Health in connection with takotsubo syndrome

Experiences, symptoms and utilization of health care

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Till minne av farmor och farfar -
ni fattas mig

ABSTRACT

Health is subjective, involves the whole person and cannot be determined by others. It is not merely the absence of disease and illness but a resource in life. Takotsubo syndrome (TS) is a form of acute, reversible heart failure that primarily affects postmenopausal women. The complete pathological mechanisms are unknown but connections to acute stress, for example accidents, public speaking or death of a close one, have been made.

The overall aim of the thesis was to build an understanding of the meaning of being affected by TS and to investigate to what extent people affected by TS utilize health care resources and its accompanying costs.

A multi-method qualitative and quantitative approach was used to gather and analyze data. In Study I and Study II 19 and 25 people, respectively, were interviewed. In Study III, questionnaires were used to compare self-reported symptoms between 48 people with TS and 79 people with myocardial infarction. In Study IV registry data on utilization of health care resources and its costs were retrieved for 58 people affected by TS.

The findings in this thesis show that the people with TS seem to live under burdensome circumstances long before the acute onset of TS and that this affects their health. Symptoms often start a few days before the acute onset and persist after discharge. Residual symptoms cause worry and make it impossible to live as desired. People affected by TS and myocardial infarction had comparable frequency and severity of symptoms 8 weeks after discharge. The average length of stay in hospital was 6,4 days and they had on average 15,6 primary or outpatient clinic contacts during the 6 months after discharge. The average direct health care cost for the period was SEK 95,071.

The conclusion from this thesis is that illness is present before the onset of TS and that the illness persists after discharge. The findings indicate that symptoms and social structures affect health. Person-centered care can be a viable option for combining medicine with the personal experience of health.

Keywords: takotsubo syndrome, health, symptoms, health related quality of life, patent reported outcome measurement, person-centered care, cost of illness

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LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I Wallström S, Ulin K, Määttä S, Omerovic E, Ekman I. Impact of long-term stress in Takotsubo syndrome: Experience of patients.
Eur J Cardiovasc Nurs. 2015. [Epub ahead of print]
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II Wallström S, Ulin K, Omerovic E, Ekman I. Symptoms in patients with takotsubo syndrome: a qualitative interview study.
BMJ Open. 2016; 6:e011820. doi: 10.1136/bmjopen-2016-011820.

III Wallström S, Ulin K, Omerovic E, Ekman I. Self-reported symptoms 8 weeks after discharge: A comparison of takotsubo syndrome and myocardial infarction.
Int J Cardiol. 224 (2016) 348-352. doi: 10.1016/j.ijcard.2016.09.052.

IV Wallström, S. Ekman, I. Omerovic, E. Ulin, K. Gyllensten, H. Health care utilization, costs, and quality of life after takotsubo syndrome.
Submitted

CONTENTS

ABBREVIATIONS

AMI	Acute myocardial infarction
BNP	B-type natriuretic protein
CoI	Cost of illness
DRG	Diagnosis-related group
ECG	Electrocardiogram
EF	Ejection fraction
EQ-5D	EuroQol-5 Dimensions
Hb	Hemoglobin
HRQoL	Health-related quality of life
MFI-20	Multidimensional Fatigue Inventory
PCC	Person-centered care
PSS-14	Perceived Stress Scale
SCAAR	Swedish Coronary Angiography and Angioplasty Registry
SF-MPQ	Short-Form McGill Pain Questionnaire
SHCQ	Somatic Health Complaints Questionnaire
TNT	Cardiac troponin T
TS	Takotsubo syndrome
VAS	Visual analog scale
WHO	World Health Organization

INTRODUCTION

Takotsubo syndrome (TS) is a relatively new and increasingly recognized diagnosis (1). As diagnosis of TS has become more common, the number of affected people who require follow-up care has increased. TS diagnosis is relatively new so knowledge is sparse about how a TS event affects health or what kind of follow-up care is needed. Health care must not only cure disease, it should also help people to regain their health and function after illness to enable them to participate in society. Furthermore, this goal should be achieved in a cost-effective way and its methods should be science-based (2). The implementation of this goal requires knowledge about health and symptoms and how they affect daily life. However, research on these issues in TS is lacking.

This thesis focuses on health before, during and after TS. It also investigates the experience of symptoms in connection with TS and how they affect health and the ability to live life as desired. The thesis also examines the utilization of care and its direct costs, from hospital admittance for acute TS onset to 6 months after discharge. All though diverse, the studies all investigate experiences of people with TS and therefore fall within the scope of health care science. Research within health care science has two main aims: to focus on curing a disease or improving the patient's life, and also to optimize care so that health care resources are focused where they are most needed.

Health

Several different definitions of health have been proposed. According to Boorse's biostatistical theory of health and disease, the medical concept of health assumes an absolute distinction between health and disease. Health is defined as statistical normality of biological function with the complete absence of pathological conditions. A distinction is made between health and well-being, which are assumed to be non-equivalent. Health, or lack thereof, may influence well-being; however, not everything that decreases well-being is considered pathological. Moreover, theoretical health (the absence of pathological conditions) is distinguished from practical health (the absence of treatable disease), but whether or not a person is healthy is still decided by others. Boorse argues that his definition of health is value free, as pathological conditions are deviations from biological design. Therefore, their recognition is a matter of natural science and not an evaluation (3). The biostatistical theory of health is a one-dimensional construct and has received much criticism of both its narrow definition of health and its claims of being value free (4)

A more common view of health shared by, among others, Nordenfelt (5) and the World Health Organization (WHO) (6), is that health is self-assessed and cannot be determined by a third party. The WHO defines health as *"a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity"* (6). Both this concept and the biostatistical theory of health describe an absolute state and an idealistic view of health, a distinction that has been debated. According to the WHO, health should be considered a resource for daily living rather than a life goal in itself (6). In contrast, Dahlberg and Segersten (7) see health as an equilibrium between freedom and vulnerability. It entails one's well-being and a capacity to pursue one's life projects (7). The ability to realize meaningful goals is also part of Nordenfelt's (5) definition of health and is in accord with the ideas of Toombs (8), who suggests that health can be consistent with disease and suffering. Toombs suggests that it is the effect of physical signs or symptoms on daily life, rather than the sign or symptom itself, that is the determining factor for health (8).

The traditional biomedical model of health and illness is based on the dualistic separation of the mind and body inspired by Descartes. It is characterized by a mechanistic understanding of the body, in which measurable and physical health is assumed to be completely separate from psychological and social processes (9). Biological concerns are viewed as more real, reliable and clinically significant than psychological ones. Despite its claims, this view of health is both culturally specific and value laden (10). Furthermore, symptoms must be correlated with signs to be valued and the process of diagnosis excludes factors regarded as irrelevant. Therefore, this model is also inherently reductionist (9).

The biopsychosocial model of health was created in an attempt to lessen reductionist thinking in medicine and to bridge the gap between the biological, psychological and social factors that influence disease and illness. According to this model, health should be understood as a combination of these three factors, rather than in purely biological terms. Biological factors include sex, genetics, comorbidities and disability. Psychological factors include personality, coping skills, attitudes and past trauma. Social factors include social support, education, family background, cultural traditions and socioeconomic status. These factors interact in both the causation and interpretation of disease and illness (11). Since its introduction, the biopsychosocial model has become popular and has been used to explain many diseases, especially when purely biomedical explanations are lacking.

However, this model has been criticized. First, the model is inherently dualistic and assumes a clear mind–body division, even though it accepts that both mind and body influence health and disease. Second, it is deterministic, as all factors are considered relatively stable over time and not easily changed. Third, its view of social factors is narrow and does not include any social structures. The biopsychosocial model ultimately places responsibility for health, disease and illness solely on the shoulders of the individual (12, 13).

One factor that is often seen as an explanation of disease is stress. The definition of stress is commonly based on the writings of Seyle (14), who defined stress as the response of the body from any demand enforced on it. Anything, both positive and negative, that created a stress response in the body is viewed as a stressor. Furthermore, he thought that all stressors created the same kind of response in the body (14). Lazarus and Folkman (15) viewed stress as the result between a person and the environment. When the environment taxes the person to that degree that the person's resources are exceeded, stress develops. When this happens the well-being of that person is endangered (15). In medical research a distinction between acute and chronic stress is often made (16).

Determinants of health

The WHO states that a person's health is not only affected by individual factors, such as disease, genetics and lifestyle, but also by environmental factors (17). At a population level, the risk of poor health and health inequalities are affected by social inequalities and by the organizational and structural aspects of these. For example, the unequal distribution of power and resources affects peoples' lives and therefore also influences their risk of poor health (18). Variations in health that are systematic, socially produced (and therefore modifiable) and unfair lead to social inequalities in health. Systematic variations are not distributed randomly but show a consistent pattern across the population. Socially produced variations are not of biological origin but arise from societal structures and interactions. Social inequities are differences that are widely considered to be unfair, because they are generated and maintained by unjust social arrangements that offend common notions of fairness (19). The determinants of these social inequalities of health may be social, economic or lifestyle-related. These determinants either increase or decrease social inequities in health and can always be influenced by political, commercial or individual choices or decisions (20).

Dahlgren and Whitehead have developed a model for understanding the main determinants of health, which they describe as a series of layers. At the center of the model are individual factors that cannot be altered, such as age, sex and genetics. The first level constitutes individual lifestyle factors, including diet, exercise and sleeping habits. The next level comprises social and community factors, for example social networks and support. The third level constitutes living and working conditions and includes education, health care services, water and sanitation, agriculture, food production and work environment. The fourth level consists of general socioeconomic, cultural and environmental conditions. These four layers of influence can be translated into four levels of policy intervention (19). This conceptual framework is an interdependent system, in which the different levels influence each other. The implementation of policies on several levels is more effective in influencing public health and can also have synergetic effects. Policy decisions on one level can be offset by a contradictory decision on another level. The framework can also be used in relation to equity. Public health focuses on the social determinants of health and, consequently, the factors at different levels of society that influence or may influence health in a positive or negative way (20).

Health-related quality of life

There are several definitions of quality of life that focus on both objective and subjective dimensions of well-being, satisfaction, life values, normality and function (21). The WHO defines quality of life as *"individuals' perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns"* (22). This defines quality of life as a multidimensional and subjective concept, which includes both positive and negative aspects of life (22). Health-related quality of life (HRQoL) is a subjective concept that encompasses the physical, social and psychological impact of a disease, illness or treatment on ability or function. HRQoL differs from overall quality of life because of its focus on the impact of a perceived health state: how people perceive aspects of life that relate to their health and how these are valued (23).

Disease, illness and sickness

Disease and illness are two important concepts related to health. The medical anthropologist Eisenberg (24) defined disease as an objective classification of pathological processes. Medical science has based the diagnostic system on this definition. In contrast, illness is a change in condition or social function experienced by the individual. Patients´ reports on symptoms is an attempt to gain an understanding of a person’s illness. A person´s experience of illness is always subjective. Furthermore, it involves not only their biological body but their whole existence. This means that an individual’s view of the world changes when they experience illness (8). Kleinman (25) has also distinguished between disease and illness, defining disease as a dysfunction of biological or physiological processes. In contrast, Kleinman considers illness to encompass psychosocial aspects, the meaning of the experienced symptoms and eventual disability. There is not always a clear connection between disease and illness and they do not have a one-to-one correspondence. Rather, an individual may have a disease without experiencing illness if they do not know about their disease or do not experience any symptoms. Similarly, a person may experience illness without having a disease; that is, they may experience symptoms in the absence of any detectable biological or physiological signs (25).

According to Toombs (8), the meaning of illness is specific to each person. Long-term illness not only involves the current context, but also considerations about the future, such as a possible deterioration in health. The experience of illness is subjective and unique; it represents the person´s reality and involves their whole existence, not just their biological body. When a person is ill, their view of both themselves and the world changes, and this is influenced by the attitudes of other people as well as the attitude of society as a whole. There is also usually a shift in perception from viewing oneself as healthy to viewing oneself as ill (8). However, it is not fruitful to view disease and illness as separate entities. Instead, they should be seen as separate aspects of the phenomenon of sickness. Sickness is a complex and fluid phenomenon. To be effective, health care must focus on the entire phenomenon of sickness and not only on disease or illness. Both the pathophysiological changes of the disease and the cultural explanations of the illness must be considered. A failure to address the meaning of a sickness for the patient may lead to a lack of understanding and dissatisfaction. Moreover, discordant explanations of sickness between health care professionals and patients may cause misunderstandings, lack of concordance or other problems in clinical care. A focus on only one aspect of sickness can lead to dissatisfaction with the care provided or undertreatment of the disease (10).

Cost of illness

Assessment of the economic burden to society of a disease or health condition is carried out by cost-of-illness (CoI) studies (26). Health economics also tries to include patients´ perspectives by measuring patient reported outcomes on health for example. This is achieved through identification, measurement and evaluation of all costs. Ideally, both direct and indirect costs are included, but transfer payments such as taxes are excluded to avoid double counting. Furthermore, intangible costs (e.g., pain, suffering and grief) are excluded because they do not directly involve a loss of output

(27). CoI studies do not compare outcomes or benefits and therefore should not be confused with economic evaluation studies, such as cost–benefit analyses. Instead, COI studies aim to assess the economic burden to society of an illness, identify cost components and describe distribution of costs (26).

Symptoms, signs and their hierarchy

For a long time, symptoms and illness narratives were the main tools by which medical diagnoses were made. Their role has become less important because of advances in technology and the development of increasingly sophisticated tools to measure signs and pathological/biological changes (28). Symptoms are always subjective (29, 30). When a symptom is perceived, a person's awareness of their body is altered and a function that has previously been taken for granted is brought to attention. The habitual equilibrium has been disturbed and this is interpreted as a bodily message (31, 32). How symptoms are perceived and a person's response to them is based on their reality (29) and includes physiological, psychological, behavioral and sociocultural components (33). This is the basis of the biopsychosocial approach, which advocates that psychological and social factors influence the illness experience and, by extension, how an individual experiences their symptoms (34). It is not uncommon for symptoms to appear in clusters and to trigger and reinforce each other (35). According to Malterud (36), symptoms are always influenced by societal norms, such as what behaviors are considered culturally acceptable in regard to sickness (36).

Symptoms and signs are often assumed to be dichotomous, with symptoms representing the subjective and personal illness experience and signs representing objectively measurable pathological changes (37). The separation of symptoms and signs was a result of scientific development and the dualistic division of mind (identity) and body. Foucault argued that this separation dehumanized the patient and opened up the body for manipulation and deconstruction. The power of judgment over the body no longer resided with the mind or the clergy, but with science and the physicians. Science claimed to produce absolute, value-neutral knowledge. Society turned to physicians as the new saviors who would abolish sickness and solve all of humanity's problems. Physicians became the priests of the body. The biological reductionism emphasized by the Enlightenment held that a person is the sum of their biological parts. By understanding the body, doctors could gain an unparalleled understanding of their patient. This view of the body, which Foucault termed the "medical gaze," could see beyond illusion, which made it authoritative and powerful. As scientific and biological knowledge increased, the meaning of symptoms and signs in relation to disease also changed. This shows that the medical gaze is not constant or neutral but is continually developing. However, despite these changes, it has managed to retain its authority and power and thus its claim of being value neutral (38).

Through the authoritativeness of the medical gaze, signs and symptoms were pulled apart and viewed as different entities. Inherent in this split is a division in terms of power and status. Signs are viewed as better and more reliable indicators of illness than symptoms, which further reduces the already diminished role of the illness narrative (37). Signs are often seen as objective facts and more veridical than symptoms, but what is often forgotten is that they are always viewed through the authoritative medical gaze (38). Malterud (37) suggests that it is impossible to distinguish between objective medical signs and subjective symptoms, as they are all interpreted through the medical gaze and are therefore subjective. Instead, she argues that symptoms and signs are essentially the same, but are assigned different values and thus credibilities. There is a hierarchy of signs. The division between signs and symptoms and their intrinsic values involves the expectation that health care professionals can interpret what is important and what is not. Diseases that lack medical signs and are based on symptom experience have lower status than diseases that can be technically measured. These conditions are often regarded as vague and not considered real diseases. Patients presenting with vague symptoms that do not fit into the diagnostic matrix run the risk of being discredited and blamed for using scarce health care resources for complaints that are not judged to be real diseases. The separation of symptoms and signs reinforces the subordinate position of the patient in the health care system (37). The complexity of the symptom experience and the difficulties in measuring symptoms impede research, which further emphasizes the secondary role and low conceptual status of symptoms (35).

Symptom distress

McCorkle and Young (39) defined symptom distress as the *"degree of discomfort from specific symptoms being experienced as perceived by the patient."* They do not differentiate between distress caused by the illness or disease itself and distress caused by treatment for the same (39). On a similar note, Rhodes and Watson (40) defined symptom distress as the degree of mental or physical suffering an individual experiences as a result of a particular symptom. Distress encompasses a wide range of feelings, including dependency, incompetence, vulnerability, apprehension, and anxiety. Rhodes and Watson (40) suggest that symptoms are subjective experiences that indicate a condition departing from normal function. Symptoms are also private; therefore, their causes are difficult to measure objectively. Symptom distress is described as the necessity of altering one's actions because of a subjective experience of illness or disease. This concept also encompasses the mental or physical suffering experienced as a result of symptoms. Several factors can amplify symptom distress, including thoughts related to the symptom, the situational context of the symptom and the mood of the person. Symptom distress hinders self-care and makes independence more difficult for the affected person (40). Symptoms are conveyed through complaints; concomitant with this is a desire to be understood (29, 30).

Symptom models

There are enough similarities between different symptoms to warrant a common analytical framework (43). Several conceptual symptom models have been constructed to try to explain how symptoms are perceived, what influences the perception of them, how they may best be managed and what consequences they have (41, 42). Although different symptom models have been developed by various research groups, they share many similarities (33, 43). The perception of symptoms is influenced by both biological and psychosocial factors, including demographic background, personality traits, culture and civil status. All these factors are seen as stable, originating from the individual or the immediate environment and preceding the symptom itself. Furthermore, the symptom experience is influenced by symptom characteristics, what value or importance a symptom is assigned and personal responses to the symptom. The development of these models has primarily focused on how concurrent symptoms can influence each other (33, 43). Although they do not always assume non-linear causes for symptoms, symptom models (like the biopsychosocial model for explaining disease) focus on the individual patient and do not consider societal or cultural influences. By extension, this also places responsibility on individuals. These models also address how symptoms should be managed. Models vary in how much emphasis they place on social, psychological and biological factors; however, all these factors must be addressed to achieve optimal symptom management. Symptom management should be a collaboration between the patient, health care professionals and, if appropriate, the patient's family. Finally, these models address what consequences the symptoms have, both for the individual and for society (41, 42).

Gender perspective

A distinction is often made between biological sex and social gender. "Sex" refers to the biological differences between men and women, such as sex organs, hormones and genetics; "gender" describes socially constructed differences, such as gender roles (44). Men and women are ascribed different roles according to their sex, and various behaviors, characteristics and tasks are often defined as either masculine or feminine. Characteristics perceived as masculine are valued more than characteristics perceived as feminine. This intrinsic power gradient results in men receiving precedence over women (44, 45). This is made possible by the societal separation of men and women. The different characteristics that are ascribed to men and women are assumed to originate in the reproductive system, which is used as the basis for this dichotomy. Women and men are assumed to be essentially different, instead of exhibiting low within-species variation. This assumed dichotomy emphasizes biological differences, rather than social structure and relationships, which are more important for the creation of gender. The creation and recreation of gender roles is a continuous process and occurs in everyday situations. Women and men define themselves as masculine or feminine through their actions. Gender relations are continually changing and the resultant behavior is not the product of gender, it *is* gender (45). Women and men live in different social spheres and are therefore subjected to different risk factors and affected by different diseases (45). In accord with this position, diseases are not viewed as merely a passive unfolding of biology. Instead, gender theory tries to understand how social structures and culture affect the body and influence both the causation and progression of disease (44, 45). In this thesis, the word "gender" is used to describe differences between men and women. However, when referring to a dichotomous, biological division between men and women, "sex" is used.

Gender in medicine and health care science

Gender medicine attempts to redefine how health, illness and disease are perceived and to understand which factors influence them. Although the social sciences can consider gender solely from a structural and social perspective, medicine and health care science must also consider the biological aspects of the body. Gender medicine emphasizes that medicine and health care science are not as value neutral as previously thought and has highlighted the lack of research on women, women's diseases and biological explanations for these diseases. This has led to a larger inclusion of women in medical research and less of a tendency to generalize results from research on (white) men to women and minorities. Although it is currently considered good practice to include both women and minorities in clinical trials, women are still excluded from clinical trials on grounds of reproductive health. Recently, gender medicine has focused on power structures and theory construction and generated critiques of biological explanations. This includes an examination of the trivialization of women's health issues. Diseases experienced more by women are often ignored by medical research or considered to have psychosomatic or psychological causes. Furthermore, gender medicine has moved from assuming that different health patterns stem from biological differences between the sexes toward explaining the differences in the diseases that affect men and women in terms of societal structures and power (46).

Health care sciences have historically considered themselves gender neutral and often do not even discuss differences between men and women. Instead, concepts such as "person," the "individual" or the "patient" are used to describe participants in research. This idealized view may lead to a disregard of power relations in both gender discourses and other social concepts, such as class and ethnicity (47).

Gender perspective on diagnosis and care

Malterud (37) has suggested that, as all medical information and all clinical judgments originate from the interpretation of medical signs, which are influenced by society and therefore not objective, diagnoses are therefore also socially constructed. The diagnostic process is influenced by the social and political context, and is gendered. As women are generally assigned a lower value and credibility than men, their illness narratives are valued less. Medical theory and practice have been created by and adapted to men through the male cultural gaze. Therefore, it is understandable that the signs and symptoms of women do not always fit this epistemology. The interpretation of signs is always influenced by the position (such as sex or class) of the interpreter (37).

There is greater knowledge about the diseases of men because they have received more research attention. Many diseases that affect women, such as chronic pain syndrome, irritable bowel syndrome and chronic fatigue syndrome, are based on symptom experience rather than technically measurable signs. They are therefore perceived as vague, assigned a low value and not seen as real diseases. Malterud (37) argues that gender bias in society contributes to privileging the diseases of men by favoring technical signs rather than symptom experience.

The previously mentioned status gradient between symptoms and signs has greater consequences for women, because they are less likely than men to be believed. Women's illness narratives have less credibility than those of men. Therefore, women's illnesses may be assigned psychosocial causes and may be trivialized. From a constructivist standpoint, the validation of medical signs is not a mechanical process and what is uncovered is not pure fact. Instead, it is a process of perception, interpretation, narrative and negotiation. Signs and symptoms are interpreted through a medical gaze that is filtered through the preconceptions of society and medicine. Diagnosis does not depend only on medical facts; it is the result of a process that involves biology, culture and social structure intertwined through language and interaction (37). Human experiences are not self-evident or linear; even bodily experiences are influenced by the lived life and societal meaning of illness and gender (37).

Gender bias within cardiovascular care

Medical diagnoses are gendered; for example, depression and TS are perceived as female diseases, whereas attention deficit hyperactivity disorder and acute myocardial infarction (AMI) are seen as male diseases. The gendering of disease may lead to a failure to recognize illness or overdiagnosis (44, 45, 48). Research shows that when physicians make diagnoses, they are more likely to give emotional explanations in female cases than in male cases when assessing constructed and otherwise identical case histories (49). Cardiovascular disease is the most common cause of death for both males and females in Sweden. Despite this, men and women do not receive the same care (48). Women receive less adequate care for AMI (50) and are less likely to receive the recommended medical treatment (51, 52). However, there is little variation between the sexes in the time before care is received (52) and mortality after an AMI has improved for both men and women, albeit at a faster rate for men (48).

Takotsubo syndrome

TS is an increasingly recognized form of acute, reversible heart failure characterized by ballooning of one of the ventricles (most commonly the left) of the heart. It was first described in Japan in 1990 as a differential diagnosis to AMI; since then, research on TS has increased (1). Different research groups have suggested and used various names for TS, including stress-induced cardiomyopathy (53), apical ballooning syndrome (54), ampulla cardiomyopathy (55) and broken heart syndrome (56). The term “takotsubo” was used in the initial publications because of the resemblance of the ventricle during end-systole to Japanese fishing pots used to trap octopus (1). The prevalence of TS has frequently been described only in relation to AMI; 1–2% of patients with suspected acute coronary syndrome are eventually diagnosed with TS. This probably underestimates the number of cases. TS affects approximately 50,000–100,000 people every year in the United States of America (1). There are no reliable figures for Sweden, but an estimation based on population would be 1,500–3,000 cases per annum in Sweden. This is in line with the estimation of 2,000 cases per annum in Sweden from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) (57).

An acute onset of extensive but transient contractile dysfunction of one of the ventricles is characteristic of TS. The signs or clinical manifestations include ST-T electrocardiogram (ECG) changes, elevated cardiac biomarkers and wall-motion abnormalities of the ventricle (58). The clinical presentation is often described as indistinguishable from that of an AMI (59). The most frequent clinical presentation of TS is chest pain followed by dyspnea (58-63), lipothymy with or without syncope (58-60, 62) and malaise (60). Chest pain is more common in patients with an AMI than in those with

TS, whereas dyspnea (59, 60), syncope and malaise are more common in patients with TS (60). In one interview study of women with TS, a variety of acute symptoms were described: pain, breathing difficulties, unconsciousness and feeling pale and cold. Interviewees described pain as having various locations and characteristics (64).

Postmenopausal women constitute the majority of affected patients; 84%–91% of cases are female and the mean age varies between 63 and 76 years (65-67). The complete pathophysiology and underlying etiology of TS are not fully understood but a catecholamine surge, often due to a stress trigger, is thought to be an important factor (1, 54). Examples of psychological stressors are bereavement, quarrels and public speaking; examples of physical stressors are medical or surgical procedures, onset of disease and accidental falls (58, 60, 61). A genetic susceptibility to TS may explain why only some individuals are affected by TS after experiencing an acute stressor (1). It has also been suggested that certain psychological factors, such as personality traits and stress coping strategies, may contribute to an increased predisposition to TS (68-70). However, some studies have found no differences between patients affected with TS and controls, or have found that patients affected by TS are psychologically robust (60, 71). It is also possible that TS is a protective response of the body against sudden cardiac death (72).

There are several contradictory explanations for the large discrepancy in TS prevalence between men and women (54, 73, 74). First, it has been suggested that males are better protected than females against the stress-induced cardiotoxicity of catecholamines. This could be an evolutionary adaptation to protect males against the presumed greater physical stress they were exposed to. This greater tolerance may also be a result of different density of adrenergic receptors in the cardiomyocyte membranes of males and females, which may lead to better protection against severe catecholamine storms in males. Neither of these hypotheses has been fully supported by experimental data so they remain speculative. Second, and contradictorily, it has been theorized that males have lower tolerance against catecholamine cardiotoxicity than females and thus survive TS less frequently than females. If males die in the acute phase, a diagnosis cannot be made because the ventricle does not have time to recover (75). This theory is supported by the fact that sudden cardiac death is more frequent in males than in females (76). Repair of damaged cardiomyocytes is also more effective in females and thus they have a better survival rate than males (77). There are no reported sex differences from animal models, but it is not clear whether this is because these studies have used animals from only one sex or because there is no sex difference in reaction to stress (75).

Knowledge of potential TS risk factors is scarce, but smoking, hyperlipidemia, alcohol abuse and anxiety states are more frequent among patients with TS than among control populations (73, 74). Furthermore, TS has been associated with a number of comorbidities: various malignancies, pulmonary disease, asthma, neurological disease and psychiatric conditions (78). It was previously thought that TS was relatively benign and had little impact on long-term survival. Recent studies have shown that both short-term and long-term survival is affected and is comparable or worse than that of patients affected by an AMI (66, 78). Mortality from cardiovascular causes is comparable between the groups. The excess mortality among patients with TS is related to non-cardiovascular or unknown causes and may stem from the above-mentioned comorbidities. However, only male sex, Killip class 3 or 4 at admission and diabetes mellitus have been shown to predict mortality (78). It was previously thought that recovery after TS is swift and complete with no residual symptoms or signs (1, 66). Ejection fraction (EF) usually recovers within 3 months but depends on the severity of the episode. However, B-type natriuretic protein (BNP) levels and ECG changes may take 6–12 months to return to normal and may remain permanently affected (1). Slower recovery also affects health. Ventricle function after 3 months is associated with physical quality of life (79). However, Compare et al (80) showed that patients with TS experienced less impact on their physical and total cardiac-related quality of life after 1 year than patients with AMI. Nonetheless, the TS group experienced greater impact on depressed mood after 1 year (80). Furthermore, some patients experience persistent symptoms, including angina, breathlessness and palpitations, after the acute episode (81).

The average length of hospital stay varies from 3.6 to 8 days across studies (82-84) but reduced between 2007 and 2012 (84). The average cost of hospital stay for patients with TS has been estimated as USD 16,723 in 2007–2011 (82) and the total average charges as USD 61,034 in 2006–2010 for patients without arrhythmias (83). Concurrent arrhythmias may increase the average inpatient cost by USD 11,334 (83). This large discrepancy may be because of the difference between costs and charges. Cost-to-charge ratios vary between 0.12 and 0.96 (85). Readmission rate during the 30 days following discharge from hospital is 11.6% (84).

Treatment of TS is based on clinical experience, as there are no randomized clinical trials to support specific treatment recommendations. Treatment is aimed at recovery of cardiac function and should be supportive to sustain life and minimize complications. Complications include acute heart failure, left ventricular outflow tract obstruction, mitral regurgitation, cardiogenic shock, arrhythmias, thrombus formation, pericardial effusion and right ventricular involvement (1). Men suffer from more of these complications than women (82). Long-term treatment should aim to prevent recurrence, but opinions about optimal medical treatments differ regarding both acute and follow-up phases (1, 86, 87). There is no evidence to guide long-term management, but at least one follow-up visit after 3–6 months is recommended (1).

RATIONALE

Swedish health care is legally required to base its practice on scientific evidence (2). Health caring sciences focus on health: how life is affected by disease, illness, symptoms and lack of health. The aim is to help people maintain or achieve health, relive suffering and alleviate the effects of disease (7). Health can be promoted through understanding the subjective illness experience, including symptoms (30). The complexity of the concepts of health and symptoms make research on them difficult. Both previous and present life situations affect the perception of symptoms, and therefore health, in other cardiac diseases (88), but little is known about life situation or self-reported symptoms in connection with TS. This knowledge is vital to provide adequate health care based on science (2).

Research has been conducted on self-reported health and symptoms in other cardiovascular diseases, but is still lacking for TS. The existing information on symptoms in patients affected by TS may not be based on self-reports but drawn from medical records or assessed by health care professionals. There is little previous research on health, life before onset, symptoms or utilization of care and its costs in connection with TS. Therefore, there is a need for further research and knowledge about factors that influence health in people affected by TS.

AIMS

Overall aim

The overall aim of the thesis was to understand the meaning of being affected by TS, personal explanations of the causes of the illness, the experience and frequency of symptoms and how they affect life and health. It also aimed to investigate to what extent people affected by TS utilize health care resources and the concomitant costs of TS.

Specific aims

Study I	The study aim was to describe and interpret patients' narratives about long-term stress experienced before onset of TS.
Study II	The study aim was to investigate the meaning of narrated symptoms in connection to TS.
Study III	The study aim was to measure and compare self-reported residual symptoms between patients with TS and AMI.
Study IV	The study aim was to describe the utilazation of health care resources, to measure direct health care costs, explore HRQoL, and distribution of costs between TS and other diagnoses among patients with TS.

METHODS

Methodological viewpoints

A full understanding of health and how it affects life requires a process of interpretation. Therefore, the overall methodological approach in this thesis is hermeneutical. All four studies include self-reported data and focus on the meaning of health in connection with TS. Scientific theory and research can never be completely neutral, as they are human endeavors influenced by pre-understanding. Moreover, knowledge and science do not arise by themselves without any human influence, and interpretation is always part of this process. A person´s situation in society, their previous experiences and societal structures all combine to shape that person's view of the world and influence their interpretation. One can never be free from one's pre-understanding, but that does not mean it should be allowed free reign. Instead, one should try to be aware and observant of one's pre-understanding to minimize its influence.

Issues of gender and social structure have often been considered subjective and unscientific by traditional medical society. In contrast, gender medicine has criticized traditional medical research for being positivistic and reductionistic. Gender medicine questions the prevailing epistemological order; traditional medical research operates within the current paradigm. Gender medicine has focused on the epistemological grounds for research and is usually influenced by a constructivist framework rather than a positivist and essentialist perspective, which assumes that differences between men and women are constant and unchangeable. A positivist viewpoint assumes that differences between men and women are independent of time and place and is likely to overlook factors such as social structures, class and ethnicity (46).

Design

To examine different aspects of health in connection with TS a multi-method design was chosen. This incorporates both qualitative and quantitative data and uses interviews, questionnaires and register data. This design was chosen to provide a comprehensive picture of health in connection with TS (89). Both inductive and deductive approaches were used and the studies contain both interpretative, explorative and descriptive elements. By combining different approaches, symptoms and experiences became the central focus, which enabled a broader, more comprehensive understanding of health in connection with TS. Qualitative and quantitative data complement each other and their combined use can produce deeper knowledge about a phenomenon. The research questions determined the choice of methods (21). The different types of data were collected independently and the analysis for each study was conducted independently. However, the findings as a whole complement each other. An overview of study design is shown in Table 1.

Study participants and data collection

All participants were invited to take part in the research after coronary angiography at Sahlgrenska University Hospital in western Sweden. The inclusion criteria for the qualitative studies were 1) established TS diagnosis in the previous 6 months; 2) be-

Table 1. Overview of the studies

	Study I	**Study II**	**Study III**	**Study IV**
Design	Interpretative	Interpretative	Descriptive	Descriptive
Data collection	Narrative interviews	Narrative interviews	Questionnaires	Register data, questionnaires
Participants	19 TS	25 TS	48 TS 79 AMI	58 TS
Sampling	Purposeful	Purposeful	Consecutive and purposeful	Consecutive
Data analysis	Phenomenological hermeneutics	Phenomenological hermeneutics	Descriptive and comparative statistics	Descriptive and comparative statistics

TS: takotsubo syndrome; AMI: acute myocardial infarction.

ing physically and mentally capable of participating; and 3) able to speak Swedish. Purposeful sampling was used to include participants of both sexes and of a wide age range. For Study I, 25 patients were asked to participate, either at hospital or by telephone after discharge; three declined, two were excluded because no narrative could be obtained, and one was excluded because they were not diagnosed with TS. The remaining 19 participants were included in the study. The interviews were conducted during 2011 and 2012, seven during the hospital stay and 12 after discharge. In two cases, a face-to-face meeting could not be arranged and these interviews were conducted via telephone. For Study II, 31 patients were asked to participate; three of these declined, no narrative could be obtained from two, and one was not diagnosed with TS. The remaining 25 interviews were included in the study. Seven of the interviews were conducted during the hospital stay and the remaining 18 were conducted after discharge. No face-to-face meeting could be arranged for two of the post-discharge interviews, so these were conducted via telephone. Data were collected during 2011 and 2012 for Study I and during 2011, 2012 and 2014 for Study II. In both studies, interviews lasted until the research question was answered (15–120 minutes) and were recorded and transcribed verbatim. The opening question was: “Can you tell me how it was when you became ill?” Follow-up questions were used for clarification and whenever the research question was not addressed spontaneously. Throughout the interviews, the interviewees were encouraged to talk freely, and interruptions were avoided as much as possible.

For Study III, which was a quantitative study measuring symptoms 8 weeks after discharge, different inclusion criteria were used for the TS and AMI groups. The inclusion criteria for the TS patients were 1) diagnosis of TS; 2) ability to speak Swedish; 3) ability to fill in the questionnaires; and 4) predicted survival of more than 6 months. As the two diseases are characterized by general age and sex differences that may influence symptom experience, the selection of the control group was based on the sex and age distribution of the selected TS participants. The inclusion criteria for the

AMI group were 1) diagnosis of AMI; 2) ability to speak Swedish; 3) ability to fill in the questionnaires; 4) predicted survival of more than 6 months; and 5) same sex and age +/−2 years as participants with TS. Patients with TS were included consecutively from May 2012 to October 2015 and patients with AMI from September 2012 to February 2016. The inclusion of participants with AMI was terminated when the groups were adequately balanced for sex and age. In total, 97 patients with TS were identified during the study period. Of those, 29 declined participation, 10 had a predicted survival of less than 6 months, five did not speak Swedish or were otherwise unable to fill in the questionnaires, two were participating in another incompatible research study, two died, and one agreed to participate but did not return the questionnaires despite reminders. The remaining 48 patients with TS were included in the study. As only patients with AMI who matched one of the included participants with TS were asked to participate, no acceptance rate data for this group were recorded. Questionnaires measuring self-reported symptoms were mailed to all participants 8 weeks after discharge. If the questionnaires were not returned within 2 weeks, telephone reminders were given.

The inclusion criteria for Study IV, which examined utilization of health care resources, were 1) having a diagnosis of TS; 2) speaking Swedish; 3) having a predicted survival of more than 6 months; and 4) living in Region Västra Götaland. In total, 110 patients with TS were identified during the study period; of those, 29 declined participation, 10 had a predicted survival of less than 6 months, five did not speak Swedish or were otherwise unable to fill in the questionnaires, two were participating in another incompatible research study, two died and four agreed to participate but were excluded from this study because they did not live in Region Västra Götaland. The remaining 58 patients with TS were included in the study. Patients were included consecutively and the inclusion period lasted from January 2012 to October 2015. Information on utilization of health care resources and their costs for each patient (measured from the day of hospital admission for TS to the end of the following 6 months) were retrieved from the Vega registry.

Data on self-reported HRQoL were collected using questionnaires. These were distributed in connection with the initial hospital stay and by mail 8 weeks and 6 months after discharge. If the questionnaires were not returned within 2 weeks, telephone reminders were made. Index values for the missing HRQoL data were imputed. Index imputation is more accurate than imputation of actual domains in smaller samples (18), so only the index scores and the visual analog scale (VAS)-scores were imputed. Values were imputed for baseline and 8 weeks, 6 months and 1 year after discharge. The values 1 year after discharge were used to strengthen the imputation and are not part of this study. The following patient characteristics were used to calculate the imputed scores: age, sex, civil status, education, country of birth, previous cardiovascular disease (myocardial infarction, angina, stroke), hypertension, current or previous nicotine use and cumulative cost.

Data on risk factors, previous diseases, comorbidities and baseline clinical characteristics were collected from electronic patient records. Table 2 (page 32) shows these data and demographic data for the participants in all four studies.

Data sources

Interviews

Research shows that interviews are an effective way of obtaining clinical knowledge (90). Narrative research investigates the conceptual stipulations of the narration and the structure and conditions of the story. This method does not seek objective truth or permanent answers. Instead, narrative studies aim to visualize the human processes that create meaning. Narrative researchers seek to obtain a deeper understanding of the inherent meaning created through the narration (91, 92). Narrative interviews are a suitable method with which to obtain descriptions of lived experience (93). The qualitative research interview provides unique opportunities to obtain new knowledge and meaning through conversation. The interview can be compared with an everyday conversation, but with one important difference: the parties are not equal. The interview has a specific purpose and the interviewer asks the questions and guides the conversation (94). The interview is created jointly by the interviewee and the interviewer, who both influence what is said and how it is said (95). The qualitative interview is a reflective dialog in which the interviewee has the opportunity to reflect on their experiences. Openness, flexibility and immediacy characterize the key approach to the interviewee (96). Lindseth and Norberg (97) have pointed out that narrative interviews are an appropriate method to obtain descriptions of lived experience. The purpose of the qualitative research interview is therefore to obtain descriptions drawn from the interviewee's lifeworld to be able to interpret and understand the meaning of the phenomenon that the interviewee describes and discusses (97). The recording and transcribing of interview data produces text that can then be interpreted (97).

Questionnaires

Questionnaires are a good way of collecting self-report data on experiences such as symptoms and health. It is important to use a reliable and valid questionnaire to ensure that it measures the concept it is intended to measure and that findings are repeatable. The structured design of questionnaires enables comparisons between groups or over time (21).

Multidimensional Fatigue Inventory

Fatigue is a multidimensional concept that encompasses several dimensions. The Multidimensional Fatigue Inventory (MFI-20) measures fatigue during the last few days and consists of 20 questions divided into five fatigue dimensions: general fatigue, physical fatigue, reduced activity, reduced motivation and mental fatigue. It provides information on fatigue intensity and can be used to generate a fatigue profile for each participant (98). Both the original and Swedish versions of the questionnaire have shown good reliability and validity (99).

Perceived Stress Scale

Stress is a complex concept. The Perceived Stress Scale (PSS-14) is a 14-item questionnaire that measures which situations the individual perceives as stressful and whether he/she views life as unpredictable, uncontrollable or overbearing. Both the original English version (100) and the translated Swedish version have been validated and deemed reliable (101).

Somatic Health Complaints Questionnaire
A wide range of residual symptoms has been described in relation to heart disease. The Somatic Health Complaints Questionnaire (SHCQ) measures the frequency of these symptoms during the latest week. It measures 13 symptoms in four domains of fatigue, breathlessness, pain and unrest and was developed and validated in Sweden (102).

Short-Form McGill Pain Questionnaire
Sensations of pain or discomfort incorporate many aspects, including location, duration, intensity and description. The Short-Form McGill Pain Questionnaire (SF-MPQ) comprises 15 sensory and affective descriptors that are rated on an intensity scale (103). A Swedish version of the questionnaire has been validated (104).

EuroQol-5 Dimensions
The EuroQol-5 Dimensions (EQ-5D) is a standardized and reliable self-report questionnaire for measuring HRQoL. It is widely used and applicable to a broad range of health conditions and treatments, settings and countries, which makes comparisons possible. The instrument provides a simple descriptive profile and a single index value for health status (105, 106).

Vega registry

The regional care Vega registry contains data on the care received by inhabitants of Region Västra Götaland. It includes data on care received from public and private caregivers both within and outside the region. Data on inpatient care, outpatient care and primary care are included, but the registry does not include data on care received from municipal care settings, such as elderly care homes and disability care services (107).

Data analysis

Phenomenological hermeneutics

The texts generated from the transcribed interviews in studies I and II were analyzed using phenomenological hermeneutics (97). This approach is inspired by and based on Ricœur’s phenomenological hermeneutics and focuses on the text. Analysis is conducted on written text or transcribed interview data (95). The goal of the analysis in phenomenological hermeneutics is to obtain knowledge and understanding of the interviewee’s perspective. This is achieved through a dialectical movement between explaining the parts of the text and understanding the whole (95, 97).

Interpretation focuses on what the text may reveal about the world and people’s experiences. This is achieved by obtaining a common and valid understanding of the text. Interpretation of the text may reveal meanings that the interviewees may not be consciously aware of (90, 97). The process of analysis within phenomenological hermeneutics consists of three separate but interwoven parts: naïve reading, structural analysis and interpretation of the whole (97). When analyzing the text, the interpreter moves between being close to the text and distancing themselves from it. At the same time, he/she must focus on what the text says and understand its meaning (95).

The first step in the analysis is the naïve reading. The texts, or interviews, are read several times so that the researcher can familiarize themselves with the material and form an initial grasp of the meaning of the text as a whole. The interpreter's mind must be open when reading the text so that it can speak to them. Naïve understanding guides the structural analysis and creates a way of entering it (93).

In the structural analysis, the text is read through systematically and meaning units are identified within the text. A meaning unit is a sequence of text, long or short, that carries a meaning relevant to the research question. Parts of the text that are not relevant to the research question are taken into consideration but are not divided into meaning units (97). The structural analysis may entail linguistic analysis or quantification of the meaning units (90). The meaning units are sorted into subthemes, which are then condensed and assembled into themes (97). Subthemes and themes may be interconnected but should still be considered separate entities as they mirror different aspects of the lived experience. The subthemes and themes are then compared to the naïve reading. If they do not cohere, a new naïve reading and one or several structural analysis should be conducted according to the hermeneutic spiral (93).

The third and last part of the analysis is the interpretation of the whole. In this part, relevant literature is included in the analysis to deepen the understanding of the meaning of the text. The interpretation of the whole is formulated from the naïve reading, structural analysis, reflections on the literature and pre-understanding, while simultaneously keeping the research question (108) and study context in mind (109). During interpretation of a text, one's pre-understanding is always present; it is impossible to free oneself from it. With the help of critical reflection, awareness of the pre-understanding may be deepened, revised and broadened. Research that takes a phenomenological hermeneutical approach conveys the meaning of lived experience as interpreted by the investigator (93).

Statistics and calculation of health care costs

Several statistical techniques were used to measure self-reported symptoms 8 weeks after discharge (Study III) and utilization of health care resources, their costs and self-reported HRQoL (Study IV). The statistical analyses were based on the frequentist statistical tradition, in which analysis does not include information from previous research. In Study III and Study IV descriptive statistics were used to calculate baseline characteristics. In Study III, the two groups were compared using independent samples t-tests for continuous variables. Because of the smaller size of the subgroups in Study IV, the Mann–Whitney U test was used to compare the continuous variables. The Pearson chi-square test of independence was used to compare categorical variables in both studies. For dichotomous variables, Yates' correction for continuity was used to compensate for the tendency of chi-square overestimation for dichotomous variables. Continuous data are expressed as mean (range) and categorical data as proportions (%).

The primary model for analysis in Study III was a multivariate adjusted complete case regression. Propensity scores were calculated to enable adjustment for differences between groups in confounding variables, such as risk factors, background and previous diseases. For the propensity score calculations, the dependent variable was TS or AMI and the independent variables were sex, age, civil status, previous AMI, previous stroke, diabetes mellitus, current and previous smoking, hypertension, EF, cardiac troponin T (TNT), and Killip class. Missing data were imputed using ad hoc imputation. When calculating the outcome measurements, linear regression was used for variables consisting of several questions combined into a total score. An ordinal regression model or polytomous universal model, which is an extension of the general linear model to ordinal categorical data, was used for single-item questions on an ordinal scale. Binary regression was used to test between-group differences in dichotomous variables. Missing outcome data were not imputed. A value of $p<0.05$ was considered significant and 95% confidence intervals were calculated. Equal variance was calculated using Levene's test; if $p>0.05$, equal variance was assumed and if $p<0.05$, the 95% confidence intervals were used to compensate for lack of homogeneity of variance. Statistical analyses were performed using SPSS 22 (SPSS Inc., Chicago, Illinois, USA).

Quantities and direct health care costs for health care encounters in Study IV were calculated both for TS diagnoses and for other diagnoses, and distribution of costs was calculated by background characteristics. Costs were calculated and presented according to 2015 values. Prior costs were updated using the Swedish health care inflation index (110). Costs for specialized health care were calculated using diagnosis-related group (DRG) weights, while primary care encounters were assigned unit costs based on national statistics on health care use and costs (111). In 2014, the cost for a visit to a primary care physician was SEK 1,397. Visits to other health care personnel were weighted as 40% of the cost of a physician visit; phone calls were weighted as one-third of the cost of a visit; and home health care as twice the cost of a visit. Indirect costs resulting from lost productivity, or intangible costs for harm and suffering, were not included in the analyses.

HRQoL was calculated as quality-adjusted life years. The health profile created from each EQ-5D response was transferred to utilities using the Swedish experience-based value set (112) and the UK general population-based value set (105). A chained truncated linear regression model was used for the imputation of missing EQ-5D data. For each missing value, 20 imputations were conducted (113). Spearman's rho was used to analyze correlations between the different EQ-5D dimensions for the complete response group. This method was chosen because of the small size of the group and the ordinal nature of the dimensions. Statistical analyses were performed using Stata 13 (Stata Corp., College Station, TX, USA) for the registry data, imputation and data on HRQoL using imputed values, and with SPSS 22 (SPSS Inc., Chicago, Illinois, USA) for medical baseline characteristics and for the non-imputed data on HRQoL.

ETHICS

The design and implementation of the studies in this thesis followed ethical guidelines and principles. The studies complied with the World Medical Association's Declaration of Helsinki (114), which states that research should contribute to welfare, must aim to benefit and not harm participants, respect the autonomy of participants and follow the principle of justice. The declaration emphasizes that invited participants should have the right to decline and end their participation of their own free will (114). Additionally, approval from the Regional Ethical Review Board in Gothenburg, Sweden, was obtained for all studies (approval reference numbers Dnr 275-11, T693-11, T580-12 and T392-15). All participants were informed of their right to decline participation and their freedom to terminate participation without having to give a specific reason. The participants were guaranteed confidentiality when the findings were presented. Informed consent was obtained from all participants before inclusion in any of the studies.

However, ethical considerations should not be limited to review board approval. The interviews and questionnaires used for data collection in this thesis focused on existential issues, such as life situation, health and symptoms, and thus could potentially lead to reflections and regrets about life. The participants were offered the opportunity for contact with a counselor if needed. Despite this, the potential risk of harm for participants was considered low and to be outweighed by the potential gain from the research.

FINDINGS

Demographic and clinical variables

The study population consisted of adults affected by TS and diagnosed by coronary angiography at Sahlgrenska University Hospital in Sweden. Study III also included a control population of patients affected by AMI. This population was selected to act as a balanced control group and matched on sex and age +/−2 years with the selected TS participants. Comparable demographic and clinical baseline data for the participants are shown in Table 2.

Table 2. Demographic and clinical baseline data for the study participants

	Study I	**Study II**	**Study III**		**Study IV**
	TS n=19	TS n=25	TS n=48 (%)	AMI n=79 (%)	TS n=58 (%)
Female sex	17	22	45 (93.8)	69 (87.3)	53 (91.4)
Mean age (range)	65 (39–84)	64 (39–84)	68 (39–86)	69 (49–87)	68 (39–86)
Married/co-habitant	11	15	27 (56.3)	46 (58.2)	31 (54.4)
Children	15	19	-	-	-
Current smoker	3	3	7 (16.3)	15 (19.0)	11 (21.2)*
Previous smoker	3	7	17 (35.4)	27 (34.2)	19 (34.6)*
Previous TS	3	3	-	-	-
Previous AMI	1	1	3 (6.3)	13 (16.5)	6 (11.1)
Previous stroke	-	-	2 (4.2)	5 (6.3)	3 (5.4)
Diabetes mellitus	2	2	1 (2.1)	16 (20.3)	3 (5.4)
Hypertension	4	6	28 (58.3)	46 (58.2)	31 (54.4)
EF mean (range)	-	46 (35–60)	43.5 (28–63)	52.4 (30–65)	-
Killip class					
I (%)	-	-	34 (70.8)	74 (93.7)	40 (70.2)
II (%)	-	-	10 (20.8)	1 (1.3)	13 (22.8)
III (%)	-	-	3 (6.3)	1 (1.3)	4 (7.0)
IV (%)	-	-	0 (0)	0 (0)	0 (0)

TS: takotsubo syndrome. AMI: acute myocardial infarction. *Nicotine use

Additional variables were collected for three of the studies. Of the 25 participants in Study II, two were also affected by chronic obstructive pulmonary disease and five had a history of anxiety or depression. The average hemoglobin (Hb) was 134 at hospitalization with a range of 79–176.

In Study III, the mean TNT for the TS group was 50 and 1,373 for the AMI group, with a range of 24–1370 and 10–10,000, respectively. Between the TS and AMI groups the following significant differences in clinical baseline data were found: diabetes mellitus (p=0.011), mean EF (p=0.000), mean TNT (p=0.002) and Killip class (p=0.000).

In Study IV, civil status was divided into more categories: of the 58 participants 5 (8.6%) were single, 12 (20.7%) divorced and 9 (15.5%) widowed. Country of birth was Sweden for 49 (84.5%) of the participants. Educational level was divided into two categories: 33 (56.9%) had primary or secondary education as their highest level and 24 (41.3%) had vocational or upper education. Two participants (3.4%) had previous angina at admission to hospital. One significant difference was found between the subgroups with complete and incomplete EQ-5D responses. More participants in the incomplete response subgroup were born in a country other than Sweden (p=0.043).

Life before onset

The interviewees with TS in Study I reported burdensome stress for a long time before acute onset of TS. The stress was characterized as low intensity, but it was unrelenting and the interviewees felt that they could not control it. Furthermore, they reported feeling much responsibility, both for practical things and for the people around them. All this led to a great deal of worry. This life situation was characterized by feelings of injustice and powerlessness to change the situation; the interviewees could not conceive of any way to ease their burden. The main theme, themes and subthemes of Study I are:

Worn down to the bone

- *Everlasting responsibilities*
  - Protecting, helping and worrying about others
  - The desired burden of busyness
- *Recurring injustice*
  - Not having needs meet
  - Disappointed to not get the same consideration in return
  - Frustrated over not being able to influence the situation
  - Sadness over how things turned out
- *Perpetual uncertainty*
  - Endurance
  - Be appropriate
  - Inner insecurity or fear

The interviewees wished that other people would step up and take more responsibility but no one ever seemed to do so. They felt that when people did help them, the tasks were often performed in a substandard way. The interviewees were always ready to step in and take over, and felt that it was easier to just do things themselves. They felt that it was their responsibility to protect others and to make sure that everything ran smoothly; this caused them a lot of worries. As part of protecting others, the interviewees did not share their own problems or concerns, as they did not want to burden others. This busyness had two functions; although it caused stress, it also gave the interviewees the satisfaction of feeling needed and appreciated. The sense of burden arose from the feeling that they could not control the influx of tasks or their content. This created mixed feelings for the interviewees because they yearned to be able to relax and trust people (Study I).

The interviewees felt that their needs were not fully met, they did not get the appreciation they thought they deserved and the appreciation they did receive was too little, too late. This led to feelings of abandonment and loneliness. The interviewees were there for others and when they did not receive the appreciation that they thought they deserved they felt disappointed. The interviewees valued hard work, attentiveness and consideration for others. Often, they felt that others did not live up to these standards and this was disappointing. They wanted others to notice their needs and to attend to them. They did not want to ask for help, and when others did not notice their needs they felt powerless. They felt that it was a great injustice when they did not receive reciprocal consideration from others. The interviewees felt unable to influence this, and that led to feelings of powerlessness, hopelessness and injustice. They felt sadness about events in their past and dwelled on these. They believed that they had always worked hard and done the right thing, but had not been rewarded for this. These events were connected with a lack of control and a sense of injustice. The interviewees continually dwelled on the past, their unsatisfactory life situation and worried about the future; this made it difficult to live in the present (Study I).

The interviewees' situation seemed static and unchangeable to them; they felt that it was best to just try and endure it. An alternative was to diminish the severity of the situation. Another survival strategy was to turn every situation into something positive; this also provided a sense of control. The interviewees felt that it was important to act appropriately and keep up appearances. They believed that there was a right way to do things, and that often they did things a little better than others. This was one reason that they did not ask for help. Another reason was a fear of refusal. Moreover, the interviewees felt an inner insecurity and fear of being insufficient. They placed high demands on themselves and others. They felt loneliness, an inner stress, and felt disconnected and misunderstood. They described these feelings as part of their personality and therefore stable. The interviewees distanced themselves from others and did not ask for help. They felt hopeless and felt that they could not influence their life situation; this exhausted their personal resources until they were on the verge of illness (Study I).

Before their acute TS onset, some of the interviewees in Study I experienced a stress trigger. However, they did not perceive this as particularly stressful, but considered it just one of a series of stressful events that constituted their life situation. Study II also revealed other symptoms in the time before the acute onset; lassitude, affected breathing and pain were the most common symptoms in this period. The interviewees did not take the pain seriously; some characterized it more as discomfort than pain. The affected breathing had a greater impact on daily life, as individuals had to limit their walking and other tasks or stop to rest. They described their breathing problems as shortness of breath, tightening of the throat, coughing and hoarseness. Some of the interviewees experienced a lack of stamina combined with shortness of breath. Lassitude was the most common symptom before onset of TS; it did not reduce with sleep and was described as general fatigue. Some kind of malaise or discomfort was also common but its descriptions varied: feeling ill, anxiety, mental slowness, feeling swollen and sweaty, feeling downhearted and amnesia. Feelings of malaise were prominent for those interviewees affected by them. Other symptoms mentioned were palpitations, fast pulse, lack of appetite without nausea and general nausea (Study II). The interviewees lived in stressful circumstances, and had felt burdened by responsibilities, injustice and uncertainty for a long time before the acute onset. An identified stress trigger was often not seen as any more stressful than their regular life. Symptoms in the period leading up to the acute onset were common, but the interviewees ignored these, giving reasons such as not wanting to bother health care professionals, not thinking the symptoms indicated anything serious or not feeling that they had time to deal with the symptom at that time (Study II).

Acute onset and hospitalization

The acute TS onset came as a shock for the interviewees; they had not considered that their symptoms could lead to actual illness. Disbelief and shock were feelings connected with falling ill. The interviewees waited until their symptoms became unbearable before they sought medical attention, even when they experienced symptoms they themselves described as serious. Even if they had lived with symptoms before the acute onset, they did not perceive themselves as ill. Instead, they viewed themselves as an active person, not as someone affected by heart disease (Study II).

The most common symptom during the acute onset was pain, but its description, characteristics, location and intensity varied between the interviewees. Pain most often occurred in the chest, back and arms. Its most common characteristic was heaviness or pressing, followed by radiating. Other characteristics mentioned were stabbing, prickling, burning, stinging and cramping. The intensity of the pain varied from discomfort to worst imaginable pain but it was uniformly described as persistent. The second most frequently described symptom was affected breathing. Descriptions used were cumbersome breathing, respiratory distress, shortness of breath, shallow breathing and gasping for breath. Tightness of the throat, hyperventilation, long exhalation, gurgling in the lungs, coughing and difficulty speaking were also mentioned (Study II).

Malaise was also a common symptom during the acute onset and was described using a variety of terms, such as feeling ill, feeling that something was wrong, feeling “yucky” or strange and feeling it in the entire body. Some participants described feeling anxious or fearful, being convinced that they would die and mentioned that the onset felt horrible or very unpleasant. Severe lassitude or tiredness that arrived suddenly and did not lessen with rest was connected with the acute onset of TS. This was a very prominent symptom for those who experienced it. Some interviewees also mentioned loss of strength in the extremities. Nausea and connected symptoms were also part of the onset. For some, this took the form of outright nausea, but others experienced associated symptoms, such as vomiting, lack of appetite, diarrhea and salivation. Other symptoms experienced in connection with acute TS onset were palpitations, tremor, diaphoresis, lipothymy, syncope, unconsciousness, amnesia, becoming quiet and finding it difficult to start tasks (Study II).

Mean HRQoL at baseline was 0.70 using the UK value set and 0.84 using the Swedish experience-based value set. This correspondes to an EQ-5D VAS score of 59.0. Problems were reported in all dimensions of EQ-5D. Significant correlations were found between mobility and self-care (p=0.039); mobility and anxiety/depression (p=0.021); usual activities and self-care (p=0.019); and pain/discomfort and anxiety/depression (p=0.044). Distribution of the scores in the different dimensions is shown in Figure 1 (page 38) (Study IV).

The length of stay in hospital was on average 6.4 days and the mean cost for a hospitalization was SEK 39,987. Most health care costs occurred during encounters where at least one of the registered conditions was in the WHO's International Statistical Classification of Diseases and Related Health Problems tenth revision (ICD) chapter IX (I00-I99 Circulatory system diseases). No pattern regarding socioeconomic factors, previous disease and risk factors could be distinguished. As only five men were included in the study, further division based on sex was deemed unreliable (Study IV). Total health care costs and their distribution among different categories of health care professionals are shown in Table 3.

Table 3. Number of contacts and mean unit costs by cost components

Care giver	Primary care		Outpatient care		Inpatient care	
	No	Unit cost SEK	No	Unit cost SEK (95%CI)	No	Unit cost SEK (95%CI)
Physician, visit	109	1397	214	2636 (2271-3001)		
Physician, indirect contact	16	466	5	0		
Nurse, visit	93	540	119	2389 (2088-2691)		
Physiotherapist and occupational therapist, visit	19	431	191	818 (762-874)		
Physiotherapist and occupational therapist, indirect contact	26	431				
Other visit	35	559	67	1151 (916-1386)		
Hospitalization			8	33,070 (25,400-40,740)	98	39,987 (33,788-46,187)

Life after onset

The symptoms experienced after discharge from hospital worried the interviewees. They believed that their disease had been resolved, but they still experienced illness. They feared that the symptoms would not be transient and that their illness would be permanent. The interviewees felt that they could not live the rest of their lives with symptoms as severe as these because the symptom burden was too great. They were not able to find much information about residual TS symptoms and this uncertainty amplified their worry. The most common residual symptom was lassitude. This was also the most burdensome symptom and had great impact on interviewees' lives. It included both lack of stamina and general fatigue and resulted in less exercise, more sleep and feeling inactive and bored. This symptom did reduce over time (Study II).

Interviewees also experienced negative effects from residual malaise. They felt that their thinking had become slow and sluggish after becoming ill. For example, they forgot things, had to write to-do lists and felt dazed (Study II).

Some of the interviewees experienced residual pain that they described as diffuse. Symptoms of affected breathing included shortness of breath, coughing, respiratory distress, long expirations and hoarse voice. Other residual symptoms were nausea with or without vomiting or related symptoms, such as changes in taste, lack of appetite, increased salivation and increased hunger, lipothymy, slow heart rate and palpitations (Study II).

The questionnaire responses showed that patients with TS experienced symptoms as frequent and as severe as those who with an AMI. The multivariate complete case regression model showed no significant differences in symptom severity or frequency between the groups (Table 4). Tiredness was the most frequent symptom for both groups. This was followed by sleep disturbance, shortness of breath during exertion and lack of energy for the TS group and shortness of breath, sleep disturbance and tiredness for the AMI group. An additional analysis was conducted using a secondary unadjusted regression model. The unadjusted model showed significant differences in frequency of headache (p=0.016) and severity of depressive symptoms (p=0.040). However, both groups scored under the cut-off point of 8. Data on descriptive characteristics of pain were also collected. The primary multivariate adjusted complete case model results showed that the participants affected by AMI more frequently described their pain as splitting (p=0.014). The between-group difference remained in the unadjusted model (p=0.005) (Study III).

Table 4. Mean frequency and severity of symptoms from the multivariate adjusted model in study III

	TS n=48 (range)	AMI n=79 (range)	β-co-efficient	95% Confidence intervals of the difference		p-value
				Lower	Upper	
Chest pain[a]	1.94 (1–5)	1.65 (1–5)	0.735	−0.278	1.748	0.155
Chest pain that limits daily activity[a]	1.43 (1–4)	1.28 (1–4)	0.345	0.896	1.586	0.286
Shortness of breath[a]	2.38 (1–6)	2.62 (1–6)	−0.084	−1.035	0.867	0.862
Shortness of breath during exertion[a]	2.96 (1–6)	3.05 (1–6)	−0.300	−1.248	0.647	0.534
Heart palpitations[a]	2.09 (1–4)	1.87 (1–5)	0.453	−0.533	1.439	0.368
Tiredness[a]	3.28 (1–6)	3.16 (1–6)	0.469	−0.483	1.420	0.335
Weakness[a]	2.78 (1–6)	2.37 (1–6)	0.832	−0.132	1.795	0.091
Lack of energy[a]	2.94 (1–6)	2.73 (1–6)	0.069	−0.874	1.012	0.886
Headache[a]	2.26 (1–6)	1.59 (1–5)	0.487	−0.519	1.494	0.343
Dizziness[a]	1.81 (1–5)	1.73 (1–5)	−0.129	−1.168	0.911	0.808
Stomach trouble[a]	2.40 (1–5)	1.96 (1–6)	0.676	−0.306	1.659	0.177
Sweating[a]	2.32 (1–5)	1.94 (1–6)	0.521	−0.466	1.507	0.301
Sleep disturbance[a]	3.17 (1–6)	2.95 (1–6)	0.082	−0.857	1.022	0.863
Anxiety[b]	7.04 (0–20)	5.71 (0–20)	−0.047	−3.182	2.207	0.721
Depression[b]	5.40 (0–17)	3.92 (0–12)	−0.143	−3.230	0.927	0.275
Stress[b]	23.36 (3–41)	22.22 (2–38)	0.036	−4.116	5.404	0.789
General fatigue[b]	13.29 (4–20)	12.51 (4–20)	−0.134	−3.605	1.177	0.317
Physical fatigue[b]	12.49 (4–20)	12.17 (4–20)	−0.169	−3.958	0.856	0.205
Reduced activity[b]	12.49 (4–20)	12.37 (4–20)	−0.111	−3.604	−1.462	0.404
Reduced motivation[b]	10.47 (4–19)	9.31 (4–18)	−0.156	−3.304	0.832	0.239
Mental fatigue[b]	10.27 (4–20)	9.26 (4–17)	0.058	−1.637	2.590	0.656

TS: takotsubo syndrome; AMI: acute myocardial infarction. [a]frequency of symptoms. [b]severity of symptoms

The 58 patients with TS had a total of 40 readmissions during the 6 months after initial hospitalization. The mean hospital stay for readmissions was 5.5 days. The total mean length of hospital stay from onset of TS to 6 months after the initial discharge was 10.2 days. The 58 patients with TS had a total of 902 primary and outpatient care contacts in the 6 months after discharge, an average of 15.6 contacts per person. The total mean direct health care costs were SEK 95,071 (95% CI: SEK 75,351–114,791). Of this, SEK 73,232 (77%) was spent on contacts in which at least one of the registered conditions was in ICD chapter IX (I00–I99 Circulatory system diseases) and SEK 64,900 (68%) was spent on contacts in which the main condition was in that ICD chapter. Other main conditions that resulted in substantial costs were in ICD chapters II (C00-D48 Neoplasms), V (F00-F99 Mental and behavioral disorders), and X (J00-J99 Respiratory system diseases). ICD code R074 (Chest pain, unspecified) was the main condition registered in 10 health care contacts, with a total cost of SEK 47,241 and cost per contact of SEK 4,724 (SEK 1025–8423). Moreover, R074 was one of several registered conditions in 172 contacts that resulted in a total cost of SEK 878,391 (Study IV).

Mean HRQoL rose after discharge and was 0.74 at 8 weeks and 0.78 at 6 months (using the UK value set), and 0.86 at 8 weeks and 0.88 at 6 months (using the Swedish experience-based value set). This corresponded to an EQ-VAS score of 68.2 at 8 weeks and 73.7 at 6 months. The score range remained large at both 8 weeks and 6 months after discharge. The following significant correlations between the different EQ-5D dimensions were found at 8 weeks and 6 months after discharge for the group with complete response. Eight weeks after discharge: between mobility and usual activities (p=0.009) and between usual activities and anxiety/depression (p=0.049); 6 months after discharge: between mobility and usual activities (p=0.002) and between pain/discomfort and anxiety/depression (p=0.008) (Study IV).

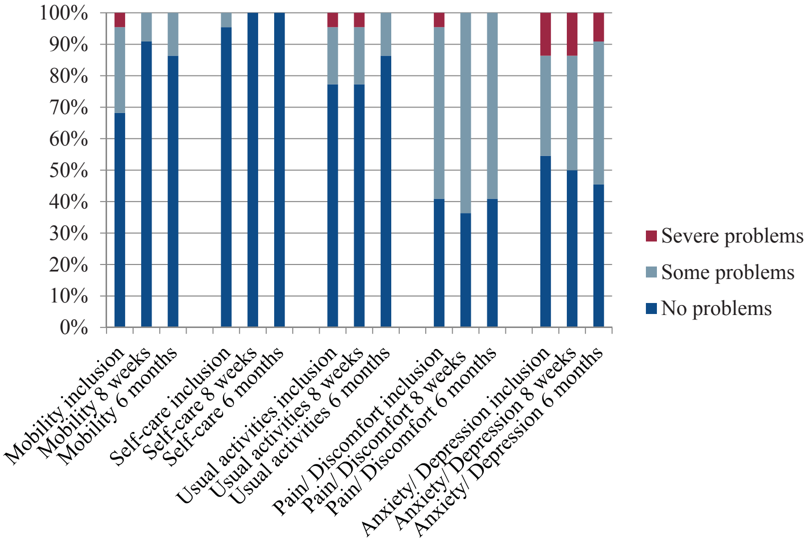

Figure 1. Comparison of the five EQ-5D dimensions from inclusion, 8 weeks after discharge, and 6 months after discharge. Sub-group with complete data.

DISCUSSION

Reflections on the findings

The findings from this thesis show that health in connection with TS is affected by several different factors. For a long time before TS onset, interviewees experienced an unsatisfactory life situation characterized by lack of control, responsibility and injustice leading to illness. This type of life situation could not be defined as healthy, as interviewees were not a state of complete physical, mental and social well-being (6), did not feel a state of equilibrium between freedom and vulnerability (7) and were unable to strive for their goals (5). These findings also illustrate that health is more than absence of disease (3). A burdensome, stressful life situation influenced interviewees' health for a long time before the onset of TS and was viewed by them as a cause of their disease (Study I). During the week leading up to the acute onset, their health was also affected by symptoms such as tiredness and breathlessness. They sought medical care when these symptoms became insufferable. After discharge from hospital, the symptoms greatly affected interviewees' health (Study II). These influences on health and their consequences will be discussed in more detail below.

Health and stress

Illness was present long before the acute onset of TS and persisted after discharge from hospital. This illness was connected to interviewees' life situation more than to individual symptoms. The life situation was burdensome and characterized by lack of control, responsibility and injustice. The interviewees thought of their burdensome life situation as an explanation for their disease (Study I). Stress is a common explanation for various diseases even when there is no clear biological evidence for its effects (13). This is especially true for diseases perceived as female. Psychological (individual) factors are more commonly used to explain women's diseases than men's diseases. An emphasis on psychological factors over societal factors places the responsibility of the illness on the individual rather than on the structural environment (44). TS mainly affects women and is associated with stress. However, whereas some studies have suggested that psychological factors can explain TS etiology (68-70), other studies have found no evidence for this (60, 71). In considering the causation of disease, the origin of the stress (e.g., psychological disposition or structural factors) is not important. Stress is caused when the environment is stressful relative to the resources available (14, 15).

Nonetheless, the interviewees cited stress and a burdensome life situation as explanations for their TS (Study I). However, other models move beyond individual, psychological factors to explain why some people experience more stress and suffer more severe consequences from it than others. Gender theory uses societal structures to explain why women suffer from more stress-related illness than men (44). According to Jónasdóttir (115), the dominant form of sociosexual relations is "love power," which is generally given voluntarily by women and is exploited by men. Men gain access to women's resources, care and love but may not return these resources. This happens under gender norms that make women incapable of building emotional reserves and authoritative social powers. This is possible because of the different stipulations for women and men. Human beings need to love and be loved to be socioexistentially confirmed; that is, to become a person. However, women do not fully control how and under which conditions they may legitimately use their capacities. The consequence of this exploitation is an exhaustion of capacities (115). The present study findings are concordant with gender theory (44) and the theoretical writings of Jónasdóttir (115). Both female and male interviewees adopted or were assigned female identities, such as taking care of and worrying about others, and organizing and taking responsibility for home life. The findings show that the interviewees gave a lot of themselves and did not feel that they received the same in return. They also needed to be busy, helpful and not be a burden to others to feel confirmed and validated as persons. Jónasdóttir (115) argues that women need to love to be confirmed; the interviewees needed to help and protect (i.e., to love) others to feel accepted. Moreover, the findings show the intrinsic power gradient in gender structure. Interviewees could not control the stipulations of how and when they assisted others, which was frustrating. The findings show that they did not fully feel part of society, a state that is also described by Jónasdóttir (115) (Study I).

Furthermore, interviewees felt trapped and felt that they could not change their circumstances. These circumstances slowly drained them of power and resources and weakened their resilience. Living under these circumstances wore the interviewees down so much that they felt their capacity was exhausted and that the smallest stressor could tip them over the edge (Study I).

Another female dominated condition that have been connected to stress and burdensome life situations is burnout. Several similarities can be seen between the lived experiences of people affected by burnout and the findings in this thesis. Both groups have been shown to experience demands and feel that these come from others (116, 117). They have a desire to help (118) and both groups perceive at least some of the demands as rewarding (116). They have no control over the influx of tasks and the demands seem never-ending, (118). Neither the people affected by burnout, nor the people affected by TS felt they had time to recuperate and were not able to relax (117). In both groups, a feeling of inadequacy emerged in relation to the demands (118). Neither group asked for help when they felt overwhelmed and when they perceived that others did not offer to help, they felt unfairly treated (117, 118). Feeling of injustice have been shown to be especially importance in people affected by burnout and the ability to let go of injustice an import factor in staying health in a context with high risk of becoming affected by burnout (109).

However, the connection of illness to stress and other psychological explanations should be made with caution. Especially, when it concerns conditions dominated by women. Psychological explanations of disease and illness can potentially place the whole burden and blame of the condition on the affected person and can also trivialize the disease by attaching an explanation with low status to it. Malterud suggests that this is especially true for women's diseases, which receive little research attention. As a consequence, there is less knowledge about these diseases, which contributes to a lack of explanatory models. Diseases that are not fully understood and that lack clear pathophysiological explanations have lower status (37).

Symptoms and health

The interviewees believed that stress and a burdensome life situation were causes of TS, and that the experienced symptoms were consequences of the disease. The findings reveal that symptoms started a week to a couple of days before acute onset. These symptoms were ignored, partly because of interviewees' life situation and partly because they were not perceived as indicating serious illness. Although the symptoms affected health, their effect was not sufficient to prompt the interviewees to act on them (Study II). This lack of response, and the reasons given for it, reflects their life situation (29, 33). When the symptoms and their effect on health became so severe that the interviewees perceived them as a sign of illness, they sought medical attention. As Leder (32) suggests, the awareness of their body changed when they experienced the symptoms and they felt that their existence was threatened (32). Although the signs of disease prompted interviewees' admittance to hospital, the symptoms affected their health, caused worry and made them seek medical attention (Study II). The findings show that patients affected by TS experience symptoms that are as frequent and severe 8 weeks after discharge from hospital as patients affected by an AMI (Study III). These residual symptoms caused much worry for the interviewees. These experiences are in accord with the literature on symptom distress (Study II).

The symptom experience and the resultant distress may have been exacerbated by lack of information about symptoms after TS (39, 40). This accords with symptom models that view the perception of symptoms as a complex interaction between personal and symptom characteristics and the value assigned to the symptoms. Concurrent symptoms may also influence and exacerbate each other (33, 41-43). Patients thought that they were cured and had interpreted the information they had received from health care professionals to mean that they would experience no residual symptoms. When they did experience symptoms, this made them feel alone and abandoned. This illustrates the lack of validity and credibility that medical professionals attribute to symptoms (37). Instead, medical professionals emphasize the lack of clinical signs of disease. As patients did not exhibit clinical signs, it was presumed that they would not experience any symptoms. The distinction was clearly made between signs, which are valued, and symptoms, which are ignored.

Aspects of experience that could not be measured and did not correlate with medical signs were not acknowledged during encounters with health care professionals. In accord with Malterud's view (37), symptoms that do not correspond with medical signs may be viewed as vague and not indicative of a real disease (and therefore discredited). Illness narratives have low credibility; they may be considered as based on psychosocial factors and therefore trivialized. This is especially likely for female-dominated diseases such as TS (37).

Despite the contrasting values and status ascribed to symptoms and signs, self-reported symptoms are good predictors of both readmission and health among patients with AMI (119, 120), and they predict long-term survival among people affected by chronic heart failure better than clinical signs (121). Furthermore, negative illness experience has been linked to increased risk of complications after AMI (122). This indicates that symptoms are not only important for patients´ well-being but are also important for survival. In addition, the connection between symptoms and HRQoL is well-established among people with coronary heart disease (88). This connection has also been made for a variety of specific symptoms, such as fatigue (123, 124), dyspnea and pain (119, 125). Even symptoms that occur only once or twice a week affect HRQoL. One reason that symptoms have such an influence on HRQoL is that they impact people's daily lives (40, 125). This accords with the findings in this thesis. Participants' symptoms hindered them from living their life as they wished to (Study II).

The little research there is shows that residual symptoms are bothersome and affect the health and quality of life of patients with TS (64). The findings from this thesis show that self-reported symptoms are intercorrelated and also correlate with mobility and the ability to perform usual activities. HRQoL was lower in the participants with TS at baseline and 8 weeks after discharge, but was comparable to that of the general Swedish female population aged 60–69 years old 6 months after discharge (112). As with self-reported symptoms 8 weeks after discharge, HRQoL 8 weeks after discharge was comparable to that of Swedish females aged 65–69 years old 6–8 weeks after discharge for an AMI (127). The predictive value of symptoms for health outcomes shows the importance of integrating symptom perception as a target for therapy (Study IV).

Social structures and health

The findings from this thesis indicate that social structures, such as gender, influence what sickness an individual is affected by, how the disease is valued, how signs and symptoms of the sickness are perceived and the utilization of health care resources (29, 30). The findings are in line with both the WHO's view of what affects health and the model by Dahlgren and Whitehead (17, 19, 20). Individual factors, such as age and sex, influence health in connection with TS; the disease mainly affects postmenopausal women. Demographics for the participants in the present studies supported this. The present findings suggest a combined influence on health of individual lifestyle factors and social and community networks. The interviewees' stressful life situation had a large impact on health; however, the strength of this influence was highly dependent on their social and community networks. Although general socioeconomic, cultural and environmental conditions influence the health of people affected by TS, for the interviewees in Study I, the impact of individual lifestyle factors and social and community networks was more obvious. One way in which societal conditions affected health in TS is through gender structures. Gender influences all aspects of life and the organization of society because it is always present and can therefore never be disregarded (18). Gender structures in society influence health because they affect the stipulations under which an individual's life situation can develop, as described by Jónasdóttir (115). As discussed above, gender structures influenced interviewees' perceptions of their responsibilities, leading to exhaustion and poor health (Study I).

The connection between health and living and working conditions, which include health care services, in the model is evident (19, 20). Health care services are directly influenced by views on illness, disease, symptoms and signs, as described by Foucault (38) and Malterud (36, 37). The status division between symptoms and illness on the one hand and signs and disease on the other influences the organization of health care services and access to them. Foucault was skeptical of the idea that power originates from a central point in society. Instead, he believed that power is dispersed and practiced in intimate and diffuse ways, most discursively through our way of speaking about and categorizing people (45). The power and authoritativeness of the medical gaze does not originate in the health care services. Rather, it is a reflection of discursive views in society as a whole. The same holds for other types of structural power, such as gender, which are changeable and can be challenged (45). The present findings cannot determine if, as Malterud (37) suggests, TS receives less research attention because it is a female-dominated disease. However, much of the research on TS is on its biomedical aspects, and there is little research on self-reported health and symptoms. This may because of the high value placed on technically measured medical signs (37, 38). As discussed above, societal power structures have consequences for the health of people affected by TS. Gender structures influence and lay the foundation of stressful life situations (115), which the interviewees themselves considered the cause of their TS. The intrinsic power gradient and status difference between symptoms and signs is evident in the scant attention paid to symptoms by health care professionals. This resulted in the interviewees feeling alone and abandoned.

Care of takotsubo syndrome

How and to what extent health is regained after an episode of illness can depend on the care received. There are no clear guidelines and sparse knowledge about the utilization of health care resources for TS (1). The findings show that most direct health care costs stem from inpatient hospital care. The total average length of hospital stay during the 6-month study period was 10 days. Of this, 6.4 days were the initial hospitalization and the rest comprised readmissions (Study IV). Previous TS studies show an average primary hospital stay of between 3.6 and 8 days (82-84). The average length of hospital stay for TS reduced between 2007 and 2012 (84).

In our sample of 58 patients, there were 40 readmissions during the 6 months after the initial discharge. A 30-day readmission rate of 11.6% was previously reported for patients with TS (84). If the readmissions in the present study are presumed to be distributed equally during the 6-month study period, the rate would be similar (11.5%) but readmission may not be equal throughout the period. The readmittance rate in Sweden the year after an AMI was 35% for females 65–75 years old and 28% for females 0–64 years old. Approximately half of these were for non-cardiovascular causes (127). Compared with this, the readmittance rate for patients with TS is substantially higher (69%) in half the time, which is likely to generate societal costs for health care. Compared with patients affected by AMI, the participants in this study experienced a longer primary stay in hospital. The median hospital stay for patients <80 years old, who were discharged alive after an AMI in Sweden, was 4 days in 2015. This had not changed since 2008 (127) (Study IV).

In addition to the initial stay in hospital and readmissions, the 58 participants with TS had 298 primary care contacts and 596 outpatient care contacts during the 6 months following discharge. On average, this is equivalent to 15.6 outpatient or primary care contacts in the 6 months following discharge. Furthermore, eight outpatient care hospitalizations were recorded. Most of the complaints in these contacts were coded in ICD chapter IX (I00–I99 Circulatory system diseases), which indicates that the utilization of health care resources was connected with TS. Most of the total costs generated from the utilization of health care resources were also linked to diseases in ICD chapter IX (I00–I99 Circulatory system diseases) and most of these costs related to subchapter I42–I49, which contains the diagnosis for TS. This indicates that much of the care that these patients utilize relates to TS or other cardiovascular diseases. Other main conditions that resulted in substantial costs were in ICD chapters II (C00–D48 Neoplasms), V (F00–F99 Mental and behavioral disorders) and X (J00–J99 Respiratory system diseases). These costs may be expected if one considers previously reported TS comorbidities (63, 74). Other comorbidities that have been connected with TS are neurologic, renal and endocrine diseases, but there were few concurrent costs related to these conditions in this sample (Study IV).

The study shows that the total average health care cost from onset to 6 months after discharge was SEK 95,071. This is equivalent to USD 11,271, based on the average exchange rate in 2015 (USD 1 = SEK 8,435) (128). This is lower than the average cost of USD 16,723 just for hospitalization reported by Khera et al. (82). The present findings showed little difference in cost of care related to age, country of birth, present or previous nicotine use. Patients with previous diagnosis of AMI, angina, stroke or hypertension had lower costs of care than those without. Men had higher costs of care than women, but because only five men were included in the study, this result should be viewed with caution and may not be reflected in a larger cohort. However, previous research shows that men suffer from more complications (82); this may be reflected in the higher cost of care in our study. Despite the small number of men in this study, the gender distribution and age was similar to that of larger cohorts (1, 59). The proportion of patients with diabetes mellitus was lower than in previous studies (63, 74) but similar to that of a larger Swedish cohort (66); this may affect the total cost of care. Despite the frequent contacts with outpatient and primary care, over half the costs arose from inpatient hospitalizations (Study IV).

Health-promoting care

The findings in this thesis show the effect of TS on health and indicate that patients' explanation of the illness does not fully accord with the biomedical research (1). For health care to be efficient, it must consider all aspects of sickness. This includes biomedical aspects, illness perceptions and symptom experience. Failure to consider these factors may lead to dissatisfaction with care and undertreatment of disease (10). The findings show that current health care fails to consider all aspects of TS. However, the present research cannot determine if this results in ineffective care or undertreatment. Nevertheless, these findings show that readmission rate are substantially higher for TS patients than for people affected by an AMI. It is evident that the lack of consideration of symptoms and illness perceptions led to ill health and unnecessary suffering for participants affected by TS.

Health care science, within which the discipline of nursing resides, emphasizes illness from a patient perspective (7, 129). It has four concepts of consensus within health care science: patient or person; health; environment; and caring or nursing, around which it aims to gain knowledge that is clinically useful (129). It compliments medicine, which focuses on disease from a biological perspective. Both perspectives are needed for treatment of disease and illness. They are not mutually exclusive, it is rather preferable if the two perspectives can be combined in health care (7). Several researchers within health care sciences (7, 130, 131) underscores the ethical responsibility of a health care professional which nurses are, to contribute to health and well-being. The point of departure for this should be the patient's or person's perspective (7). With this perspective on health care science, and consequently also nursing and caring, it is the responsibility of nurses as a profession to listen to the patient and their experience of illness and health.

Taking the point of departure in the patient narrative in order to fully grasp and understand the illness experience person-centered care (PCC) also includes the mutual understanding and agreement on how to plan and perform the care. PCC takes its philosophical foundation and view of people from personhood (132, 133). The reduction and deconstruction of people and the division between symptoms and signs and illness and disease that has enabled progress in medical science has also rendered medicine having difficulties to integrate the person's life situation in the process of diagnosing and treating disease. This reductionism and deconstruction is totally incompatible with the ethics of personhood (133). A person cannot be divided into parts or considered separate from their body (134).

According to Ricœur (135, 136), a person has awareness, meaning, a will, self-respect, self-esteem, a sense of self and capabilities. Ricœur described all people as capable: humans are *homo capax*. This capability goes hand in hand with vulnerability. A capable person has responsibility for his or her own actions. A person does not become a person alone, rather this always happens in relationship with others. In interactions with others, a person can reflect upon themselves and grow. A person cannot be understood by examining their parts (135, 136). Instead the narrative can be used to gain understanding about a person (95). The (illness) narrative is the foundation of PCC. It should be a personal narrative about illness and how it affects life. The illness narrative constitutes the foundation of a partnership between the patient and the health care professionals (132, 133). A person is always in an institutional, existential and cognitive inferior position in relation to health care professionals when they are in need of care (133).

The partnership is an attempt to counteract the asymmetry in the relationship between health care professionals and the person in need of care, and it enables dialog and shared decision making. A health care plan, which integrates the personal illness narrative and medical knowledge, should be made in partnership between the patient and health care professionals. Another aspect of PCC is documentation. This ensures the sustainability of the illness narrative and the partnership and makes them less dependable on specific health care professionals. Furthermore, the documentation gives legitimacy to the narrative and partnership. Through these processes, PCC attempts to combine reductionist medicine with the holistic view of a patient as first of all and always being a person while also being a patient including also important information from medicine such as biomarkers, imaging et cetera (132, 133). The use of PCC (132) does reduce symptoms and improve self-efficacy (137) and quality of life (138) in addition to reducing the length of hospital stay (139), lower health care costs (140) in patients with cardiac diseases. However, the present findings indicate that there are still some aspects that need further work to develop and clinically implement PCC.

First, the role of the patient narrative and the personal symptom experience within it needs to be guarded. Symptoms greatly impact personal health and without emphasis on them PCC would not stay person-centered. However, nurses and other health care professionals are active in a medical paradigm, which values signs . It is therefore a risk that focus unintentionally shifts from illness experience to clinical signs. One contributing factor to this may be lacking knowledge and understanding of the illness experience and the importance of symptoms. This could lead to misinterpretation of symptoms or that they are omitted in the health care plan. A deficient language of symptoms may also be an important factor. Insufficient language to describe symptoms, or the misconception that symptoms cannot be described, may lead health care professionals to translate the social suffering symptoms entail into bodily dysfunction as a way of handling them. The risk of focus shifting from personal illness experience to medical signs is further enhanced by the current diagnostic system, which is a hinder for PCC. Medical diagnoses are most often based on signs of disease rather than the personal illness experience as well as resources for health. Person-centered integrative diagnosis has been seen as a potential replacement of the current ICD-system in order to bring the whole person to the foreground in care (141). Either way, the health care professional need to take the patient narrative as seriously as bio-markers and imaging results (142). Viewing symptoms and signs not as different entities but as a hierarchy of the same phenomenon (37) could help health care professionals to better integrate symptom experience into PCC.

Second, societal structures and their impact on health need to be integrated into health care approaches. One definition of health is the ability to strive and realize meaningful life goals (5). Context is important for the ethical pursuit of a good life, which can be seen as entailing health. Ricœur defined a person's ethical intentions as "aiming at the 'good life' with and for others in just institutions." If the institutions are not just, the pursuit of health is hindered (135, 136). When focus is placed on a person and their uniqueness emphasized, structural aspects are easily forgotten. The narrative is always interpreted (90-92) and if health care professionals are not aware of these structures and do not reflect on them, their preconceptions may overly influence the interpretation of the narrative and therefore also the partnership and documentation. Without reflection, preconceptions based on societal structures may be interpreted as personal characteristics and the institution may not be just. If these aspects are taken into consideration, PCC could be a viable way to organize care for people affected by TS that incorporates their health and factors that affect it, such as life situation, symptoms, illness and societal structures. It also has the potential to be cost effective.

Methodological considerations

Qualitative and quantitative methods complement each other and are appropriate for different research questions. The study aim should always guide what method is chosen (21). The chosen methods fulfill the overall aim of the thesis and are therefore appropriate. In qualitative research, the primary aim is not to seek an objective truth or final answer that can be generalized without reflection. Instead, the aim is to visualize the processes of people to create meaning and describe and understand a phenomenon (91, 92). When choosing the setting and sample for a qualitative study, it is important to consider the potential richness of the information. A small number of participants may generate a large amount of data for analysis (21). However, to guarantee the trustworthiness of qualitative studies, several issues need consideration.

According to Lincoln and Guba (143), these are credibility, dependability, confirmability and transferability. Credibility refers to confidence in the truth of the findings (143). The phenomenological hermeneutic approach does not seek one single truth. There is always more than one way to interpret a text. However, every possible interpretation is not equally probable (95). Credibility consists of two aspects: the study should be conducted in a way that enhances the findings and steps should be taken to demonstrate credibility. Follow-up questions were used during the interviews in Study I and Study II to ensure understanding. The interpretation was based on original source material. Credibility is also strengthened by the richness of the data. Dependability refers to whether the findings are consistent and could be repeated. The participants' diagnoses were validated by a cardiologist, which ensures the dependability of the sample. Moreover, several researchers cooperated in the interpretation of the text to ensure the dependability of the findings.

The third aspect of trustworthiness is confirmability, which refers to the neutrality or objectivity of the findings; that is, whether they are shaped by the interviewees (143). Pre-understanding can never be totally avoided and always has some influence on the analysis. However, within phenomenological hermeneutics, it should be contained and reflected upon to minimize its influence over the interpretation (97). The researcher conducting the interviews had little clinical experience of cardiology, which decreases the pre-understanding about people affected by TS. The last aspect of trustworthiness is transferability. This refers to the possibility of extrapolating the findings. The applicability to other settings or groups is increased by large samples, diversity in age, sex and background of the interviewees and the richness of the data (143). Interviews are a good method through which to acquire knowledge about personal experiences, and phenomenological hermeneutics was developed to explore lived experiences (97). Therefore, the methods for data collection and analysis were deemed appropriate to answer the research questions in Study I and Study II.

In quantitative studies, validity and reliability are often discussed. Validity refers to whether an instrument measures what it is intended to measure and reliability refers to the consistency of what is measured (21). All questionnaires used in this thesis are well established and have been used extensively before. Moreover, they have all been validated in Swedish and have shown good validity and reliability. Although none of these questionnaires have been tested on people affected by TS, no appropriate alternative questionnaires that had been tested on people affected by TS could be found. With the exception of the SHCQ, all questionnaires are general and have been used in studies of people with cardiovascular diseases. The use of self-reported symptom measures further strengthens the validity of the findings (Study III). The validity and reliability of the Vega registry have been shown to be good (107, 144). Costs were calculated based on DRG codes and averages and were not exact costs. These estimates are used to reimburse health care so they were deemed sufficiently accurate. Furthermore, this is the best available method to calculate costs, as exact costs for every visit or hospitalization are not recorded in Sweden (Study IV).

No significant differences could be found in the primary multivariate adjusted complete case regression model at the set significance level of $p<0.05$. This may be because there is little difference in self-reported symptoms in people affected by TS and those affected by AMI. However, it may also indicate a type II error (21). In that case, a greater number of participants would have resulted in significant between-group differences in self-reported symptoms. To minimize the risk of type II errors, a power calculation was conducted before the start of the study. This indicated that a sample size of 46 participants would be sufficient to show a difference in general fatigue at a significance level of $p<0.05$ (Study III).

CONCLUSION

The thesis findings show that people affected by TS experienced illness long before the acute onset of TS and that their illness was connected to a burdensome life situation. Societal structures may have contributed to this situation occurring. Participants viewed their life situation as a cause of their disease. Furthermore, these findings show that after discharge from hospital, the health of people who had experienced TS remained affected. They experienced comparable frequency and severity of symptoms as people who had been affected by an AMI and these symptoms caused worry and affected health. Moreover, they had frequent contacts with health care professionals after their discharge from hospital.

In order for health care to be efficient, it must consider all aspects of sickness. This includes biomedical aspects, illness perception and symptom experience. Failure to do so may lead to dissatisfaction with care and under treatment of disease and illness. PCC takes the patient narrative as a point of departure in order to fully grasp and understand the illness experience and medical signs. PCC also includes the mutual understanding and agreement on how to plan and perform the care. It is the ethical responsibility of health care professionals to contribute to health and well-being. PCC has the potential, with the consideration of social structures and guardiancy of the inclusion of the personal symptom experience, to enable this for people affected by TS.

IMPLICATIONS FOR CARE

From health care professionals perspective this thesis shows the importance of including more perspectives than the biomedical in care. It is the ethical responsibility of health care professionals to contribute to health and well-being. To facilitate the restoration of health, health care professionals need to consider the patient's entire life situation. This includes symptom experiences, views on sickness (both in general and for TS specifically) and structural factors. The findings show that people differ in their experience of health in connection with TS. It is important that health care professionals are aware of this and realize that self-reported symptoms and health may not correlate with measurable signs of TS severity.

Health care professionals and the organizations they work in are not immune to social structures and normative influences. Awareness of the discursive medical perspective and medical gaze is therefore important in the successful integration of personal views of illness and health in care. This awareness if equally important to policy makers. Limited by normative structures, preconceptions based on societal structures run the risk of being interpreted as individual characteristics, which may result in unequal and unjust care. PCC emphasizes the narrative and personal experience of sickness and uses that as a basis for designing individual health plans. Focusing on the personal need and resources of each patient enables the potential optimization of care beyond social structures and preconceptions, both in terms of health economics and maximizing health. Addressing symptoms and other health issues may also lessen the need for readmittance, which would be a health economic gain.

FUTURE PERSPECTIVE

The thesis findings indicate the following areas for future research. Symptom experience needs to be an integrated part of the care of patients with TS. However, research is needed on how best to integrate symptom narratives into clinical practice. More research, both qualitative and quantitative, is needed to investigate self-reported symptoms for longer after discharge from hospital and to examine their consequences for health and the ability to live life as desired. These aspects should be integrated into guidelines for treatment and follow-up care for patients affected by TS. It would be very useful to include more men in future studies. This would enable comparisons between the sexes, which this thesis was unable to fully address.

Furthermore, this study found that patients perceived a stressful life situation as the cause of their sickness. This is something that health care professionals need to be aware of and to address when meeting patients. Further health economic evaluations of the consequences of TS are also needed. Research investigating if a person-centered approach is viable for people affected by TS is also needed. The goal of such an approach would be to integrate symptom experience, views on TS causation and life situation into care and to investigate if these factors impact self-reported health and ability to perform daily activities.

SAMMANFATTNING PÅ SVENSKA

Takotsubo syndrom är en form av akut, reversibel hjärtsvikt som främst drabbar kvinnor efter klimakteriet. Insjuknandet liknar det vid hjärtinfarkt, både vad gäller symptom och kliniska tecken. Den medicinska återhämtningen har betraktats som snabb och vistelsen på sjukhus brukar vara några dagar till en vecka. Diagnosen är relativt ny och drabbar uppskattningsvis 1 500-3 000 personer i Sverige varje år. Det är inte helt kartlagt vad som orsakar takotsubo syndrom eller varför många fler kvinnor än män drabbas men det finns kopplingar till akut stress. Trots kopplingen till stress är lite känt om livssituationen före insjuknandet. Vidare saknas kunskap om egenskattade symptom och hälsa före, i samband med och efter det akuta insjuknandet samt hur mycket och vilken typ av vård som används och dess kostnader.

Avhandlingens övergripande syfte var att skaffa en förståelse om vad det innebär att drabbas av takotsubo syndrom. Flera olika metoder användes för att samla in och analysera data. Information om tidigare livssituation, symptom, förklaringsmodeller till insjuknandet och hur detta påverkade hälsan samlades in med hjälp av intervjuer. Information om symptom och hälsa i samband med insjuknandet och efter utskrivning från sjukhus samlades även in med enkäter. Information om användning av vård och dess kostnader hämtades från register. Avhandlingen och dess studier utgår från att hälsa och symptom är personliga upplevelser som inte kan bedömas av andra personer men som påverkas av yttre faktorer såsom livssituation, levnadsförhållanden och sociala strukturer i samhället. Avhandlingen visar att personerna som drabbats av takotsubo syndrom upplevde ohälsa i form av en betungande livssituation långt innan det akuta insjuknandet. De intervjuade ansåg själva att detta var en bidragande orsak till att de blev sjuka. Några dagar till en vecka innan det akuta insjuknandet började intervjupersonerna känna av symptom i form av till exempel andfåddhet, trötthet och smärta. Antingen så sågs inte symptomen som ett tecken på någon allvarlig sjukdom eller så kände inte de intervjuade att de hade tid att söka vård. Trots att de redan haft symptom och besvär tidigare kom de akuta symptomen som till exempel smärta, andfåddhet, utmattning, illamående och allmän sjukdomskänsla som en överväldigande chock. De kände då de att detta var något allvarligt som de inte skulle klara av på egen hand. Efter sjukhusvistelsen hade de intervjuade många kvarstående symptom, såsom trötthet, minskad uthållighet, smärta, allmän sjukdomskänsla och andfåddhet. De kvarvarande symptomen hade stor påverkan på hälsan eftersom de skapade oro och gjorde att de intervjuade inte kunde leva som de önskade. De intervjuade hade förstått det som att deras hjärta var läkt och att de nu var friska. Tanken på att leva resten av livet med så svåra symptom skrämde dem.

Personer som drabbats av takotsubo syndrom har lika frekventa och svåra symptom som personer som drabbats av en hjärtinfarkt. Självskattad hälsa var lägst vid insjuknandet för att sen öka under de följande sex månaderna. Spridningen inom gruppen var emellertid stor, vissa skattade hög hälsa medan andra skattade låg. Ungefär hälften hade problem med smärta eller obehag och ångest eller depression vid insjuknandet samt åtta veckor och sex månader efter utskrivning. Det fanns ett samband mellan dessa vid alla tre tillfällena. Den genomsnittliga vårdtiden för takotsubo syndrom var 6,4 dagar. Under de sex månader som följde utskrivningen hade gruppen om 58 personer 40 återinläggningar på sjukhus och i genomsnitt 15,6 öppen- och primärvårdskontakter. Den totala genomsnittliga kostnaden för vården från insjuknandet fram till sex månade efter utskrivning från sjukhus var 95 071 kronor. Av detta härrörde 77% till vårdkontakter med någon hjärtrelaterad diagnos. Avhandlingen bidrar med kunskap om självskattade symptom och hälsa, tidigare livssituation och nyttjande av vård hos personer som drabbats av takotsubo syndrom. Resultatet tyder på att sociala strukturer har betydelse för den egenupplevda hälsan. Den här kunskapen är viktig för att kunna utveckla en vård som svarar an på de behov som finns och stödja dessa patienter i att återfå sin hälsa. En möjlig väg för att kunna kombinera den medicinska vården med personernas egna upplevelser av sin hälsa och ohälsa är person-centrerad vård.

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