either a uni-dimensional or a multi-dimensional tool only. Thirst was most often self-assessed using a uni-dimensional tool such as the VAS (Albert et al., 2013; Aliti et al., 2013; Holst et al., 2008a, 2008b; Philipson et al., 2010; Waldréus et al., 2011). Only one study utilised a multi-dimensional tool, i.e., TDS (Reilly et al., 2010). However, findings from this study are very limited as only the abstract of the trial was published (Reilly et al., 2010).

Uni-dimensional tools

Uni-dimensional tools measure a single dimension of the patient's symptom experience such as intensity. While this eliminates responder burden, uni-dimensional tools can oversimplify patient symptom experience. Uni-dimensional tools most often used are the VAS and the NRS.

Visual Analogue Scale/Numeric Rating Scale

The VAS and the NRS have been widely used and validated in pain and breathlessness research (Gift, 1989; Gift & Narsavage, 1998). Both have the advantage of being administered to patients' quickly, easily and subjectively. It avoids imprecise descriptive terms seen in the categorical scales (Gift, 1989). However, depending on the patient's interpretation, the anchoring text can influence the scores. At present, the VAS and the NRS have not been validated specifically for thirst.

There are certain disadvantages to the VAS which must be considered. While it can be quickly administered, the VAS is more demanding and requires greater cognitive skills (concentration, understanding and language skills) compared to the NRS. In fact, up to 26% of patients find it confusing. In addition, it is often difficult for some patients to convert a very subjective sensation such as thirst to a straight line (Gift, 1989). Mistakenly placing an × or a circle across the line may result in invalid results (Nordgren & Sörensen, 2003). Teaching patients how to use the scale or detailed instructions at the top of the scale was often provided to overcome this disadvantage (Gift, 1989; Guyatt, Townsend, Berman, & Keller, 1987). Nonetheless, this may be inadequate to overcome difficulties associated with accurately recalling previous sensations such as the amount of change experienced since the last measurement (Carlsson, 1983). This is often observed in patients with difficulties remembering previous experiences such as the elderly (Carlsson, 1983).

Moreover, problems in recording change in scores after repeated measurements may also arise (Gift, Plaut, & Jacox, 1986). However, success in recording change may be dependent on the patient population being studied (Carlsson, 1983). For instance, it is more likely to obtain stable measurements from patients with chronic diseases compared to patients with continuous changing sensations (Greenleaf, 1992). Patient expectations may also influence their scores (Welch, 2002). Patients are more likely to report a decrease in pain after receiving an intervention. However, this can be easily solved by using absolute values rather than change scores (Gift et al., 1986). Lastly, VAS was found to be less reproducible in comparison to NRS (Wilcock, Crosby, Clarke, & Tattersfield, 1999). However, the NRS is not necessarily linear. In comparison to a change from 1 to 2, a single point change from 7 to 8 may represent a greater subjective increase (Gift & Narsavage, 1998).

There are many benefits in using the VAS. It can be applied to measure different aspects or dimensions of thirst such as intensity (severity of thirst), distress (how much distress does thirst causes) and the timeframe (did the patient experience thirst now, over the past 24 hours and over the past 2 weeks) (Gift, 1989; Johnson, Oxberry, Cleland, & Clark, 2010). Therefore, it can also be applied as a multi-dimensional measure to assess thirst. In terms of its ability to measure thirst, the VAS is relatively similar to the TDS, i.e., one dimension remains unassessed. For example, the VAS may measure thirst intensity, distress and timeframe but not the frequency dimension. The choice to use one of either tool is still largely dependent on the researcher's familiarity and preference.

Multi-dimensional tool

Multi-dimensional tools assess multiple dimensions or component of symptoms experienced by

the patient. It gives a broader understanding of not just the intensity of the symptom but also the frequency of the symptom and its impact on the patient (distress).

Thirst Distress Scale

The TDS is a validated six-item scale based on a conceptual framework encompassing thirst distress, thirst duration and frequency (Welch, 2002). It was developed to provide a multi-dimensional measurement of thirst in patients undergoing haemodialysis. Similar to the VAS and the NRS, the TDS is also relatively easy to administer. Each item was scored based on a four-point Likert scale which assessed the relevance of thirst ranging from 1 (not relevant) to 4 (extremely relevant) (Welch, 2002). The patient can circle the number that best represents their subjective rating. The scores are summed which provided an overall individual score of 6 (no abnormal thirst) to 24 (thirst almost always present) (Welch, 2002). Thirst intensity is not measured in this scale; therefore it can be used alongside a uni-dimensional tool such as the VAS or the NRS to provide better overall representation of the patient's thirst experience.

Conclusion and recommendations

This review has shown that in order to better understand thirst, identify the causes of thirst, its prognostic significance in CHF and devise an effective management plan, there is a need for valid and reliable tools to measure thirst. At present, there are only three measurement tools utilised in studies examining thirst in patients with CHF. However, the following tools have not been validated for use in CHF patients. The VAS has been used primarily to measure thirst intensity in recent studies. This measurement tool is very easy and quick to administer to patients. It also has the advantage of being applied to measure various aspects of thirst, i.e., distress and timeframe (frequency and duration). However, using a uni-dimensional tool in conjunction with a multi-dimensional tool may be beneficial to capture all dimensions of thirst. The use of qualitative methodology combined with a quantitative study design will add more depth to our understanding of the patient's thirst experience. A consistent approach of measuring thirst in patients with CHF may help collate prevalence data needed to understand thirst in CHF. Consequently, developing management strategies to combat this bothersome symptom and improve patient's quality of life.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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A survey of views and opinions of health professionals managing thirst in chronic heart failure

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Background: Thirst is a common and burdensome symptom of chronic heart failure (CHF) which affects adherence to self-care practices specifically fluid restriction. Despite this, there is no standard clinical practice for managing the symptom of thirst. *Aims and objectives*: The aim is to identify the current strategies recommended by health professionals to help relieve thirst in CHF patients and their perceived usefulness of these strategies. *Methods*: A survey was distributed to attendees of the 8th Annual Scientific Meeting of Australasian Cardiovascular Nursing College. *Results*: There were 42 of 70 respondents to the survey. The majority (33 of 40; 82.5%) had recommended various strategies to alleviate thirst. The most recommended strategy was ice chips (36 of 38; 94.7%). Overall, the respondents reported 'some use' in all of the strategies. *Conclusion*: Information from this survey may help in the incorporation of thirst-relieving strategies into evidence-based guidelines; further improving the quality of care of patients.

Keywords: cardiovascular; self-care; survey; symptom control

Introduction

Chronic heart failure (CHF) is the syndrome describing the failure of the heart to maintain adequate circulation to meet the metabolic demands of the body (National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand, 2011). Structural and functional abnormalities resulting in impaired cardiac filling and ejection have mostly been implicated in conjunction with neurohormonal dysregulation (Cotter, Felker, Adams, Milo-Cotter, & O'Connor, 2008). Despite recent developments in medical treatment, many patients are still burdened with symptoms which affects their quality of life (Waldréus, Hahn, & Jaarsma, 2013; Waldréus, Sjöstrand, & Hahn, 2011). Patients with CHF experience a number of symptoms such as fatigue and shortness of breath. Among these symptoms, thirst is a common complaint in patients and the most rarely addressed.

Thirst is a subjective perception described by various sensations including dry mouth, lips and throat, light-headedness, tiredness, headache, loss of appetite and feeling of an 'empty'

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stomach (Kenney & Chiu, 2001). It has been defined as a 'desire to drink caused by physiological and behavioural cues as a result of deficit in water' and is one of the most common and troublesome symptoms of CHF (Waldréus et al., 2011, 2013). Several factors which promote thirst include the CHF condition, prescribed medications and self-care practices (Waldréus et al., 2013). Increased activation of neurohormonal systems often observed in CHF can stimulate the central thirst centre in the lateral hypothalamus (Curtiss, Cohn, Vrobel, & Franciosa, 1978; Epstein, Schrier, & Abraham, 1999; Packer, 1988; Unger & Li, 2004), xerostomia (dry mouth) and loss of body water from diuretic therapy to treat fluid retention also enhances thirst (Waldréus et al., 2013). Self-care practices such as weighing daily and fluid restriction are crucial in the management of CHF. Self-care involves cognitive decision-making based on the recognition of signs and symptoms, and processing these within the context of existing knowledge and prior experiences (Dickstein et al., 2010). However, self-care practices such as fluid restriction may also increase patient's perception of thirst (Holst, Strömberg, Lindholm, & Willenheimer, 2008a, 2008b; Philipson, Ekman, Swedberg, & Schaufelberger, 2010). Although thirst is vital in maintaining body homeostasis, in a chronic state such as CHF, thirst is potentially detrimental and is one of the main reasons for non-adherence with fluid restricted therapy (Holst et al., 2008a, 2008b; Unger & Li, 2004). Non-adherence with fluid restriction can lead to excessive fluid ingestion which can result in significant hyponatraemia manifesting clinically with lassitude and confusion in the most severe cases (Arieff, Llach, & Massry, 1976), as well as symptoms of fluid overload with symptoms of oedema, shortness of breath and fatigue (Krum et al., 2006; National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand, 2011). In more serious instances, pulmonary oedema may result (Krum et al., 2006; National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand, 2011).

To date, there is no prevalence data of thirst in CHF (Waldréus, van der Wal, Hahn, van Veldhuisen, & Jaarsma, 2014); however, findings from a study of symptom prevalence and symptom burden demonstrate symptoms such as dry mouth as much more prevalent compared to symptoms thought to be typical such as systemic oedema and a lack of appetite (Zambroski, Moser, Bhat, & Ziegler, 2005). Dry mouth was present in over 70% of patients in the study (Zambroski et al., 2005). It was reported to be frequent and severe and was quite a bit distressing in a third of patients (Zambroski et al., 2005). In addition, information from medical records also show a 9% frequency of persistent thirst in the last six months of life (Nordgren & Sörensen, 2003). Despite the enormity of this problem, there is very little scientific literature on thirst as a symptom (Allida et al., 2015) and there is no standard management of thirst in the clinical care setting. Thus, our aim was to (1) identify current strategies recommended by health professionals to their patients with CHF suffering from thirst and (2) identify their perceived usefulness of these strategies.

Methods

Design, setting and sample

This study utilised a descriptive study design. The survey was a brief questionnaire developed by the investigators using Survey Monkey™ which sought to assess the effectiveness of various strategies recommended to patient with CHF to relieve their thirst. The paper survey was distributed to the attendees of the 8th Annual Scientific Meeting of the Australasian Cardiovascular Nursing College, Gold Coast, Australia during one session on the first day of the conference in February 2014.

Measurements and item generation

Items were generated for the survey through a literature review (Allida et al., 2014) and piloting to minimise ambiguity and redundancies. This 3-item survey was adapted from another survey (Newton, Davidson, & Sanderson, 2012). Permission to reproduce these survey items was approved by the corresponding author. The survey was distributed in English. The survey ascertained basic demographics related to profession and primary area of specialty. Respondents were asked if they had recommended any strategies to help alleviate thirst to their patients suffering from CHF. For those who ticked 'yes' they had recommended any strategies, they were then asked if they had recommended to use the following; artificial saliva, ice chips, chewing gum, small sips of water, peppermint/buttermilk flavoured candies, cold water with a slice of lemon, lozenges and ice cold water. If they had recommended any of these strategies, they were asked what their perception is of the use of the following; some use, unsure or useful. In addition, they were also asked if they had recommended 'other' strategies not mentioned in the survey and specify what these strategies were. As this survey was adapted from a previously valid and reliable survey, the investigators did not feel the need to further validate this survey.

Data collection

The survey distribution was performed by two of the authors who also attended the conference. The paper survey was placed on all the delegates' chair during the session and were invited by the convenor to participate. A participant information sheet detailing the purpose of the study and what is involved in participating was attached at the front of the survey. A participant consent statement was also included and respondents were asked if they agree to participate in the survey. After agreeing to participate, the attendees were given time to complete the survey. At the end of the session, the surveys were collected from the attendees.

Ethical considerations

Ethics approval was received from the University of Technology, Sydney Research Ethics Committee. Subsequently, the conference committee approved the circulation of the survey.

Data management and analysis

The responses from the paper survey were entered into the online-based survey in Survey Monkey™. Data generated from this were exported into an Excel spreadsheet. Descriptive analyses were used to describe the sample and the responses to study variables. Data are reported as number (percentage) unless otherwise stated.

Results

Forty-two of 70 (58%) attendees completed the survey. The majority of the respondents were registered nurses (14 of 39; 36%) (Figure 1); with a primary area of specialty in coronary (19 of 40; 48%) and CHF care (18 of 40; 45%). Figure 1 presents the full results; demonstrating the other healthcare professionals that responded to the survey. Responses were received from Australian and New Zealand-based conference attendees with the majority of responses from Australia (37 of 40; 93%).

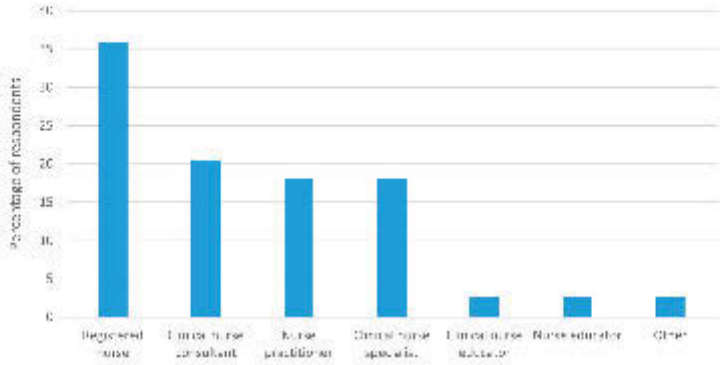

Figure 1. Professions of the respondents at the conference.

Strategies recommended to CHF patients

The majority of the respondents had recommended various strategies to alleviate thirst (33 of 40; 83%). The most recommended strategy to relieve thirst was ice chips (36 of 38; 95%). Peppermint/buttermilk flavoured candies were the least recommended strategy. Chewing gum was recommended by 20 of 33 (61%) respondents. The full result is presented in Figure 2.

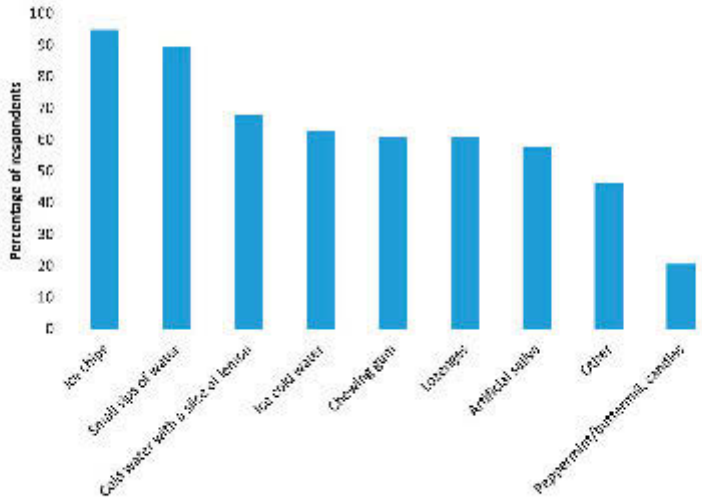

Figure 2. Percentage of health professionals recommending various strategies to relieve thirst.

Perceived usefulness of the recommended strategies

Based on their clinical judgement, the respondents reported 'some use' in all of the strategies. With ice chips as the most frequently recommended strategy, it was only reported to have 'some use' (18 of 36; 50%) in relieving patient's thirst by most of the respondents who had recommended this strategy. While some respondents have also reported ice chips as useful in alleviating their patient's thirst (12 of 36; 33%). In terms of the least recommended strategy, peppermint/buttermilk flavoured candies were predominantly reported to have 'some use' (4 of 7; 57%) in managing patient's thirst. The full result is presented in Figure 3.

Other strategies used to relieve thirst

Some respondents reported recommending 'other' (21 of 39; 54%) strategies apart from the list of strategies provided in the survey. The most common 'other' strategies include freezing fruits in ice cube trays or prepared ice blocks (Table 1). Some health professionals had also recommended developing a fluid plan to divide daily fluid intake and keeping a diary to remember it.

Discussion

Thirst is a common and troublesome symptom of CHF. To date, there is no standard clinical practice to manage thirst. Most of the thirst literature and clinical trials were conducted in people with malignant disease and end-stage renal disease. However, the strategies investigated in these populations may potentially be useful in alleviating thirst in CHF. As clearly demonstrated by the survey, CHF health professionals have recommended similar strategies to help relieve patients' thirst. Useful thirst-relieving strategies includes artificial saliva, chewing gum, peppermints, lozenges and ice chips. Incorporation of these strategies into evidence-based guidelines may improve thirst management in CHF, consequently; improving adherence to fluid restriction. However, as demonstrated most clinicians are either unsure or not convinced of their usefulness. The results also showed variability in perceived usefulness of the interventions which is expected as patients

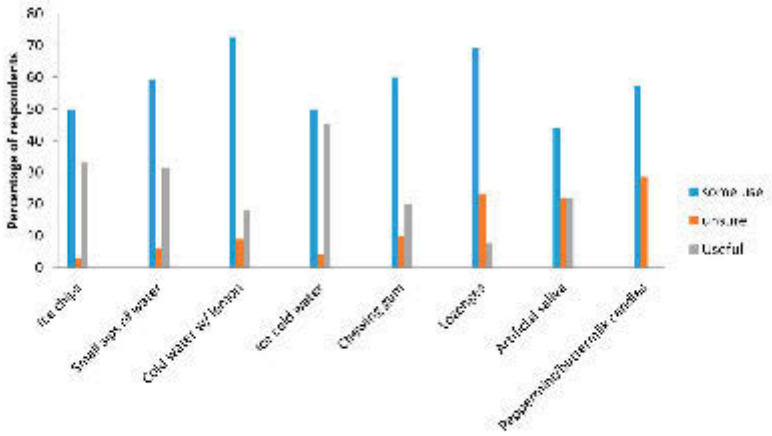

Figure 3. Perceived efficacies of various strategies.

Table 1. Other strategy used to relieve thirst specified by health professionals.

- Pacing out fluid across the day
- Some food, for example, small amounts of watermelon
- Freeze grapes, fruits, etc. in ice cube trays
- Drink small amounts often, for example, ½ a cup of tea
- Don't drink sweet drinks (real or artificial sugar)
- Avoid salty foods
- Iced fruit jellies
- Other commercially available liquids from pharmacy
- Distraction
- Mouthwash
- Washing mouth out and spitting water out
- Sipping from a bottle of ice water as it melts during the day
- Ice cubes
- Decanting fluid out of allowance into small bottle
- Sugar-free lozenges
- Spray atomizer water
- Fluid plan – breakfast, lunch and dinner; measure and divide total day intake – no sugary drinks
- Mints

experience relief from thirst differently. While some may experience relief for many hours, others only remain thirst free for an hour. Health professionals are often told varying effects of the intervention by their patients, as a result they can only report what they have been told. Future studies should aim at identifying the views of the patients on the usefulness of various strategies to relieve thirst. In addition, systematic investigation of these strategies through appropriately powered randomised trials is crucial in implementing these strategies in clinical and community care settings. The results of this survey were used to inform the design and the intervention of a clinical trial aiming to help relieve thirst in people with CHF; currently undergoing recruitment.

The results also show that some respondents also reported recommending 'other' strategies not listed in the survey (21 of 39; 54%). The most common strategies were freezing fruits in ice cube trays or home-made/prepared ice blocks. Moreover, some health professionals had also recommended developing a fluid plan to divide/distribute daily fluid intake and keeping a diary to remember it. Findings from a qualitative, descriptive study which examined compliance in CHF patients showed similar results. Patients reported using home-made 'ice-lollies' or ice cubes to prevent thirst (Van der Wal, Jaarsma, Moser, van Gilst, & van Veldhuisen, 2010). In addition, 66% (10 of 15) of patients also stated that they measure and distribute the amount of fluid they used throughout the day (Van der Wal et al., 2010). Other tips against thirst also included the advice to use less sugar (Van der Wal et al., 2010) which is aligned with the recommendations of health professionals in this survey.

This survey has also identified that nurses play an important role in the management of thirst. The patient/nurse relationship constitutes trust which enables discussion of problems related to fluid restriction, thirst and adherence. This then allows for advice to be given to patients on how to manage thirst and fluid restriction. Findings from the study by Van der Wal et al. (2010) show that patients do adapt some of the strategies they are advised (Van der Wal et al., 2010). Therefore, patient–nurse communication should be further encouraged in clinical practice.

Limitations

Our response rate of 58% (42 of 70) is better compared to other surveys of professional practice (Baldwin, Allgulander, Bandelow, Ferre, & Pallanti, 2012; Culshaw, Kendall, & Wilcock, 2012;

Daniel, Ndetan, Rupert, & Martinez, 2012; Newton et al., 2012; To et al., 2012; Weil, Gold, McIver, Rotstein, & Philip, 2012). However, it is still likely that the response rate of our survey would have been further improved had we been able to distribute our survey on both days of the conference or to another conference. Due to this respondents were limited to Australasian Cardiovascular Nursing College members who attended the conference. Secondly, as there were no similar studies to our survey, comparisons of our findings was difficult.

Another limitation in this study was the descriptive nature of the study design. Descriptive studies present the possibility for the lack of objectivity as the questions in this survey were predetermined and prescriptive. The use of a Likert scale also poses a disadvantage which involves its uni-dimensionality. Attitudes of the population for one particular item are vast and multi-dimensional. Therefore, providing three to five options of choice fails to measure the true attitudes of respondents. In addition, it is likely that respondents' answers to the previous questions will influence the next. Although these limitations are evident, Likert scale was chosen as it is easily understood and very easy to code when accumulating data. It is also unrestrictive in terms of how participants can respond to questions as opposed to yes/no. Convenience sampling used in this study is also another limitation. While this is efficient, it poses risk of bias which can lead to inaccuracy of our study findings. And lastly, in order to reduce respondent burden and improve the response rate of the survey, the investigators only collected information based on country of residence as opposed to states. As CHF management may vary between states in Australia, it may have been useful to obtain information of the states the respondents were from.

Conclusion

This survey shows that various strategies to relieve thirst are recommended to CHF patients. However, most healthcare professionals are unsure of their efficacy. Therefore, systematic evaluation of these methods is warranted. Although, strategies such as ice chips and chewing gum were reported useful in alleviating thirst by most healthcare professionals, identifying patients' perception of these strategies is crucial to provide useful insight on patient preferences. More research is needed to investigate the efficacy of these strategies in relieving thirst.

Relevance to clinical practice

Thirst greatly affects non-adherence to self-care practices such as fluid restriction. As demonstrated in this survey, there are many thirst-relieving strategies that clinicians can recommend or have recommended to patients. Systematic evaluation of these strategies is essential in incorporating these strategies into evidence-based guidelines to improve patient's quality of care.

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