Health-related quality of life after cardiac arrest

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Health-related quality of life after cardiac arrest

ABSTRACT

Background
Cardiac arrest is a major health problem worldwide. For many of the afflicted, cardiac arrest is the natural end of life. For others, it is an unexpected event suddenly striking in the middle of life. During the last decades, major efforts in treatment have contributed to more people surviving their cardiac arrest. However, previous research has mainly focused on survival, while the knowledge about health-related quality of life in survivors is sparse. Hence, there is a need for more research in order to extend the knowledge about the living situations among survivors and their spouses. For example, factors associated with health-related quality of life are not sufficiently investigated. Knowledge about such factors is important in order to develop interventions and to be able to improve post cardiac arrest care. In addition, existing research shows incongruent results concerning differences in characteristics and survival between men and women. In order to provide equitable care between sexes, further studies are warranted.

Aim
The overall aim of this thesis was to increase the knowledge of survival and health-related quality of life among people suffering cardiac arrest with focus on sex and other related factors. The specific aims were: to describe in-hospital cardiac arrest events with regard to sex and investigate if sex is associated with survival after controlling for known predictors and interaction effects (study I), to describe health status and psychological distress among in-hospital cardiac arrest survivors in relation to sex (study II), to investigate factors associated with health-related quality of life among cardiac arrest survivors treated with an implantable cardioverter defibrillator in relation to sex, and to compare their health-related quality of life with a general population, (study III) and to investigate if type D personality and perceived control among cardiac arrest survivors and their spouses were associated with their own and their partners’ health-related quality of life (study IV).

Methods
The general design in all studies (I-IV) was quantitative, cross-sectional and correlational. This thesis is based on four different data collections. Data was systematically collected using national quality registries (I and II) or by sending questionnaires to survivors (III and IV) and their spouses.
Health-related quality of life after cardiac arrest (IV), treated at several different hospitals in Sweden. The sample size varied between 126 and 990 across the studies. The outcomes and explanatory study variables were chosen with respect to Wilson and Cleary's conceptual model of health-related quality of life. The main outcome variables were survival after resuscitation, survival at hospital discharge, survival at 30 days post cardiac arrest (I), and health-related quality of life measured by the Hospital Anxiety and Depression Scale (II and III) and the EuroQol-5 dimensions (II-IV). In this thesis descriptive and inferential statistics were applied. The main statistics consisted of logistic and linear regression analyses, and structural equation modelling.

Results
Male sex was associated with a better chance of survival to hospital discharge, but no associations between sex and survival after resuscitation or at 30 days were identified. More men than women received resuscitation attempts when suffering an in-hospital cardiac arrest (study I). Health-related quality of life among most cardiac arrest survivors was good (II-IV), even when compared to a general population (III). However, a significant proportion reported low health status and symptoms of anxiety and depression (II and III). Women reported worse health-related quality of life compared to men, and female sex was associated with poorer health-related quality of life in the multiple regression models (II and III). Several additional factors were identified to be associated with poorer health-related quality of life: being unemployed, having a type D personality, perceiving less control, suffering from more comorbidities and suffering from more ICD-related concerns (III). In addition, older age was associated with poorer (EQ VAS) or better (HADS Anxiety) health-related quality of life, depending of outcome measure (II). Moreover, perceived control and type D personality among the survivors were associated with health-related quality of life among their spouses, but not vice versa.

Conclusions
Although, sex does not appear to be an important predictor for survival, the difference between men and women regarding the proportion of resuscitation attempts should be further investigated. The majority of survivors and their spouses report good health-related quality of life similar to general populations. However, a substantial proportion suffer from health problems. Since women in general report worse health-related quality of life compared to men a higher proportion of women may be in need of support. Several factors associated with worse health-related quality of life were identified and might be used during follow-up and rehabilitation. For example, identifying type D personality might be important when screening patients at risk for health problems. Perceiving
more control could be targeted by health-supportive interventions, for example person-centered care. Healthcare professionals should make efforts to identify survivors at risk of poor health-related quality of life and offer individualized support when needed. Characteristics among survivors were associated with health-related quality of life in their spouses. Including spouses in follow-up care is therefore important. Wilson and Cleary's conceptual model for health-related quality of life appears to be applicable for choosing outcomes in cardiac arrest research and might be helpful when designing interventions to improve post cardiac arrest care.
LIST OF PAPERS

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals.


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## ABBREVIATIONS

<table>
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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>APIM</td>
<td>Actor-Partner Interdependence Model</td>
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<td>CA</td>
<td>Cardiac Arrest</td>
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<tr>
<td>CAD</td>
<td>Coronary Artery Disease</td>
</tr>
<tr>
<td>CAS</td>
<td>Control Attitude Scale</td>
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<tr>
<td>COSCA</td>
<td>Core Outcome Set for Cardiac Arrest</td>
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<tr>
<td>CPC</td>
<td>Cerebral Performance Category</td>
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<tr>
<td>CPR</td>
<td>Cardiopulmonary Resuscitation</td>
</tr>
<tr>
<td>DS-14</td>
<td>Standard Assessment of Social Inhibition, Negative Affectivity, and Type D Personality</td>
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<td>EQ-5D-3L</td>
<td>EuroQol 5 dimensions 3 levels</td>
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<tr>
<td>EQ-5D-5L</td>
<td>EuroQol 5 dimensions 5 levels</td>
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<td>HADS</td>
<td>Hospital Anxiety and Depression Scale</td>
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<td>HRQoL</td>
<td>Health-Related Quality of Life</td>
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<tr>
<td>ICD</td>
<td>Implantable Cardioverter Defibrillator</td>
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<td>ICDC</td>
<td>ICD-related Concerns</td>
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<tr>
<td>IHCA</td>
<td>In-Hospital Cardiac Arrest</td>
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<td>ILCOR</td>
<td>International Liaison Committee on Resuscitation</td>
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<tr>
<td>OHCA</td>
<td>Out-of-Hospital Cardiac Arrest</td>
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<tr>
<td>PCC</td>
<td>Person Centered Care</td>
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<tr>
<td>PROM</td>
<td>Patient-Reported Outcome Measure</td>
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<tr>
<td>QoL</td>
<td>Quality of Life</td>
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<tr>
<td>SRCPR</td>
<td>Swedish Register of Cardiopulmonary Resuscitation</td>
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<tr>
<td>VAS</td>
<td>Visual Analogue Scale</td>
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<tr>
<td>VF</td>
<td>Ventricular Fibrillation</td>
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<td>VT</td>
<td>Ventricular Tachycardia</td>
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<td>WHO</td>
<td>World Health Organization</td>
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INTRODUCTION

Cardiac arrest (CA), can be defined as “the cessation of cardiac mechanical activity, confirmed by the absence of detectable pulse, unresponsiveness and apnoea (or agonal, gasping respirations)”, and is a significant health problem worldwide. The most common aetiology of CA is coronary artery disease (CAD). For many of the afflicted, cardiac arrest is the natural end of life. However, for others it’s an unexpected, traumatic event, suddenly striking in the middle of life. Prompt resuscitation is crucial to saving their lives.

Through research, clinical guidelines and implementation of best practice, afflicted patients have successfully been resuscitated to survive the acute phase of CA. Today, there is extensive knowledge of which interventions are associated with survival and therefore we can provide evidence-based treatment, with more and more people surviving their CA. However, there are weaknesses in the follow-up care, support and rehabilitation. Most research has focused on evaluating effects on survival while knowledge on well-being and life situation, including health-related quality of life (HRQoL), among survivors and their partners is sparse. Due to the life-threatening nature of suffering a CA, such event is likely to have an impact on HRQoL in both survivors and their partners. However, factors associated with HRQoL have not been thoroughly explored. Therefore, developing interventions to improve care is difficult. Consequently, a structured post CA care is missing in many hospitals and other healthcare settings. In addition, although a vast majority of those suffering CA with attempted resuscitation are men, the effects of sex on survival and HRQoL have not been sufficiently investigated.
BACKGROUND

**Cardiac arrest – demographical and clinical characteristics**

In Europe, approximately 350,000 persons suffer from an out-of-hospital cardiac arrest (OHCA) annually, whereas the prevalence of in-hospital cardiac arrest (IHCA) is unknown. In Sweden, approximately 5,500 people suffer from an OHCA and 2,500 from an IHCA with attempted resuscitation annually. During recent decades, major improvements in survival rates have been reported and more than 1,400 people (600 after OHCA vs. 800 after IHCA) survived CA in Sweden during 2017. Survival rates in Sweden are higher after an IHCA (approximately 30%) compared to an OHCA (approximately 10%), and are comparable to most countries in Europe, Australia and North America. In Sweden, the majority of patients suffering a CA with a resuscitation attempt are men (OHCA 69% and IHCA 62%), the mean age is 67 (OHCA) and 71 (IHCA) years respectively and most CAs are due to cardiac diseases, CAD in particular. CAD is the most common cause of death in the world.

The best prognosis for survival is for patients suffering witnessed CA due to ventricular fibrillation (VF) or ventricular tachycardia (VT), i.e. a CA treatable with defibrillation, receiving prompt resuscitation efforts. Approximately 30% of patients suffering CA have a shockable initial rhythm. Previous research has demonstrated differences in characteristics and survival between men and women, but results are incongruent. A recent study from Japan, including almost 400,000 patients suffering OHCA, did not find any sex differences in survival when controlling for confounders, such as initial rhythm and aetiology. In contrast, a review from 2015 reported better chance of survival in women suffering an OHCA. In IHCA, women seem to have a lower proportion of shockable initial rhythm, but a slightly better chance of surviving IHCA compared to men. However, this association could be dependent on age, as higher survival rates may occur only among younger women, where protective effects of estrogen has been suggested to be a contributing factor. In contrast, a recent Swedish cohort study reported no differences in characteristics and outcome between men and women.

**Treatment of cardiac arrest**

Every fifth year, consensus on treatment recommendations is presented by the International Liaison Committee on Resuscitation (ILCOR). These recommendations are the basis for international guidelines.
of surviving seems to be highly dependent on the time elapse from CA to evidence-based interventions, usually described as four links of “The chain of survival” (Figure 1). These interventions/links are: 1) early recognition and call for help, 2) early cardiopulmonary resuscitation (CPR), 3) early defibrillation and 4) post resuscitation care. The first link highlights the importance of promptly identifying CA and calling the dispatch center (OHCA)/alerting the medical emergency team (IHCA) for help. If early CPR is initiated the chance of survival increases two to three times (OHCA). In Sweden, more than 70% of OHCA patients receive CPR prior to the arrival of the ambulance, and more than 70% of patients suffering IHCA receive CPR within one minute. When defibrillation is performed within three minutes from CA more than 70% of patients with VF may survive, but the chance of survival decreases by 10% for every minute elapsed. Outside hospital, 24% of patients with VF are defibrillated prior to ambulance arrival. In-hospital 85% are defibrillated within three minutes.

The most central parts of post-resuscitation care are identifying and treating the cause of CA and close monitoring of vital signs, preferably at an intensive care unit. As part of post resuscitation care a substantial group of the patients are treated with target temperature management (35%), percutaneous coronary intervention (50%), and an implantable cardioverter defibrillator (ICD, 23%) post OHCA in Sweden. Among patients suffering OHCA about 25% are admitted alive to the hospital, and of these about 50% survive to 30 days post CA. Among those with return of spontaneous circulation and admitted to hospital, but subsequently dying in-hospital, the most common cause of death is related to hypoxic brain injury. Therefore multimodal neurological prognostication is important to be able to optimize care, choose the most relevant level-of-care, including withdrawal of life-sustaining treatment, and give information to relatives. Most of patients still alive at 30 days, regardless of place (OHCA or IHCA), have been reported to have good cerebral outcome when assessed with the Cerebral Performance Category (CPC) Scale (CPC 1 or 2). This scale has received criticism for being crude, but is the most used
assessment for reporting neurological outcome in CA survivors. Less than 10% of all CA survivors in Sweden are reported to have poor cerebral outcome (CPC 3 to 5) at 30 days according to assessments made with the CPC Scale.

Post cardiac arrest follow-up and rehabilitation
In the 2015 guidelines from the European Resuscitation Council, a short section describing follow-up and rehabilitation is presented, recommending a structured follow-up, including information (oral and written), screening for cognitive and psychological problems and referral to support and specialized care if needed. Since the numbers of survivors (potentially in need of support) is constantly increasing, there may be reasons to include follow-up and rehabilitation as a fifth link in the chain of survival. However, the knowledge of evidence-based interventions, as well as current practices, is sparse. A recently published survey reports weaknesses in structure and variability in post CA care and follow-up in Sweden. Fewer than half of the Swedish hospitals had routines for following up with CA survivors, and in the case of existing routines, these were not always applied. In addition, relatives were not always included in follow-up care. The most common routine was to offer a visit to an outpatient cardiology reception unit. Since this survey was conducted, Swedish guidelines have been published by the Swedish resuscitation council, potentially contributing to improving care.

Rehabilitation efforts depend on aetiology and may often therefore include secondary prevention of CAD, e.g. antihypertensive- and lipid-lowering drugs, smoking cessation, exercise, and stress reduction. For patients with long-term cognitive impairments, further evaluation by occupational therapist and/or a neuropsychologist is common. For the minority with severe brain injury, referral to a specialized rehabilitation centre might be applicable. Such rehabilitation might be effective for increasing patient independency in daily activities and for decreasing burden among relatives. However, for the majority (with mild-moderate impairments) learning adjustment strategies and compensatory techniques might be sufficient.

Experiences of life after cardiac arrest
Surviving a life-threatening condition such as CA will affect the lives of both survivors and their partners. In qualitative studies, survivors have described the event as a confrontation with death, and as a sudden trauma striking unexpectedly in the middle of everyday life. Survivors have described their experiences as waking up in chaos, in a struggle to find meaning and to regain control. Their memory loss is often extensive, their bodily functions altered and they often have to adjust their daily activities to a variety of health problems. Survivors also describe fear of
Health-related quality of life among cardiac arrest survivors

Having suffered a CA is likely to affect different aspects of HRQoL among survivors. Since most CAs are caused by a cardiovascular disease, survivors may be at risk of suffering cardiac complications. In addition, brain injury develops within minutes after the cessation of blood flow and may explain other possible complications seen among survivors. Although, severe brain injuries are uncommon, mild to moderate cognitive impairments have been reported in as many as 30-50% of the survivors. Mild impairments are often not detected by health care professionals if merely standard measures, e.g. the CPC Scale, are used. In addition, psychological distress (such as anxiety, depression and post-traumatic stress disorder) and fatigue are frequently reported among survivors. Such complications may affect the ability to perform daily activities, participation in society and HRQoL. A review on psychological distress by Wilder-Schaaf et al. reports high prevalence of anxiety (range 13-61%) and depression (range 14-45%) in previous studies. However, Wilder-Schaaf also report major methodological variability in relation to measures used, time of measurement and settings.

Another review by Elliot et al. concludes that HRQoL among survivors appears to be good or at least acceptable, but also reports major variations between different studies and highlights a need for larger studies. This has been confirmed by more recent studies with larger number of participants. However, although HRQoL in general is good, significant proportions report serious health problems. Some studies report that suffering a CA has negative effects on HRQoL, and that survivors have poorer HRQoL compared to general populations. Other studies have not been able to report any differences.

Almost all research on HRQoL has included OHCA survivors only. The few studies including IHCA survivors are small and the results are inconclusive. This group of patients differs from OHCA with regard to being older and suffering more comorbidities. However, they receive earlier treatment. Therefore, this group may have different health
problems as well as care needs. This thesis will include populations from both contexts.

Factors associated with health-related quality of life

Only few larger population-based studies have investigated HRQoL among survivors. Even less is known about factors associated with HRQoL after surviving a CA. One of the first studies exploring such factors was published by Wachelder et al. in 2009. In their study, older age, being woman, being treated with percutaneous coronary intervention and not being treated with targeted temperature management were significantly associated with better HRQoL or higher levels of societal participation. In a more recent Australian study by Smith et al., better health status before CA, working before CA, suffering a CA witnessed by the emergency medical services personnel and having a shockable initial rhythm were identified as factors associated with better functional status among survivors. A longitudinal study by Verberne et al., identified not having a partner, suffering cognitive or functional problems, suffering anxiety or depression as being associated with worse physical or mental HRQoL post CA. Similar factors were identified in a previous study by Moulaert et al. However, most of the identified factors can be considered belonging to the domain of HRQoL they were reported to be associated with, i.e. cognitive and functional problems as a part of physical HRQoL, and anxiety or depression as a part of mental HRQoL. A more recent study from France by Geri et al., identified younger age, being man, having good neurological recovery and being independently in daily activities as factors associated with better HRQoL. This is one of the first studies identifying sex as a significantly independent associated factor for HRQoL in CA survivors. In addition, in a recently published Australian study, female OHCA survivors appear to report poorer functional outcome and HRQoL compared to men.

Although women appear to be at higher risk of suffering health problems, there is a lack of knowledge of the influence of sex on HRQoL in CA survivors and their relatives, especially when suffering an IHCA. In other diseases and conditions, sex is often reported to be an important determinant of survival and HRQoL. In addition, interactions of sex with disease prevalence, health-related behaviors, utilization and experiences of healthcare appear to be common. Moreover, women are often underrepresented in research, especially in cardiovascular studies. In cardiovascular diseases, the symptoms of women are underrecognized and their treatment less likely to be provided according to guidelines, when compared to men.

Survivors are likely to be in need of social support when recovering from CA. Therefore characteristics and reactions among their partners might be important factors. Studies in other populations have reported that survivors and partners are likely to affect each other’s health. These
aspects have not been explored in CA populations. In general, little is known about HRQoL in relatives to CA survivors, although psychological distress has been reported.\(^72\) \(^73\) In a study by Wachelder et al., stress reactions and anxiety were even more common among relatives, mostly partners, compared to the survivors.\(^54\) In a study from 2018, overall HRQoL among partners two years post CA was reported to be good and similar to a general population. However, 30% of partners still experienced trauma-related stress, in particular those witnessing the CA.\(^74\) A few factors associated with post-traumatic stress disorder (PTSD) in partners of CA survivors were identified by Zimmerli et al. These factors were: being woman, previous history of depression and if the family considered ICU treatment as insufficient.\(^72\) Factors associated with other dimensions of HRQoL are not thoroughly explored.

The prevalence of type D personality (distressed personality) is reported to be 28% in people suffering CAD. A person with type D personality is characterised by perceiving negative emotions (negative affectivity) and not being willing to share these emotions with others out of fear of being rejected (social inhibition).\(^75\) Type D personality is reported to be associated with a higher risk of mortality and morbidity in patients with CAD.\(^76\) In addition, associations with poorer HRQoL are identified in a variety of cardiovascular diseases.\(^77\) However, knowledge of the importance of type D personality for HRQoL in CA survivors is lacking.

In patients suffering CAD, perceiving more control is reported to be associated with better HRQoL, but such aspects have not previously been investigated in CA survivors.\(^78\)

**Differences between men and women suffering cardiac arrest**

In this thesis, potential sex differences among people suffering CA were investigated. Sex refers to the biological attributes of the participants, and associations of sex with physical, psychological and social factors are explored, using binary responses (man/male or woman/female).\(^68\) According to the Health and Medical Service Act (1982:763), the aim of the Swedish healthcare and public medical service is “good health and care on equitable terms for the entire population”.\(^79\) However, there are unmotivated differences between men and women in Swedish healthcare. The inequity, i.e. care is not provided fair in relation to patients’ needs, appears to be particularly related to the care relationship being asymmetric, which stress the importance to recognize mutual dependency and aspects of power in the relationship in order to plan and individualize patient care. The differences in care might also be explained by health care personnel generalizing about patients’ needs and resources related to their sex.\(^80\) Therefore, studying sex differences is important.
Previous research reports incongruent results concerning differences in characteristics and survival between men and women suffering CA. Moreover, despite the fact that a vast majority of existing research in different areas shows that female sex is associated with poorer HRQoL,\textsuperscript{81-87} only a few studies have investigated HRQoL after CA in relation to sex. A few studies show that women surviving OHCA report more problems with psychological distress or lower HRQoL compared to men,\textsuperscript{52,65,67} while other studies found no such differences.\textsuperscript{48,50,66} No studies have investigated these aspects for IHCA survivors. In order to provide equitable and better care, further studies are warranted.
CONCEPTUAL FRAMEWORK

Health-related quality of life

Quality of life (QoL) is an important outcome in healthcare research, but consensus is lacking with regard to its definition. However, QoL is mostly defined as a multidimensional concept including domains like ability/function, happiness/satisfaction, goal achievement and/or social capability. According to the World Health Organization (WHO), QoL is the position in life as perceived by the individuals themselves. This should be related to the culture and value systems in which they live, but also to their own personal beliefs, goals and expectations. QoL is also defined by WHO as a complex, broad concept affected by the individual’s health.

Most definitions and models of QoL include the following health dimensions: 1) physical health, 2) psychological health, 3) social health and 4) functional health. There is no consensus regarding the definition of health either.

Traditional definitions have mostly included merely biological/physical dimensions and the absence of disease, while more recent definitions, e.g. within caring sciences, often take a more holistic approach, including more aspects of human life. According to the WHO, health is a multidimensional concept, defined as a state of complete physical, psychological and social well-being, and not only absence of disease/infirmity. The definition is often criticized for its absoluteness, and adjustments including e.g. “adaption to challenges” have therefore been suggested.

In the absence of a clear definition for QoL in its general sense, the term HRQoL is today more frequently used for evaluating the impact of disease and the effects of healthcare interventions from the perspective of the patients. Although QoL, health (or perceived health status) and HRQoL often are used interchangeably, HRQoL can be more distinctly defined as the parts of an individual’s QoL that are related to, or affected by, the health domains. Aspects of QoL not explicitly related to health, e.g. cultural and political aspects are often excluded. In general, most researchers agree that relevant domains may vary. However, most definitions (or instruments) include physical, psychological and social domains. In addition, general- or overall self-perceived health is often included. As an attempt to categorize what HRQoL instruments might measure, Wilson and Cleary have developed a conceptual model for the dimensions included in HRQoL and their relationships. Their model were revised by Ferrans et al. in 2005. In this thesis the revised version is used (Figure 2).
Figure 2. Linking clinical variables with health-related quality of life: a conceptual model of patient outcomes, IB Wilson and PD Cleary, JAMA, 1995, revised by C Ferrans et al., Journal of Nursing Scholarship, 2005. Copyright by JAMA. Used with permission.

The main components are presented as five boxes in the middle of the model. The first box includes biological and physiological variables, e.g. the function of organs or diseases and provides a basis for the model. The second box includes symptom status, referring to all symptoms (physical and psychological) experienced by the individual. The third box includes functional status, referring to the individual’s physical, psychological and social functioning. The fourth box includes the general health perceptions, referring to the integration of the previous boxes as experienced by the individual. The fifth box is the overall QoL, i.e. how happy or satisfied the individual is with life as a whole. These components are also related to characteristics of the individual him-/herself (e.g. sex, age, personality and preferences) and characteristics of the environment (e.g. social and psychological support).\textsuperscript{98,99} The revisions made by Ferrans et al. included adding arrows from “characteristics boxes” to the “biological box” and removing a box called “non-medical factors” associated with overall QoL in the original model.\textsuperscript{99} In the model, most assessments (boxes 2-5) are based on the individual’s own perceptions. Consequently, they should be based on patient-reported outcome measures (PROM). However, they might also be supported by more objective measures (boxes 1-3).

Measures of HRQoL are more frequently used in the context of CA. In a statement from ILCOR in 2008, health-related outcomes are considered
especially important when performing CA research and when providing care for CA survivors.\textsuperscript{38} Recently another ILCOR advisory statement, the Core Outcome Set for Cardiac Arrest (COSCA) was published. This initiative was performed in close collaboration with researchers, clinicians, patients and their partners, and aimed at finding relevant outcomes for cardiac arrest research and follow-up. According to the publication, reporting of CA should include outcomes measuring survival, neurological function and HRQoL, e.g. the EuroQol 5 dimensions 5 levels (EQ-5D-5L).\textsuperscript{100}

The overall theoretical rationale for this thesis is based on Wilson and Cleary's conceptual model (the revised version). HRQoL is defined as a holistic multidimensional concept including dimensions of QoL related to health, and should be based on individual perceptions. The study variables in this thesis are chosen with respect to the model, in order to include physical, psychological and social aspects of HRQoL, in addition to general health status.

\textit{Health-related quality of life after cardiac arrest}
RATIONALE OF THE THESIS

Most CA research has focused on prognosis and survival, while the knowledge about the living situation and HRQoL among survivors and their partners is sparse. Despite that HRQoL assessments are commonly used to investigate the impact of a disease on life, little is known about CA survivors. In addition, almost all research investigating HRQoL is performed in populations where the CA occurred in an out-of-hospital context and with a small number of participants. Hence, there is a need for larger studies investigating HRQoL among survivors, especially including those suffering IHCA.

During the last decades, major efforts in CA treatment have contributed to increased survival. However, there are weaknesses in the follow-up care, support and rehabilitation. One explanation could be that factors associated with HRQoL are not sufficiently investigated. Knowledge about such factors is important in order to develop interventions and to be able to improve post CA care. For example, although CA survivors and their partners are likely to affect each other’s HRQoL, such aspects are not previously investigated. Special attention should also be given to potential sex differences, since a few existing studies report worse HRQoL among women surviving OHCA compared to men. However, the results are incongruent and no studies to date have investigated these aspects for IHCA survivors. In addition, previous research reports incongruent results also concerning differences in characteristics and survival between men and women. In order to provide improved and equitable care, further studies are warranted.
AIM OF THE THESIS

The overall aim of this thesis is to increase the knowledge of survival and HRQoL among people suffering CA with focus on sex and other related factors.

Specific aims

- To describe IHCA events with regard to sex and investigate if sex is associated with survival after controlling for previously known predictors and interaction effects (study I)
- To describe health status and psychological distress among IHCA survivors in relation to sex (study II)
- To investigate factors associated with HRQoL among CA survivors treated with an ICD in relation to sex, and to compare their HRQoL with a general population (study III)
- To investigate if a distressed personality and perceived control among cardiac arrest survivors and their spouses were associated with their own and their partner’s HRQoL (study IV)
METHODS

In order to increase the knowledge of survival and HRQoL among people suffering CA, with focus on sex and other related factors, various methods were used (Table 1).

<table>
<thead>
<tr>
<th>Table 1. Overview of the methods in study I-IV</th>
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<tr>
<td>Study</td>
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APIM=Actor-Partner Interdependence Model, CA=Cardiac Arrest, CPR=Cardiopulmonary Resuscitation, EQ-5D-3L=EuroQol 5 dimensions 3 levels, EQ-5D-5L=EuroQol 5 dimensions 5 levels, HADS=Hospital Anxiety and Depression Scale, IHCA=In-Hospital Cardiac Arrest, ICD=Implantable Cardioverter Defibrillator, SRCPR=Swedish Register of Cardiopulmonary Resuscitation

Design

The general design in all studies (I-IV) was quantitative, cross-sectional and correlational. This thesis is based on four studies, using different samples of data from CA populations, to describe and investigate survival (I) and HRQoL (II-IV) among survivors (II-IV) and their partners (IV), with focus on sex (I-III) and other related factors (I-IV). In order to increase generalizability, a multicenter design was used in studies II-IV. Data was systematically collected using national quality registries (I and II) or by sending study specific questionnaires to survivors (III and IV) and their partners (IV), treated at several different hospitals in Sweden. The outcomes and the other study variables were chosen with respect to Wilson and Cleary’s conceptual model of HRQoL.98 99
The Swedish Register of Cardiopulmonary Resuscitation
More than 90% of the emergency hospitals in Sweden report data to the Swedish Register of Cardiopulmonary Resuscitation (SRCPR). The registry data consists of all reported CAs where any resuscitation efforts are performed.

The registry is internet-based (https://shlrsjh.registercentrum.se/) and clinics report data by using three protocols: 1) patient baseline information and CA events, 2) follow-up data on post resuscitation care, hospital discharge, survival at 30 days post CA and CPC scoring, and 3) PROMs at 3-6 months. The third registration includes e.g. PROMs measuring HRQoL (EQ-5D-5L and Hospital Anxiety and depression Scale, HADS). In addition, a scoring of cerebral function (CPC Scale) is conducted based on information from the conversation and/or patient records. The registry is validated by random inspections of the data, performed by the National Registry Committee.

The Swedish ICD and Pacemaker Registry
All Swedish patients receiving treatment with an ICD or other pacemaker device are included in the Swedish ICD and Pacemaker registry (https://www.pacemakerregistret.se), aiming at improving patient safety and quality of care. The registry contains data on e.g. the reason of treatment, implantation procedures, and patient characteristics and outcome.

Participants and data collection
The participants in study I and II were recruited from the SRCPR. The participants in study III and IV were recruited using contact information from the Swedish ICD and Pacemaker Registry and the SRCPR respectively.

In study I, all CAs where any resuscitation efforts were performed, i.e. starting chest compressions or giving defibrillation, were included. Data was collected using the first and second SRCPR protocol at a single county hospital between January 2007 and June 2011. This resulted in 286 CA events included and analyzed. The hospital is located in a middle-sized Swedish town in the south-east of Sweden, and the treatments and outcomes of CA at this hospital were similar to most hospitals in Sweden. Outcomes and predictors were selected with consideration to prior research and the aim of the study. The associations between sex and survival were tested using all three survival outcomes in the SRCPR, i.e.
after resuscitation attempt, at hospital discharge and at 30 days post arrest. In addition, in a sub-analysis performed to investigate the proportion of attempted resuscitations with regard to sex, 1193 CA events (with or without resuscitation attempts) at the hospital were included and analyzed. For this sub-analysis, data from a two-year period (from January 2009 to December 2010) was collected from hospital medical records.

Study II is the first report from the SRCPR using national patient-reported data (third protocol) on HRQoL. Also, data from protocol one and two were used for characteristics and as explanatory variables. All patients suffering an IHCA in Sweden and surviving to three months were eligible for inclusion. A questionnaire including the EQ-5D-5L and the HADS, together with an invitation to a telephone follow-up (based on the questionnaire) was sent to the survivors. The follow-up calls were performed by resuscitation coordinators or cardiac rehabilitation nurses depending on hospital organization. Patients ≥18 years of age surviving a CA were included. Survivors with obvious signs not being able to comply with the requirements of the registration, e.g. severe cognitive dysfunction, language difficulties, severe physical illness and severe psychological illness were excluded. Data for the study was collected between August 2013 and December 2015. In total, 47 emergency hospitals (64% of all eligible hospitals) in Sweden contributed with data. During this period, 594 of 773 (77%) eligible IHCA survivors were followed up and included in the study. There were no age or sex differences between participants and non-participants. However, non-participants had a worse CPC score (p<0.001) at hospital discharge. The EQ-5D-5L and the HADS were used as outcome variables to investigate associations between sex and HRQoL.

Study III included CA survivors treated with an ICD. This study was a part of a larger follow-up on ICD-recipients in Sweden. Survivors were recruited from the Swedish ICD and Pacemaker Registry. All eligible adults in the 2011 registry were sent an invitation to participate (n=5535). Those completing the informed consent were sent a questionnaire including demographics, e.g. age, sex, cohabitation, occupation and education, and self-reported measures for HRQoL (EuroQol 5 dimensions 3 levels, EQ-5D-3L and HADS), perceived control (Control Attitude Scale, CAS), personality (Standard Assessment of Negative Affectivity, Social Inhibition and Type D Personality, DS-14), and ICD-related Concerns (ICDC). In total, 3 067 patients (55% response rate) returned the questionnaire. Patients with a CA, i.e. suffering VF according to the registry were included in the present study (n=990). The EQ-5D-3L and the HADS were used as outcome variables to investigate associations with potentially related factors. HRQoL was also compared to a general Swedish population, matched for
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age and sex. A county council in the southeast of Sweden collected the general population data, by using a postal questionnaire including the EQ-5D-3L. A stratified randomized sample (n=13,440) of the total county population, ages 18-84, was selected and 7,238 responded (54%). To make the two groups comparable, they were stratified according to sex and age (5 years interval). After that, 1,000 persons in the general population data file were randomly selected from each stratum to match the same proportion in the CA group.

Study IV was a part of a longitudinal study investigating several aspects of HRQoL among CA survivors and their relatives. The inclusion of survivors was performed during telephone follow-up at 3-6 months post CA (protocol 3 for the SRCPR). In addition to inclusion criteria in the registry (studies I and II), patients should have suffered a CA with cardiopulmonary etiology. Short expected survival and/or difficulties to understand study instructions were criteria for exclusion of both survivors and their relatives. The survivors themselves chose if relatives should be asked for participation. Relatives should be ≥18 years of age. The inclusion was performed at Kalmar county hospital, Linköping university hospital, Sahlgrenska university hospital, Gothenburg, Vrinnevi hospital, Norrköping and Central hospital, Växjö. All included survivors and their relatives were sent a questionnaire at 6, 12 and 24 months after CA. Among 317 eligible patients, 66 declined participation and 39 accepted participation but did not return the questionnaire. For the main study this resulted in 67% of patients responding (n=212). No significant differences in age or sex between participants and non-participants were detected. In the present study, partner relationships and their associations with HRQoL at baseline (6 months after the CA) were investigated. Therefore, exclusively CA survivors with a partner were included, in total 126 dyads, i.e. 126 CA survivors and 126 partners. When presenting and discussing the APIM and the results, the term spouse is used for defining: a cohabiting partner, a husband or a wife. The questionnaire consisted of a consent form and demographic data of e.g. age, sex, cohabitation and occupation. In addition, self-reported measures of HRQoL (EQ-5D-5L), perceived control (CAS) and personality (DS-14) were included. The EQ-5D-5L was used as an outcome variable to investigate associations between HRQoL and dyadic relationship.
Outcome variables

Survival
According to the advisory statement (COSCA) from ILCOR, survival should be assessed at least at hospital discharge or at 30 days after CA. Within the SRCPR, survival is recorded on three occasions: 1) after completed resuscitation attempt, 2) at hospital discharge and 3) at 30 days. In this thesis, all three survival outcomes are used (study I). Survival is naturally the biological basis for the concept of HRQoL.

The EuroQol 5 dimensions
The EuroQol 5 dimensions questionnaire was developed by the EuroQol-group between 1987 and 1991. It includes a descriptive system and a visual analogue scale (EQ VAS). The descriptive system includes five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) as a generic measure of health status or HRQoL. The five dimensions can be used for describing a health state profile and to calculate a preference-based index with a maximum level of 1 (best possible health). Higher index values indicate better health status and negative values respresent a health state worse than death. The original questionnaire (EQ-5D-3L) used a 3-level scale for rating the presence and severity of health problems. For the revised 5-level version (EQ-5D-5L), introduced in 2009, the responders rate their status for each dimension on a five-point scale, ranging from 1 “no problems” to 5 “extreme problems.” The EQ VAS constitues an overall measure of health status with a range from 0 (“the worst health you can imagine”) to 100 (“the best health you can imagine”). In addition, the EQ-5D may be used for health-economical calculations. Although acceptable validity has been reported for the 3-level version, e.g. in cardiac patients, it has been criticized for lacking responsiveness and sensitivity. In addition, major ceiling effects have been reported, especially in general populations. These psychometric problems were the basis for revising the questionnaire and introducing the 5-level version. In 2013, Janssen et al. published a multi-country study evaluating the psychometric properties of the EQ-5D-5L compared to the EQ-5D-3L in different groups of patients suffering chronic conditions, e.g. cardiovascular disease. Overall, the 5-level version showed improved psychometric properties compared to the 3-level alternative with regard to missing values, ceiling effects and discriminatory power. The 3-level version (but not the 5-level version) has previously been applied in CA populations. However, the 5-level version is a recommended outcome according to the COSCA statement. In this thesis the EQ-5D-3L (study
III) and the EQ-5D-5L (studies II and IV) are both used as outcome measures of self-perceived general health status (part of HRQoL).98

The Hospital Anxiety and Depression scale
The HADS has been developed as a screening measure to detect symptoms of anxiety and/or depression.106 In total, HADS consists of 14 items. Seven of these items measure anxiety and seven measure depression. For each item, there are four response categories, ranging from 0–3. The responses within each domain (anxiety or depression) are summarized, resulting in two total scores ranging from 0 to 21. Higher scores indicate more symptoms of anxiety and/or depression. Different cut-off scores have been suggested and applied.45 In this thesis the following are used: normal (0–7), mild (8–10), moderate (11–14) and severe (15–21).106 The HADS are well validated and good measurement properties are previously reported in medical patients.107 It has also been applied in CA populations.44 In this thesis the HADS (studies II and III) is used as an outcome measure of the psychological domains of HRQoL.98

Additional measurements

The Control Attitudes Scale
The CAS has been developed to measure the self-perceived level of control among patients suffering different cardiac diseases and their relatives. In total, the instrument consists of four items, two measuring perceived control and two measuring perceived helplessness.78 Patients and relatives rate their responses from “not at all” to “very much” (a score from 0-7). A total score (from 4-28) are then calculated and lower values indicate less perceived control. The CAS has been validated showing acceptable psychometrical properties,108 but has not previously been applied in CA populations. In this thesis the CAS was tested as a factor potentially associated with HRQoL (studies III and IV).

The Standard Assessment of Social Inhibition, Negative Affectivity, and Type D Personality
The DS-14 is an instrument for detecting social inhibition, negative affectivity, and type D personality in a person.75 Having a type D personality was previously reported to be associated with an increased risk of suffering health-related problems in CAD patients.76 77 Seven items measure social inhibition and seven measure negative affectivity, using a response scale from 0 (“false”) to 4 (“true”), resulting in a total score from 0-28. A person with type D personality has a score of ≥10 on both “subscales”, according to a proposed cut-off. The DS-14 are reported to
have good measurement properties\textsuperscript{109} and is widely used in patients with cardiac diseases,\textsuperscript{77} but have not previously been used for CA survivors and their relatives. In this thesis the DS-14 were tested as a factor potentially associated with HRQoL (studies III and IV).

**The ICD-related concerns**

The ICD-related concerns (ICDC) is constructed to measure concerns related to having an ICD implanted. The instrument consists of eight items, e.g. “I am worried about my ICD firing”, with responses from 0 (“not at all”) to 4 (“very much”). The item responses are summarized to a total score from 0 to 32, with higher scores indicating more ICD-related concerns.\textsuperscript{84} The measure has previously been used in studies including patients implanted with an ICD,\textsuperscript{110} but has not been previously used in CA survivors. In this thesis ICD-related concerns is tested as a factor potentially associated with HRQoL (study III).

**The Cerebral Performance Category Scale**

The CPC Scale is an observer reported outcome measure of neurological outcome after brain injury, e.g. after suffering CA. The patients are rated on an ordinal scale from 1 (“conscious with no or minor neurological disability”) to 5 (“brain dead”). The scale is often dichotomized into “good outcome” (CPC 1-2) or “poor outcome” (CPC 3-5). People with “good outcome” are able to perform independent activities of daily life, while those with “poor outcome” are not. The CPC Scale is widely used in CA research and has been recommended in guidelines for reporting CA research since 1991.\textsuperscript{1}

**Data analyses**

In this thesis, various statistical analyses were applied, depending on the specific aims and properties (level and distribution) of data. Descriptive statistics were used, and data was presented by numbers and percentages, mean values (M) and standard deviations (SD), or by medians (Md) and quartiles (Q1-Q3) with regard to characteristics and distribution of data.

To compare group differences between men and women or survivors and spouses, chi-square statistics or Fisher’s exact test were used on nominal data, independent sample t-test or the Mann-Whitney U test were used for interval/ratio and ordinal data respectively.

To test the associations between sex and survival (study I), hierarchical logistic regression analyses were performed. All three survival outcomes in
the SRCPR were tested as outcome variables: after resuscitation attempt, at hospital discharge and at 30 days post arrest. The regression analyses were performed in three blocks: 1) sex as the only explanatory variable, 2) including previously reported important covariates, e.g. initial rhythm and time to treatment, and 3) including a multiplicative interaction term for sex and age. Due to violation of non-dependency, i.e. nested data since 15 patients suffered more than one CA, all regression models were re-analyzed using robust variance estimates, a method relaxing the requirement of the observations to be independent, to examine that this violation had not biased the findings.

To investigate the associations of sex and other factors on survivors HRQoL (studies II and III), linear regression analyses were performed. Four HRQoL outcomes were tested: EQ index, EQ VAS, HADS Anxiety and HADS Depression. In study II, the regression analyses were performed in three blocks (hierarchal regression): 1) including sex as the only outcome variable, 2) including age as a covariate and 3) including a multiplicative interaction term for sex and age. To investigate factors associated with HRQoL in survivors treated with ICD (study III), the regression analyses were performed in two steps: 1) univariate regression analyses between each explanatory variable and outcome variable, and 2) multiple linear regression analysis including all explanatory variables (forced entry method) in order to identify significantly independent variables controlling for the other outcome variables. Categorical explanatory variables with more than two categories (e.g., education) were entered as dummy coded variables in the models, with one as reference category. \( R^2 \)-statistics was used to estimate explained variance in the outcome variable. No problems with multicollinearity between the explanatory variables were detected, in any of the regression models, according to the variance inflation factor. Further, in study III, survivors were clustered depending on time from CA/ICD-implantation to completing the questionnaire and then compared using Kruskal-Wallis one-way ANOVA (non-parametric one-way ANOVA on ranks). Participants (those suffering CA) were also compared to a general population, matched for age and sex using Mann-Whitney U test.

The Actor-Partner Interdependence Model (APIM, Figure 3) was used to investigate if personality and perceived control in CA survivors and their spouses were associated with their own and their partner’s HRQoL (study IV). The APIM is an interpersonal conceptual model for analyzing nonindependent dyadic data. A dyad could be defined as an interpersonal system of two partners, which should be considered simultaneously. A partner relationship involves two people sharing a romantic notion manifested through dating, cohabiting, or marriage.
In the example (Figure 3), the patient actor effect is the impact of the patient’s explanatory variable on his/her own outcome variable, whilst the patient partner effect is the impact of the patient’s explanatory variable on his/hers spouse’s outcome variable, e.g., HRQoL. Likewise, the spouse’s actor effect refers to the impact of the spouse’s explanatory variable on his/hers outcome variable, whilst the spouse’s partner effect refers to the impact of the spouse’s explanatory variable on the patient’s outcome variable. For this thesis, (study IV) structural equation modelling (path analyses) was used to estimate actor and partner effects. In total, four different models were conducted using perceived control or type D personality as the explanatory variable and EQ index or EQ VAS as the outcome variable. Perceived control was used as a continuous variable while type D personality was dichotomized.

The level of statistical significance was set to \( p < 0.05 \) in all studies. All statistical analyses were performed using Stata 12.1 - 14.2 (StataCorp LP, College Station, TX, USA) and Mplus Version 8.2 (Muthén & Muthén, Los Angeles, CA, USA).

**Ethical considerations**

This thesis and the included studies are designed according to and conform with the principles of the Declaration of Helsinki,\(^{11,14}\) e.g., the principles of autonomy and respect for human rights. Studies I, III and IV were approved by the Regional Ethical Review Board in Linköping (No. 2013/70-32, 2011/434-31 and 2103/235-31) and study II was approved by the Regional Ethical Review Board in Gothenburg (No. 406-13).
Since studies I-III were based on registry data or previously collected data, there were no possibilities to influence the data collection for these studies. When designing study IV, potential risks, burdens and benefits for the participants were taken into account, e.g. when designing the questionnaire. It could be experienced as burdensome to answer a questionnaire, especially if you are not feeling well, e.g. suffer from fatigue after a CA event. Therefore, the included questions and measures were chosen with careful consideration with regard to length, difficulty and total number of questions. Also, the baseline questionnaire was sent 6 months after CA not to add burden during the first months of recovery.

Within the SRCPR (studies I and II), all included patients surviving their CA receive an information letter about them being registered, the purpose of the registry, what data is registered and how data is managed, e.g., according to confidentiality, and applicable legislations. The letter also provides information about who is responsible for the registry and contact details in case of questions, or if they would like an excerpt from the registry or withdraw their data. For study II, patients received an invitation to a telephone interview together with a questionnaire. The invitation letter highlighted that participation was voluntary. All data material from the interview was entered online into the registry database.

If the patient chose to participate and completed the registry interview (study II), they were informed of the possibility for them and their relatives to participate in study IV. If they agreed to participate, they received written information and a consent form together with the baseline questionnaire (study IV).

In Study III, all registered adult patients implanted with an ICD in the Swedish ICD and Pacemaker Registry during 2011-2012 were invited by sending them an information letter and a consent form. Only those returning the form received the study questionnaire. All participants (studies III and IV) were informed that they could withdraw participation at any time without any explanation, and that withdrawal would not in any way affect further care. They were also granted full confidentiality. The obtained study material (questionnaires) was coded and kept stored, only available to members of the research team. The code keys were kept separated from the questionnaires.
RESULTS

Characteristics of participants
The majority of those suffering CA in all studies were men (63.3–85.7%), with an overall proportion of 67.7%. Their mean age varied from 65.6 (SD=12.3) to 74.1 (SD=12.6). An overview of participants' characteristics (studies I-IV) is presented in Table 2.

### Table 2. Characteristics of participants (study I-IV)

<table>
<thead>
<tr>
<th></th>
<th>Study I (n=286)</th>
<th>Study II (n=594)</th>
<th>Study III (n=990)</th>
<th>Study IV—Survivors (n=126)</th>
<th>Study IV—Spouses (n=126)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, M (SD)</td>
<td>74.1 (12.6)</td>
<td>68.8 (12.9)</td>
<td>65.6 (12.3)</td>
<td>66.0 (11.2)</td>
<td>64.4 (10.9)</td>
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<tr>
<td>Sex, n (%)</td>
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<tr>
<td>Male</td>
<td>196 (68.5)</td>
<td>276 (45.9)</td>
<td>772 (78.0)</td>
<td>108 (85.7)</td>
<td>19 (15.1)</td>
</tr>
<tr>
<td>Female</td>
<td>90 (31.5)</td>
<td>218 (54.1)</td>
<td>218 (22.0)</td>
<td>18 (14.3)</td>
<td>107 (84.9)</td>
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<tr>
<td>Place of cardiac arrest, n (%)</td>
<td></td>
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<tr>
<td>IHCA</td>
<td>288 (100)</td>
<td>75 (59.5)</td>
<td>75 (59.5)</td>
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<tr>
<td>OHCA</td>
<td>110 (38.5)</td>
<td>51 (40.5)</td>
<td>51 (40.5)</td>
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<tr>
<td>Initial rhythm, n (%)</td>
<td></td>
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<tr>
<td>Shockable (VT/VF)</td>
<td>110 (38.5)</td>
<td>320 (58.9)</td>
<td>990 (100.0)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Non shockable (Asystoli/PEA)</td>
<td>176 (61.5)</td>
<td>274 (41.1)</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Self-rating scales</td>
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<tr>
<td>Perceived control (CAS), Md (Q1-Q3)</td>
<td>-</td>
<td>-</td>
<td>20 (16-23)</td>
<td>21 (16-24)</td>
<td>18 (16-21)</td>
</tr>
<tr>
<td>Type D personality (DS-14), n (%)</td>
<td>-</td>
<td>-</td>
<td>140 (14.5)</td>
<td>16 (12.7)</td>
<td>23 (18.3)</td>
</tr>
</tbody>
</table>

CAS=Control Attitudes Scale for measuring perceived control, DS-14=Instrument for detecting type D personality, IHCA=In-Hospital Cardiac Arrest, OHCA=Out-of-Hospital Cardiac Arrest, PEA=Pulseless Electrical Activity, Type D personality=Combination of negative affectivity and social inhibition (≥10 on both scales), VT=Ventricular Fibrillation, VT=Ventricular Tachycardia

In-hospital cardiac arrest survival with focus on sex
In total, 288 IHCA events were analyzed from a sex perspective (study I). The majority of participants were men (68.5%) and the mean age was 74.1 (SD=12.6) years (Table 2). Women were significantly older than men (M=77.1 years vs. 74.1 years, p<0.006). In addition, women more often suffered a CA without cardiac etiology compared to men (63.8% vs. 51.1%, p<0.043). Men had more often a previous diagnosis of cancer compared to women (13.8% vs. 3.6%, p<0.012). In 53.5% of the cases, the patient survived the resuscitation attempt, 37.4% were discharged alive, and 35.0% were still alive at 30 days post CA (Table 3).
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Table 3. Survival after in-hospital cardiac arrest in relation to sex (study I)

<table>
<thead>
<tr>
<th>Outcome variable (n, %)</th>
<th>All (n=286)</th>
<th>Men (n=196)</th>
<th>Women (n=90)</th>
<th>OR (SE)* †</th>
<th>95% CI for OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival after resuscitation</td>
<td>153 (53.5)</td>
<td>111 (56.6)</td>
<td>42 (46.7)</td>
<td>1.72 (0.64)</td>
<td>0.83-3.55</td>
</tr>
<tr>
<td>Survival at hospital discharge</td>
<td>107 (37.4)</td>
<td>80 (40.8)</td>
<td>27 (30.0)</td>
<td>2.69 (1.26)*</td>
<td>1.08-6.72</td>
</tr>
<tr>
<td>Survival at 30 days post CA</td>
<td>100 (35.0)</td>
<td>74 (37.8)</td>
<td>26 (28.9)</td>
<td>2.11 (0.99)</td>
<td>0.84-5.29</td>
</tr>
</tbody>
</table>

CA=Cardiac Arrest, †Logistic regression analyses
*Odds Ratio for sex (being man) adjusted for age, initial rhythm, time to treatment, witnessed CA, medical treatment, intubation, cardiac etiology, CA daytime

Before adjustment of age, initial rhythm, time to treatment, witnessed CA, medical treatment, intubation, cardiac etiology, CA daytime, sex was not associated with better chance of survival. After adjusting for covariates in the logistic regression model, male sex was significantly associated with better chance of survival at hospital discharge (p<0.05), but not with survival after resuscitation or at 30 days post CA (Table 3).

In addition, having a shockable initial rhythm, suffering a witnessed CA, and not being intubated, were significantly associated with better chance of survival for all survival outcomes. Moreover, younger age, shorter time to treatment and not receiving medical treatment were associated with better chance of survival to hospital discharge and survival to 30 days. No interaction effects for sex and age were found, i.e. the multiplicative interaction term was non-significant for all three survival outcomes.

The proportion of CA with a resuscitation attempt compared to CA without resuscitation was higher among men compared to women (14.8% vs. 6.2%, p<0.001).

Health-related quality of life among cardiac arrest survivors with focus on sex and other related factors

In the period for study II, from August 2013 to December 2015, 594 IHCA survivors (773 eligible, 76.8% response rate) in Sweden completed a PROM registration in the SRCPR. All of them were included in the study. The mean age of the participants was 68.8 (SD=12.9) years and the majority were men (63.3%) (Table 2). Women were significantly older (Md=73 years vs. 69 years, p<0.001), more likely to suffer CA with non-cardiac or unknown etiology (33.5% vs. 17.6%, p<0.001), and were less likely to be found in a shockable initial rhythm (51.5% vs. 63.3%, p=0.007). They also had poorer neurologic outcome according to the CPC Scale at 3–6 months post CA compared to men (p=0.006).

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The median values for EQ VAS and EQ index among survivors were 70 (Q1-Q3=50-80) and 0.78 (Q1-Q3=0.67-0.86) respectively (Table 4). Women reported significantly more problems than men in all EQ-5D-5L dimensions except for self-care, i.e. mobility (p=0.004), usual activities (p<0.001), pain/discomfort (p<0.001), and anxiety/depression (p<0.001). Based on the HADS, a minority of the survivors reported symptoms of anxiety (≥8, n=87, 14.6%) and/or depression (≥8, n=77, 13.0%).

Sex (female sex) was significantly associated with worse HRQoL (measured by EQ-5D-5L and HADS) in the unadjusted regression models. The associations remained after adjusting for age (Table 4). Older age was significantly associated with worse (EQ VAS) or better (HADS Anxiety) HRQoL, depending on outcome. No interaction effects were found for any of the outcome variables when the multiplicative interaction term for sex and age was included. The adjusted regression models in Study II explained 2-6% of the total variance in HRQoL (Table 5).

Table 4. Health-related quality of life among participants in relation to sex (study II-IV)

<table>
<thead>
<tr>
<th>IHCA survivors (study II)</th>
<th>All patients</th>
<th>Men</th>
<th>Women</th>
<th>B (SE)</th>
<th>95% CI for B</th>
</tr>
</thead>
<tbody>
<tr>
<td>EQ VAS, Md (Q1-Q3)</td>
<td>70 (50-80)</td>
<td>75 (55-80)</td>
<td>65 (50-80)</td>
<td>-5.58 (1.78) **</td>
<td>-9.03 to -2.13</td>
</tr>
<tr>
<td>EQ index</td>
<td>0.78 (0.67-0.86)</td>
<td>0.79 (0.69-0.87)</td>
<td>0.75 (0.61-0.81)</td>
<td>-0.08 (0.02) ***</td>
<td>-0.11 to -0.04</td>
</tr>
<tr>
<td>HADS Anxiety</td>
<td>2 (0-5)</td>
<td>2 (0-5)</td>
<td>3 (1-6)</td>
<td>1.21 (0.32) ***</td>
<td>0.59 to 1.84</td>
</tr>
<tr>
<td>HADS Depression</td>
<td>2 (1-5)</td>
<td>2 (1-4)</td>
<td>3 (1-6)</td>
<td>0.77 (0.30) **</td>
<td>0.16 to 1.38</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CA survivors with an ICD (study II)</th>
<th>All patients</th>
<th>Men</th>
<th>Women</th>
<th>B (SE)</th>
<th>95% CI for B</th>
</tr>
</thead>
<tbody>
<tr>
<td>EQ VAS, Md (Q1-Q3)</td>
<td>80 (69-90)</td>
<td>79 (69-89)</td>
<td>80 (70-90)</td>
<td>1.13 (1.32)†</td>
<td>0.55 to 2.74</td>
</tr>
<tr>
<td>EQ index</td>
<td>0.85 (0.79-1.00)</td>
<td>0.85 (0.73-1.00)</td>
<td>0.85 (0.75-1.00)</td>
<td>0.06 (0.02)</td>
<td></td>
</tr>
<tr>
<td>HADS Anxiety</td>
<td>3 (1-6)</td>
<td>2 (1-5)</td>
<td>4 (1-6)</td>
<td>-0.14 (0.19)†</td>
<td>0.09 to 1.01</td>
</tr>
<tr>
<td>HADS Depression</td>
<td>2 (1-4)</td>
<td>3 (1-6)</td>
<td>1.5 (1-4)</td>
<td>-0.23 (0.23)†</td>
<td>-0.53 to 0.24</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IHCA &amp; OHCA survivors (study IV)</th>
<th>All patients</th>
<th>Men</th>
<th>Women</th>
<th>B (SE)</th>
<th>95% CI for B</th>
</tr>
</thead>
<tbody>
<tr>
<td>EQ VAS, Md (Q1-Q3)</td>
<td>80 (70-85)</td>
<td>80 (70-89)</td>
<td>75 (60-80)</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>EQ index</td>
<td>0.80 (0.74-1.00)</td>
<td>0.80 (0.70-1.00)</td>
<td>0.74 (0.69-0.80)</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Spouses of CA survivors (study IV)</th>
<th>All patients</th>
<th>Men</th>
<th>Women</th>
<th>B (SE)</th>
<th>95% CI for B</th>
</tr>
</thead>
<tbody>
<tr>
<td>EQ VAS, Md (Q1-Q3)</td>
<td>80 (70-90)</td>
<td>80 (70-90)</td>
<td>80 (75-90)</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>EQ index</td>
<td>0.79 (0.76-0.86)</td>
<td>0.79 (0.78-1.00)</td>
<td>0.79 (0.76-0.86)</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>

*HRQoL measured by EQ-5D-5L in study II & study IV, EQ-5D-3L in study III and HADS in study II & III
EQ VAS=EuroQol Visual Analogue Scale, HADS=Hospital Anxiety and Depression Scale, ICD=Implantable Cardioverter Defibrillator, IHCA=In-Hospital Cardiac Arrest, OHCA=Out-of-Hospital Cardiac Arrest, n/a=not applicable
Linear regression analyses
Beta value for sex (being woman) adjusted for age, *Beta value for sex (being woman) adjusted for age, education, employment, cohabiting, time since ICD-implant, sum of comorbidities, received ICD-shocks, ICD-related concerns, perceived control and type D personality
*p<0.05, **p<0.01, ***p<0.001
In the CA survivors implanted with an ICD (n=990, study III), 22% were women. The mean age of the participants was 65.6 years (SD=12.2), the majority were retired (n=689, 68.3%) and lived with someone else (n=798, 90.9%). The time since they received their ICD was in mean 5.7 (SD=4.1) years and a minority (n=392, 40.2%) had experienced an ICD shock. A type D personality was detected in 14.5% (n=140). Women were significantly younger (p<0.001) and more likely to be working outside the home (p<0.001). Their time since ICD-implantation was longer (p<0.001), they reported fewer comorbidities (p=0.009), more ICD-related concerns (p=0.032), and less perceived control (p=0.015) compared to men.

No significant differences in sex or age were detected when comparing the CA survivors to the general population, matched for age and sex. However, there were significantly more CA survivors with a university degree (22.4% vs. 28.1%, p=0.008) and significantly fewer with an employment outside home (40.9% vs. 25.6%, p<0.001) compared to the general population. In total, the median values for EQ VAS and EQ index were 80 (Q1-Q3=69-90) and 0.85 (Q1-Q3=0.73-1.00) respectively. In relation to time since ICD-implantation, no significant differences in HRQoL (EQ-5D-3L) were found. A minority of the participants reported symptoms of anxiety (≥8, n=149, 15.5%) and/or depression (≥8, n=72, 7.4%) in study III.

Table 5. Factors associated with health-related quality of life (study II-III)

<table>
<thead>
<tr>
<th>Outcome variable (HRQoL)</th>
<th>Factors independently associated with worse HRQoL in the final regression models</th>
<th>R²-values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IHCA survivors (study II)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EQ index (EQ-5D-5L)</td>
<td>being woman***, older age*</td>
<td>0.03</td>
</tr>
<tr>
<td>EQ VAS</td>
<td>being woman**, younger age***</td>
<td>0.06</td>
</tr>
<tr>
<td>HADS Anxiety</td>
<td>being woman***, younger age**</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>CA survivors with an ICD (study III)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EQ index (EQ-5D-3L)</td>
<td>being woman***, unemployment***, suffering more comorbidity***, suffering more ICD-related concerns*, perceiving a lower level of control***, having a type D personality***</td>
<td>0.27</td>
</tr>
<tr>
<td>EQ VAS</td>
<td>unemployment***, suffering more comorbidity***, suffering more ICD-related concerns*, perceiving a lower level of control***, having a type D personality***</td>
<td>0.30</td>
</tr>
<tr>
<td>HADS Anxiety</td>
<td>being woman*, unemployment***, suffering more comorbidity***, suffering more ICD-related concerns*, perceiving a lower level of control***, having a type D personality***</td>
<td>0.54</td>
</tr>
<tr>
<td>HADS Depression</td>
<td>being woman*, unemployment***, suffering more comorbidity***, suffering more ICD-related concerns*, perceiving a lower level of control***, having a type D personality***</td>
<td>0.34</td>
</tr>
</tbody>
</table>

CA=Cardiac Arrest, EQ VAS=EuroQol Visual Analogue Scale, HADS=Hospital Anxiety and Depression Scale, HRQoL=Health-Related Quality of Life, ICD=Implantable Cardioverter Defibrillator, IHCA=In-Hospital Cardiac Arrest, R²-values=variance in the outcome explained by the model

*Linear regression analyses
**Tested variables age and sex; *Tested variables sex, age, education, employment, cohabiting, time since ICD-implant, sum of comorbidities, received ICD-shocks, ICD-related concerns, perceived control and type D personality

*p<0.05, **p<0.01, ***p<0.001
In the unadjusted univariate regression models sex, age, education, cohabitation, employment, comorbidity, ICD-related concerns, receiving ICD-shocks, perceived control, and type D personality were significantly associated with HRQoL measured by the EQ-5D-3L (EQ index and EQ VAS) and/or the HADS (Anxiety and Depression). In the adjusted multiple regression models for EQ index and EQ VAS, unemployment, suffering more comorbidity, suffering more ICD-related concerns, perceiving a lower level of control, and having a type D personality were independently associated with worse HRQoL. Sex (female sex) was independently associated with EQ index but not with EQ VAS (Table 4). The final models explained 27% of the variance in EQ index and 30% in EQ VAS (Table 5).

In the adjusted regression models for HADS Anxiety and HADS Depression, unemployment, suffering more comorbidity, suffering more ICD-related concerns, perceiving a lower level of control and having a type D personality were independently associated both with more symptoms of anxiety and depression (worse psychological HRQoL). In addition, sex (female sex) was independently associated with more symptoms of anxiety, but not depression (Table 4). The final models explained 44% of the variance in HADS Anxiety and 34% in HADS Depression (Table 5).

Compared with the general population (using the EQ-5D-3L) the CA survivors implanted with an ICD reported significantly better HRQoL, measured by EQ index (Md=0.85, Q1-Q3=0.73-1.00 vs. Md=0.80, Q1-Q3=0.73-1.00, p<0.001) and fewer problems in the dimension pain/discomfort (Md=1, Q1-Q3=1-2 vs. Md=2, Q1-Q3=1-2, p<0.001). In contrast, the CA survivors reported significantly more problems in the dimensions mobility (Md=1, Q1-Q3=1-2 vs. Md=1, Q1-Q3=1-2, p=0.002) and usual activities (Md=1, Q1-Q3=1-1 vs. Md=1, Q1-Q3=1-1, p<0.001). There were no differences detected for the dimensions self-care or anxiety/depression.

In study IV, 126 survivor-spouse dyads were included. The mean age for CA survivors and their spouses was 66.0 (SD=11.2) and 64.4 (SD=10.9) respectively. In the majority of the dyads the survivors were men and the spouses were women (n=107, 84.9%). The spouses reported significantly lower levels of perceived control (p=0.001) and more negative affectivity compared to the survivors (p=0.007). No significant differences between spouses and survivors were detected for social inhibition, type D personality and HRQoL (measured by EQ index and EQ VAS). The median values for EQ index and EQ VAS among all participants was 0.79 (Q1-Q3=0.75-0.87) and 80 (Q1-Q3=70-90) respectively.
In the APIM, significant actor effects for perceived control on HRQoL among survivors were detected. More perceived control was associated with better HRQoL (EQ VAS, $\beta=0.53$, $p<0.001$ and EQ index, $\beta=0.48$, $p<0.001$). In contrast, no significant actor effects were found for perceived control on HRQoL in spouses. A significant positive partner effect for perceived control among survivors on their spouses’ HRQoL was detected for EQ VAS, i.e., more perceived control in the survivor was associated with better HRQoL in the spouse ($\beta=0.20$, $p<0.05$), but not for EQ index. No significant partner effects for perceived control in spouses were displayed. More details of the APIM are presented in Figure 4a and Figure 4b.

Figure 4a and 4b. Actor partner Interdependence model with perceived control (CAS) as explanatory variable and EQ VAS or EQ index as outcome variable. $E_1$=measurement error for survivor, $E_2$=measurement error for spouse, ns=non-significant, *$p<0.05$, **$p<0.01$, ***$p<0.001$
Significant actor effects for type D personality on HRQoL were detected for the survivors (EQ VAS, $\beta=-0.36$, $p<0.001$ & EQ index, $\beta=-0.34$, $p<0.001$) and the spouses (EQ VAS, $\beta=-0.18$, $p<0.05$). For both groups, having a type D personality was associated with worse HRQoL. In addition, a significant negative partner effect for type D personality in survivors on their spouses’ HRQoL was detected (EQ VAS, $\beta=-0.24$, $p<0.01$), i.e. type D personality in the survivor was associated with poorer HRQoL in the spouse. No significant partner effects for type D personality in spouses were displayed. More details are presented in Figure 5a and Figure 5b.

Figure 5a and 5b. Actor partner Interdependence model with type D personality as explanatory variable and EQ VAS or EQ index as outcome variable. E1=measurement error for survivor, E2=measurement error for spouse, ns=non-significant, $^*p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$
DISCUSSION

The overall aim of this thesis was to increase the knowledge of survival and HRQoL among people suffering CA with focus on sex and other related factors. In summary, the major findings are: 1) survival to hospital discharge, but not after resuscitation or at 30 days, was better among men compared to women, 2) more men than women received a resuscitation attempt when suffering an IHCA, 3) using self-reported outcome measures, HRQoL among most CA survivors appears to be good even when compared to a general population, 4) women reported worse HRQoL compared to men, and female sex was independently associated with poorer HRQoL in the multiple regression models, 5) older/younger age (depending on outcome), being unemployed, suffering more comorbidities, perceiving less control, having a type D personality and suffering from more ICD-related concerns were identified to be associated with poorer HRQoL, and 6) perceived control and type D personality among the survivors were associated with HRQoL among their spouses, but not vice versa.

In-hospital cardiac arrest survival with focus on sex

Male sex was associated with an increased chance of survival to hospital discharge in the final regression model. However, no associations were identified between sex and survival after resuscitation attempt or at 30 days post arrest. Therefore, sex does not appear to be an important predictor for survival among patients receiving in-hospital resuscitation. However, the results are in contrast to other Swedish studies reporting an advantage in survival for women suffering IHCA. Moreover, a systematic review found that women had an increased chance of survival when adjusting for clinically important differences, e.g. initial rhythm. The explanation for these differences are not obvious. One possible reason is that the data in study I was from a single hospital, and may differ compared to other Swedish hospitals. In larger studies where sex is associated with survival, such findings might lack clinical relevance despite statistical significance. An extensive American study found “being woman of child-bearing age” to be a positive predictor for survival. In the above study, no differences in survival were identified between older men and women. In addition, all patients from 44-56 years were excluded. Therefore the results are difficult to compare to study I, since almost all women in study I were above child-bearing age.
The proportion of IHCAs with a resuscitation attempt compared to IHCAs without resuscitation was higher among men. In CA research in general, the majority of included patients, i.e. patients receiving resuscitation efforts when suffering CA, are men. However, only a few studies have compared those not receiving treatment. The results correspond with results from Herlitz et al. In their study, resuscitation attempts were started significantly more often in men (14%) compared to women (11%). No significant differences between men and women in an evaluation of the justification to start resuscitation were detected. However, no evaluation of those not receiving resuscitation was performed. In study I, the women receiving resuscitation were older than the men and less likely to have a CA with cardiac etiology, which might explain some of the differences. A study by Becerra et al. did not find any differences when comparing men and women with regard to do-not-attempt-resuscitation decisions. However, they reported relatives to be frequently involved and important in making such decisions. Since women in general live longer compared to men, they are more likely to be alone when becoming seriously ill and admitted to hospital. It is possible that the absence of a spouse could influence therapy wishes and do-not-attempt-resuscitation decisions, resulting in fewer women receiving resuscitation. According to the results in study I, one could pose the question as to whether women are under treated and/or men are over treated, which in turn might indicate that women receiving treatment is a more selective group with higher chances of survival. Since no data was available regarding e.g., age and etiology among those not receiving resuscitation, the results should be interpreted with caution. However, the potential sex differences and equity in treatment of CA should be further investigated.

Health-related quality of life among cardiac arrest survivors with focus on sex and other related factors

This thesis includes two of the largest studies so far exploring HRQoL in CA populations. Overall, regardless of study population, i.e. IHCA survivors, OHCA survivors, CA survivors implanted with an ICD, and spouses of CA survivors, HRQoL among the majority appears to be good, and is comparable to Swedish general population data, patients suffering CAD, patients implanted with an ICD, and to previous population-based CA studies. Suffering a CA is hypothetically more likely to impact HRQoL compared to suffering other diseases and conditions, due to its existence-threatening nature and possible emotional and cognitive consequences. However, the results indicate that most CA survivors are doing well according to the measures of HRQoL applied in this thesis. CA survivors might be grateful for having “a second chance at life” and perhaps
therefore value their life differently compared to others. However, although the majority reported good overall HRQoL and few/minor health-problems in studies II-IV, the variation was great and a significant proportion of the participants reported poor HRQoL, e.g. 25% of the participants in study II reported an EQ VAS score of 50 or lower. These patients might gain from targeted health-related support, e.g. counselling, cognitive training and learning adjustment strategies, and regular specialized follow-up.

The IHCA survivors in study II rated their HRQoL, measured by EQ VAS, lower compared to the participants in study III and IV. This indicates that IHCA survivors might differ in characteristics and outcomes from OHCA populations. Compared to the CA survivors in study III, and to other studies exploring HRQoL in large OHCA populations, e.g. two Australian studies,\(^{50, 52}\) EQ VAS was lower among our IHCA participants. These differences might be explained by timing of measurements, differences in culture or post CA care. However, since a preliminary report from the SRCPR displays EQ VAS ratings among Swedish OHCA survivors similar to those reported in the Australian studies, it is more likely that differences are due to characteristics, e.g. higher age and more comorbidity among IHCA survivors.\(^3\) Study III is the first to report better HRQoL, measured by EQ index, compared to the general population. This result might be due to them being a selective group of survivors, receiving active surgical treatment and being invited to regular hospital follow-up by specialized healthcare providers. The ICD itself might also contribute to more perceived control and better HRQoL. However, also in this study, a significant proportion suffers from various health-problems (e.g. >15% suffer from anxiety according to the HADS), which might affect the recovery after CA.

In general, women reported worse HRQoL compared to men (studies II and III) irrespective of outcome (EQ-5D or HADS). Female sex was also independently associated with poorer outcome in most of the adjusted regression models. This corresponds to other studies on OHCA survivors\(^{44, 50, 52}\) and general populations.\(^119\) One possible explanation could be that women may experience worse health due to more responsibility in family- and other social activities. In addition, since women in general live longer than men, they are more likely to live alone when suffering a CA, and therefore at higher risk of experiencing loneliness and not having family support.\(^122\) Health-problems in the dimensions anxiety/depression, mobility and usual activities may partly be explained by the consequences of being alone, e.g. due to dependency on others to participate in social activities. Experiencing loneliness has also been more commonly reported
Health-related quality of life after cardiac arrest among women in general Swedish populations. However, although "being cohabitant" showed some significantly univariate associations with better HRQoL in study III, this was not an independently significant factor for better HRQoL in any of the adjusted regression models. This is in contrast to the study by Verberne et al. where “not having a partner” was independently associated with worse HRQoL. Although significant associations between sex and HRQoL were identified, the effect size in terms of explained variance ($R^2$) was small, indicating other factors being of more importance for explaining the variance in HRQoL.

In addition to sex, several factors independently associated with HRQoL were identified in studies II and III. Age was independently associated with HRQoL in study II. Older age was associated with worse general health status (EQ VAS), while younger age was associated with more symptoms of anxiety (HADS). Similar results have been reported in patients with CAD. Older people are more likely to suffer from comorbidities and physical limitations. In contrast, they might be less anxious compared to younger people, since their adjustments in daily life after suffering a CA are fewer.

Only a few studies have investigated factors associated with HRQoL in CA survivors, identifying factors like e.g. sex, age and unemployment which corresponds to the results in this thesis. However, this thesis contributes by identifying factors previously not investigated in CA populations. Unemployment, having more ICD-related concerns, perceiving less control, having a type D personality, and suffering more comorbidity were significantly associated with worse HRQoL in all four final multiple regression models in study III. These models explained between 27-54% of the variance in the outcome, indicating that the included explanatory variables are important for HRQoL in CA survivors implanted with an ICD and might therefore be used in follow-up screening and post CA care. A review on factors associated with HRQoL in CAD patients concluded that psychosocial factors are important, especially those possible to adjust. Some of the identified factors are probably not modifiable, but can be used to identify those at risk of suffering lower HRQoL. However, it might be possible to promote e.g. the sense of control and self-efficacy by offering person-centered care, based on the patient’s narrative and individual health goals. In addition, regular hospital visits to specialized healthcare professionals, stress reductive therapy and CPR training might be helpful to perceive more control and improve HRQoL for all CA survivors.
In study IV, type D personality and perceived control displayed significant actor effects with HRQoL among survivors. Type D personality also displayed a significant actor effect for spouses’ HRQoL. Moreover, type D personality and perceived control among survivors were associated with HRQoL in their spouses, i.e. significant partner effects were found.

The results regarding actor effects in survivors correspond to study III, where associations with HRQoL were identified for both type D personality and perceived control. Study IV contributes by suggesting that these results are transferable to CA survivors in general, not only those treated with an ICD. No other CA studies have investigated these aspects, but similar associations have been identified in CAD patients.

The results from study IV are in contrast to other dyadic studies in cardiovascular populations, where partner effects of spouses’ characteristics on patients’ HRQoL are more commonly reported. The results indicate that spouses appear to be sensitive to characteristics of their partners (the survivors), but not vice versa. When much initial focus after suffering CA probably is put on the survivors, their spouses might consider it necessary to conceal their own problems and needs. Since survivors might suffer from cognitive problems they might not be sensitive to reactions in their spouses. The differences could also be a consequence of the measures used in clinical studies being more suitable for patients.

Cardiac rehabilitation, including stress management and social interactions, has been reported to reduce type D characteristics and improve HRQoL in patients suffering from CAD. Psychosocial risk factors (e.g. type D personality) are also reported to obstruct the effects of rehabilitation and secondary prevention when suffering CAD. In CAD patients, more perceived control is also associated with fewer cardiac complications. In addition, CPR training increased the level of perceived control in spouses of CA survivors. Efforts to increase a sense of control might therefore be an important target for supporting HRQoL in both CA survivors and spouses. A systematic review concluded that dyadic psychological interventions had positive effects in CAD patients and their spouses. Such interventions contributed to better HRQoL and lower blood pressure among patients, and reduced psychological distress among their spouses. The results from study IV indicate that including spouses in post CA care is important, especially in survivors with type D personality, perceiving low levels of control.
Applying Wilson and Cleary’s conceptual model
Clinical variables, both explanatory and outcome, can be linked and their relationships discussed according to Wilson and Cleary’s conceptual model of HRQoL. The survival outcomes used in this thesis provides a natural and obvious biological basis for HRQoL, as the first of the model’s main components (biological variables). Comorbidity is also applicable as a biological explanatory variable. In the second main component (symptom status), study variables measuring symptoms of anxiety and depression (HADS) and ICD-related concerns might be located, while the third main component (functional status) might include CPC-score (observer reported outcome), employment, and problems reported in the health dimensions included in the EQ-5D (patient reported outcome). Further, for the fourth main component (general health perceptions), the measures of self-perceived general health status, i.e. the EQ index and the EQ VAS are applicable. In this thesis, no measures were used to assess the overall QoL (the fifth main component), including e.g., QoL related to happiness or life satisfaction. In order to include characteristics of the individual, the explanatory variables sex, age, type D personality, perceived control, and education were applied, while cohabitation and characteristics (type D personality and perceived control) of the spouse were included as explanatory variables to assess characteristics of the environment (Figure 6).

Figure 6. Linking clinical variables with health-related quality of life: a conceptual model of patient outcomes (including identified associations in this thesis, displayed as golden arrows), IB Wilson and PD Cleary, JAMA, 1995, revised by C Ferrans et al., Journal of Nursing Scholarship, 2005. Copyright by JAMA. Used with permission.
The biological variable comorbidity was associated with symptom status measured by HADS and the general health perceptions measured by EQ index and EQ VAS, indicating that biological variables are significant for predicting aspects of HRQoL in CA populations, which is also suggested in the original model. Symptom status measured by ICD-related concerns was associated with other psychological symptoms measured by the HADS. However, ICD-related concerns were also associated with general health perceptions (EQ index and EQ VAS). Functional status measured by employment status was also associated with general health perceptions.

Associations were also identified for characteristics of the individual (age, sex, type D personality, and perceived control) with both symptom status and general health perceptions. These associations were also described in the original model. In contrast, characteristics of the environment measured by type D personality and perceived control in spouses, were not associated with any of the outcomes in the CA survivors. Characteristics of the environment (spouses) might not be that important for HRQoL in survivors at 6 months post CA (because of reasons already discussed). It is possible that such characteristics are more important for survivors living without a spouse, or that other environmental factors are of greater significance compared to those included in this thesis. A systematic review by Ojelabi et al., investigating the empirical evidence supporting the use of Wilson and Cleary’s model in chronic diseases, found the model to be suitable for evaluating HRQoL in e.g. patients with CAD and heart failure. In general, symptom status was considered having most impact on overall QoL. However, environmental factors were not evaluated in their review. More studies are needed to investigate the effects of environmental factors on HRQoL in general and in CA survivors in particular. Another systematic review of various HRQoL models by Bakas et al. reported Wilson and Cleary’s model to be adequate and useful for research and clinical purposes regardless of population.

In general, the model appears to be applicable for studying CA survivors and their spouses. Most of the features of the original model were supported by the results in this thesis, and most of the explanatory variables were significantly associated with the outcomes explaining considerable proportions of the variance. However, more research is needed to cover all parts of the model, e.g. by further studying characteristics of the individual and the environment and overall QoL. In addition, casual, mediation and moderation effects of different parts of the model are unknown, and should be further investigated in CA survivors. However, Wilson and Cleary’s model might guide CA researchers when choosing outcomes and designing health-supportive interventions. A study
evaluating the model in CAD patients found anxiety and depressive symptoms to have most impact on HRQoL, and the authors recommend including psychological aspect in clinical practice. Such recommendation is in agreement with the guidelines for post CA follow-care.

According to the philosophical foundations behind person-centered care (PCC), human identity is created by the narrative, and developed in the relationship to ourselves, to others and to society. Therefore, humans should be understood from individual, interpersonal and structural societal perspectives. Knowledge and research should be built on the meeting between objective and subjective measures, implying a dialectical and multidimensional understanding of HRQoL e.g., by using conceptual models like the one created by Wilson and Cleary.

**Methodological considerations**

This thesis is based on four studies using a quantitative approach to increase the knowledge of survival and HRQoL among people suffering CA with focus on sex and other related factors. Quantitative methods are suitable for describing and investigating characteristics and outcomes in a large number of participants, allowing to generalize findings to similar populations. They include statistical analysis of data, allowing e.g. between-group comparisons and investigating associations between study variables. Data from various CA populations and well-established statistical methods were used in order to strengthen the results. The cross-sectional design of this thesis does not allow any casual conclusions. However, it adds new knowledge and provides an important starting point for further research, e.g. prospective designs and intervention development. To combine the methodology with a more qualitative approach would probably have been beneficial to collect more detailed information, and increase the in-depth understanding of life after CA for survivors and their spouses.

Quantitative measures should be valid and reliable, i.e. they should be characterized by having good measurement properties. An instrument with good validity measures what it is supposed to measure (e.g. HRQoL) while reliability refers to the consistency of its measurements, i.e. how well it measures. The EQ-5D and the HADS have not been psychometrically evaluated in CA populations, but are commonly used instruments, well validated in several other populations. The outcomes were chosen with regard to Wilson and Cleary’s conceptual model for HRQoL. The choice of outcomes is also supported by the COSCA guidelines for
reporting CA research and the European guidelines for resuscitation. In this thesis, focusing on life after CA, a more long-term follow-up of survival would have been a desirable supplement.

The EQ-5D and the HADS are generic measures, not previously validated in CA populations. The EQ-5D could be criticized for reporting only a few dimensions of HRQoL. However, its simplicity makes EQ-5D suitable for registries and registry studies. In addition, it allows for comparisons with other groups of patients and with general populations. The EQ-5D-3L version has been reported to have acceptable validity and reliability in cardiac patients and has also previously been used in CA populations. However, problems with responsiveness and ceiling effects have been reported. The new 5-level version used in studies II and IV has shown improved psychometric properties compared to the 3-level version, and has potential to constitute a more sensitive and responsive measure. The use of the EQ index may also be discussed. Since it is weighted, based on preferences of the general population, one can argue that it does not constitute a PROM, and should be used for economical calculations. Another limitation is that EQ-5D has no recommended cut-off for what is a good (or bad) HRQoL, making it difficult to interpret results. In a Swedish study, using the EQ-5D to compare HRQoL in homeless people to the general population, the general population data was similar to the results in this thesis. When their participants answered an additional five-level (very good, good, fair, poor, and very poor) question of self-reported health, merely a quarter of the general population considered their health as worse than good. Therefore, in this thesis, HRQoL among survivors was considered as good if it was approximately similar compared to the general population.

In addition, the most appropriate cut-off for HADS is debated. The HADS is a well-validated, widely used screening instrument for psychological distress. However, both EQ-5D and HADS are not validated in CA survivors or their spouses and could be criticized for having unknown capacity to detect truly relevant aspects of HRQoL in these populations. Hence, there is a need for condition-specific measures in order to better evaluate health-promoting interventions and improve care. Although subjective self-reported measures of HRQoL are likely to be affected by daily stressors, they provide important knowledge from the perspective of patients and their spouses.

In study I, registry data from a single hospital was used. A strength is that the sample includes all patients suffering CA at the hospital during the
study period. The sample size might be considered small as logistic regression requires large samples, often 500 observations or larger.\textsuperscript{142} However, the sample size was considered sufficient, at least to identify medium to large effects,\textsuperscript{142} as 15 to 20 observations were provided for each explanatory variable.\textsuperscript{143} Studies II and III are based on nationwide data with large numbers of participants and their sample size are sufficient to detect a medium effect based on the following parameters: $f^2=0.15$, $\alpha=0.05$, $1-\beta=0.95$. The sample size in study IV could also be considered small. Since study IV was a part of a larger longitudinal study, no a priori power analysis was conducted. However, since the APIM is a simple model that includes only one explanatory variable, the sample size were considered sufficient.\textsuperscript{112} In summary, the sample size in studies II and III are sufficient, while sample size could be considered a limitation in studies I and IV. A small sample size increases the risk of making a type II error (“false negative”) and not detecting small effects.

Insufficient sample size might constitute a threat against external validity. However, more important is whether the sample is representative for the population. Since the hospital data (study I) regarding e.g. treatment and survival did not differ from nationwide data, the results could probably be generalized to other hospitals with similar size and organization. The number of non-participants in studies II and III is a potential limitation with regard to external validity. Also, the reasons for some survivors declining participation are unknown. However, a fairly large proportion of non-responders may not necessarily imply problems with external validity if they have similar characteristics as respondents. In study II, no differences in age or sex between participants and non-participants were detected. In contrast, since there was difference in CPC score between participants and non-participants, the findings may not be generalized to the survivors with the poorest cognitive outcome. This is a known problem also reported and discussed in previous CA studies.\textsuperscript{49, 50} One way of solving this problem had been to allow proxy ratings of HRQoL or visiting patients at home. In CA research, difficulties in including those with the poorest functional outcome might lead to overestimation of HRQoL in both survivors and spouses.

For the additional analysis in study I, regarding patients suffering CAs with no resuscitation attempt, no data for a longer time period than two years was accessible. Nor could this variable be controlled for age, which definitively is a limitations. More research is needed to investigate the equity in care, e.g. by examining the characteristics among patients not receiving resuscitation from a sex perspective.
A variety of statistical analyses were applied. They were chosen depending on specific aims and properties (level and distribution) of data. Since data in general was categorical (nominal or ordinal), or not normally distributed, non-parametric statistics were used for most analyses. However, the linear regression models used in studies II and III, and the structural equation modelling in study IV are based on parametric statistics. In these studies, ordinal self-reported outcomes (EQ-5D and HADS) are used. This choice might be criticized. An alternative would have been to dichotomize the outcomes and instead use logistic regression models. However, there is no established cut-off for the EQ-5D and the best cut-off for HADS are debated. Moreover, those participants rating their HRQoL close to the cut-off would have been at risk of being incorrectly evaluated.

Clinical implications

Much knowledge has previously been gathered about CA survival and predictors associated with survival outcomes. However, the influence of sex on survival is repeatedly debated. This thesis contributes to this discussion. Sex does not appear to be an important predictor for survival after suffering an IHCA among those receiving resuscitation. Therefore, the patient’s sex should not influence CA treatment (e.g. duration of resuscitation) or do-not-attempt-resuscitation decisions. However, the difference between men and women with regard to proportion of receiving resuscitation efforts needs to be much further elaborated, in order to ensure equity in care.

In contrast to survival, little is known about life after CA for survivors and their spouses. This thesis contributes with new knowledge about their HRQoL in general, and associated factors in particular. HRQoL among survivors is generally good. Therefore, fear of low HRQoL in survivors should not influence do-not-attempt-resuscitation orders or other treatment decisions. However, the great variation among survivors is important knowledge for clinical care. Poor self-reported HRQoL is associated with increased risk of both morbidity and mortality, which suggests an importance of employing such measures in post CA follow-up to find those in need of support. Identifying predictors for HRQoL is important to improve follow-up care. Several of the factors identified to be independently associated with HRQoL might be used in clinical care in order to screen for those at risk of suffering health problems. For example, since female CA survivors in general suffer from poorer HRQoL compared to men, special attention should probably be given to their health problems during post CA follow-up. However, there are other factors contributing to explaining the variation in HRQoL, of which some were independently associated with the outcome in most of the final multivariate regression
models, e.g. comorbidity, personality and perceived control. These factors are therefore potentially more important to consider in clinical care. Moreover, both EQ-5D and HADS appear to be applicable as follow-up outcome measures for CA survivors and their spouses during post CA care.

The results in this thesis suggest the importance of a structured and individualized post CA care where spouses are included. However, post CA care appears to be inequitable in terms of hospital differences, and mainly focused on cardiovascular problems. In addition, spouses are not always invited to participate. In current guidelines for CA, nurses are important in coordinating the follow-up care for patients and their relatives. According to the Swedish Society of Nursing, PCC is considered to be one of six core competencies in nursing. Since PCC aims at acknowledge the patient’s narrative, including experiences of suffering CA in order to identify and support individual health-related goals in partnership with patients and relatives, it promotes a holistic and individualized approach to CA survivors, their HRQoL and need of support. Therefore, equity in healthcare (e.g. between men and women) can be increased by implementing PCC. In previous studies, PCC is reported to increase self-efficacy to control cardiac symptoms and to improve experiences of care, e.g. regarding information and family involvement, in patients with CAD. Therefore, implementation of PCC is potentially helpful also in post CA care. Applying a person-centered approach to post CA care would probably be more inclusive to aspects important to the afflicted patients themselves, and might help to achieve equitable care.

**Further research**

- Investigating equity (e.g. between men and women) in CA treatment, especially with regard to those not receiving resuscitation
- Further investigating factors (pre-, intra-, and post CA) associated with HRQoL in CA populations, e.g. by using additional variables included in the conceptual model by Wilson and Cleary and by investigating casual associations
- Investigating longitudinal variations and explanatory variables for HRQoL
- Exploring experiences of life after CA among survivors and relatives by using qualitative designs
- Developing psychosocial interventions in order to improve HRQoL
- Validation of recommended PROMs for CA, e.g. EQ-5D-5L and HADS
- Developing condition-/disease specific PROMs for CA
CONCLUSIONS

The overall aim with this thesis was to increase the knowledge of survival and HRQoL among people suffering CA with focus on sex and other related factors. Sex does not appear to be an important factor for survival among patients suffering CA where resuscitation is attempted. The difference between men and women regarding the proportion of resuscitation attempts and equity in care should be further investigated to clarify whether the differences are medically and ethically justifiable, or a sign of inequitable care. Although the majority of survivors and their spouses report HRQoL at similar levels as general populations, a substantial proportion suffer from health problems. Women report worse HRQoL compared to men. Therefore, a higher proportion of women may be in need of support. Several additional factors associated with lower levels of HRQoL, e.g. having a type D personality and perceiving less control, were identified. These factors might be used when screening patients for health problems and when developing health promoting interventions. Healthcare professionals should make efforts to identify survivors at risk of poor HRQoL and offer individualized targeted support when needed. Characteristics among survivors were associated with HRQoL in their spouses, but not vice versa. Including spouses in follow-up care is therefore important. Wilson and Cleary’s conceptual model for HRQoL appears to be applicable for choosing outcomes in CA research and might be helpful when designing interventions to improve post CA care.
SVENSK SAMMANFATTNING

Vad handlar avhandlingen om?
Avhandlingen handlar framförallt om livssituationen hos de personer som drabbats av och överlevt ett plötsligt oväntat hjärtstopp, framförallt utifrån deras hälsorelaterade livskvalitet, men också om könsskillnader och andra faktorer som skulle kunna påverka livskvaliteten.

Varför är detta ämne viktigt att studera?

Vilka frågor ville avhandlingen besvara?

Hur genomfördes studierna?
Avhandlingen bygger på fyra delstudier, som tillsammans bidrar till att besvara syftet och frågorna. Dessa studier bygger på data från nationella

**Vilken kunskap har avhandlingen bidragit med?**


Även om kön inte verkade ha någon avgörande betydelse för chanson att överleva, behöver skillnaderna mellan män och kvinnor när det gäller andelen som får behandling med hjärt-lungräddning undersökas vidare för att säkerställa en jämlik vård. Majoriteten av överlevarna skattar sin hälsorelaterade livskvalitet som god. Däremot är andelen som upplever allvarliga hälsoproblem viktig att uppmärksamma i vården efter hjärtstopp. Eftersom kvinnor skattar lägre livskvalitet än män kan en högre andel kvinnor vara i behov av stödinsatser. De faktorer som visade ett samband med sämre livskvalitet kan användas av vårdpersonalen för att identifiera patienter som är i behov av stöd. Eftersom personer i parrelationer kan påverka varandra är det viktigt att överlevarnas partners involveras i uppföljningen och vården efter hjärtstopp.
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Health-related quality of life after cardiac arrest


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Papers

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