

From DEPARTMENT OF MEDICINE UNIT OF HEART AND
LUNG DISEASES

Karolinska Institute, Stockholm, Sweden

**SEX AND GENDER DIFFERENCES IN PATIENTS UNDERGOING ABLATION
OF ATRIAL ARRHYTHMIAS**

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**Karolinska
Institutet**

Stockholm 2018

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Published by Karolinska Institute.

Printed by Eprint AB

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ISBN 978-91-7831-133-0

SEX AND GENDER DIFFERENCES IN PATIENTS UNDERGOING ABLATION
OF ATRIAL ARRHYTHMIAS

THESIS FOR DOCTORAL DEGREE (PhD)

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TO MY BELOVED FAMILY,

AND IN LOVING MEMORY OF

INGRID AND WALDEMAR

KARLENSTEDT

Det är först då fågeln kastar sig ut i den fria rymden som han känner att han har vingar.

– C. Wagner

ABSTRACT

Background: Women and men differ in the prevalence of arrhythmias. Furthermore, there are sex and gender differences in referral for ablation, symptom severity, health-related quality of life (HRQOL), functional impairment and response to treatment, risk factors, and outcomes.

Aim: This thesis studies sex and gender differences in referral, treatment, outcome, symptom, HRQOL, and functional impairment in patients undergoing cardiac ablation of atrial fibrillation and paroxysmal supraventricular tachycardia (PSVT).

Method: The thesis is based on four studies. Study I and II are observational prospective studies based on questionnaires before and six months after ablation. Study I include 214 (109 women) patients referred for PSVT ablation and Study II includes 242 (121 women) patients with atrial fibrillation referred for pulmonary vein isolation (PVI). The following questionnaires were used: Symptom Checklist: Frequency and Severity, Short Form 36, and Sickness Impact profile. Referral patterns and socio-economic data and symptom duration were evaluated with a separate questionnaire. In Study III, 700 patients (359 women) who had undergone AV-nodal junction (AVJ) ablation between 1990 and 2010 were retrospectively studied. Data were sampled from medical records, the Swedish ICD and Pacemaker Registry, and from the National Patient Registry kept by the National Board of Health and Welfare. Study IV was conducted with 80 (40 women) patients randomized either to an active or a standard pain treatment during PVI using cryo- or radiofrequency energy. Evaluation of the two treatments strategies was assessed with a questionnaire based on the Pain-O-Meter.

Results: In Study I, although women had more PSVT symptoms, they were referred in mean six years later than the men. In addition, women more often reported they were not believed when describing their arrhythmia symptoms and were consequently more often diagnosed with stress and anxiety. In Study II, no such sex difference was found, but women were more symptomatic, assessed a lower HRQOL and a greater functional impairment than the men. Furthermore, women more often received drug treatment and were less often than men referred for cardioversion before ablation. In Study III, heart failure was present in more men than women before the AVJ ablation. When indication presented before ablation, women less often than men received implantable cardioverter-defibrillator (ICD) or cardiac resynchronization therapy (CRT). There were no differences between the sexes regarding primary cause of death, and cardiovascular mortality was the most common cause of death. The main parameter influencing survival was age at the time of AVJ ablation. In Study IV, over 90% of the patients experienced pain during the PVI. Premedication and regular administration of analgesic resulted in less pain and fewer drug administration occasions. Women experienced more pain than men regardless of energy type, cryo - or radiofrequency energy.

Conclusion: All four studies showed that there were sex and gender difference in either referral, morbidity, symptom, HRQOL, functional impairment or response to treatment. Women with PSVT and atrial fibrillation were treated more conservatively than men. Women with PSVT were referred for curative ablation later than men despite having more symptoms. Symptoms due to PSVT in women were more often incorrectly diagnosed as panic attacks, stress, anxiety, or depression. Furthermore, women with atrial fibrillation were more symptomatic, assessed a lower HRQOL and a greater functional impairment but despite that, were more seldom referred for cardioversion before PVI. Women less often received CRT or ICD implantation even when indication was present before AVJ ablation. We found no sex differences regarding survival or primary cause of death after AVJ ablation. The main factor influencing survival was age at the time of ablation. Women experienced more pain than men during PVI, but an active regular supply of analgesic and sedative drugs reduced pain and discomfort during PVI in both sexes.

LIST OF SCIENTIFIC PAPERS

- I. Carnlöf C, Iwarzon M, Jensen-Urstad M, Gadler F, Insulander P. Women with PSVT are often misdiagnosed, referred later than men, and have more symptoms after ablation. *Scand Cardiovasc J.* 2017 Dec;51(6):299-307.
- II. Carnlöf C, Iwarzon M, Jensen-Urstad M, Gadler F, Insulander P. Gender differences in referral, symptoms, HRQOL and functional impairment in patients with atrial fibrillation before and after for pulmonary vein isolation. In manuscript.
- III. Carnlöf C, Insulander P, Jensen-Urstad M, Iwarzon M, Gadler F. Atrio-ventricular junction ablation and pacemaker treatment: a comparison between men and women. *Scand Cardiovasc J.* 2018 Jun;52(3):120-126
- IV. Carnlöf C, Insulander P, Jensen-Urstad M. An active supply of analgesics during pulmonary vein isolation reduces pain. *Scand Cardiovasc J.* 2014 Feb;48(1):35-40.

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LIST OF ABBREVIATIONS

AAD	Antiarrhythmic drugs
AF	Atrial fibrillation
AVJ	Atrio-ventricular junction
AVNRT	Atrio-ventricular nodal reentrant tachycardia
AVRT	Atrio-ventricular reentrant tachycardia
BiV	Biventricular
CRT-D	Cardiac resynchronization therapy- defibrillator
CRT-P	Cardiac resynchronization therapy-pacemaker
ECG	Electrocardiogram
EF	Ejection fraction
ESC	European Society of Cardiology
FAT	Focal atrial tachycardia
HF	Heart failure
HRQOL	Health related quality of life
ICD	Implantable cardioverter-defibrillator
LV	Left ventricular
NRS	Numerical rating scale
PAF	Paroxysmal atrial fibrillation
POM	Pain-O-Meter
PSVT	Paroxysmal supraventricular tachycardia
PVI	Pulmonary vein isolation
QOL	Quality of life
RF	Radiofrequency
RV	Right ventricular
SCL	Symptom Checklist-Frequency and Severity Scale
SF-36	Short Form-36
SIP	Sickness Impact Profile
VAS	Visual analogue scale
WHO	World Health Organization

1 INTRODUCTION

1.1 BRIEF HISTORY

The beating heart and irregular heartbeats have impressed and fascinated people for more than two thousand years. In the fifth century before Christ, the Chinese physician Pien Tsíó made a significant breakthrough laying the foundation of the pulse theory in the identification and treatment of cardiac arrhythmias (1). In this theory, the pulse was studied as a reflection of cardiac activity and the pulse beat as a diagnostic and prognostic criterion of pathology. His theory compared the human body to a stringed instrument where a skilled observer could detect both harmony and dissonance (1). This was one of the first pulse theories, but many more studies of the pulse have been described through the history, starting in ancient Egypt, Greece, and Arabia. Arrhythmia disturbance and pulse analysis have also been described in music and paintings. In the early 1800s, Ludwig van Beethoven set his own cardiac rhythm disturbance to music in the piano sonata opus 8, “Les adieux”. The Dutch artist J. S. Steen (1626-1679) made several paintings in oil showing physicians analysing the pulse in sick women (1).



The Doctor's Visit" by Jan Steen

A first attempt to obtain an electrocardiogram (ECG) from the body surface was made by A.D. Waller (1856-1922) as early as 1887 (2). He published his work in *The Journal of Physiology* but the clinical significance of his discovery of the ECG curve was not recognized at the time. Twenty years later, W. Einthoven (1860- 1927) identified and named four waves (P, Q, R, S) in each ECG when he experimented with the recently invented string galvanometer. The discovery with waves in the ECG was crucial for future studies of cardiac disturbances. In 1924, W. Einthoven won the Nobel Prize in Medicine for his work with the string galvanometer (3).

Willhelm His (1863-1934), living and working in Germany, studied the heart and metabolic conditions. In animal experiments, he found that if the atrium was separated by septum, a dissociated heart rhythm would occur. In a work from 1893, he described the structure that today carries his name, His bundle (1). His bundle constitutes the extension of the AV node that divides into the right and left branches in the ventricle (4).

1.1.1 Treatment breakthroughs

In 1981, Scheinman et al. performed the first intentional atrio-ventricular junction (AVJ) ablation on a human to control refractory supraventricular arrhythmias (accidental AV block had been reported earlier) (5). The technique used was a portable defibrillator with standard electrodes that delivered a high-energy direct current shock (300-500 J) that created a complete AV block. In the late 1980s, the use of direct current shock was replaced with safer radiofrequency energy (6, 7). In Sweden, ablations of arrhythmias with radiofrequency (RF) energy have been a routine treatment since the early of 1990s.

On 8 October 1958 at Karolinska University Hospital, Åke Senning implanted the first pacemaker in a patient with total atrioventricular block (8). In 1980, Mieczyslaw Mirowsky implanted the first automatic cardioverter defibrillator (ICD) in a human, which was placed in the abdomen due to its size (9). In 1993, the first ICD placed in pectoralis was introduced (9).

1.2 DEFINITIONS

1.2.1 Gender and sex

The terms gender and sex are often used equivalently, but there is an important distinction.

The World Health Organization (WHO) define the terms as follows:

“Sex” refers to the biological and physiological characteristics that define men and women and “Gender” refers to the socially constructed roles, behaviours, activities, and attributes that a given society considers appropriate for men and women. (<http://www.who.int/gender/whatisgender/en/>)

WHO further states that “male” and “female” are sex categories, and “masculine” and “feminine” are gender categories:

Women menstruate while men do not, men have testicles while women do not, women have developed breasts that are usually capable of lactating, while men do not, and men generally have more massive bones than women.

(<http://www.who.int/gender/whatisgender/en/>)

In addition, the sex categories cannot be changed, whereas gender characteristics are changeable:

In the United States (and most other countries), women earn significantly less money than men for similar work. In Viet Nam, many more men than women smoke, as female smoking has not traditionally been considered appropriate.

(<http://www.who.int/gender/whatisgender/en/>)

An example of a changed gender characteristic recently made news headlines. Before 2018, in Saudi Arabia women were not allowed to drive cars and this restriction was used as an example of gender characteristics by the WHO: “In Saudi Arabia men can drive cars while women cannot” (<http://www.who.int/gender/whatisgender/en/>). However, as of 2018, women are now allowed to drive cars in Saudi Arabia (10).

According to the Sex and Gender Equity in Research (SAGER) guidelines, developed by the European Association of Science Editors, the term sex and gender should be used carefully to avoid confusion (11). The term sex (male or female) should be used only as a biological classification, and the term gender (masculine and feminine) should be used only as a social and cultural characteristic (11). In this thesis we have strived to consistently use the terminology recommended by SAGER.

1.2.2 Quality of life and Health-related quality of life

Quality of life (QOL) as a concept has been used in a variety of areas for a long time. The concept can be traced back to the Greek philosophers. According to Rustoen (1993), the concept of QOL derives from a speech given in 1964 by the US President Lyndon B Johnson: “The criterion of progress cannot be sought in the banking book but in the quality of the life we live” (12).

Quality of life is an ambiguous term, so it is difficult to define. The concept often includes satisfaction with everyday life, both past and present. An individual’s QOL can be affected by economic conditions, physical environment, education, employment, cultural

opportunities, and psychological and physical well-being. The World Health Organization (WHO) defines QOL as follows:

An individual's perception 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. It is a broad-ranging concept, affected in a complex way by the person's physical health, psychological state, personal belief and social relationships to salient features of their environment (13).

<http://www.who.int/healthinfo/survey/whoqol-qualityoflife/en/>.

Health status is related to the QOL concept in science, but in the clinical care it has been limited to Health-Related Quality of Life (HRQOL). HRQOL refers mainly to function and well-being related to health, illness, and treatment. The concept includes both positive and negative experiences of a medical condition. The focus is on the individual in a health care context and thus contributes to the individual aspect considered in the care and treatment. Specifically, HRQOL relates to a patient's ability to adapt to her illness, resources, and needs (13).

1.2.3 Symptoms

The definition of "symptom" derives from the Greek word "symptoma", which means "anything that has befallen one". In an international dictionary, the word symptom is defined as "the subjective evidence of disease or physical disturbance observed by a patient" (14). Symptoms are only known by the person experiencing the symptoms. Fever or high blood pressure can be measured and observed by others and are "signs" of disease. The disease itself, can produce symptoms. Symptoms can also be produced by side effects or toxicities of a treatment or arise from comorbid medical conditions or acute injuries. Symptoms often occur in clusters and have been shown additive in their impact on for example cancer patients (15).

A routine assessment of the patient's self-reported symptom burden and HRQOL with validated instruments can be beneficial for physicians when deciding on a treatment and can be an indicator of the patient's recovery and treatment outcome. It is important that patients assess their symptoms themselves to avoid the risk of underestimation. Earlier studies have

shown that healthcare professionals tend to underestimate symptoms such as pain and rate the patient's symptom lower than the patient herself (16-18).

A patient's own assessment reflects the patient's daily health status. In oncology practice, self-assessment has been shown to be a beneficial strategy, improving the clinician's ability to predict unfavourable clinical events. Both the clinician's and the patient's perspectives are central, complementary, and provide meaningful information (19, 20).

1.3 ARRHYTHMIA

There are several differences between men and women in the presentation of electrophysiology and cardiac arrhythmias (Table I) (21, 22). One of the first to describe the differences in the heart rhythm between men and women was H. Bazett. In 1920, Bazett found that women had higher heart rate at rest and longer QT interval than men (23). These findings have been confirmed in later reports (24, 25). In a large population-based study (over 5 000 participants), women's average resting heart rate was 3-5 beats higher than men's (24). Women also have shorter QRS duration, sinus-node recovery time, and AV nodal refractoriness, and faster conduction through the AV node (26, 27). Stress produces a more pronounced effect on the AV node and on the sinus node in women, whereas men react with a more pronounced effect on ventricular electrophysiologic properties. Certain gender differences in cardiac electrophysiologic properties seem to be intrinsic. After autonomic tone inhibition, women have higher heart rate and shorter AV nodal refractoriness but longer QT and JT intervals and longer effective refractory period in the right ventricle (28).

This difference in AV nodal refractoriness may partly explain why women often have faster heart rate during atrial fibrillation and supraventricular tachycardia. Factors such as differences in body habitus and autonomic nervous system are also important (29). Moreover, female hormones are known to affect the calcium and potassium channel, which may prolong the QT interval and therefore increase the risk of arrhythmic events (22).

Table I. Examples of sex differences in electrophysiological properties and arrhythmias

Electrophysiological properties	Male predominance	Female Predominance
<i>Heart rate</i>		3-5 beats higher heart rate at rest in women
<i>Sinus node recovery time</i>		Shorter in women
<i>QRS-complex</i>		Narrower and lower voltage in women
<i>Q-T interval</i>		10 -20 ms longer in women (longer during menstruation period)
Arrhythmia type		
<i>Bradyarrhythmia</i>	High-Degree AV-block Carotid sinus syndrome	Sinus node disease
<i>Supraventricular tachyarrhythmias</i>	Atrial fibrillation AV reentrant tachycardia	AV nodal reentrant tachycardia
<i>Ventricular tachyarrhythmias</i>	Ventricular tachycardia Brugada syndrome Sudden cardiac death	Long QT syndrome Torsade's de pointes

1.3.1 Atrial fibrillation

Atrial fibrillation (AF) is the most common supraventricular tachyarrhythmia. In a 2006 report from Rotterdam, the estimated lifetime risk to develop AF was one in four among middle-aged adults in Europe (30). Risk factors for developing AF are primarily age, hypertension, heart failure (HF), and valve disease (31-33). AF is one of the major causes of HF, stroke, dementia, cardiovascular morbidity and sudden cardiac death, and high health costs (34-36). The recommended treatment strategies from the European Society of Cardiology (ESC) 2016 regarding AF includes rate and rhythm control, stroke prophylaxis, and life style changes are shown in Figure I (34).

1.3.2 Rhythm control of atrial fibrillation

In patients with AF who experience severe symptoms and low HRQOL despite a good ventricular rate control, restoring sinus rhythm may be necessary (37). As a first-line therapy, anti-arrhythmic drug (AAD) therapy is generally recommended (38). In patients who continue to have recurrent episodes of atrial fibrillation despite medical therapy or have complications associated with AAD, PVI has shown to substantially decrease symptoms and improve the HRQOL (39, 40). PVI performed in experienced centres has shown to be more effective than AAD therapy (41-44). In younger patients with paroxysmal AF, PVI as a first line treatment has shown to be cost-effective (45).

1.3.3 Rate control of atrial fibrillation

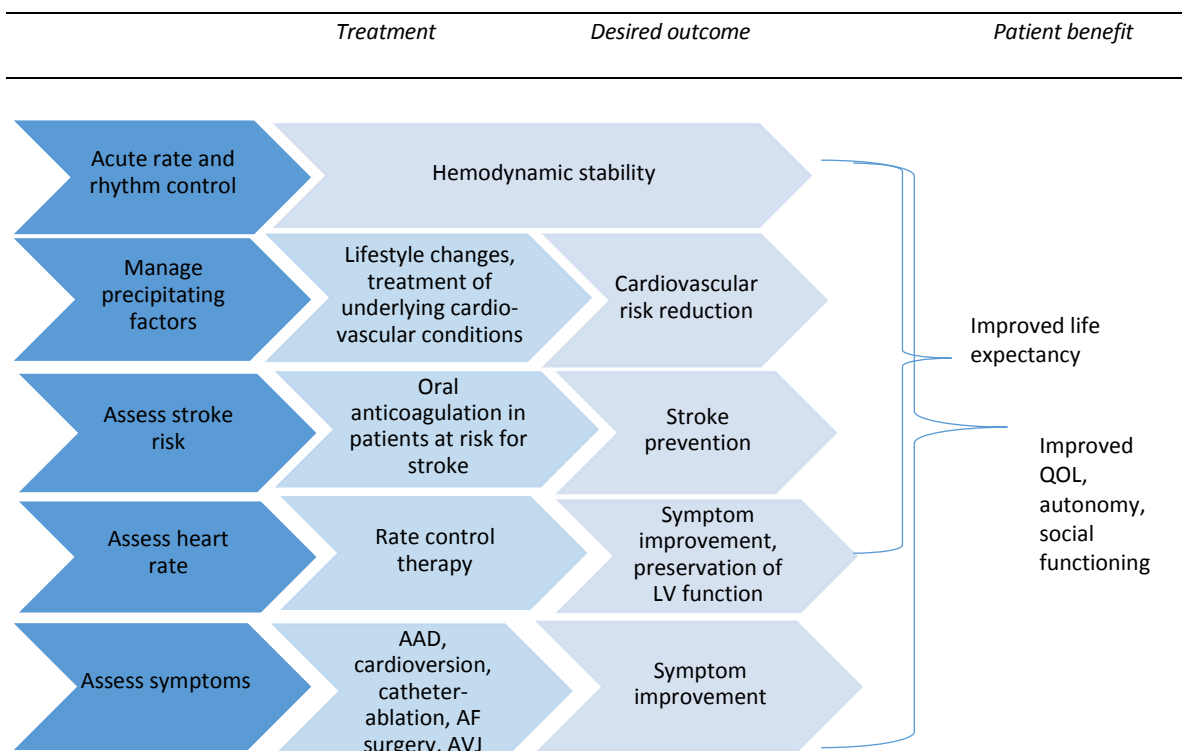
If medication fails, pacemaker implantation and AVJ ablation has shown to control rate and symptoms. The procedure is uncomplicated with a low long-term mortality risk and complication rate, but the patients will be pacemaker-dependent for the rest of their lives (46). According to current guidelines, AVJ ablation should be considered in patients nonresponsive or intolerant to rate and rhythm control (34).

To avoid negative effects and dyssynchrony, a pacemaker system with a left ventricular electrode to achieve biventricular (BiV) pacing may be implanted (47). The choice of pacing therapy depends on the ejection fraction (EF) and the individual patient characteristics (48, 49). Cardiac resynchronization therapy (CRT) reduces mortality and hospitalization and improves cardiac function in patients with severely depressed EF ($<35\%$) and QRS duration (≥ 120 ms) (50).

In patients with HF who receive CRT, it is important that the percentage of BiV pacing is $>90\%$ and AVJ ablation may be needed to achieve full effect of CRT in HF patients with AF and rapid conduction (51).

In selected patients, the ejection fraction has shown to improve after the AVJ ablation (52-54). On the contrary, a negative effect of permanent pacemaker stimulation is dyssynchronous movement patterns of the ventricles. This might lead to an impaired EF and development of HF, especially in patients with previous impaired cardiac function (55). In this group of patients, an increased mortality after the AVJ ablation has been found (56). Ozcan et al. found several independent predictors for sudden death after AVJ ablation: diabetes mellitus, New York Heart association functional class (\geq II), earlier ablation, ventricular arrhythmia, mitral or aortic stenosis, aortic regurgitation, and chronic obstructive pulmonary disease (57).

Figure 1. Adapted and modified from 2016 European Society of Cardiology of AF management strategies (34)



1.3.4 Atrial fibrillation and sex and gender differences

There are sex and gender differences in prevalence, complications, and treatment of AF. The prevalence for AF is higher in men than women but women have a similar or higher incidence of stroke and death due to AF (32, 58). Moreover, women with AF are less likely to receive specialist care, rhythm control therapy, cardioversion, or catheter ablation than men despite current guidelines (34, 59). The reasons for this discrepancy between men and women are unknown. The outcomes of catheter ablation seem to be equally effective in women and men, but overall complications are significantly higher among women (60, 61). In a large register study (nearly 90 000 patients), women were 1,5 times more likely to have major adverse events such as vascular access complications, pericardiocentesis, and post procedure bleeding requiring transfusion (61). Obesity, diabetes, hypertension, renal failure, chronic pulmonary disease, cerebrovascular accident, and older age were also more common in women than men (61).

In a registry study from Germany, data from 9 576 patients (39% women) with AF were studied, showed that women experienced more severe symptoms than men during AF. The women had higher heart rate, more frequent palpitations, severer shortness of breath, chest pain, and dizziness (62). Only 16% of the women were completely free of symptoms before pharmacological treatment compared with 27% of the men. This finding supports previous

reports, which were less comprehensive (39, 63). These studies also show that AF patients estimated their HRQOL lower than the normal population before pharmacological treatment was initiated (39, 63). In the 2005 RACE study, Rienstra et al. reported a lower HRQOL and more symptoms due to AF in women than in men (64). In 2000, Paquette et al. found that the women with AF had worse physical functioning than men independent of other concomitant heart diseases and age. In contrast, AF had a less negative effect on the mental and general well-being in women compared to men (65).

1.3.5 Paroxysmal supraventricular tachycardia

Atrio-ventricular nodal reentrant tachycardia (AVNRT) and atrio-ventricular reentrant tachycardia (AVRT) constitute about 90% of all regular paroxysmal supraventricular tachycardias (PSVT). PSVT episodes are characterized by a sudden start and stop. The heart rate is typically between 140-250 beats per minute (66). Symptoms due to the high rate are therefore often similar to the symptoms of AF: palpitations, shortness of breath, fatigue, dizziness, syncope, and angina and in certain cases myocardial infarction (67, 68). The difference is that episodes of AVNRT and AVRT very seldom are asymptomatic because no rate modifying effect is possible in the AV node. Ablation has been the treatment of choice in these arrhythmias since the late 1990s and has a high success rate and a very low complication rate (66, 69).

1.3.6 Paroxysmal supraventricular tachycardia – sex and gender differences

Women have a higher risk for AVNRT than men (Table I) (66). On the contrary, AVRT is more common in men. Previous studies show that women are referred for ablation several years later than men despite more severe symptoms (70, 71). It is unknown whether the reason for this discrepancy is caused by a patient's or a doctor's delay. Because symptoms during episodes of PSVT often resemble what is experienced in panic disorder and other psychiatric conditions, PSVT might be misinterpreted as anxiety attacks or panic disorder. Moreover, women seem to be at a higher risk than men of being incorrectly diagnosed and incorrectly treated (68, 72, 73).

1.3.7 Pain and sex differences

Men and women differ in response to pain. Earlier research has demonstrated greater pain prevalence among women compared to men (74). Large-scale epidemiological studies across multiple geographic regions found that pain is reported more frequently by women than by men (74). There are several physiological systems that may affect analgesics and pain (e.g., hormones, body fat, liver metabolism, and immune responses) (75-78). There also seems to be an age component as many common pain conditions increase during the puberty, especially in women (79). Moreover, psychosocial and sociocultural mechanisms affect how pain is handled (80). Robinson et al. reported that both women and men believed that men are less willing to report pain than woman. This gender role expectation may contribute to sex differences in experimental pain (81).

1.3.8 Pain and cardiac ablation

During cardiac ablation, effective analgesic and sedation is necessary to carry out the procedure safely and pain free. (82). Catheter cryo balloon ablation compared to radiofrequency (RF) seems to be better tolerated and less painful (83). The most common way to reduce discomfort and anxiety during ablation is to use conscious intravenous sedation and analgesia (84). Usually, this is administered by trained nurses under the supervision of a physician at the electrophysiology laboratory (84). This approach maintains spontaneous respiration so anaesthesia services are not needed (84).

2 OVERALL AIM

The overall aim of this thesis was to study sex and gender differences in referral, treatment, outcome, symptom, HRQOL, and functional impairment in patients undergoing cardiac ablation of atrial fibrillation and PSVT.

2.1 SPECIFIC AIM

Study I. With a gender perspective, Study I specifically evaluates morbidity, HRQOL, symptoms, and functional impairment in patients with PSVT before and six months after ablation and the patients' experiences and perspectives of their ablation referral.

Study II. With a gender perspective, Study II evaluates morbidity, HRQOL, symptoms, and functional impairment in patients with AF before and six months after PVI and the patients' experiences and perspectives of their ablation referral.

Study III. Study III evaluates possible sex bias in patients with AF receiving AVJ ablation regarding indication and choice of pacing system and compares differences between the sexes with respect to complications, morbidity, and long-term mortality.

Study IV. Study IV evaluates whether a more active supply of analgesic and sedative drugs reduce pain and discomfort during PVI. Furthermore, this study evaluates sex differences in pain perception and compares standard radiofrequency with cryo energy ablation.

3 PATIENTS AND METHODS

3.1 PATIENTS AND SELECTIONS

The participants in the studies were all referred for cardiac ablations to the cardiology department at Karolinska University Hospital between 1990 and 2015. Patients were excluded if they could not read, write, or understand the Swedish language, had cognitive disturbances, or did not return a signed informed consent.

3.2 OVERVIEW OF THE STUDY DESIGN

Study	I	II	III	IV
Number of patients	214 (109 women)	242 (121 women)	700 (359 women)	80 (40 women)
Design	Prospective observational study	Prospective observational study	Retrospective longitudinal registry study	Randomized interventional study
Including period	February 2013 - May 2015	February 2013 - January 2016	January 1990 - December 2010	April 2007 - January 2011
Data collection method	Patients file, SF-36* SIP**, SCL***, Questionnaire regarding the referral process	Patients file, SF-36* SIP**, SCL***, Questionnaire regarding the referral process	Patients file, local ablation registry, Swedish ICD and Pacemaker Registry, Patient Registry kept by the National Board of Health and Welfare	Patients file, Questionnaire regarding experienced pain, Pain-O-Meter
Data analyses	Descriptive and statistical analyses	Descriptive and statistical analyses	Descriptive and statistical analyses	Descriptive and statistical analyses

*Medical Short Form 36, **Sickness Impact Profile, ***Symptom Checklist: Frequency and Severity Scale

3.3 QUESTIONNAIRES

Two types of questionnaires were used: general and symptom-specific questionnaires. General questionnaires identify and compare patient groups and symptom-specific questionnaires are used for individual patients and special conditions (85). The purpose and/or research question determines the choice of questionnaires: What it is you want to measure and why? If a questionnaire is too general, it may exclude significant areas.

3.3.1 Medical Short Form 36

For the last few decades, the most common general questionnaire used for patients with arrhythmias has been the *Medical Short Form 36 (SF-36)*. This questionnaire has been translated into Swedish and adapted and evaluated at the School of Care Sciences, Sahlgrenska University Hospital in Gothenburg. This was done in collaboration with the International Quality of Life Assessment as a project to match the original U.S. Medical Outcomes Study Short-Form Health. SF-36 is based on the WHO's health concept defined in 1948 and is widely used in public health and epidemiological research (86, 87). Unlike the symptom-specific instruments, SF-36 is less sensitive to small variations and changes. SF-36 measures eight health domains with five functional scales and three well-being scales. The five functional scales measure the degree of dysfunction and the three well-being scales cover the whole spectrum from negative to positive health. In addition to these eight subscales, there are also two summary scales – Physical health (PCS) and Mental health (MCS) – calculated from the eight scales weighted into the two measurements (Table II) (88).

Table II. SF-36 scales

Definitions of Lowest and Highest Scores

Scale	Items	Lowest possible (floor)	Highest possible (ceiling)
Physical Health /functional scales			
Physical Functioning (PF)	10	Limited a lot in performing all physical activities including bathing or dressing due to health	Performs all types of physical activities including the most vigorous
Role- Physical (RP)	4	Problems with work or other daily activities as a result of physical health	No problems with work or other daily activities as a result of the physical health
Role -Emotional (RE)	3	Problems with work or other daily activities as a result of emotional problems	No problems with work or other daily activities as a result of emotional problems
Social-Functioning (SF)	2	Extreme and frequent interference with normal social activities due to physical or emotional problems	Performs normal social activities without interference due to physical or emotional problems
Bodily Pain (BP)	2	Very severe and extremely limiting pain	No pain or limitations due to pain
Mental Health/well-being scales			
Mental Health (ME)	5	Feelings of nervousness and depression all the time	Feels peaceful, happy, and calm all the time
General Health (GH)	5	Evaluates personal health as poor and believes it is likely to get worse	Evaluates personal health as excellent
Vitality (VT)	4	Feels tired and worn out all the time	Feels full of pep and energy all the time

Modified from the Swedish Manual and Interpretation Guide (86).

3.3.2 Symptom checklist: Frequency and Severity scale

Symptom Checklist: Frequency and Severity Scale (SCL) version 3 was developed by Bubien and Jenkins in 1996 to measure symptoms in patients with cardiac arrhythmias (39). SCL is presently one of the most frequently used symptom-specific instruments for arrhythmia patients (85, 89). In patients with dual pacemakers, the SCL has been used to evaluate the mode switch function. In addition, SCL has been used to measure the outcome after isthmus ablation, ICD, and concomitant AF, AF after AVJ ablation, as well as in long-term follow-up in patients who have undergone ablation of supraventricular tachycardia (89-94).

SCL has not previously been translated into Swedish, validated, or reliability tested. Nevertheless, SCL together with the Swedish SF-36 have been used for comparison when developing new symptom specific arrhythmia instruments in Sweden (95-97). Therefore, simultaneously with the studies in this thesis, the SCL was translated into Swedish and psychometric properties were evaluated with exploratory factor analyses for use in patients with AF, atrial flutter, and paroxysmal tachycardia (Submitted for publication).

3.3.2.1 Translation procedure, face, and content validity of the SCL

Translation procedure followed the steps recommended by the WHO (98). The steps included forward translation of the SCL from English to Swedish performed by a person familiar with English-speaking language, face and content validity assessment by expert panel, and face validity in sample with a pre-test on a target population. The Swedish SCL was tested by six patients referred for cardioversion and by six patients referred for PSVT ablation. The patients were interviewed with the “think aloud method” and were asked to evaluate the intelligibility of the questions (99). The forward-backward translations using the WHO’s recommendations yielded no differences in the descriptions of the items in the SCL. Thereafter, the author, Louise Jenkins, gave permission to use the Swedish version of the SCL. According to the authors of SCL, the reliability of the two scales (frequency and severity) of the SCLs should be calculated using Cronbach’s alpha to estimate the internal consistency at each data collection point. Values obtained were for both Study I and II: $> .87$ for the frequency and $> .89$ for the severity scale.

3.3.3 Sickness Impact Profile

Sickness Impact Profile (SIP) measures the self-rated functional capacity to perform daily activities in chronic and acute medical conditions. The instrument was developed by Bergner et al. in the United States and was translated and validated for Swedish conditions by Sullivan et al. (100, 101). The instrument includes 136 items that form 12 scales. Points can be shown as total index (i.e., all 12 categories merged) for the physical and psychosocial index along with the remaining five categories or for the twelve-part categories separately. In Study I and II we chose to use the following ten scales: ambulation, mobility, emotional behavior, communication, work, sleep and rest, social interaction, alertness behavior, home management, recreation, and pastime (Table III). The excluded items were body care and food intake. We judged these questions unfit in our specific study population, and the exclusion of the items did not affect the validity of the scale. Lower values indicate less

functional impairment. SIP has previously been used in studies for patients with arrhythmia (102, 103).

Table III. Dimensions and categories and number of claims at each category in Sickness Impact Profile

Dimension/Category	Number of claims
Physical function	
Ambulation	12
Body Care and Movement*	23
Mobility	10
Psychosocial function	
Social Interaction	20
Alertness behaviour	10
Emotional behaviour	9
Communication	9
Independent categories	
Sleep and Rest	7
Eating*	9
Work	9
Home management	10
Recreation and Pastimes	8
Total	136

- Excluded dimensions in study I and II

3.3.4 Pain-O-Meter

In Study IV, the pain was assessed during the ablation with the Pain-O-Meter (POM). The instrument is well-validated, based on the visual analogue scale (VAS) and the McGill Pain questionnaire (12). Conventionally, the POM is a hard-plastic tool with the VAS scale that has a list of sensory and affective words that describe the experience of pain and a picture of a body. In Study IV, we turned the POM instrument details into a picture of a body where patients could mark the location of their pain. We also used the POM word description of the overall dimension (appendix 4).

3.4 STUDY I AND II

Study I and II had the same design – descriptive observational studies based on questionnaires that included patients who were referred for their first cardiac ablation due to PSVT in Study I and AF in Study II. Before the start of the studies, six patients during cardiac ablation-related hospitalization were interviewed using a half-structured questionnaire regarding their experience with their referral for the arrhythmia (appendix 1). These patients were not included in the latter study. The interviews were taped and transcribed verbatim. After the transcribed interviews were analysed, the following themes were found: anxiety and worries not believed or being treated impolitely when seeking health care. A questionnaire was constructed including the two themes as well as questions regarding referral patterns, socioeconomic data, and symptom duration (appendix 2). Arrhythmia symptoms were evaluated with the SCL, the HRQOL with SF-36, and the functional impairment with SIP at baseline and six months after ablation. All questionnaires were sent home to the patient together with an informed consent and information and about the study less than 30 days prior to the ablation.

3.5 STUDY III

In Study III, all included participants (700) had undergone AVJ ablation between January 1990 and December 2010 and the data were collected from the institution's ablation register at the Karolinska University Hospital. Information about the pacemaker system and complications due to the implant was retrieved from the Swedish ICD and Pacemaker Registry. Patient files were used for clinical data, indication, and concomitant disease. Data regarding mortality, primary cause of death, and out clinic visits due to HF, stroke, or ventricular tachycardia were obtained from National Patient Registry kept by the National Board of Health and Welfare. The diagnosis codes shifted during the follow-up periods. For data between 1990 and 1996, the ninth revision of the International Classification of Diseases (ICD9) coding for diagnosis was used; for data between 1997 and 2012, the tenth revision of the ICD (ICD10) coding was used (Table IV).

Table IV. International Classification of Diseases

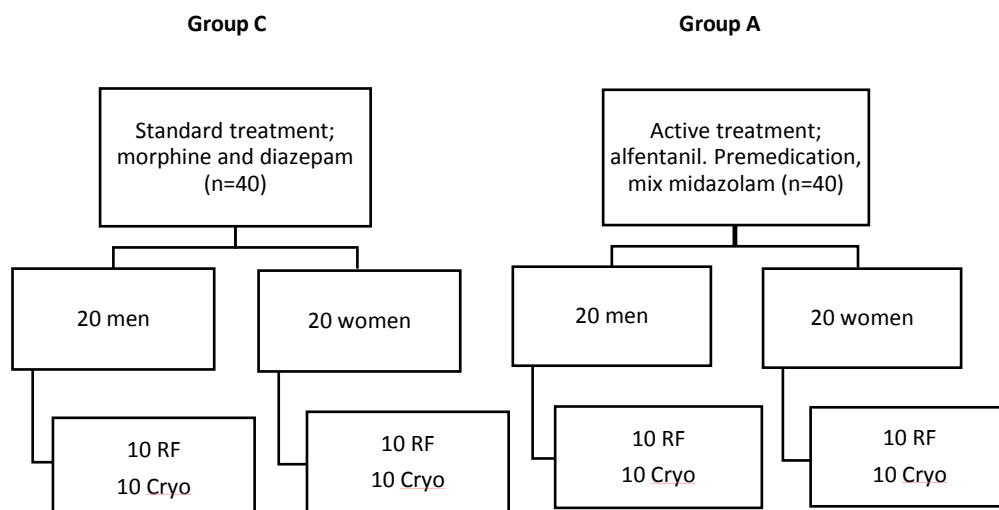
Diagnose codes	ICD-9 (1990–1996)	ICD-10 (1997–2012)
Stroke	430–438	I60-I69
Atrial fibrillation	427D	I48
Heart failure	428	I50-0.09
Ventricular tachycardia	427B	I47:0–9
Ventricular fibrillation	427E, 427D	I49.0
Cardiac arrest	I46.0	427F

For data between 1990 and 1996, the ninth revision of the International Classification of Diseases (ICD9) was used. For data between 1997 and 2012, the tenth revision of the International Classification of Diseases (ICD10) was used for coding the causes of death.

3.6 STUDY IV

Study IV included 80 patients – 40 men with mean age 56 (range 23-72) and 40 women with mean age 63 (range 50-76) – scheduled to undergo PVI. The participants were randomized into two pharmacological treatments. They were randomized in groups with an equal number of men and women. One group (A) received a more active analgesic strategy and the control group (C) was offered standard treatment and received analgesic and sedatives on request. The participants in group A were given midazolam 30 min before the procedure; thereafter, they received medication according to a predetermined protocol (appendix 3). The choice of RF energy versus cryo energy was done at the discretion of the electrophysiologist and not randomized. The groups were balanced to achieve the same number of men and women in each group. Patients with long-standing persistent AF were all treated with RF energy (Figure II).

Figure II. Overview of randomization in Study IV



The control group (C) was offered standard treatment and received analgesic and sedatives on request. The active group (A) had a premedication 30 min before the ablation and thereafter according to a predetermined protocol.

4 DATA ANALYSIS

Table V. Overview over statistical analyses used in the thesis

Function	Statistical method	Study I	Study II	Study III	Study IV
Summary and descriptions of observations division	Descriptive statistics, mean standard deviation, or number and percentage	✓	✓	✓	✓
Comparison of nominal data	Fisher's exact test	✓	✓	✓	✓
Analyse of differences between two groups	Unpaired t-test, (Student's t-test, parametric test)	✓	✓	✓	✓
Analysis of survival and the effect on explaining variables	Cox regression			✓	
Analysis of correlations between two or more variables (non-parametric)	Spearman's correlation coefficient	✓	✓		✓
Linear regression analysis					✓

A p-value of <0.05 was considered significant. The statistical analyses were conducted using IBM SPSS statistics 22 and 24 for Windows (SPSS, Inc., Chicago IL) and R version 3.1.1. R Core Team (2014). R: A language and environment for statistical computing. R Foundation for Statistical Computing Vienna, Austria.

5 ETHICAL CONSIDERATIONS

The studies in this thesis followed the ethical principles outlined in the declaration of Helsinki for medical research on human subjects (104). All participants gave their written informed consent (Study I, II, and V) apart from Study III where only the patients alive at the follow-up could provide their consent. Considerations were taken concerning the deceased patients and it was judged that no harmful effect would be caused by including their data in the study.

Permission to perform research in the clinical setting was obtained from the head of the clinic. The studies were also approved by the Regional Institutional Ethics Committee at the Karolinska Institute: Study I and II Dnr, 2011/1903-32/2; Study III 2010/914-31/1, 2012/1390-32; and Study IV Dnr. 2006/632-31, EU-nr 2006-004415-22.

The research in this thesis also conforms to the ethical principles for nursing research recommended by the Northern Nurses' Federation. These principles include autonomy, beneficence, non-maleficence, and justice (105).

The principle Autonomy: With respect for the participant's autonomy and integrity, all patients were able to decide whether they wanted to participate in the studies after receiving written and verbal information about the studies. Participation was entirely voluntary, and all patients received information about the right to withdraw from the research project without this decision affecting their continued care. All data were handled in a way to ensure confidentiality.

The principle of beneficence: The patients included in the four studies did not benefit from participating, although the results may eventually improve treatment of arrhythmias and improve equality between the sexes in health care, referral, choice of pacemaker system, and analgesia during ablation procedures.

The principle of non-maleficence: We did not recognize any negative consequences of participating in the studies and did not find any risks that could harm the patients.

The principle of justice: All eligible patients in Study I, II, and IV had the same chance to participate and were asked to participate. The aim was an equal number of the sexes in the studies to secure adequate comparison. Consequently, this strategy increased the inclusion period since fewer women than men are referred for ablation of AF.

6 RESULTS

6.1 STUDY I

Study I included 214 (109 women) referred for ablation due to PSVT: 43% were referred for ablation at first consultation, 83% were referred by specialists working in hospitals, and 4% were referred by their general practitioner. ECG-documented tachycardia was available in 78% of the women and in 90% of the men ($p = .03$). Compared to men, women had a longer history of symptomatic arrhythmia before ablation.

More women than men stated they were not taken seriously when they expressed concern about their tachycardia symptoms (17% vs. 7%, $p = .03$). From the patient's perspective, physicians more often incorrectly interpreted women's symptoms as anxiety, stress, panic attacks, or depression, delaying referral for ablation.

There were minor differences between the sexes in HRQOL and functional impairment at baseline, but women had more symptoms and scored higher on both scales of the SCL. At six months, women were still more symptomatic than men and their HRQOL improved less. There were no socioeconomic differences between men and women regarding level of education, income, or comorbidities.

6.2 STUDY II

A total of 242 (121 women) patients referred for PVI were studied – 74% with paroxysmal and 26% with persistent AF. There were no differences between the sexes with respect to proportion of paroxysmal/persistent AF, comorbidity, duration of AF, or acceptance of ablation when offered. Women were in mean three years older, had failed more drugs, and had less often undergone cardioversions before PVI. Women also had more symptoms, scored higher in both scales of the SCL, scored lower in all components in SF-36, and scored higher in five categories of the SIP at baseline. At six months, women were still more symptomatic and had improved less in HRQOL than men, although there were no differences in the SIP categories except for in home management.

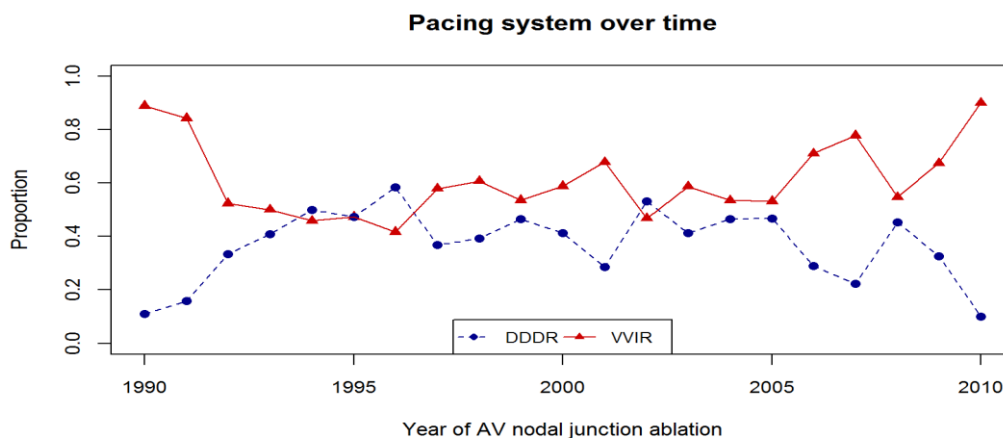
6.3 STUDY III

This retrospective register study included 700 patients (359 women) who had undergone AVJ ablation between 1990 and December 2010. The women were older than the men at the time of ablation and more often had an indication of PAF and had a pacemaker programmed to

DDDR. HF was present in 44% of the men and in 28% of the women. In HF patients, CRT-pacemaker was implanted before ablation in 42% of the men and in 18% of the women. Women less often than men received ICD or CRT even when there was an indication present. Complications in form of perforation or infection of the pacemaker or ICD system were seen in 6% of the men and 3% of the women. EF decreased slightly in the whole study group with no differences between the sexes. In addition, there were no differences in the RV-pacing group or the CRT group even though the CRT group was too small to show any significant difference between CRT and conventional pacing regarding impact on EF.

During the follow-up, 366 patients died after a mean of 78 ± 26 months. Time to death after the ablation was shorter for patients ablated after 2001 compared to the group ablated before 2001. The patients ablated after 2001 were older, had more co-morbidities, and had their pacemaker programmed to VVIR more often, indicating a more advanced disease, which may explain the increased mortality in this group (Figure III.) There were no differences between the sexes regarding primary cause of death. Cardiovascular mortality was the most common cause of death (26%), coronary diseases 13%, HF 6%, stroke 3%, and AF 3%. The main factor influencing survival was age at the time of ablation.

Figure III.



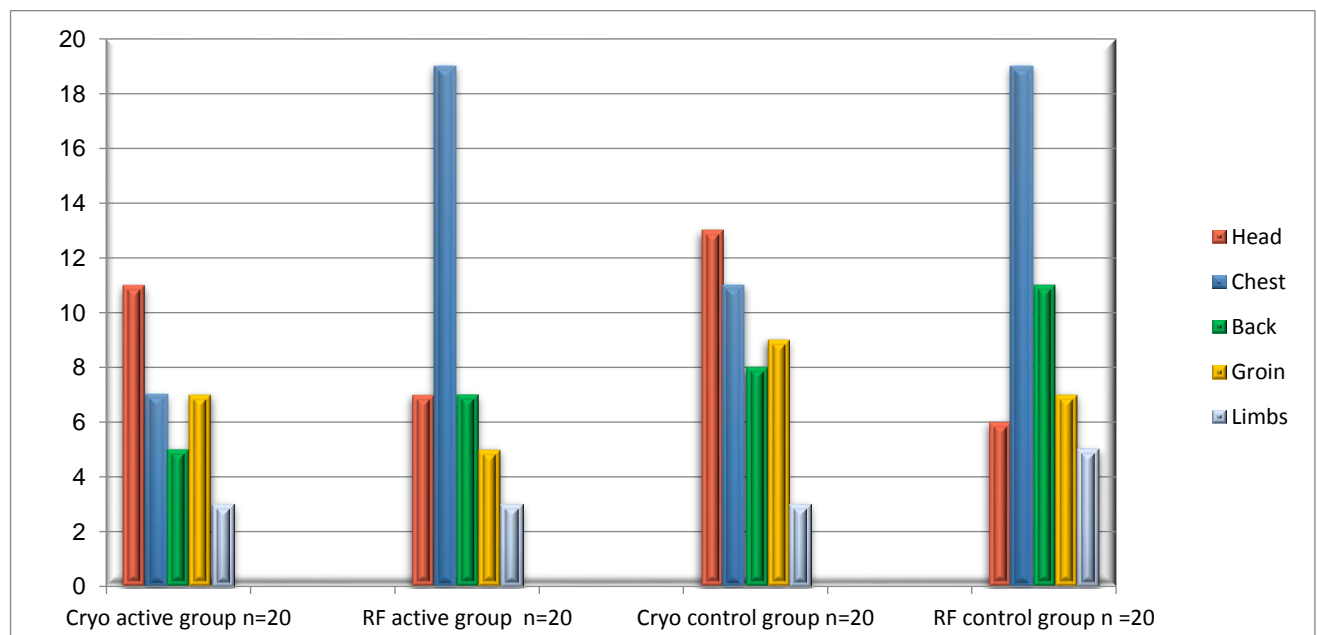
At the beginning of the follow-up, mainly VVIR systems were implanted. Between 1993 and 2005, the use of DDDR increased to equal of the use of VVIR systems. After 2005, the use of VVIR system increased again, indicating a sicker population.

6.4 STUDY IV

In Study IV, a total of 80 (40 women) patients were included. The results show that almost all patients (91%) experienced pain during the PVI. Premedication and regular administration of analgesic resulted in fewer drug administration occasions and less pain measured as numeric rating scale (NRS). Women experienced more pain than men regardless of energy type. Cryo energy ablation was experienced less painful compared with RF energy. There were no differences between men and women in the location of pain. The chest was the most frequently reported region during RF energy ablation. Half of the patients in the cryo energy group experienced pain located on the forehead. A side effect of PVI due to the long procedure time was back pain (not related to ablation application per se), which was reported by 31 of the 80 patients. Furthermore, 14 of the patients reported that they had pain in their limbs due to the long procedure time and the post ablation period when they were confined to bed (Figure IV). Procedure time was similar for the group receiving active treatment compared with that for the group receiving standard treatment.

Most frequently used sensory description of the pain was burning, pressing, or stabbing. The affective description of the pain was that it felt troublesome and irritating. Four patients also described their pain as torturing. All these patients were in the RF energy group and three of them had received the more active pain strategy.

Figure IV. Localization of pain in the different study groups



7 GENERAL DISCUSSION

7.1 PRINCIPAL OBSERVATIONS

The following list are our principal observations:

- Women's symptoms during PSVT were more often incorrectly interpreted as anxiety, stress, panic attacks, or depression compared to men.
- Gender discrepancy found in the referral for curative PSVT ablation was not seen in AF patients referred for PVI.
- HRQOL improved more for men than for women after PVI.
- Sex bias was evident in the choice of pacing system before AVJ ablation.
- EF decreased slightly in the whole cohort after AVJ ablation.
- More active supply of analgesic and sedative drugs should be used to reduce pain and discomfort during the PVI procedure.

The following section discusses these main observations. More detailed discussion regarding methodology are given in each paper.

7.2 COMPARISON WITH OTHER STUDIES

7.2.1 Referral

The results of Study I indicate that symptoms due to PSVT often are incorrectly diagnosed as panic attacks, stress, anxiety, or depression. These misdiagnoses delay referral for ablation, especially for women. Similar results have been described in other studies (68, 72). PSVT and panic disorder is known to coexist, and the symptoms are much alike (68, 106).

Palpitations during PSVT are commonly associated with anxiety and panic disorder are characterized by sudden attacks of intense fear, palpitations, and tachycardia and may therefore be misdiagnosed.

Other causes for referral delay may be a wish to record the tachycardia on ECG as documentation, but many times the arrhythmia ceased before it could be verified. In Study I, 78% of the women and 90% of the men had a documented episode of arrhythmia when they were referred for ablation. These results are in accordance with earlier reports (107, 108). Lessmeier et al. (1997) found that inappropriate rhythm detection techniques (Holter instead of event monitoring) delay the diagnosis of PSVT (72). The ambition to document the tachycardia on ECG is contrary to the ACC/AHAA/ESC guidelines from 2003 (the most

recent guidelines during the period of the present study). The guidelines state that if symptoms and clinical history indicate that an arrhythmia is paroxysmal and resting 12-lead ECG gives no clue for the arrhythmia mechanism, further diagnostic tests for documentation may not be necessary before referral for an invasive electrophysiological study and/or catheter ablation (66). It is reasonable to presume that this ambition to document a tachycardia episode on ECG results in an unnecessary delay for both men and women.

Study II found no differences between the sexes regarding time in AF before referral for PVI. In addition, Study II found that the women had not more comorbidities than the men even if they were older at the time of the ablation. This indicates a more aggressive treatment strategy than reported in other studies. These studies found that women were older and had more comorbidities before PVI and were referred later than men (60, 61, 109, 110).

7.2.2 Gender discrepancies in the choice of pacemaker system

In Study III, a long-term follow-up study (20 years) of patients undergoing AVJ ablation, we found gender discrepancies in the choice of pacemaker system before the ablation. Women with HF less often received CRT or ICD even when indication was present. Similar disparity has earlier been reported by Alaeddini et al. (111). Women had consistently higher rates of hospital admission for HF, but CRT-P and CRT-D were used less frequently in women than in men (111). The reason for this gender disparity in using CRT devices are unknown. Linde et al. also reported in a large retrospective register study that the proportion of CRT was lower in women, but CRT was equally underused in both sexes (112).

7.2.3 Decreased EF after AVJ ablation

We found a slightly decreased EF in the whole cohort after AVJ ablation despite the use of CRT. Similar results have been reported predominantly in patients with previous HF (113). One reason may be that the RV pacing caused left ventricular (LV) dyssynchrony, and thus decreased EF. Similar results have been reported in several studies before (114-117). Brignole et al. compared RV, LV, and BiV pacing and found only modest or no favourable effect with LV and BiV pacing sites (118).

7.2.4 Analgesic and sedation to reduce pain during PVI

The PVI procedure can be long lasting and relatively painful (84). Almost all patients in our study experienced less pain during PVI with cryo technique than with RF energy. This result agrees with other studies (82, 83, 119). Moreover, the PVI procedure may also cause discomfort and anxiety (84). Our result in Study IV shows that the pain was not solely caused by the ablation; 39% of our patients experienced backpain and pain from the limbs due to the long period they were confined to bed during and after the procedure.

We used intravenous sedation so the patients, despite their depressed level of consciousness, could respond to verbal commands and physical stimulation (120). General sedation has the disadvantages that it requires the presence of full anaesthesia support, which can cause scheduling difficulties. A third alternative is to use deep sedation with the goal to keep the patient in deep sedation while maintaining spontaneous ventilation throughout the procedure. Kottkamp et al. showed that deep sedation during ablation can be performed in environments with experienced electrophysiologists and nurses specially trained and with long experience with sedation and analgesia (121). This is not always achievable and cannot be generally used in EP labs without this special competence.

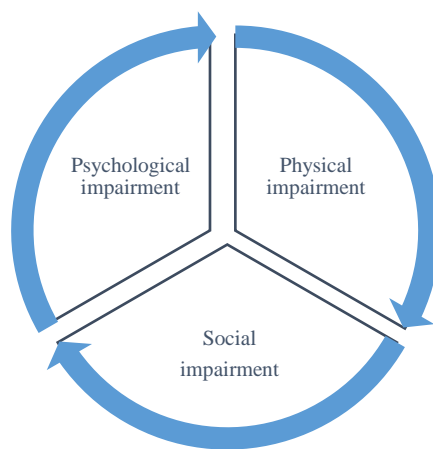
7.2.5 HRQOL, symptoms and functional impairment

In Study I and II, HRQOL was impaired in the patients before the cardiac ablation but improved after the procedure. However, the HRQOL improved more for men than for women. Women also were more symptomatic and reported more functional impairment than men. They were also more symptomatic after PSVT as well as after PVI ablation than the men. It is unclear why this is the case. If the symptoms are caused by supraventricular premature beats, the clinical experience is that symptomatic premature beats diminish gradually during the first six months after ablation. However, since women are more symptomatic to tachycardia per se, it is reasonable to assume that they also experience more symptoms due to premature beats after ablation (70, 107). In Study I, we compared women 50 years and younger with those older than 50 years just to clarify that the symptoms were not post-menopausal symptoms. We found no differences regarding symptoms after ablation in the two groups.

Individuals who experience severe symptoms and functional impairment and a low HRQOL caused by arrhythmia sometimes find the simplest daily activities difficult. Even if they do

not have symptoms between the attacks, earlier studies show that the memory of arrhythmia attacks may have negative impact on activities and ambitions (85). Concerns about whether an arrhythmia will start can affect and limit the individual in several ways, for example, her tendency to make longer trips. Some choose to travel only within the country and to places where hospital access is easy to find (Figure V). Bohnen et al. showed that the quality of life of close relatives was also influenced negatively because of the uncertainty and anxiety for his/her partner (122). Similar results were presented in a Swedish study by Dalteg et al. (123).

Figure V. Description of the effect of impaired HRQOL in arrhythmia patients



Physical impairment: symptoms such as fatigue, palpitations, irregular heart beats, and dizziness.

Social impairment: unwillingness to travel, go to the cinema, and visit friends because of the fear of an arrhythmia episode.

Psychological impairment: stress, anxiety, and depression.

Evaluation of arrhythmia symptoms can be difficult. Many patients have underlying heart diseases that can produce symptoms such as weakness, light headedness, and dyspnoea, symptoms that are also very common during arrhythmia. Moreover, patients with chronic diseases, especially women, feel that they are not being listened to and taken seriously when seeking medical care (108). Patients with PSVT often have a long history of numerous visits to doctors and/or hospital emergency departments. In many cases, the arrhythmia had expired before it could be verified by ECG. This may result in avoiding seeking help when experiencing new tachycardia episodes. Wood et al. describes this situation as follows:

An ambiguity when and where the next arrhythmia episode will start and/or how long the episode will last. A need to "cover up" and deal with the symptoms so that everything seems normal in front of relatives or colleagues (108).

This reaction might lead to self-treatment:

To self-try to find causal factors to prevent new episodes to occur and to experiment and try different strategies to shorten or get a current episode to a halt e.g. with different types of breathing exercises, yoga, straining or dip your face in cold water (108).

7.3 POTENTIAL MECHANISM

7.3.1 Sex differences in studies

Differences in biology between women and men have been described in the report "Exploring the Biological contributions to Human Health" (2001) by The Institute of Medicine in the United States. They state when it comes to the sciences of medicine and clinical practice, sex is an important issue and must be taken into consideration (124).

Although women traditionally been underrepresented in trials, results have been extrapolated to the female population that assume identical results in men and women. If studies only include men, they should explain why and how this introduces limits to the generalizability of the study (76).

Men more often than women are referred for cardiac ablation due to AF. This leads to an underrepresentation of women in cardiac ablation studies and might lead to insufficient knowledge of treatment outcome in women and lack of sex-specific recommendations and under-utilization of existing guideline-based therapies for women (125). In the German ablation registry, only 33% of the cohort were women (126). This is in accordance with data from the Swedish ablation registry and our clinical experience.

7.4 STRENGTH AND LIMITATION

Study I and II were based on questionnaires. The response rate was 56% in Study I and 65% in Study II. There is some uncertainty performing studies with only questionnaires. How honest are the patients? Have the patients answered the questionnaires themselves? Are there too many questions for patients to answer? Did the patients who denied participation have more or fewer symptoms than those who chose to participate? We assume that the participating patients are representative.

Study III was based on data from the hospital's ablation register, medical records, and data from the National Patient Registry (NPR) kept by the National Board of Health and Welfare. The sources of register data are both a strength and a weakness. Sweden is unique because the social security number (a personal identification number assigned to all legal residents and citizens) gives researchers the ability to freely retrieve data from the NPR. This is an advantage in comparison with other countries when retrospectively studying morbidity, mortality, and causes of death. Another advantage of this type of study compared to randomized studies is that register studies capture data from real life practice in larger and unselected cohorts.

Although register studies are inexpensive, and cost effective, they have limitations which is a weakness. The duration of specific diseases or diagnoses are often uncertain. Diagnoses are usually attached to patients their entire lives. Hence, it is not always possible to determine whether the reason for a patient's visit to an out-patient clinic is, for example, HF or some other diagnosis. Another limitation is that recorded data are not always complete and may in some instances be incorrect. Over the years, the routines for medical records and data recorded in registries have changed as has what is considered a normal range for various lab tests, including echocardiography. Therefore, when comparing data from 1990 with data from 2010, the conclusions should be made with some caution.

8 CONCLUSIONS OF THE THESIS

- Women with PSVT are referred for curative ablation later than men despite more symptoms.
- Symptoms due to PSVT are often incorrectly diagnosed as panic attacks, stress, anxiety, or depression, misdiagnoses that delay referral for ablation, especially for women.
- Women with AF are more symptomatic and report worse HRQOL and functional impairment than men, but there are no differences in the duration of the AF before the PVI or when referred for ablation when indicated.
- Women are still more symptomatic after both PSVT and PVI ablation than men.
- Indication, choice of pacing system, and morbidity differed between the sexes in patients with AF treated with AVJ ablation.
- EF decreased slightly in the whole study cohort after AVJ ablation.
- There were no sex differences regarding survival or primary cause of death after AVJ ablation. The main factor influencing survival was age at the time of ablation.
- Women less often than men received treatment with ICD and/or CRT when indication was present before AVJ ablation.
- An active regular supply of analgesic and sedative drugs reduce pain and discomfort during PVI in both sexes.
- Women experience more pain than men during PVI.

9 CLINICAL IMPLICATIONS TO ACHIEVE A MORE EQUAL HEALTH CARE FOR THE SEXES

- 1) It is necessary to include and describe results for both sexes in clinical and cardiovascular studies. We found several differences between the sexes and this knowledge may help us to tailor a good health care in the daily work with arrhythmia patients.
- 2) There seems to be major differences in how physicians interpret tachycardia symptoms in men and women leading to differences in referral patterns. Therefore, it is of great importance to increase and improve the information to achieve equality between the sexes in treatment and referral according to existing guidelines with respect to the arrhythmia disease.
- 3) Our results indicate a need for a systematic approach for implementation of guidelines and for person-centred health care for arrhythmia patients (127, 128). A tailored integrated education program involving the patient might solve some issues. To correct misperceptions of the arrhythmia and treatment, education programs addressing the HRQOL should be developed within a multidisciplinary team of allied health professionals (129). Person-centred care integrates education and shared decision making with the patients. This may be of particular value in the management of patients with arrhythmia (130). The need to prevent and treat arrhythmia patients effectively where women's and men's needs are evaluated is necessary to avoid increasing health costs and to increase the benefits for individual patients.

10 SVENSK SAMMANFATTNING

Bakgrund Kvinnor och män skiljer sig åt vad gäller prevalens av förmaksarytmier. Tidigare studier har visat det också finns könsskillnader i remittering, handläggning, symtombörda, hälsorelaterad livskvalitet (HRQOL), funktionsnedsättning, riskfaktorer och resultat av olika behandlingsalternativ vid paroxysmal supraventrikulär takykardi (PSVT) och förmaksflimmer.

Syfte Det övergripande syftet med denna avhandling har varit att studera genus- och könsskillnader i remittering, behandling, symtom, HRQOL och funktionsnedsättning, riskfaktorer och resultat hos patienter som genomgår ablationsbehandling av PSVT eller förmaksflimmer.

Metod Avhandlingen bygger på fyra studier. Studie I och II är prospektiva observationsstudier baserade på enkäter och medicinska journaler, före samt sex månader efter ablationsbehandling. I Studie I ingick 214 (109 kvinnor) patienter remitterade för ablation av PSVT. I Studie II ingick 242 (121 kvinnor) patienter med förmaksflimmer remitterade för lungvensisolering. Följande enkäter användes i Studie I och II: Symtom Checklista: frekvens och svårighetsgrad, SF-36 samt Funktionsschema. Remitteringsgång, socioekonomiska data samt symtomduration utvärderades med ett separat frågeformulär. I studie III ingick 700 patienter (359 kvinnor) som genomgått His-ablation mellan åren 1990 till 2010. Studien baserades på registerdata insamlade från patientjournaler, svenska ICD- och pacemakerregistret och från det nationella patient- och dödsregistret som tillhandahålls av Socialstyrelsen. I Studie IV randomiserades 80 (40 kvinnor) patienter antingen till en aktiv eller standardiserad smärtbehandling under lungvensisoleringen med kryo- eller radiofrekvensenergi. Utvärderingen av de två behandlingsstrategierna utvärderades med en enkät baserad på Pain-O-Metern.

Resultat Kvinnorna med PSVT i Studie I upplevde mer symtom, men remitterades för ablationsbehandling i genomsnitt sex år senare än männen. Dessutom rapporterade kvinnorna att de oftare inte kände sig trodda när de sökte hjälp och beskrev sina arytmsymtom. De fick oftare diagnoser såsom stress och ångest. I studie II fanns inte samma könsskillnad hos förmaksflimmerpatienterna gällande remitteringen, men kvinnorna var mer symtomatiska, skattade en lägre HRQOL och en större funktionsnedsättning än männen. Dessutom hade kvinnorna oftare fått pröva fler läkemedel och blev mindre ofta än männen remitterade för elkonvertering före lungvensisoleringen. I studie III hade fler män än kvinnor en diagnos med hjärtsvikt före His-ablation. När indikationen fanns erhöll kvinnorna mindre ofta än männen mer avancerade pacemakersystem såsom ICD eller CRT-system före His-ablationen. Det förelåg ingen skillnad mellan könen när det gällde den primära dödsorsaken efter His-ablationen. Den vanligaste dödsorsaken för bägge könen var hjärta- och kärlsjukdom och den viktigaste parametern som påverkade överlevnaden var ålder vid tidpunkten för His-ablationen. I studie IV upplevde 90 % av patienterna smärta under lungvensisoleringen. Premedicinering och regelbunden administrering av smärtstillande läkemedel resulterade i

mindre smärta och färre läkemedels administrationstillfällen. Kvinnorna upplevde mer smärta än männen oavsett energityp, kryo- eller radiofrekvensenergi.

Slutsatser Alla fyra studier visade genus och/eller könsskillnader i antingen remittering, sjuklighet, symptom, HRQOL, funktionsnedsättning eller resultat av behandling. Kvinnorna med PSVT och förmaksflimmer behandlades mer konservativt än männen. Kvinnorna med PSVT remitterades för botande ablationsbehandling flera år senare än männen, trots mer symptom. Arytmisymtomen hos kvinnorna blev oftare felaktigt diagnostiserade såsom panikattack, stress, ångest, eller depression. Kvinnorna med förmaksflimmer upplevde mer symptom, skattade en lägre HRQOL och en större funktionsnedsättning före lungvensisoleringen än männen. Trots detta, blev de mer sällan remitterade för elkonvertering före lungvensisoleringen. Kvinnorna erhöll mindre ofta de mer avancerade pacemakersystemen såsom CRT-eller ICD även när indikationen fanns före Hisablationen. Det fanns inga könsskillnader när det gäller överlevnad eller primär dödsorsak efter Hisablationen. Den viktigaste faktorn som påverkade överlevnaden var ålder vid tidpunkten för ablation. Kvinnorna upplevde mer smärta än männen under lungvensisoleringen, men en aktiv regelbunden tillförsel av smärtstillande och lugnande läkemedel minskade smärtan och obehaget under ablationen för båda könen.

11 ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to all of you who have supported and believed in me during these years and my doctoral studies and made this thesis possible.

In particular, I would like to thank the following persons.

Per Insulander, my principal supervisor: Thank you for all support and encouragement and your patience with me when my patience was long gone. Thank you for answering all the questions I had along the way and your valuable guidance in research that you always found time to share with me. Without your support from the beginning to the end, this thesis would never have been written.

Marie Iwarzon, my co-supervisor, thank you for all your support and help and all your deep knowledge of questionnaires and health-related quality of life. Thank you!

Fredrik Gadler, my co-supervisor and boss. Thank you for your positive support and for giving me the opportunity and time to perform my research despite all staffing problems.

Michael Melin, my mentor. Thank you for interest in my work and wellbeing. One day we will have that lunch.

Mats Jensen-Urstad, one of the first who introduced me to research, thank you for providing me with time to perform it and giving me lots of good advice along the way.

Eva Hägglund, thank you for your encouragement and for all inspiring discussion about life, statistical issues, and the future and for just being there when I needed you. It has been great to have you by my side along this journey.

Nicola Drca, for all the laughs and for just being such a jolly good fellow. Life is so much easier when people like you are around.

Cecilia Linde, former head of the Department of Cardiology, Karolinska University Hospital for promoting and showing interest in my research.

Fanny Edfeldt, Hanna Carnlöf, and Gunilla Förstedt, thanks for all hours you helped me with the data logging and distribution of all mail.

Minna Bergman, for verbatim type the interviews in the that were used in Study I and II.

Andreas Vaitsis, thank you for your valuable help with the statistic course. I would never have managed to complete the course without you.

The staff at the EP lab, nurses and doctors for excellent assistance with Study IV.

Christer Wredlert, for always helping me out when I have computer problems. Often with just one finger touch, and for teaching me to say NO and NOW!

All my dear friends at the echo laboratory, Aristomenis Manouras, Christina Oliveira Da Silva, Linn Vang and Elif Günyeli for your extraordinaire competence and for always finding your time to help me with my study patients.

My colleagues Karin Hellkvist and Terhi Wallebom for your support, positive encouragement and giving me time to perform my research when I most needed it.

Irene Saviaro, do not ever stop to be my personal helpdesk! Your help through the years with data programs and the coffee machine have been invaluable.

Anita Furö and Monica Broberg, thank you for your support with rooms and your interest in my research and wellbeing.

All my friends and colleagues at the Heart and Vascular Theme –none mentioned, none forgotten.

My physiotherapist, Anders Lånström, for keeping me in shape and on my feet during the two last years.

My late father and mother who never stopped believing in me. You would have been so proud. I miss you.

To my family – my husband, Lars, children Calle, Anders and Hanna, grandchildren Victor, Anton, Lova and William, and daughters-in-law Amanda and Isabelle – you are the joy and help me keep the right balance in my life.

I will also express my gratitude to the funders. This research work was supported by grants from the Women and Health Foundation, 1.6 Million Club, The Swedish Heart and Lung Association, the Department of Cardiology, Karolinska University Hospital, and allied Health Professions within Cardiology.

Finally, thanks to all the patients who took their time to answer the questionnaires.

12 APPENDIX

Appendix 1) Intervjuguide till studie I och II

Appendix 2) Avslutande frågor angående remittering Studie 1 och II

Appendix 3) Studieprotokoll till smärtstudien Studie IV

Appendix 4) Frågeformulär till smärtstudien Studie IV

Appendix 1. Intervjuguide till studie I och II

Presentation av mig, syftet med intervjun, arbetar du el studerar?

Kan du berätta/ beskriva om första gången du kände att något var annorlunda?

Sökte du hjälp vid det tillfället?

Vilken sorts hjälp och var?

Har du väntat länge på att söka hjälp? Hur länge då?

Hur blev du bemött/ betrodd?

Vad fick du för besked?

Fick du några råd om hur du vid ev. återkommande besvär skulle agera?

Hur/vad kände du då?

När fick du din diagnos?

Vilken sorts information fick du om din hjärtsjukdom; skriftliga? Muntliga?

Har du ätit några mediciner för att lindra dessa och i så fall vilka?

När var första gången du blev informerad om att dina hjärtbesvär kunde botas?

Har du väntat länge på behandling?

Hur frekventa har dina hjärtbesvär varit?

Vilken behandling föreslogs?

Har du känt dig tveksam till denna behandling?

Har du och sökt information via internet? Anhöriga/närstående? Litteratur?

Hemsidor? Annat?

Hur har dina hjärtbesvär påverkat ditt liv?

Begränsningar? Bilkörning, socialt umgänge familjen, semestrar?

Sjukskrivning/ Arbete %? Hur mkt?

Ångest? Oro? Annat?

Vilket stöd alt hjälp har du fått i samband med detta?

Vilka besvär/symtom har du haft under hjärtklappningsattackerna?

Därefter se: SCL saknar du något symtom?

Appendix 2 Avslutande frågor Studie I och II

1. Hur lång tid har du haft besvär med hjärtrusningar? Antal <input type="text"/> månader <input type="text"/> år Jag har aldrig känt några hjärtrusningar <input type="checkbox"/> Kommentar: _____	
2. Hur många gånger har du sökt <u>akut på sjukhus</u> för dina hjärtrusningar? <input type="text"/> Antal gånger	
3. Hur många gånger har du sökt <u>öppenvården</u> för dina hjärtrusningar? <input type="text"/> Antal gånger (T.ex. Distriktsläkare, företagshälsovården, hjärtspecialist)	
4. <u>Var</u> ställdes rätt diagnos? Akutmott. <input type="checkbox"/> Vårdcentralen <input type="checkbox"/> Hos hjärtspecialist <input type="checkbox"/> Annat: _____	
5. <u>Vem</u> ställde rätt diagnos? Akutläkare <input type="checkbox"/> Distriktsläkare <input type="checkbox"/> Hjärtspecialist <input type="checkbox"/> Annan: _____ Kön på den som ställde rätt diagnos: Kvinnlig läkare <input type="checkbox"/> Manlig läkare <input type="checkbox"/>	
6. Hur många gånger har du behövt söka läkare för att få <u>rätt diagnos</u>? Fick rätt diagnos vid första läkarkontakten <input type="checkbox"/> <u>Antal läkarbesök:</u> Distriktsläkare <input type="checkbox"/> Privatläkare <input type="checkbox"/> Hjärtspecialist <input type="checkbox"/> Kommentar: _____	
7. Hur lång <u>tid</u> tog det att få rätt diagnos? <input type="text"/> månader <input type="text"/> år	

8. Hur upplever du att du har blivit bemött i öppen vården när du sökt vård för dina hjärtrusningar? Flera svar kan vara aktuella.

- ☐ Ej sökt öppenvård för mina hjärtrusningar. Gå vidare till fråga 9
- ☐ Jag fick ett bra bemötande av både kvinnliga och manliga läkare
- ☐ Jag är fullkomligt nöjd, kunde inte varit bättre
- ☐ Ganska bra
- ☐ Blev bemött bra av kvinnliga läkare
- ☐ Blev inte bemött bra av kvinnliga läkare
- ☐ Blev bemött bra av manliga läkare
- ☐ Blev inte bemött bra av manliga läkare
- ☐ Jag upplevde inte att sjukvårdspersonalen trodde på mig när jag sökte för mina hjärtbesvär
- ☐ Jag upplever att jag blivit felaktigt diagnosticerad

Vilken diagnos fick du? _____

Annat: _____

9. Hur upplever du att du har blivit bemött när du sökt vård för dina hjärtrusningar på akut-mottagning? Flera svar kan vara aktuella.

- ☐ Ej sökt på akutmottagning för mina hjärtrusningar. Gå vidare till fråga 10
- ☐ Jag fick ett bra bemötande av både kvinnliga och manliga läkare
- ☐ Jag är fullkomligt nöjd, kunde inte varit bättre
- ☐ Ganska bra
- ☐ Blev bemött bra av kvinnliga läkare
- ☐ Blev inte bemött bra av kvinnliga läkare
- ☐ Blev bemött bra av manliga läkare
- ☐ Blev inte bemött bra av manliga läkare
- ☐ Jag upplevde inte att sjukvårdspersonalen trodde på mig när jag sökte för mina hjärtbesvär
- ☐ Jag upplever att jag blivit felaktigt diagnosticerad

Vilken diagnos fick du? _____

Annat: _____

10. När du hade fått den rätta diagnosen; vilken behandling blev du erbjuden?

- ☐ Läkemedelsbehandling
- ☐ Läkemedelsbehandling och elkonvertering
- Antal gånger du blivit elkonverterad
- ☐ Läkemedelsbehandling i väntan på ablationsbehandling
- ☐ Ablationsbehandling direkt

Annat: _____

11. Vilka läkemedel har du prövat för dina hjärtrytmrubbningsbesvär?

- | | |
|--|---|
| <input type="checkbox"/> Seloken/ Metropolol/ Tenormin | <input type="checkbox"/> Sotalol/ Sotacor |
| <input type="checkbox"/> Tambocor | <input type="checkbox"/> Rytmonorm |
| <input type="checkbox"/> Kinidin | <input type="checkbox"/> Disopyramid/ Durbis |
| <input type="checkbox"/> Mulfajq | <input type="checkbox"/> Verapamil/ Isoptin/ Cardizem |
| <input type="checkbox"/> Amiodarone/ Cordarone | <input type="checkbox"/> Digoxin/ Lanacrist |
| <input type="checkbox"/> Annat | <input type="checkbox"/> Inga läkemedel |

12. Fick du information om hur du skulle agera vid ev. ny hjärtrusning?

- ☐ Ja, vilken _____
- ☐ Jag behövde inte någon information, jag visste hur jag skulle agera.
- ☐ Hade önskat mer information

Kommentar: _____

13. Fick du information om hur dina hjärtrusningar kunde komma att inverka på ditt dagliga liv?

- ☐ Ja ☐ Delvis ☐ Nej

Kommentar: _____

Till sist:

Är du man eller kvinna?

☐

Man

☐

Kvinna

Vilket år är du född?

I vilket land är du född: _____

I vilket land är din mor född: _____

I vilket land är din far född: _____

Civiltillstånd☐

Gift, sambo, bor med maka/make/partner

☐

Gift men bor ej med maka/make/partner

☐

Ensamstående

☐

Änka/ änkan

Vilken är din högst avslutade utbildning?

☐

Grundskola/ folkskola

☐

Gymnasium/ realskola

☐

Universitet/ högskola

☐

Annan ange vad _____

Vad har varit din huvudsakliga sysselsättning de senaste 12 månaderna?

☐

Fast anställd/ tillsvidareanställd

☐

Arbetat som vikarie eller timanställd

☐

Egen företagare

☐

Tjänstledig eller föräldraledig

☐

Studerande, praktiserande

☐

Arbetsmarknadsåtgärd, arbetslös

☐

Ålderspensionär

☐

Långtidssjukskriven (mer än tre månader)

☐

Sjuk -/ aktivitetsersättning (förtids-, sjukpensionär)

Annat: _____

I vilken grad har du arbetat _____ % av heltid

Appendix 3

EudraCT-nummer:2006-004415-22

Studieprotokoll

Premedicinering i form av Mixtur Midazolam 1mg/ml, 7ml peroralt vid 70 kg (max 10 ml) ges cirka 20 minuter före undersökningen på avdelningen innan transport till elektrofysiologiska laboratoriet.

Inför katetreringen:

- Fem minuter innan ges injektion Rapifen 0,5 ml 1mg/ml intravenöst.

Före ablation:

- Två minuter innan ges injektion Midazolam 1ml (1 mg/ml) samt injektion Rapifen 0,5ml (1mg/ml).
- Ovanstående dosering upprepas var 30:e minut under hela ablationsproceduren.

Dokumentation av administrerat läkemedel och tidpunkt fylls i patients läkemedelsjournal enligt sjukhusets rutiner. Vid katetreringstillfället samt under var 15:e minut under ablationsbehandlingen får patient skatta sin upplevda smärta enligt VAS-skalan.

Appendix 4

Vi ber dig hjälpa oss att förbättra och utvärdera smärtbehandlingen för patienter som genomgår ablationsbehandling mot rytmrubbningar.

Enkäten tar endast några minuter att fylla i och vi är tacksamma om du besvarar följande frågor:



Man ☐ Kvinna ☐ Ålder.....

1) Kände du någon smärta under själva ingreppet Ja ☐ Nej ☐

2a) Om ja, hur skulle du vilja skatta din smärta när den var som värst under ingreppet enligt nedanstående skala

0 1 2 3 4 5 6 7 8 9 10
 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ 
Ingen smärta Värsta tänkbara smärta

2b) Hur skulle du skatta den genomsnittliga upplevd smärta

0 1 2 3 4 5 6 7 8 9 10
 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ 
Ingen smärta Värsta tänkbara smärta

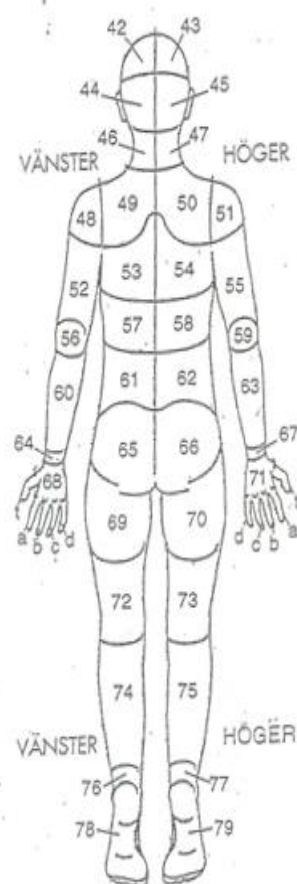
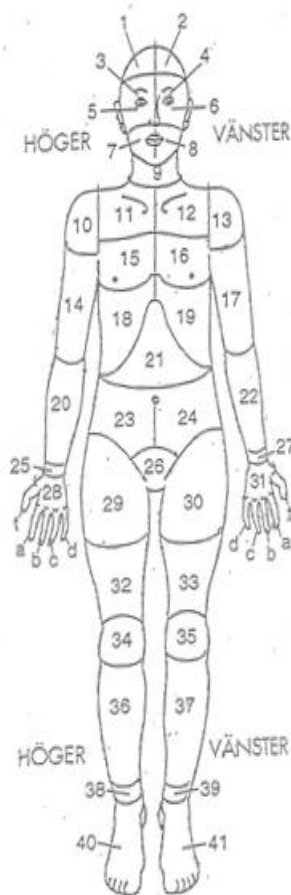
3) Hur skulle du vilja beskriva smärtan:

- Skärande ☐
- Molande ☐
- Stickande ☐
- Klämmande ☐
- Krampaktig ☐
- Sönderslitande ☐
- Värkande ☐
- Svidande ☐
- Brännande ☐
- Ömmande ☐
- Gnagande ☐
- Tryckande ☐



4) Hur upplevde du smärtan:

- Irriterande ☐
- Skrämmande ☐
- Besvärlig ☐
- Kvävande ☐
- Mördande ☐
- Odräglig ☐
- Fruktansvärd ☐
- Tröttande ☐
- Oroande ☐
- Outhärdlig ☐
- Torturerande ☐

5) Kan du rita in på figurerna var det gjorde ont?



6) Hur nöjd är du med den smärtbehandling du fick i samband med din ablationsbehandling

	0	1	2	3	4	5	6	7	8	9	10	
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Mycket missnöjd												Mycket nöjd

7) Här har du möjlighet med egna ord kommentera varför du satt dina kryss där du gjorde. Du kan också skriva ned andra eventuella synpunkter som kan hjälpa oss att bli bättre på vårt omhändertagande.

.....

.....

.....

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.....

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Tack för hjälpen!

Ansvariga för denna enkät är:

Leg ssk Carina Camlöf

Överläkare Mats Jensen-Urstad

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