MASTER'S THESIS
Master in Biomedicine

"Anxiety and depression in relation to levels of N-terminal B-type natriuretic peptides in patients treated with implantable cardioverter defibrillators"

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By

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Betina Cecilia Eide Blad

Abstract

Background: Implantable cardioverter defibrillator (ICD) is an effective preventive treatment for ventricular arrhythmias and is recommended in the guidelines for patients at high risk. Higher prevalence of anxiety and depression has been reported in patients treated with ICD, particular after receiving ICD shock. N-terminal pro-B type natriuretic peptide (NT-proBNP) is a widely used diagnostic and prognostic biomarker in heart failure, and NT-proBNP robustly reflects the severity of the disease. The association between the prevalence of anxiety and depression in participants with ICD, when accounting for concentrations of NT-proBNP as a surrogate for disease severity, is not known.

Objective: The main purpose of the current study is to assess the relation between mental distress and disease severity, as indicated by NT-proBNP concentrations, in patients treated with ICD at risk of ventricular arrhythmias.

Method: This is a cross-sectional substudy, where 178 (75%) of the participants from the SMASH-1 study at Akershus University Hospital were included. Blood samples were drawn from the participants, and concentrations of NT-proBNP were analyzed by a commercial immunossay. Each participant completed a questionnaire that consisted of Hospital Anxiety and Depression Scale (HADS) and Florida Shock Anxiety Scale (FSAS), in order assess the prevalence of anxiety and depression.

Results: The mean age was 66.9 years±9.9, and 89% of the participants were men. 18 (10.1%) participants were classified with depression (HADS-D sumscore ≥8), 23 (12.9%) participants with anxiety (HADS-A sumscore ≥8) and 69 (38.8%) participants had shock related anxiety (FSAS sumscore ≥12). Dyspnea (OR 10.8 [95% CI 2.3-50.5] p=0.002) and palpitations (OR 4.5 [95% CI 1.2-16.9] p=0.02) were independently associated with depression while female gender was associated with shock related anxiety (OR 3.8 [95% CI=1.1-13.3] p=0.03). Consentrations of NT-proBNP were not associated with depression, anxiety or shock-related anxiety. Previous shock was not related with the patient related outcomes in the study population.

Conclusion: Dyspnea and palpitations were associated with depression, and female gender was seen as determinant for development of shock related anxiety. Concentrations of NT-proBNP were not associated with mental distress. In addition, no significant association between previous shock and depression, anxiety or shock related anxiety was seen.

Keywords: ICD, CHD, Heart Failure, Anxiety, Depression, Quality of Life, HADS, FSAS

Sammendrag

Bakgrunn: Implanterbar hjertestarter er en effektiv behandling for ventrikulære arytmier. Høyere forekomst av angst og depresjon hos pasienter med implanterbar hjertestarter, spesielt etter å ha fått støt, er tidligere sett. N-terminalt pro-B-type natriuretisk peptid (NT-proBNP) er en mye brukt diagnostisk og prognostisk biomarkør i hjertesvikt, som i tillegg reflekterer sykdommens alvorlighetsgrad. Sammenhengen mellom forekomst av angst og depresjon hos pasienter med implanterbar hjertestarter, hvor NT-proBNP indikerer sykdomsgraden, er ikke kjent.

Formål: Hovedformålet med denne studien er å studere forholdet mellom psykiske lidelser og alvorlighetsgraden ved konsentrasjoner av NT-proBNP, hos pasienter behandlet med implanterbar hjertestarter på grunn av økt risiko for ventrikulære arytmier.

Metode: Denne studien var en tverrsnittsstudie, hvor 178 (75%) av deltakerne fra SMASH-1 studien ved Akershus Universitetssykehus, ble inkludert. Blodprøver ble tatt av deltakerne, og nivåer av NT-proBNP ble analysert ved bruk av et kommersielt immunoassay. Hver deltaker besvarte ett spørreskjema som bestod av Hospital Anxiety and Depression Scale (HADS) and Florida Shock Anxiety Scale (FSAS), for å studere forekomsten depresjon og angst hos studiedeltakerne.

Resultater: Gjennomsnittsalderen til deltakerne var 66,9 år ± 9,9, hvor 89% av deltakerne var menn. 18 (10,1%) deltakere hadde depresjon (HADS-D sumscore ≥8), 23 (12,9%) deltakere hadde angst (HADS-A sumscore ≥8), mens støtrelatert angst (FSAS sumscore ≥12) ble sett hos 69 (38,8%) av deltakerne. Dyspne (OR 10.8 [95% CI 2.3-50.5] p=0.002) og palpitasjoner (OR 4,5 [95% CI 1,2-16,9] p=0,02) var uavhengig forbundet med depresjon mens kvinnelig kjønn var uavhengig assosiert med sjokkrelatert angst (OR 3.8 [95% CI 1,1-13,3] p=0,03). NT-proBNP var ikke forbundet med depresjon, angst eller støtrelatert angst. Tidligere støt var ikke assosiert med de studerte psykologiske lidelsene i studiepopulasjonen.

Konklusjon: Dyspné og palpitasjoner var assosiert med depresjon, og kvinnelig kjønn var assosiert med sjokkrelatert angst. Konsentrasjoner av NT-proBNP var ikke forbundet med depresjon, angst eller støtrelatert angst hos pasienter med implanterbar hjertestarter. I tillegg ble det ikke observert en signifikant sammenheng mellom tidligere støt og depresjon, angst eller støtrelatert angst.

Keywords: Implanterbar hjertestarter, Koronar hjertesykdom, Hjertesvikt, Angst, Depresjon, Livskvalitet, HADS, FSAS

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List of Abbreviations

AF	Atrial Fibrillation
AUH	Akershus University Hospital
ALS	Amyotrophic Lateral Sclerosis
ANP	Atrial Natriuretic Peptide
AV-node	Atrioventricular node
BNP	B-type Natriuretic Peptide
BMI	Body Mass Index
CHD	Coronary Heart Disease
CRF	Case Record Form
AF	Atrial Fibrillation
AUH	Akershus University Hospital
ALS	Amyotrophic Lateral Sclerosis
ANP	Atrial Natriuretic Peptide
AV-node	Atrioventricular node
BNP	B-type Natriuretic Peptide
BMI	Body Mass Index
CHD	Coronary Heart Disease
CRF	Case Record Form
CV	Coefficient of Variation
DCM	Dilated Cardiomyopathy
ECG	Electrocardiography
ELICA	Electrochemiluminescenece Immunoassay
ESC	European Society of Cardiology
FSAS	Florida Shock Anxiety Scale
G	G-force
HADS	Hospital Anxiety and Depression Scale
HCM	Hypertrophic Cardiomyopathy
HF	Heart Failure
HFmrEF	Heart Failure with mid-range Ejection Fraction
HFpEF	Heart Failure with preserved Ejection Fraction
HFrEF	Heart Failure with reduced Ejection Fraction
ICD	Implantable Cardioverter Defibrillator

ID	Identity
IQR	Interquartile Range
K2-EDTA	Dipotassium Ethylenediaminetetraacetic Acid
LDL	Low Density Lipoproteins
LVEF	Left Ventricle Ejection Fraction
NT	Amino terminal
NT-proBNP	N-terminal pro-B type Natriuretic Peptide
NYHA	New York Heart Association functional classification
MI	Myocardial Infarction
p	p-value
QoL	Quality of Life
RAAS	Renin-Angiotensin-Aldosterone System
RCF	Relative Centrifugal Force
Rho	Correlation coefficient
$Ru(bpy)_3^{2+}$	Tris (2,2-bipyridyl)ruthenium(II)
SA	Supraventricular Arrhythmias
SA-node	Sinoartrial node
SBP	Systemic Blood Pressure
SCD	Sudden Cardiac Death
SD	Standard Deviation
SMASH-1 study	Scandi navian Multicenter study to Advance risk Stratification in Heart disease-1 study
SPSS	Statistical Package for the Social Sciences
VA	Ventricle Arrhythmias
VF	Ventricle Fibrillation
VT	Ventricle Tachycardias
WHO	World Health Organization

1.0 Introduction

1.1 Structure and function of the heart

The main function of the heart is to pump oxygenated blood to the organs and the cells, pump deoxygenated blood to the lungs for gas exchange and maintain the systemic blood flow and pressure (1). The heart is an irregular cone shaped fibro muscular hollow organ, enclosed in a fibroserous sac (the pericardium). The heart is divided into four heart chambers, including an atrium and a ventricle on each side (Figure 1-1) (1). The left ventricle is three times as thick as the right ventricle, and the lumen appears to be circular when compared to the D-shaped lumen in the right ventricle (1). The heart consists of three separate layers: endocardium is the inner layer, the middle layer is myocardium, which includes the actual muscle cells of the heart (myocytes), and epicardium is the outer layer, the inner layer of pericardium (2). The myocytes are contractile cells in the myocardium that make the heart contract (2). Four heart valves, fibrous rings, are localized between the heart chambers to prevent the blood from flowing backwards (3). The heart valves are connected to the heart wall by small muscles; the papillary muscles (3). The tricuspid valve is localized between the right atrium and right ventricle, the pulmonary valve connects the right ventricle with the pulmonary artery, the mitral valve is between the left atrium and left ventricle, and the aortic valve is localized between left ventricle and aorta (1). By passive filling from the veins and coordinated contractions in the right atrium, blood is pumped into the right ventricle and from there the blood is pumped to the lungs. After gas exchange the blood is transferred into the left atrium and further to the left ventricle through passive filling and atrial contractions during the diastole (1). Finally, the blood is pumped out to the rest of the organs by contractions in the left ventricle in the systole (2).

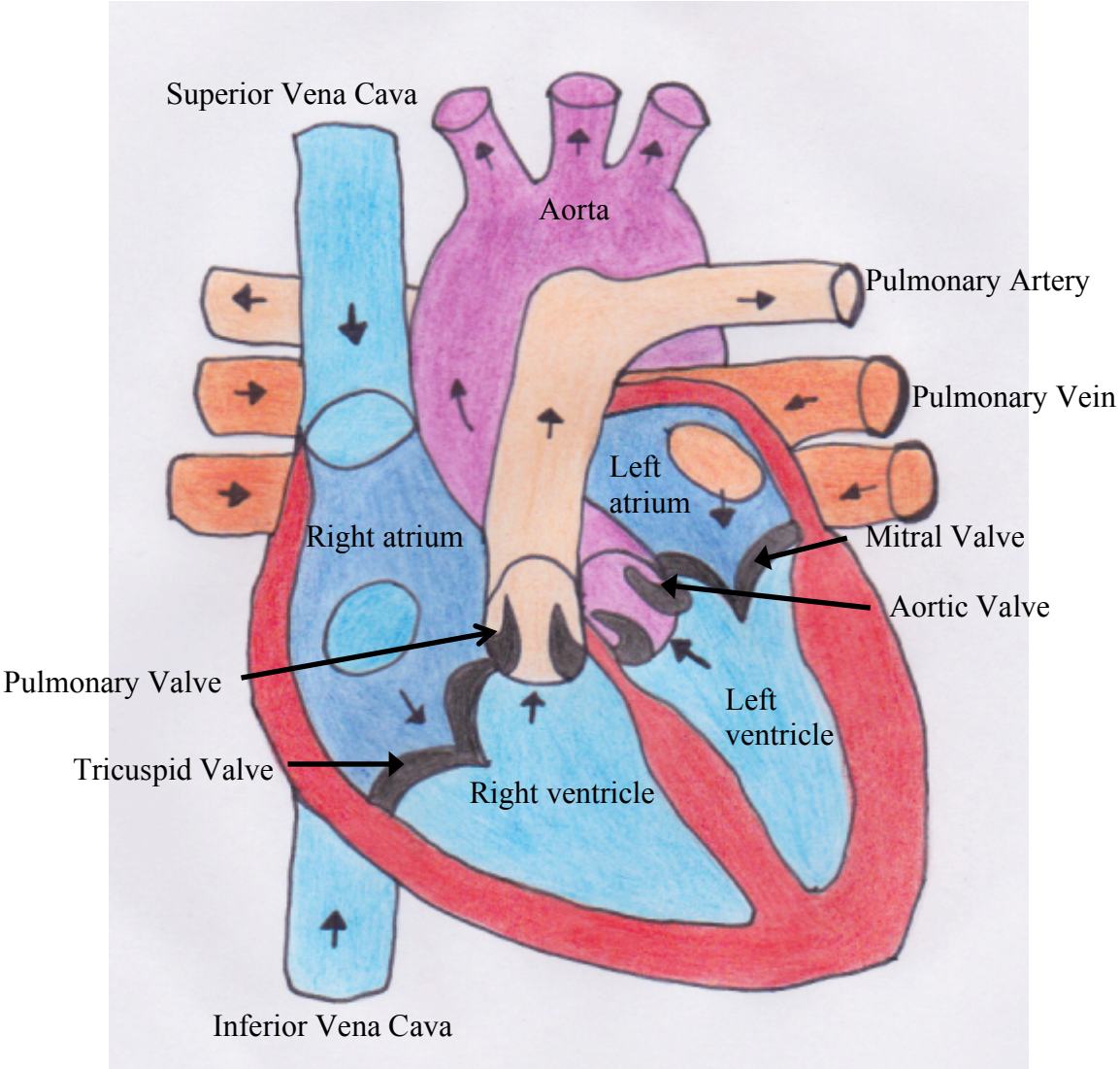

Figure 1-1: The interior anatomy of the human heart. Frontal section.

Electrical impulses controlled by the automatic nervous system coordinates the contractions of the heart (2). The Sinoatrial (SA) node is localized in the right atrium and consists of specialized cells (Figure 1-2) (2). This node function as a pacemaker, firing approximately 70 times per minute at rest and transports the electrical impulses to the atrial myocytes, resulting in depolarization and atrial contractions (2). The electrical impulses are further transferred to the atrioventricular (AV) node in the left and right atrium by conducting fibers (2). From here the signals follows the bundle of His down to the left and right bundle branch (1). The Purkinje fibers transfer the electrical impulses from the bundles to the myocytes in the left and right ventricles, resulting in ventricular contractions (1).

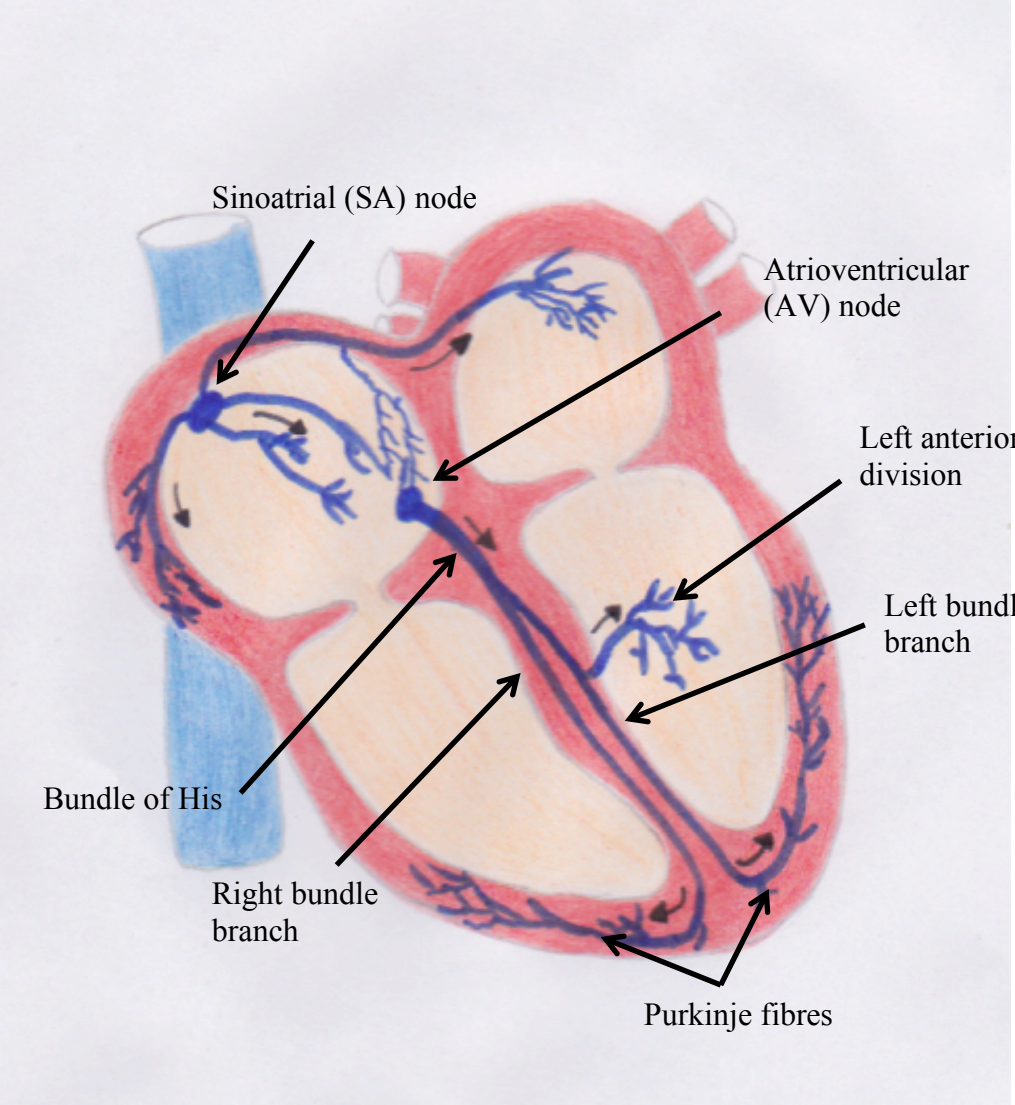

Figure 1-2: The electrical pathway in the human heart. Frontal section.

1.2 Indication and comorbidities in patients treated with ICD

Coronary heart disease (CHD) is the main cause of heart failure (HF) (3). HF is a central criterion in selecting patient requiring treatment with implantable cardioverter defibrillators (ICD) as primary prevention for ventricular arrhythmias (VA) (4, 5). Patients who have already experienced VA may require treatment with ICD as secondary prevention for new events of VA and sudden cardiac death (SCD) (5).

1.2.1 Coronary heart disease

CHD is the leading cause of death and disabilities in the western world (3). In the Unites states accounts CHD for 1 of 6 deaths, whereas 45% of cardiac deaths in Norway are caused by CHD (3, 6). CHD includes a wide range of clinical presentations, ranging from asymptomatic CHD, stable or unstable angina pectoris, to myocardial infarction (3). The main risk factors of CHD are increased high-density lipoprotein cholesterol ratio, hypertension, smoking and electrocardiographic abnormalties (3).

Atherosclerosis is the main mechanism for development of CHD (7). Plaque formation narrows the diameter in the coronary arteries by invasion of cholesterol, especially low-density lipoproteins (LDL), of the intima in the arterial wall (3). Furthermore, monocytes are attracted to the intima, as they infiltrate and further develop as macrophages in order to obtain a foam-like look when receiving nutrition from LDL (3). The macrophages excrete inflammatory substances that stimulate smooth muscle cells, fibrous tissue and the arterial wall to grow (3). Over time will the plaque continue to grow, and consequently the blood vessels narrows (3). Atherosclerotic arteries loose the ability to dilate which cause wall rupture, formation of thrombosis and cessation of the blood supply, resulting in myocardial infarction (MI) (8). During MI, the myocytes become necrotic due to ischemia and leaves scars in the myocardium, causing decreased myocardial contractility and risk of HF, a feared complication for MI patients (9). The extent of the infarct determines the HF severity, based on the degree of decreased levels of functional myocytes (10).

1.2.2 Heart Failure

1.2.2.1 Definition

HF is considered more as a syndrome than a disease (11). The condition is defined in several different ways, which indicate the complexity of the condition when considering both symptomology and pathophysiology. The European Society of Cardiology (ESC) defines HF as “an abnormality of cardiac structure or function leading to failure of the heart to deliver oxygen at a rate commensurate with the requirements of the metabolizing tissues, despite normal filling pressures (or only at the expense of increased filling pressures)” (11). HF usually develops from adaptive mechanisms that have become maladaptive (3). MI, persistent hypertension or cardiomyopathies are the most common causes of HF (10). CHD and hypertension accounts for ≥90% of the HF events in the western world (10). Between 1990

and 2015 were 40 million individuals diagnosed with HF worldwide (12). HF is prevalent in 1%-2% of the adult population (13).

1.2.2.2 Categorization of heart failure

HF is characteristically a chronic condition where the symptoms may deteriorate due to intermittent conditions such as infections, over-hydration or MI, known as decompensated HF (13, 14). ESC defines acute HF as "a rapid onset of, or change in, symptoms and signs of HF" (13). Acute HF includes patients who have HF symptoms for the first time, de novo acute HF, and patients who experience a worsening of a known cardiomyopathy, acute decompensated HF (15). Stable chronic HF is diagnosed when the patients have been treated for the clinical symptoms and the condition has been unchanged the last month (13).

HF can either be left sided, right sided, or biventricular (16). Right sided HF is less common and severe (16). In left sided HF, the left ventricular ejection fraction (LVEF) (% of blood pumped by the left ventricle) is used when categorizing HF as either HF with reduced ejection fraction (EF≤40%, HFrEF) or HF with preserved ejection fraction (EF≥50%, HFpEF) (16). Additionally, HF with a mid-range ejection fraction (HFmrEF), ejection fraction between 40%-49%, has in the later years served as an intermediate definition for HF (16). The prevalence of HFrEF and HFpEF are about equal, but the demographic distribution is different. HFrEF is overly represented in men with CHD and history of MI (17). In contrast, HFpEF is more prevalent in elderly women with hypertension, obisety, diabetes and/or atrial fibrillation (18, 19).

HFrEF is also referred to as systolic HF and is defined as "a pathophysiological state in which an abnormality of cardiac function is responsible for the failure of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues" (20). Cardiomyopathias and arrhythmias are among the common causes of systolic HF (20). Diastolic dysfunction, on the other hand, is the primary underlying mechanism of HFpEF, and is seen as a consequence of increased resistance in filling one or both ventricles (21). The decreased ability to fill the ventricles leads typically to symptoms of congestion such as dyspnea, peripheral edema and exercise intolerance (21). Diabetes, hypertension and CHD are the leading causes of diastolic dysfunction (3). Valvular failure and cardiomyopathies are also frequent causes of diastolic dysfunction, especially in elderly patients (3). Systolic and diastolic dysfunction should not be seen as isolated pathophysiological events, since they are

often observed together (3).

1.2.2.3 Pathophysiology of heart failure

The pathophysiology of HF is characterized by structural alterations in the heart and a dysfunctional neurohormonal system (3). Due to adaptive mechanisms in a healthy heart, cardiac output and blood pressure remains largely unaffected dispite transient disturbances in contractility or hemodynamics (10). Thus, these mechanisms contribute to immediate hemodynamic benefits. However, in HF these mechanisms are overactive and become malfunctional as a consequence of protracted activation of the adaptive mechanisms (10).

Cardiomyopathy is characterized by structural and functional abnormalities in the myocardium of the ventricle, which can be explained by flow-limiting coronary artery disease or abnormal loading conditions (22). Cardiomyopathy is divided into two subgroups, hypertrophic cardiomyopathy (HCM) and dilated cardiomyopathy (DCM) (23). HF is seen as a severe and prevalent complication due to both HCM and DCM (23, 24). ESC defines HCM as “presence of increased wall thickness in the left ventricle, and cannot be explained only by abnormal loading conditions” (25). Myocardial fibrosis, morphologic abnormalities in the mitral valve apparatus and electrocardiographic abnormalities can also be seen in patients with HCM (25). DMC is defined by ESC as “the presence of left ventricular dilatation and left ventricular systolic dysfunction in the absence of abnormal loading conditions (hypertension, valve disease) or coronary artery disease sufficient to cause global systolic impairment” (22). In addition, dilation and dysfunction in the right ventricle is prevalent in patients with DMC (22). CHD and myocardial infarction are causes of development of DCM, in addition to valvuar dysfunction (10, 22). In such conditions, the myocardial contractility may still be good, but the hemodynamic is unable to meet the body´s metabolic needs due to mechanical failure (10).

Activation of the neurohormonal system is an important mechanism in HF (26). Persistent sympathetic activation and reduced perfusion of the kidneys stimulates the neurohormonal system, which includes activation of the Renin-Angiotensin-Aldosterone System (RAAS) (26). RAAS is the regulatory system for cardiovascular and renal function (27). Angiotensin II is the mediator, while Renin, Aldosterone and Angiotensin 1-7 contributes to the system with other vital functions (3). An overactive RAAS is the most important neurohormonal mechanism behind development of HF (27). RAAS is activated early during HF as a

compensatory mechanism, and as the condition persists the RAAS system become maladaptive by increased levels of Angiotensin II (27). Increased concentrations of the Angiotensin II results in vasoconstriction, contractions of the arterioles, and consequently to reduced blood flow in the body and therefore reduced capability to maintain the level of oxygen in the cells (3). Increased secretion of Aldosterone by Angiotensin II intensifies the retention of salt and water in the body, and increase the levels of intracellular calcium (3). Also important in the neurohormonal system during HF are atrial natriuretic peptides (ANP) and B-type natriuretic peptides (BNP) (26). In a healthy patient, ANP is primarily released from the atrium, whereas BNP is released from the left ventricle (26). During HF, large amounts of ANP and BNP are secreted from the left ventricle most importantly due to wall stress (28). While ANP is more rapidly secreted due to storage of the natriuretic peptide in atrial granules, are BNP, especially N-terminal pro-B type natriuretic peptides (NT-proBNP), secreted in lower frequencies due the natriuretic peptide are synthesized as a consequence of acute stretch of the left ventricle wall (29). NT-proBNP will be covered in detail later in the thesis.

1.2.2.4 Risk factors of development of heart failure

Risk factors associated with HF are mainly the same risk factors related to CHD, and includes increased age, obesity, hypertension, diabetes and smoking (4, 30).

The incidence of HF increase from 10.6/1000 person-years in the age group 65-69 years, to 42.5/1000 person years in the age group over 80 years (31). Higher age is also associated with worse outcome of HF (13). Obesity is associated with the risk of developing left ventricular hypertrophy and dilatation, resulting in increased risk of HF (32, 33). There is a 5% increased risk for development of HF for each unit increment in body mass index (BMI) for men, whereas the same risk is 7% for women (34). Overweight women have 50% higher risk of HF, compared to women with normal BMI, while obese men have 90 % higher risk of HF compared to non-obese men (34). Hypertension is identified as one of the most significant mechanic causes of HF (35). Because of increased blood pressure due to higher resistance in the arteries, the left ventricle remodel from circular to spherical shape as a consequence of increased ventricular volume (36). The Framingham study showed a fourfolds higher risk of HF in hypertensive younger men (<65 years) compared to men without hypertension, and the same risk was threefolds higher for younger women with hypertension (37). In addition, increased pulse pressure (difference between systolic and

diastolic blood pressure), an indicator for arterial stiffening, is seen as a risk factor of HF in elderly patients (≥65 years) (38). Diabetes is another risk factor for development of HF (39). Development of coronary atherosclerosis, diabetic cardiomyopathy and shared comorbidities are the main mechanisms causing HF in diabetic patients (40). Concentric remodeling and hypertrophy of the left ventricle is seen to be common alterations in the myocardium in patients with diabetes, whereas the alterations can trigger HF (41). Diabetic patients with HF have higher risk of hospitalization and mortality, compared to non-diabetic patients with HF (39). Last, cigarette smoking is a well-known risk factor for atherosclerosis and CHD in general, but also directly for HF (11, 42, 43). 30% of deaths due to CHD and HF in the Unites Stated are caused by smoking, and the risk is dose-related (44).

1.2.2.5 Symptoms of heart failure

HF is typically characterized by symptoms such as dyspnea, orthopnea and edema in lower limbs (4). Symptoms of HF occur due to the reduced ability to empty venous reservoirs (backward failure) or because of reduced output from the ventricles (forward failure) (3). Backward failure is a result of failure in one or both ventricles to fill and eject blood normally (4). Patients with backward failure experience edema, orthopnea and dyspnea due to elevated venous pressure and pulmonary congestion (4). Forward failure is caused by reduced cardiac output to the lungs (right side failure), or to the periphery (left side failure), which results in decreased systemic blood pressure and fatigue (4). The severity of HF symptoms is usually classified according to the New York Heart Association (NYHA) functional classification, based on symptoms during different degrees of physical activity (Table 1-1) (13). Class I represents asymptomatic HF (no limitation in physical activity) in patients diagnosed with HF by cardiac imaging. Patients with the most severe symptoms are classified as NYHA IV, including HF symptoms at rest and vast limitations during activity (13).

Table 1-1: The New York Heart Association (NYHA) functional classification of HF (45).

Class	Patient symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause fatigue, palpitation or dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation or dyspnea.
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of HF at rest. If any physical activity is undertaken, discomfort increases.

1.2.2.6 Outcome of heart failure

HF is annually the direct cause of over one million hospitalizations in the United States and Europe (46, 47). Worsening of HF is the most prevalent cause of hospitalization among these patients (46). Moreover, the incidence of hospitalizations and mean age of the patients admitted for HF is increasing, partially due to an aging population (46).

SCD accounts for 35%-50% of deaths in patients with HF (48). HF is associated with a fivefold risk of SCD compared to non-HF patients (49). The rapid onset of ventricular arrhythmias (VA) in patients with HF is the main mechanism behind the elevated risk of SCD in this population (49). The incidence of SCD increases with age, and men have a fourfold higher risk of SCD compared to women (20). Previous MI, infections, increased blood pressure, increased BMI and increased cholesterol levels are other significant risk factors of SCD (20). The mortality rate is particularly high the first days after hospitalizations due to HF, and has been reported to be between 4%-7% the first 11 days (4, 14). Furthermore, 10-20% of the patients hospitalized due to HF are dead after 30 days (14). One-year survival after HF onset is approximately 70% (14). The survival prognosis for patients with HFrEF and HFpEF have over time evolved differently. In contrast to patients with HFpEF, where there are still no therapy that improves outcome, the survival rate for HFrEF patients has increased the last decades as a result of clinical implementation of several multiple evidence-based drugs and device therapies that have shown to improve outcome (19, 47). However, absolute survival of HF remains poor (46).

1.2.3 Cardiac arrhythmias

Cardiac arrhythmias are categorized according to the location and rate of the arrhythmias (10). Tachycardia is an abnormally fast cardiac rhythm, defined as more than 100 heartbeats per minute at rest, where bradycardia is an abnormally slow cardiac rhythm with fewer than 60 heartbeats per minute (10). Supraventricular arrhythmias (SA) origin from the atrium and atrial fibrillation (AF), which is uncoordinated activation of the atria, is the most common SA (50). VA occurs in the ventricles and concerns ventricular tachycardia (VT) and ventricular fibrillation (VF) (10). VF is uncontrolled cardiac rhythms due to a storm of electrical signals from different origins in the ventricles at the same time (10). During VT, the lower part of the cardiac electrical pathway takes over as pacemaker, due to increased amounts of electrical signals from one origin in the ventricles (10). VA is the main cause of SCD, and consequently a common and feared complication for patients with HF (9, 10, 51). SBP is usually not maintained during VA, which may result in syncope and sudden death if not treated (9). Ischemia, HF, side effects of drugs and disruptions in blood electrolytes are the most frequent causes of VA (52).

1.3 Implantable cardioverter defibrillator

Implantable cardioverter defibrillator (ICD) is an effective treatment for primary and secondary prevention of SCD due to VA (53, 54). Dr. Mirowski and Dr. Mower published the first report regarding ICD treatment in 1970 (55). 10 years later was the first ICD implanted in a 57-year old woman who survived cardiac arrest due to myocardial infarction (MI), and today are millions of patients treated with ICD (56). Longitudinal studies have shown ICD treatment to significantly reduce SCD in patients at high risk (57, 58). Compared to antiarrhythmic drug therapy, ICD treatment is superior regarding efficacy and prolonged survival in patients resuscitated after VA (59). EF ≤30%, cardiac arrhythmias (mainly VA), channelopathies, cardiomyopathies, prior MI, long QT syndrome is the main criteria for ICD implantation (5).

The ICD device function both as a pacemaker and defibrillator, and consist of a pulse generator and one or two wires connected to the atrium or/and the ventricles (Figure 1-3) (60). Memory chips for storage of electrographic data, voltage converters and resistors, and integrated circuits for analyzes of the heart rhythm and delivery of the therapy, are the main parts of the pulse generator (61, 62). The ICD is implanted in a pocket in the subcutaneous tissue, right under the clavicle, and the wires are connected to the heart on the outside or in

the ventricles via the aorta (57, 58). The function of the ICD is based on recognition of different heart rhythms (63). The device is programmed to deliver overdrive pacing or electric shock to convert the rhythm if it recognizes VA (63).

Figure 1-3: Two ICDs with pulse generators. One ICD without wires, and one ICD with two wires (60). The figure is reproduced with permission from Medtronic.

The electric shock from the ICD is categorized as either appropriate or inappropriate, according to whether the cardiac rhythm detected was an artifact or VA (63). 75% of the spontaneous ICD shocks are appropriate (63). The most frequent causes of inappropriate shocks are ICD malfunction, wire fracture or sinus tachycardia (58, 64).

1.4 NT-proBNP

NT-proBNP is the amino-terminal part of the prohormone BNP, synthesized as a preprohormone consisting of 134 peptides with a signal cleavage sequence (65). After the first enzymatic cleavage is the prohormone 108 amino acids long, and the second cleavage results in to units: the amino-terminal (NT) fragment consisting of 76 amino acids, and the active 32 amino acids long carboxyl-terminal unit (65, 66). NT-proBNP binds to the natriuretic receptor-A, a guanylyl cyclase A receptor, and mediates the reduction of blood pressure in conditions with volume excess by preventing sympathetic outflow, inhibiting production and activation of vasoconstrictor peptides, reduce excess salt and water retention, and stimulate vascular relaxation (67, 68).

NT-proBNP is widely used as a diagnostic biomarker for HF and has been shown to have high sensitivity, specificity, stability and analytic performance (69-71). NT-proBNP is secreted into the plasma from the myocardium in the left ventricle under both normal circumstances and myocardial dysfunctions (28, 68). The myocytes secret NT-proBNP as a consequence of the myocardial wall stress, which is typically seen secondary to volume overload (28). The NT-proBNP concentrations are reported up to 200 to 300 folds higher in patients with HF compared to healthy individuals (72). In addition, the circulating plasma concentrations of NT-proBNP increase linearly to the severity of the cardiac dysfunction in both elderly and younger patients (73). NT-proBNP has proven particularly valuable in separating patients with HF from other causes of acute dyspnea (74). Additionally, NT-proBNP has been demonstrated to be associated with the risk of cardiac arrythmias, although without convincing accuracy (75-77). NT-proBNP has a strong prognostic value as an independent predictor of mortality and morbidity in patients with heart failure and after cardiac arrest (78). NT-proBNP concentrations also reflect the severity of HF (79, 80).

1.5 Patient related outcome measures

World Health Organization (WHO) defines mental health as ”a state of well-being in which every individual realizes his or her own potential, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to her or his community” (81). Thoughts and feelings are a part of the human biology, whereas as people we meet, experiences and events can change how we feel, and how we perceive and cope with our lives (82). Everyday feelings can become destructive; such as sorrow develops to depression and fear becomes anxiety (81).

1.5.1 Depression and anxiety

Depression is a mood disorder where the patients often have the feeling of being in a negative emotional state over a longer period of time (83). Long lasting grief after a negative life event, repeated stress or several negative life adjustments are the main triggering factors of depression (82). Decreased vulnerability and heredity of depression can explain why some patients develop depression without having experienced any major negative life events (82). The main symptoms of depression are lowered mood, lack of interest and enjoyment of most activities, reduced energy and fatigue. Other symptoms such as increased or decreased appetite, reduced concentration, and negative thoughts about the future or the person himself

may be present (83). In addition, psychomotor impairments such as slow body movements, weakness and decreased responsiveness are often seen in patients with depression (82). Depression can be mild, moderate or deep, and deep depression is often recurrent (84). Anxiety may be common in patients with depression, consenquently the two conditions may be difficult to distinguish (82).

Anxiety is a mental disorder characterized by distress, fear and panic (82). Physical symptoms such as palpations, sweat, dizziness, difficulties of breathing, shivering and restlessness occurs due to hyperactivity in the sympathetic nerve system, and are referred to as symptoms due to the "fight or flight-response" (82). The natural physiologic function of anxiety is to survive threats, but can occur as dysfunctional in relation with biologically increased vulnerability or maladaptation of fear (82). Fear is an adaptive response and due to hyperactivity in the sympathetic nerve system in inexpedient situations, the brain perceive situations as more threatening that in reality it is (85). Patients with anxiety often perform actions in order to avoid threatening situations and as a consequence could the anxiety be maintained or reinforced (84). Trauma, congenital vulnerability, insecure childhood environment and heredity of anxiety disorders are common factors for development of anxiety (84).

1.5.2 ICD and mental distress

Patients treated with ICD experience a worsening of quality of life (QoL) and mental health after receiving shock from the ICD (86). It is estimated that approximately 20% of patients treated with ICD experience anxiety and/or depression (87). Fear of shock, pain, concerns regarding device failure and fear of being alone if the ICD fires, are the main determinants of reduced mental health in the ICD population (88). Maladaptation of coping strategies in order to mentally increase the control of the ICD, such as avoiding behavior, monitoring symptoms or being constantly on the alert, are usually seen in patients treated with ICD (88, 89).

Patients who have experienced shock have 1.6 times higher risk of anxiety, compared to patients who have never received a shock (90). In addition, the patients with increased ICD related concerns have 5.0 times higher risk of anxiety (90). Patients who have experienced two or more inappropriate shocks have higher levels of anxiety related to shock, compared to the patients who experienced one or none inappropriate shocks (90). These findings are supported by a study that identified an association between high number of shocks and

symptoms of depression (91). However, Thylén et al. presented concerns related to the ICD to have a bigger impact on psychological distress than the actual shock (90). In addition, the severity of HF is seen to predict higher levels of anxiety in the ICD population (92). The association between lower age and higher levels of anxiety is widely discussed. Lower age and female gender is associated with higher levels of shock related anxiety, but a systematic review from 2015 could not, due to conflicting reports, conclude that age was a significant determinant of anxiety in patients treated with ICD (93-96).

The attitude towards technology is strongly associated with mental distress in patients treated with ICD (97). The psycological outcomes are related to the degree of positivism towards technology dependence (97). Patients with a positive view on their cardiac diagnosis adjusts better to their ICD, compared to patients with a negative view (88). Sears et al. investigated if a management program for ICD treatment could reduce psychological stress among ICD recipients who have received shock (98). The study concluded that structural inventions involving ICD education and cognitive behavioral strategies could reduce psychological distress and increase QOL (98).

Summarized, previous studies have demonstrated a higher prevalence of anxiety and depression in patients treated with ICD. However, the association between anxiety and depression and disease severity, according to concentrations of NT-proBNP, is not established.

2.0 Aims of the study

The main purpose of the current study is to assess the relation between mental distress and disease severity, as indicated by NT-proBNP concentrations, in patients treated with ICD at risk of ventricular arrythmias. The specific objectives are:

1) To assess the prevalence of anxiety and depression in patients treated with ICD.
2) To assess whether anxiety or depression is associated with concentrations of NT-proBNP.
3) To assess whether previous shock from the ICD is an independent determinant of anxiety or depression, adjusting for concentrations of NT-proBNP (surrogate for disease severity).

3.0 Methodology

3.1 Study design

This master thesis is a substudy of the ongoing "Scandinavian Multicenter study to Advance risk Stratification in Heart disease" (SMASH-1) study. The SMASH-1 study is a prospective, observational study conducted by the Cardio Thoracic Research group at Akershus University Hospital (AUH), Lørenskog. An additional site at Stavanger University Hospital was a part of the study, but only participants from AUH were included in the current substudy. The main purpose of the SMASH-1 study was to assess the relations between established and novel circulating biomarkers and the incidence of ventricular arrhythmias, through establishment of an extensive biobank of patients with ICD (Appendix 1). The specific aims of the study was to evaluate the prognostic value of secretoneurin as an indicator of the incidence of ventricular arrhythmias in patients with ICD, and to evaluate established and novel echocardiographic parameters in association to ventricular arrhythmias and circulating biomarkers.

The current study is a cross-sectional observational study with a quantitative approach. A cross-sectional study design determines exposure and outcome at the same period of time (99). Cross-sectional studies are easy, quick and less expensive compared to studies by other designs. In addition, cross-sectional studies are often hypothesis generating, as the study design is not strong enough to confirm incidence or causality due to the limited duration of the study (99).

3.2 Study population

The participants in the current study were included from the SMASH-1 study cohort at AUH. Patients treated with ICD, who had annual or biannual routine device check at the cardiology outpatient clinic, were asked to participate in the SMASH-1 study. Participants over 18 years treated with ICD who signed a written informed consent, and without any of the exclusion criteria, were eligible for the study (Table 3-1).

Table 3-1: The inclusion and exclusion criteria for the SMASH-1 study (Appendix 1).

Inclusion criteria	Exclusion criteria
Patients ≥ 18 years	Participation in other interventional trials
Current ICD treatment	Previously included in this study
Signed written informed consent	Unable to sign a written informed consent and unwilling/unable to comply with the protocol
	Known or suspected terminal cancer
	Neurological condition with short life expectancy; for example Amyotrophic lateral sclerosis (ALS)
	History of non-compliance to medical management and patients who are considered as potentially unreliable by the investigator
	Drug- or alcohol abuse the last 12 months. Assessed by the investigator during the screening phase.
	Surgical or medical condition that may impair the patients ability to participate in the study

3.3 Study protocol

The potential participants for the SMASH-1 study were contacted by a study nurse via phone prior to the routine device check at AUH. The purpose of the contact was to give the patients information regarding the SMASH-1 study and to schedule a visit for study inclusion. The baseline visit was scheduled right before or after the routine device check, in order to reduce the number of hospital-visits for the participants. Additional information regarding the study and consent form was given to the patient in person or sent by mail (Appendix 2).

The SMASH-1 study comprised of two study visits; the baseline visit (visit 1) and the 1-year follow-up visit (visit 2). The protocol was similar for the visits and included clinical interview, blood sampling, measures of vital parameters (blood pressure, respiratory frequency and heart rate) and resting electrocardiography (ECG). The clinical data from the visits were registered in case report forms (CRF) (Appendix 3 and 4). Questions regarding cardiac events since visit 1 was added to the CRF for visit 2. Only clinical data from the baseline visit was used in the current substudy.

3.4 Data collection

249 participants from the SMASH study were asked to participate in the current substudy, either at the SMASH baseline visit or by phone prior to the visit. Consent forms with information regarding the substudy and the study questionnaires were given to the potential participants at the SMASH consultation (Appendix 5 and 6). The participants who accepted to participate in the substudy by phone received the consent forms and questionnaires by mail. A stamped envelope was attached to all of the distributed questionnaires, allowing the participants to return their answers as easy as possible. Reminders were sent to the participants who didn´t answer after their first distribution. The questionnaires are described in detail later in this thesis.

The signed consent forms and completed questionnaires were labeled with the same participant ID as in the SMASH study, when received at the Research Division at AUH. The written consent forms were stored in a locked binder at AUH, as it included sensitive and confidential information. The completed questionnaires were stored in a separate binder.

3.4.1 Baseline procedure and serum sampling

The equipment used to the blood sampling included:

- Hand sanitizer with 85% alcohol
- Disinfection swaps with 70% isopropyl alcohol
- Tourniquet
- Winged “butterfly” needle, 0.80 x 19 mm
- Vacutainers (described in detail below)
- Vacutainers rack
- Micropore tape
- Cotton balls
- Rubber glows
- Needle disposal box

Before a participant was called into the room where the visit took place, the equipment was found and placed at a movable table next to the chair for blood sampling. A piece of adhesive tape was prepared with a cotton ball to make sure that blood residues didn´t leaked from the participant after the venipuncture. The participant had to first confirm the name and personal identity number, in order for the study nurse to identify the participant with the person identifications on the vacutainers. After the hands was washed with soap and water, the nurse searched for a good vein to puncture. The tourniquet was tightened around the participant´s overarm, approximately 10cm over the elbow joint. When an appropriate vein was identified and palpated, the nurse sanitized her hands with disinfectants and the puncture area was wiped with a disinfection swab. Further, the needle was assembled before the vein was punctured, and the vacutainer was connected to the “butterfly” needle. The tourniquet was further loosened in order to prevent hemolysis. After all of the vacutainers was filled up, the needle was pulled out and secured with its security mechanism before it was thrown into the needle disposal box. Finally, the adhesive tape with the cotton ball was attached over the puncture area.

16 vacutainers, comprising a total of 91 ml blood, was filled during the blood sampling. After a vacutainer was filled up it was immediately flipped 6-8 times in order for the material in the vacutainer to react with the blood. The vacutainers was filled in this specific order:

- 7 x 5ml Serum glass without gel (BD Vacutainer® #367615)
- 2 x 4ml serum glass with gel (Greiner Bio-One Vacuette® #454067R)
- 2 x 4ml lithium-heparin glass (Greiner Bio-One Vacuette® #454029)
- 1 x 4ml K2-EDTA glass (Greiner Bio-One Vacuette® #454209)
- 4 x 6ml K2-EDTA glass (Greiner Bio-One Vacuette® #456043)
- 2 x 6ml K2-EDTA glass (Greiner Bio-One Vacuette® #456043).

2 x 6ml K2-EDTA vacutainers were labeled before they were stored in a freezer measured to -80ºC, right after the blood samples were drawn. The labels included the participants study ID, material, and visit number (1 or 2). These blood samples will be used for genetic analyzes once the SMASH-1 study is completed. 7 x 5ml serum vacutainers without gel was left at room temperature to coagulate for 30-60 minutes, and subsequently centrifuged for 15 minutes in room temperature at 2000 RCF (G). 500µl serum from the vacutainers was pipetted over to 20 x 0.5ml aliquots (Sarstedt #72.730.003) with 20 red caps (Sarstedt # 65.716.003). Further, 2 x 4ml Lithium-heparin vacutainers and 4 x 6ml K2-EDTA vacutainers were centrifuged at 4° in 20 minutes at 1920 RCF (G). 500µl lithium-heparin plasma was pipetted into 6 x 0.5ml aliquots with six green caps (Sarstedt #65.716.005). 500µl K2-EDTA-plasma was pipetted into 16 x 0.5ml aliquots with purple caps (Sarstedt #65.716008). All of the aliquots were labeled with “SMASH 1”, participants study ID, visit number (1 or 2), material and aliquot number, and the caps were marked with the participants study ID before the blood sampling. Finally, all of the aliquots were stored in the same freezer as the 6ml K2-EDTA vacutainers. 1 x 4ml K2-EDTA glass and 2 x 4ml serum glass with gel were labeled with the same information as for the 6ml K2-EDTA vacutainers and sent to the central laboratory at AUH for analysis of NT-proBNP and creatinine directly after the blood sampling.

3.4.2 Analysis of NT-proBNP

The analysis of NT-proBNP was done by the commercially available electrochemiluminescenece immunoassay (ECLIA) (Elecsys, proBNP II, Roche Diagnostics, Mannheim, Germany) on the Cobas e801 platform, at the central laboratory at AUH (100). ECLIA use a sandwich technique based on monoclonal and polyclonal antibodies from sheep, where the reaction complex is detected by emission of light (100). Room tempered serum (20-25ºC) from the blood samples was used as analysis sample. The reagents used in the analysis are listed in Table 3-2. This analysis method was standardized according to Elecsys proBNP analysis 03121640190 (100).

Table 3-2: The reagents used in the analysis of NT-proBNP. All of the reagents were produced by Roche Diagnostics, Mannheim, and distributed by Roche Diagnostics AS, Norway (100).

Reagents	Contents	Product number
Reagent A	12.4ml Streptavidin coated microparticles 0.72 mg/ml **21.0ml Anti-NT-proBNP-As-biotin**: Biotinylated polyclonal anti-NT-proBNP-antibody (sheep), phosphate buffer pH 7.4, 44 mmol/L **19.7ml Anti-NT-proBNP-As-$Ru(bpy)_3^{2+}$:** Polyclonal anti-NT-proBNP-antibody (sheep) marked with a ruthenium complex (Tris 2,2-bipyridyl)ruthenium(II)-complex ($Ru(bpy)_3^{2+}$)	07027664190
Reagent B	Diluent Universal	07299001190
Reagent C	PreClean M	06908853190
System reagents	ProCell M CleanCell M	06908799190 04880293190

The analysis procedure (100):

Analysis total time: 9 minutes

Total amount of the analysis sample (blood sample + reagents): 9µl

Analysis instrument: Cobas e801 from Roche Diagnostics

1) Biotinylated monoclonal NT-proBNP-specific antibodies and polyclonal NT-proBNP antibodies with a ruthenium complex, were added to the NT-proBNP sample. As a consenquence, many sandwich complexes were generated during the first incubation.

2) Streptavidin coated microparticles were further added to the sample, whereas the microparticles connected with the sandwich complex by interactions between the streptavidin and biotin during the second incubation.

3) Further, the reaction mixture was taken up by a target cell, whereas the immunocomplexes were captured on the surface of an electrode due to the microparticles. ProCell M was added to the solution in order to prevent interference between unbounded antibodies and the sample, by removing the unbounded material.

4) A chemiluminescence reaction was initiated by adding voltage to the electrode, whereas the emission of light from the immunocomplex was detected and measured by a photomultiplier. The level of emission was equal to the concentration of NT-proBNP.

5) The analysis machine calculated the NT-proBNP concentration in each sample, either in pmol/L or pg/mL. The units can be converted by the following calculation:

pmol/L x 8.457= pg/mL or ng/L x 0.118=pmol/L

The concentrations were determined by a calibration curve, made up of a 2-points calibration and a master curve that was read into the instrument via the reagent barcode.

3.4.3 Assessment of NT-proBNP

The reference values for NT-proBNP for detection of HF are presented in Table 3-3. The standardized measurement unit for NT-proBNP was changed from pmol/L to ng/L October 2nd 2017 at the central laboratory at AUH. The NT-proBNP values in SMASH-1 study were reported in pmol/L for all the participants until 1st of October. 10 participants had the NT-

proBNP values mentioned as ng/L. In the current study are the NT-proBNP values reported, according to ESC, as ng/L by multiplying the values mentioned in pmol/L with 8.457 (101).

Precision is the ability to reproduce the same result each run, where the coefficient of variation (CV) is the measure of analytic precision (102). CV measures the distribution of the variation in a data set with this formula (102):

$$\frac{\text{Standard deviation}}{\text{Mean}}$$

Analyses with a high CV have low precision, whereas high precision is seen as low CV in the analysis (102). The CV was measured at 97ng/L and 515ng/L for the NT-proBNP analysis, and CV was equal to 10% or lower for both concentrations (100). The lower detection limit of NT-proBNP was 5ng/L and the highest level of detection was 35 000ng/L (100).

Table 3-3: Standardized reference values of NT-proBNP for detection of HF according to age intervals (100).

Age	Women	Men
18- 44	≤130 ng/L	≤86 ng/L
45-54	≤245 ng/L	≤121 ng/L
55-64	≤287 ng/L	≤210 ng/L
65-74	≤349 ng/L	≤376 ng/L
≥75	≤738 ng/L	≤486 ng/L

3.5 Questionnaires

3.5.1 Hospital Anxiety and Depression Scale

Hospital Anxiety and Depression Scale (HADS) is a reliable and useful questionnaire widely used by clinicians to assess anxiety and depression (103, 104). A previously validated Norwegian version of HADS was used in the current study to assess the prevalence of anxiety and depression (103, 104) (Appendix 6). The questionnaire consisted of questions regarding general symptoms of depression (HADS-D) and anxiety (HADS-A), whereas the questions labeled with even numbers represented HADS-D and the questions with odd numbers represented HADS-A (103). The participants ticked off one of the answer options that matched with the statement they recognized themselves in. The wording of the answers varied according to the questions, but all the answers were graded according to how often the participants experienced the statements in the questionnaire, from 0 (no symptoms) to 3 (often symptoms) (104). The total sumscore was calculated for each participant (104). If a value was missing or the participant had ticked off two or more values, the item was recorded as missing.

3.5.2 Florida Shock Anxiety Scale

The Florida Shock Anxiety Scale (FSAS) is a questionnaire designed specifically for patients treated with ICD, in order to give a quantitative measure of the patients level of anxiety and concerns related to the ICD (105). A previously validated Norwegian version of FSAS was used in the current study (Appendix 6). The questionnaire consisted of 10 item regarding concerns related to the ICD. The questions addressed daily activities; physical activities, sexual activity, if the participants were afraid of receiving an ICD shock when he/she was alone, avoidance of certain feelings and concerns of not knowing when the ICD would fire (105). The participants answered by ticking off on a 5-point Likert scale, where the numbers 1-5 was linked to how often the participants experienced inexpedient thoughts regarding their ICD and everyday life. 1= not at all, 2=rare, 3= occasionally, 4= often and 5= all the time (105). The total score of the FSAS questionnaire was calculated for each participant, based on the independent score from each item (105). Analogously to the scoring of HADS, missing values were not registered.

3.6 Statististical methods

The statistical analyzes of the data were primarily based on descriptive statistics. The quantitative variables were calculated and presented as mean±standard deviation (SD) for parametric variables, median (quartile 1 to quartile 3) for non-parametric variables and absolute number (% of total) for categorical variables. Continuous variables were analyzed in order to assess for differences between the groups and thus reject the null hypothesis (106). Independent-samples T-test for one selection was used to assess the continuous variables that were normally distributed: age, SBP, LVEF, heart rate and BMI. Concentrations of NT-proBNP and creatinine were tested by Mann-Whitney *U* test for non-parametric data, due to no normal distribution of the variables, where a right skew in the distribution was found (106). The CRF used in the SMASH-1 study obtained various information regarding medical history, symptoms and clinical status, whereas variables such as palpitation, dyspnea, history of HF and history of diabetes etc. was dichotomized into yes/no variables prior the categorical analyzes. Chi Square test was performed in order to assess for difference between the categorical variables (106): shock (Y/N), depression (Y/N), anxiety (Y/N) and shock related anxiety (Y/N). In order to dichotomize anxiety and depression by the HADS questionnaire, the recommended cut-off values for the sumscore was ≥8 for both (HADS-A) and (HADS-D) (103). The cut-off value for the FSAS sumcore (shock related anxiety y/n) has not previously been assessed, whereas the investigator of the current study determined the total FSAS score as ≥12 (lowest total sumscore for participants that reported to have any kind of ICD concerns). Multivariate logistic regression models were used in order to evaluate what variables were significantly associated with anxiety and depression (106). The selection of variables used in the multivariate regression was based on Spearman´s correlation, where variables with $p<0.05$ were included (106). The levels of reliability in the questionnaires were calculated by Chronbach´s alpha, and the validity in the study was assessed by controlling for data and coding errors in the data set by a manually check. The significance level was set at a two-tailed p-value <0.05. The statistical analysis, data management and documentation were performed by the statistical software IBM SPSS statistics, version 23 (IBM, SPSS INC., Chicago, III, USA). Microsoft Excel for Mac, version 14.5.4 (2010), was used to design figures and tables.

3.7 Ethical considerations

The current study has been approved by the Regional Committees for Medical and Health Research Ethics (Appendix 7 and 8). Reference number: 2015/2080. The Research Council of Norway funded this study (study number: 250585/F20) together with internal funding from the Cardio Thoracic Research Group at AUH. Due to no collaboration with companies or persons with financial or personal gain, the current study had no conflict of interest.

The Declaration of Helsinki is a collection of ethical principles to guide clinicians involved in medical research, concerning identifiable human material or identifiable data, to act in the participants best interest (107). The declaration is widely used by researchers in order to protect and ensure respect for the participants life, health, privacy and confidentiality (107). In addition, the guidelines emphasize the importance of appropriate scientific education, training and quality for the clinicians conducting a study (107). The current study was performed in accordance to the Declaration of Helsinki. As an important point in the declaration, the participants in the study signed a written informative consent, allowing them to participate in the study (107). Information regarding aims of the study, methods, benefits and risk, conflict of interest and other important aspects of the study was attached to the written consent form. The information was presented in Norwegian in an understandable manner without the use of complicated medical terminology. The informed consent forms was voluntarily signed by participants who were physically and mentally capable to understand the information regarding the study, and able to give a written consent (107). The participants were informed that they could withdraw the consent and end their participation in the study at any time. No reward of any kind was given to the participants.

4.0 Results

4.1 Study population

236 of the 249 participants in the SMASH-1 study were invited to participate in the current substudy (Figure 4-1).

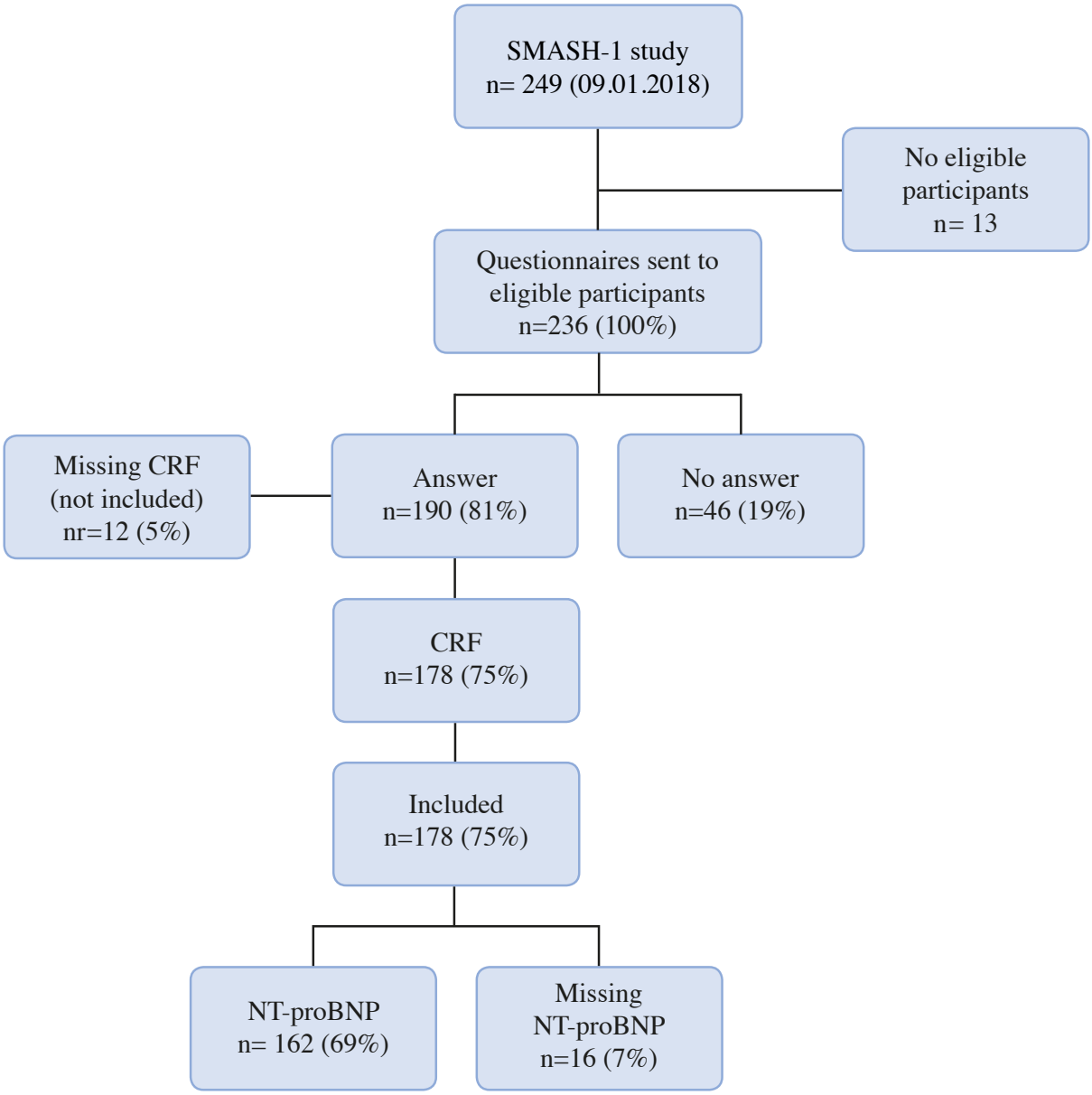

Figure 4-1: Flowchart of the data collection in the current study population.

A total of 249 participants were enrolled in the SMASH-1 study at the time of the second questionnaire distribution in the current substudy (finalized January 9th 2018). 236 participants were eligible for the present study after excluding 13 participants due to death, missing addresses and withdrawn consents. 190 (81%) of the 236 participants completed and submitted the questionnaires, whereas the remaining 46 (19%) participants did not reply after receiving a reminder. The clinical characteristics were recorded in the CRF and this baseline information was completed for 178 (75%) participants, which comprised the current study population.

The mean age of the study population was 66.9±9.9 years, with a range of 36 to 85 years. 19 (11%) of the participants were women and 159 (89%) were men, and the mean age was comparable between the genders (Table 4-1). The participants had a mean BMI of 27.1±4.1 kg/m^2, a mean SBP of 130±20 mmHG and a mean heart rate of 62±10 BPM. 81.4% of the participants had a history of HF, 84.2% had previous VA, 59.4% had a history of AMI and 42.9% had AF, whereas diabetes was identified in 20.2% of the study participants. Dyspnea was found in 15.9% of the participants, 41.2% had palpitations and 40.7% participants had experienced syncope. The mean LVEF assessed by echocardiography was 41.8±10.2%. The median NT-proBNP concentration was 518 (IQR 211-1211) ng/L, whereas the median creatinine concentration was 88.0 (IQR 77.0-106.5) µmol/L.

Table 4-1: Baseline characteristics of the study population.

	Total (n=178, 100%)	**Male** (n=159, 89%)	**Female** (n=19, 11%)	**p-value¶**
Age (years)	66.9±9.9	67.4±9.7	62.4±10.7	0.06
Heart rate (%) [a]	62±10	62±11	60±9	0.33
Body mass index (kg/m2)	27.1±4.1	27.5±4.1	26.0±4.1	0.16
Left ventricle ejection fraction (%) [c]	41.8±10.2	41.3±10.3	45.8±8.6	0.07
Systolic blood pressure (mmHg)	130±20	130±20	123±21	0.14
Current and former smoker	122 (68.5%)	108 (67.9%)	14 (73.7%)	0.79
Diabetes mellitus (type 1 and 2)	36 (20.2%)	33 (20.8%)	3 (15.8%)	0.76
Chronic obstructive pulmonary disease	17 (9.6%)	14 (8.8%)	3 (15.8%)	0.39
Cardiac artery disease [a]	115 (66.9%)	108 (70.1%)	7 (38.9%)	0.01
Cardiomyopathy [a]	156 (89.7%)	140 (90.3%)	16 (84.2%)	0.42
Valvular disease [a]	45 (25.4%)	40 (25.3%)	5 (26.3%)	1.00
Symptoms:				
Dyspnea (NYHA III+IV) [a]	28 (15.9%)	25 (15.9)	3 (15.8%)	1.00
Palpitations [a]	73 (41.2%	57 (36.1%)	16 (84.2%)	<0.001
Presyncope	93 (52.2%)	79 (49.7%)	14 (73.7%)	0.05
Syncope [a]	72 (40.7%)	65 (41.1%)	7 (36.8%)	0.80
History of:				
Heart failure [a]	140 (81.4%)	127 (83.0%)	13 (68.4%)	0.12
Atrial fibrillation [a]	76 (42.9%)	71 (44.9%)	5 (26.3%)	0.14
Acute myocardial infarct [a]	104 (59.4)	98 (62.8%)	6 (31.6%)	0.12
Ventricular arrhythmias [a]	150 (84.2%)	132 (84.1%)	18 (94.7%)	0.31
Laboratory measurements:				
NT-proBNP (ng/L) [b]	518 (211-1211)	512 (211-1378)	600 (241-1006)	0.94
Creatinine (µmol/L) [a]	88.0 (77.0-106.5)	90.0 (79.0-109.0)	75.0 (66.0-87.0)	<0.001

Data presented as numbers (%), mean (SD) or median (interquartile range).
¶= p-value for comparison between the groups with Chi-square for categorical variables, Independent-samples T-test for continuous parametric variables and Mann-Whitney *U* test for non-parametric variables.
[a]<5% missing, [b]<10% missing, [c]<15% missing

4.2. Patient related outcomes

Table 4-2 gives an overview over the distribution of the physiological outcomes between the genders in the study population. The amount of participants classified with depression (HADS-D sumscore ≥8) in the total population was 10.1 %, and there were no difference between men and women (9.4% vs. 15.8%, p=0.41). Similarly, there was no difference in the prevalence of anxiety (HADS-A sumscore ≥8) between the genders (13.2% men vs. 10.5%, p=1.00). The proportion of shock related anxiety (FSAS sumscore ≥12) was higher among the female participants, compared to the male participants (70.6% vs. 36.3%, p=0.008).

Table 4-2: Overview of the distribution of the psychological outcomes between the genders.

		Gender		
	Total (n=)	**Male (n=)**	**Female (n=)**	**P-Value (<0.05)**
Depression (HADS-D ≥8)	18 (10.1%)	15 (9.4%)	3 (15.8%)	0.41
Anxiety (HADS-A ≥8)	23 (12.9%)	21 (13.2%)	2 (10.5%)	1.00
Shock related anxiety (FSAS ≥12) [1]	69 (38.8%)	57 (36.3%)	12 (70.6%)	0.008

Data presented as numbers (%)
[1] =missing 4 participants

4.2.1 Depression

4.2.1.1 Baseline characteristics

The mean age of the participants with depression was 66.5 years±9.9 years, which was comparable to the age of the participants who did not have depression (p=0.86) (Table 4-3). Dyspnea (classified as NYHA III & IV, p<0.001) and palpitations (p=0.02) were more prevalent in participants with depression, compared to participants without depression. No difference in history of presyncope was found between the groups (p=0.80), but history of syncope was more prevalent in the depressed participants (p=0.01). History of HF (p=0.20), VA (p=0.72), AMI (p=0.31), diabetes (p=0.21) and AF (p=1.00) was not different between the participants with vs. without depression. Numerically higher values of NT-proBNP were seen in the participants with depression (median 698 [IQR 272-1828] ng/L vs. median 478 [IQR 209-1162] ng/L), however without significant differences (p=0.29).

Table 4-3: Baseline characteristics of the participants stratified by depression.

	Depression		
	Depression (HADS-D sumscore ≥8) n=18, 10.1%	**No depression (HADS-D sumscore <8) n=160, 89.9%**	**p-value¶**
Age (years)	66.5 ±9.9	66.9±9.9	0.86
Gender (male)	15 (8.4%)	144 (80.9%)	0.41
Body mass index (kg/m^2)	27.3±4.3	27.3±4.1	0.96
Heart rate (beats per minute) [a]	68±13	61±10	0.05
Systolic blood pressure (mmHg)	127±25	130±19	0.62
Left ventricular ejection fraction (%) [c]	39.0±9.2	42.1±10.3	0.20
Symptoms:			
Dyspnea (NYHA III+IV) [a]	9 (52.9%)	19 (11.9%)	<0.001
Palpitations [a]	12 (66.7%)	61 (38.4%)	0.02
Presyncope	10 (55.6%)	83 (51.9%)	0.80
Syncope [a]	12 (70.6%)	60 (37.5%)	0.01
History of:			
Heart failure [a]	16 (94.1%)	124 (80.0%)	0.20
Ventricular arrhythmias [a]	14 (82.4%)	136 (85.5%)	0.72
Acute myocardial infarction [a]	13 (72.2%)	91 (58.0%)	0.31
Diabetes mellitus (type 1 and 2)	6 (33.3%)	30 (18.8%)	0.21
Atrial fibrillation [a]	8 (44.4%)	68 (42.8%)	1.00
Laboratory measurements:			
NT-proBNP (ng/L) [b]	698 (272-1828)	478 (209-1162)	0.29
Creatinine (µmol/L) [a]	87.5 (77.5-116.5)	89.0 (77.0-108.0)	0.74

Data presented as numbers (%), mean (SD) or median (interquartile range).
¶= p-value for comparison between the groups with Chi-square for categorical variables, Independent-samples T-test for continuous parametric variables and Mann-Whitney *U* test for non-parametric variables.
[a]<5% missing, [b]<10% missing, [c]<15 missing

4.2.1.2 Items related to depression

Answers HADS- D:

Question #2 “Glede over ting” (n=176): 105 (59.6%) of the participants enjoyed things “definitely as much”, compared to the two participants (1.1%) who did not at all enjoy things as they did before, and 63 (35.8%) participants reported that they didn´t enjoy things quite as much as they used to.

Question #4 “Le og se det morsomme i situasjoner” (n=178): 135 (75.8%) participants could laugh and see the funny side of things, but 34 (19.1%) participants answered “not quite so much now”. Eight (4.4%) participants could “definitely not quite so much now” laugh and see the funny side in things, whereas the remaining one (0.5%) participant had no ability at all to do this.

Question #6 “Godt humør” (n=178): One participant (0.5%) reported to never be in a good mood. On the other hand, 132 (74.1%) of the participants experienced to be mostly in a good mood, 35 (19.6%) participants were in a good mood quite often and the remaining 10 (5.6%) participants reported to have a good mood sometimes.

Question #8 “Alt går langsommere” (n=172): Whereas 65 (37.7%) participants had never experienced the feeling of being slowed down, had 84 (47.8%) participants this feeling from time to time. 10 (5.8%) participants felt slowed down very often and 13 (7.5%) of the participants had this feeling almost all the time.

Question #10 “Utseende” (n=174): Regarding the participants thoughts about their appearance, had seven (4.0%) participants lost their interest on their appearance and six (3.4%) participants didn´t care as much as they should. 100 (57.4%) participants did care as much as they always have done, whereas the remaining 41 (23.5%) participants felt they didn´t care enough.

Question #12 “Ser med glede frem hendelser og ting” (n=173): 113 (65.3%) participants reported that they looked forward to things “as much as I ever did”. Five (2.8%) participants reported that they didn´t look forward to things, besides six (3.4%) participants answered “definitely less than I used to”.

Question #14 “Glede seg over en god bok, radio/Tv-program” (n=176): 144 (81.8%) of the participants could often enjoy a good book or a radio/ TV-show, four (2.2%) participants could only do this quite rarely, whereas 21(11.9%) participants reported to enjoy a good book or something on the radio/television from time to time. The remaining seven (3.9%) participants could enjoy the mentioned activities very rare.

4.2.2 Anxiety

4.2.2.1 Baseline characteristics

The baseline characteristics of the participants with and without anxiety are presented in Table 4-4. Participants with anxiety had a mean age of 65.1±9.6 years, which was not different from the participants without anxiety (p=0.35). A higher mean heart rate was identified in participants with anxiety, compared to the participants with no anxiety (p=0.04). In addition, lower LVEF was seen in the participants with anxiety (p=0.01). No difference between prevalence of dyspnea was seen between the groups (p=0.75). History of VA was comparable between the participants with and without anxiety (p=1.00). 21 (95.5%) of the participants with anxiety had HF, whereas HF was identified in 119 (79.3%) participants without anxiety (p=0.08). Concentrations of NT-proBNP were similar in participants with and without anxiety: median 541 (IQR 203-1150) ng/L vs. median 512 (IQR 211-1234) ng/L, p=0.97).

Table 4-4: Baseline characteristics of the participants stratified by anxiety.

	Anxiety		
	Yes (HADS-A sumscore ≥8) n=23, 12.9%	**No (HADS-A sumscore <8) n=155, 87.1%**	**p-value¶**
Age (years)	65.1±9.6	67.2±10.0	0.35
Gender (Male)	21 (11.8%)	138 (77.5%)	1.00
Body mass index (kg)/m2)	26.8±4.3	27.4±4.1	0.54
Heart rate (beats per minute) [a]	67±13	61±10	0.04
Systolic blood pressure (mmHg)	123±18	131±20	0.72
Left ventricle ejection fraction (%) [c]	36.5±9.5	42.6±10.1	0.01
Symptoms:			
Dyspnea (NYHA III+IV) [a]	4 (18.2%)	24 (15.6%)	0.75
Palpitations [a]	14 (60.9%)	59 (38.3%)	0.06
Presyncope	16 (69.6%)	77 (49.7%)	0.11
Syncope [a]	12 (54.5%)	60 (38.7%)	0.17
History of:			
Heart failure [a]	21 (95.5%)	119 (79.3%)	0.08
Ventricular arrhythmias [a]	19 (86.4%)	131 (85.1%)	1.00
Acute myocardial infarction [a]	15 (65.2%)	89 (58.6%)	0.65
Diabetes mellitus (type 1 and 2)	6 (26.1%)	30 (19.4%)	0.41
Atrial fibrillation [a]	11 (50.0%)	65 (41.9%)	0.49
Laboratory measurements:			
NT-proBNP (ng/L) [b]	541 (203-1150)	512 (211-1234)	0.97
Creatinine (µmol/L) [a]	88.0 (78.0-108.0)	88.5 (76.7-108.0)	0.87

Data presented as numbers (%), mean (SD) or median (interquartile range).
¶= p-value for comparison between the groups with Chi-square for categorical variables, Independent-samples T-test for continuous parametric variables and Mann-Whitney *U* test for non-parametric variables.
[a] <5% missing, [b]<10% missing, [c]<15% missing

4.2.2.2 Items related to anxiety

Answers from HADS-A:

Question #1 “Nervøs eller anspent” (n=176): 97 (55.1%) of the participants had not felt tense or “wound-up”. Two (1.1%) participants were tense or “wound-up” mostly, 67 (38.0%) had experienced these feelings sometimes, whereas 10 (5.6%) participants had often felt tense or “wound-up”.

Question #3 “Urolig følelse” (n=176): One (0.5%) participant answered “very definitely and quite badly ” on the question regarding having a frightened feeling as if something quite badly is going to happen, where 112 (63.6%) participants had not experienced this feeling. Question #5 “Hodet fult av bekymringer” (n=172): 188 (68.6%) participants answered that they had worrying thoughts once in a while, 38 (22.0%) participants had these thoughts occasionally, nine (5.2%) participants reported to have these thoughts “a lot of the time”, and seven (4.0%) participants had worrying thoughts a great deal of the time.

Question #7 “Sitte i fred og ro,” (n=176): 08 (61.3%) participants reported that they could sit at ease and feel relaxed, while two (1.1%) participants had no ability to do this. Six (3.4%) of the participants could not sit down in ease and feel relaxed often, and the remaining 60 (34.0%) participants answered “usually” on this question.

Question #9 “Urolig og sommerfugler i magen” (n=175): Two (1.1%) participants answered that they had a “frightened feeling” very often. 100 (57.1%) of the participants had not experienced this feeling, 63 (36.0%) had this feeling from time to time and 10 (5.7%) participants had the feeling of “butterflies in the stomach” quite often.

Question #11 “Rastløs” (n=174): 73 (41.9%) participants reported no experienced feeling of being restless, whereas 71 (40.8%) participants didn´t have this feeling often. 27 (15.5%) participants had the restless feeling quite often and the remaining three participants (1.7%) were restless very often.

Question #13 “Panikk” (n=174): Two (1.1%) participants experienced a feeling of panic very often and five (2.8%) of the participants had panic quite often. 130 (74.7%) participants had not experienced panic, whereas 37 (21.2%) participants did not have this feeling often.

4.2.3 Shock related anxiety

4.2.3.1 Baseline characteristics

66.2±10.4 years was the mean age of the participants with shock related anxiety, which was comparable to the participants with no shock related anxiety (p=0.51) (Table 4-5). There were a larger amount of women among the patients with shock related anxiety compared to those without (68.0% vs. 43.8%, p=0.008). No difference in heart rate (p=0.83), SBP (p=0.35) or LVEF (p=0.62) was found between participants with vs. without anxiety. Palpitations were identified to be more prevalent in participants with shock related anxiety (p=0.02). Participants with no shock related anxiety had numerically lower median concentrations of NT-proBNP (median 448 [IQR 211-1116] ng/L), compared to the participants with shock related anxiety (median 567 [IQR 203-1234] ng/L), however the difference was not significant (p=0.77).

Table 4-5: Baseline characteristics of the participants stratified by shock related anxiety.

	Shock related anxiety		
	Yes (FSAS sum score ≥12) (n=69, 38.8%)	**No** (FSAS sum score <12) (n=105, 59.0%)	**p-value¶**
Age (years)	66.2±10.4	67.3±9.5	0.51
Gender (male)	57 (32.0%)	100 (56.2%)	0.008
Body mass index (kg/m2)	27.2±4.3	27.3±4.0	0.87
Heart rate (beats per minute) [a]	62±12	61±9	0.83
Systolic blood pressure (mmHg)	128±20	131±20	0.35
Left ventricle ejection fraction (%) [c]	41.5±9.9	42.3±10.5	0.62
Symptoms:			
Dyspnea (NYHA III+IV) [a]	13 (19.1%)	14 (13.5%)	0.39
Palpitations [a]	35 (50.7%)	35 (33.7%)	0.02
Presyncope	40 (58.0%)	52 (49.5%)	0.28
Syncope [a]	30 (44.1%)	40 (38.1%)	0.43
History of:			
Heart failure [a]	55 (82.1%)	81 (80.2%)	0.84
Ventricular arrhythmias [a]	59 (86.8%)	87 (83.7%)	0.66
Acute myocardial infarction [a]	42 (60.9%)	59 (57.8%)	0.75
Diabetes mellitus (type 1 and 2)	13 (18.8%)	21 (20.0%)	1.00
Atrial fibrillation [a]	26 (38.2%)	48 (45.7%)	0.35
Laboratory measurements:			
NT-proBNP (ng/L) [b]	567 (203-1234)	448 (211-1116)	0.77
Creatinine (µmol/L) [a]	87.0 (78.2-106.7)	89.0 (76.0-108.0)	0.67

Data presented as numbers (%), mean (SD) or median (interquartile range).
¶= p-value for comparison between the groups with Chi-square for categorical variables, Independent-samples T-test for continuous parametric variables and Mann-Whitney *U* test for non-parametric variables.
[a] <5% missing, [b] <10% missing, [c]<15% missing

4.2.3.2 Items related to shock related anxiety

Answers from FSAS:

Question #1 “Trene” (n=172): One (0.5%) participant answered “ all the time” on the question regarding having concerns related to exercise due to potential firing of the ICD, whereas eight (4.6%) participants had this concern often. 108 (62.7%) participants were not afraid to exercise, 36 (20.9%) participants had this feeling rarely and 19 (11.0%) participants reported to have concerns related to exercise occasionally.

Question #2 “Være alene når min ICD gir støt” (n=174): 119 (68.3%) participants were not afraid of being alone if the ICD fired, but two (1.1%) of the participants who answered this question reported that they were afraid to be alone all the time. 35 (20.1%) participants had this concern rarely, 10 (5.7%) answered occasionally whereas eight (4.6%) participants had often the concern of being alone.

Question #3 “Unngår bli sint eller opprørt” (n=168): Two (1.1%) participants avoided being angry or upset in order to reduce the risk of triggering the ICD to fire, compared to the 131 (77.9%) participants who reported that they did not avoid these emotions. 25 (14.8%) participants avoided being angry or upset rarely, six (3.5%) participants avoided these emotions occasionally, and four (2.3%) participants avoided these emotions often.

Question #4 “Ikke vite når min ICD vil gi støt” (n=173): Five (2.8%) participants were bothered all the time by not knowing when the ICD could fire, five (2.8%) participants had this concern often, 12 (6.9%) occasionally, 23 (13.2%) had this concern rarely, while 128 (73.9%) participants had never been bothered of this concern.

Question #5 “Ikke vite om ICD vil gi støt når den skal” (n=173): 137 (79.1%) of the participants were not worried that the ICD potentially could not fire if needed, but three (1.7%) participants had this concern all the time. Only two (1.1%) participants reported to have this concern often.

Question #6 “Redd for å ta på andre” (n=172): 164 (95.3%) participants stated that they were not afraid to touch others out of fear of giving them shock if the ICD fired, whereas five (2.9%) participants had this concern rarely. One (0.5%) participant had the concern of touching others all the time and two (1.1%) participants had this concern occasionally.

Question #7 “Tiltrekke oppmerksomhet” (n=173): No concern regarding drawing attention if the ICD fired was reported by 148 (85.5%) participants, whereas four (2.3%) participants stated to be bothered by this concern all the time. One (0.5%) participant had this concern often.

Question #8 “Støt når hjertet banker raskt” (n=171): Three (1.7%) participants were concerned all the time for a potential firing of the ICD when they felt the heart beat too fast. On the other hand, 111 (64.9%) participants had not this though. The concern was reported by four (2.3%) participants to be prevalent often, while 18 (10.5%) had this concern occasionally. The remaining 35 (20.4%) participants had the concern of ICD shock if the heart beat too fast rarely.

Question #9 “Uønskede tanker om ICD” (n=172): 139 (80.8%) of the participants who answered the question regarding unwilling thoughts regarding a potential firing of the ICD, did not have these thoughts. 23 (13.3%) participants had unwilling thoughts rarely, six (3.4%) reported to have these thoughts occasionally, three (1.7%) participants had often unwilling thoughts about the ICD, whereas one (0.5%) participant had unwilling thoughts all the time.

Question #10 “Seksuelt aktiv” (n=166): The most prevalent shock related concern in the study population was the concern of being sexual active because the ICD could potentially fire. Six (3.6%) participants reported that they had this concern all the time, compared to the 137 (82.5%) participants who reported never have the concern of being sexual active. Three (1.8%) participants had this concern often, five (3.0%) were concerned occasionally and 15 (9.0%) participants were rarely concerned of being sexual active.

4.2.4 Previous shock

4.2.4.1 Baseline characteristics

Table 4-6 presents the baseline characteristics of the participants with vs. without previous ICD shock. Participants who had experienced shock had a mean age of 67.5±10.1 years, whereas 66.5±10.1 years was the mean age for the participants who had not experienced previous shock (p=0.66). Syncope was found to be more prevalent in participants with experienced shock, compared to the participants with no previous shock (p=0.02). No difference in history of HF was found between the groups (p=0.76). A history of VA was more prevalent in the group of participants with previous shock vs. no previous shock (p=0.02). Numerically higher concentrations of NT-proBNP (median 719 [IQR 334-2609] ng/L) were seen in the participants who had experienced shock, compared to the participants who had not experienced previous shock (median 448 [IQR 203-1132] ng/L). However, the difference between the concentrations of NT-proBNP did not reach statistical significance (p=0.07).

Table 4-6: Baseline characteristics of the participants stratified by experienced shock.

	Experienced ICD shock		
	Yes (n=23, 12.9%)	**No (n=142, 79.8%)**	**p-value¶**
Age (years)	67.5 ±10.1	66.5±10.1	0.66
Gender (male)	20 (11.2%)	128 (72.0%)	0.71
Body mass index (kg/m2)	26.2±2.7	27.5±4.4	0.07
Heart rate (beats per minute) [a]	62±8	62±10	0.92
Systolic blood pressure (mmHg)	133±26	129±18	0.49
Left ventricle ejection fraction (%) [c]	41.2±10.3	42.1±10.3	0.72
Symptoms:			
Dyspnea (NYHA III+IV) [a]	0 (0.0%)	25 (17.9%)	0.02
Palpitations [a]	8 (34.8%)	59 (41.8%)	0.64
Presyncope	13 (56.5%)	76 (53.5%)	0.82
Syncope [a]	15 (65.2%)	54 (38.3%)	0.02
History of:			
Heart failure [a]	19 (86.4%)	112 (81.2%)	0.76
Ventricular arrhythmias [a]	23 (100.0%)	115 (82.1%)	0.02
Acute myocardial infarction [a]	14 (60.9%)	83 (59.7%)	1.00
Diabetes mellitus (type 1 and 2)	6 (26.1%)	27 (19.0%)	0.41
Atrial fibrillation [a]	13 (56.5%)	56 (39.7%)	0.17
Laboratory measurements:			
NT-proBNP (ng/L) [b]	719 (334-2609)	448 (203-1132)	0.07
Creatinine (µmol/L) [a]	96.0 (83.0-126.0)	87.0 (75.5-104.5)	0.11

Data presented as numbers (%), mean (SD) or median (interquartile range).
¶= p-value for comparison between the groups with Chi-square for categorical variables, Independent-samples T-test for continuous parametric variables and Mann-Whitney *U* test for non-parametric variables.
[a]<5% missing, [b]<10% missing, [c]<15% missing

4.3 Previous shock and patient related outcomes

The prevalence of depression was not different between the participants with experienced shock and the participants with no previous shock (8.7% vs. 9.2%, p=1.00) (Figure 4-2, Panel A). Further, the distribution of anxiety in participants with experieces shock was comparable to the proportion of participant anxiety that had not experienced previous shock (17.4% vs. 10.6%, p=0.30%). As for depression and anxiety, no difference of shock related anxiety was seen between the groups (47.8% vs. 38.0, p=0.35). The distribution of gender between the groups is presented in figure 2, Panel B and C.

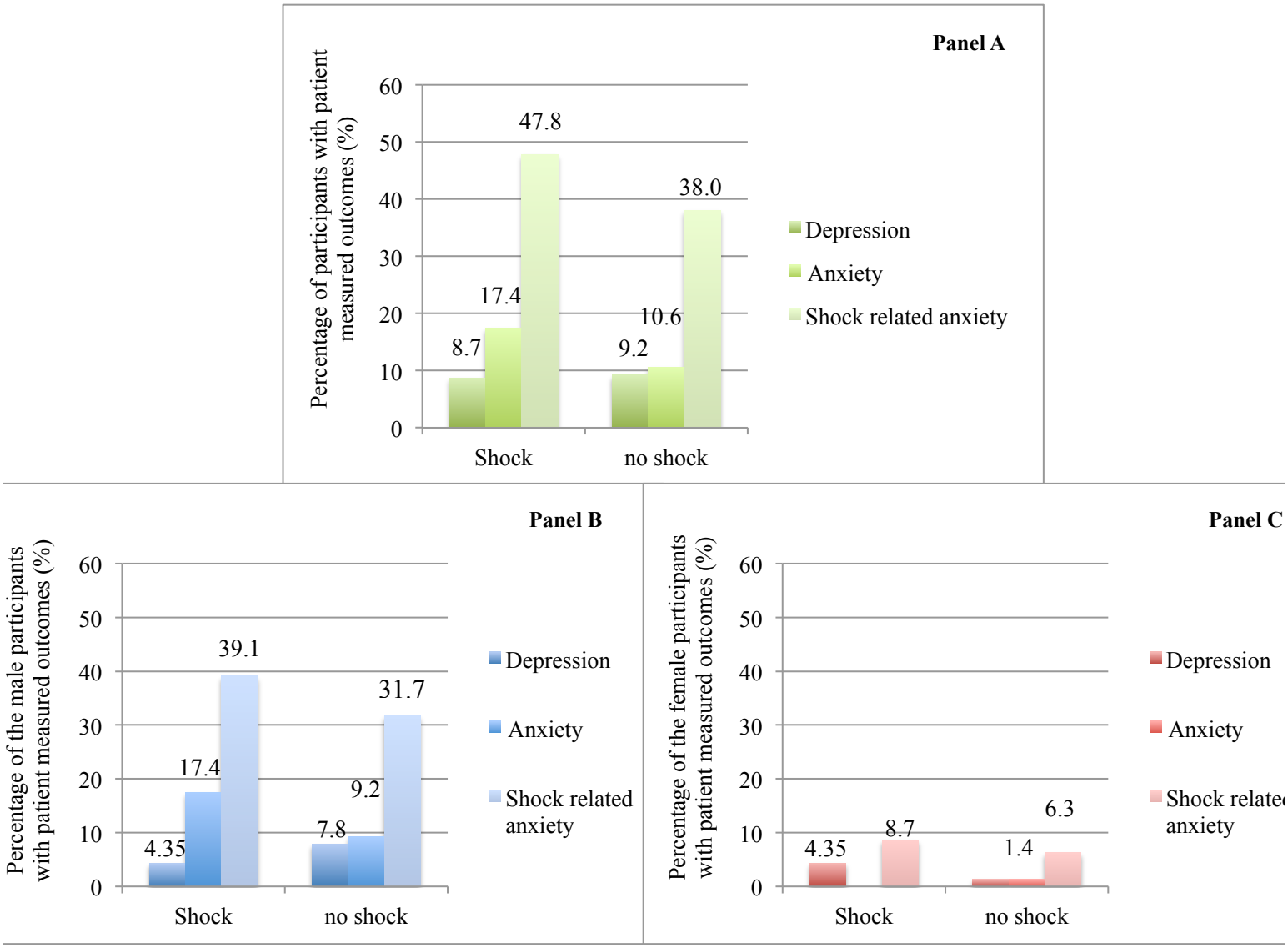

Figure 4-2: Panel A presents the amount of participants with patient measured outcomes in relation to previous shock vs. no previous shock, calculated as percentage from the respective shock /no shock groups. The gender distribution of the patient related outcomes in relation to previous shock vs. no shock are presented in panel B and C. The gender distribution is calculated from panel A.

4.4 Predictors of depression, anxiety and shock related anxiety

4.4.1 Depression

After the initial analyzes using Spearman's correlation to assess for colinearity and association to the outcome, we included previous shock, dyspnea, heart rate, LVEF, palpitations and NT-proBNP in the logistic regression analyzes for depression. The covariates in the regression model explained 5.1% of the variation in depression among the study participants (R^2= 0.051). Presence of palpitations (p=0.02), heart rate (p=0.01) and dyspnea (NYHA class, p=<0.001) were significantly associated with depression in participants treated with ICD in the univariate models (Table 4-7A). After adjusting for the other variables, palpitations (OR 4.5 [95% CI 1.2-16.9] p=0.02) and dyspnea (OR 10.8 [95% CI 2.3-50.5.] p=0.002) remained associated to depression, while heart rate did not (p=0.37). The participants had four times higher risk of depressions when having palpitations, whereas the risk of depression was eleven times higher if the participants were classified as NYHA III or IV, compared to the participants with NYHA I or II. NT-proBNP was excluded as variable after the first regression analysis, in order to check if the concentrations of the biomarker had any influence on the results. As identified in the first regression analysis, concentrations of NT-proBNP did not influence the results from the regression analyzes.

Table 4-7A: Presentation of the univariate and multivariate analyzes of determinants for depression.

	Depression			
Covariates	**Unadjusted OR (95% CI)**	**p-value**	**Adjusted OR (95%CI)**	**p-value**
Previous shock, yes vs. no	0.9 (0.1-4.4)	0.94	1.4 (0.2-7.7)	0.68
Dyspnea (NYHA III+IV), yes vs. no	8.2 (2.8-24.0)	<0.001	10.8 (2.3-50.5)	0.002
Heart rate (%)	1.0 (1.0-1.1)	0.01	1.0 (0.9-1.0)	0.37
Palpitations, yes vs. no	3.2 (1.1-9.0)	0.02	4.5 (1.2-16.9)	0.02
LVEF (%)	0.9 (0.9-1.0)	0.23	0.9 (0.9-1.0)	0.81
NT-proBNP (ng/L)	1.2 (0-8-2.0)	0.26	1.2 (0.6-2.3)	0.49

4.4.2 Anxiety

Previous shock, dyspnea, heart rate, palpitations, syncope and NT-proBNP were included as covariates in the regression analyzes for anxiety (Table 4-7B). The regression model explained 4.8% of the variability in anxiety among the study participants (R^2= 0.048). In the univariate analysis, heart rate (p=0.01) and palpitations (p=0.04) was found to be associated with anxiety. None of the variables were significant associated with anxiety in the multivariate analysis. Moreover, association between the variables and anxiety were not seen after adjusting for NT-proBNP.

Table 4-7B: An overview of the results from the univariate and multivariate analyses of anxiety in the ICD population.

	Anxiety			
Covariates	**Unadjusted OR (95% CI)**	**p-value**	**Adjusted OR (95%CI)**	**p-value**
Previous shock, yes vs. no	1.7 (0.5-5.9)	0.34	1.5 (0.3-6.7)	0.59
Dyspnea (NYHA III+IV), yes vs. no	1.2 (0.3-3.8)	0.75	0.7 (0.1-4.2)	0.78
Heart rate (%)	1.0 (1.0-1.0)	0.01	1.0 (0.9-1.0)	0.31
Palpitations, yes vs. no	2.5 (1.0-6.1)	0.04	2.3 (0.7-7.3)	0.15
Syncope, yes vs. no	1.9 (0.7-4.6)	0.16	2.6 (0.8-8.7)	0.10
NT-proBNP (ng/L)	1.0 (0.6-1.5)	0.94	0.9 (0.5-1.5)	0.69

4.4.3 Shock related anxiety

Table 4-7C presents the results from the univariate and multivariate regression analyses for shock related anxiety. Previous shock, NT-proBNP, palpitations and gender were included in the analyses. The covariates explained 5.3% of the variability of shock related anxiety in the study population (R^2= 0.053%). Palpitations (p=0.02) and gender (p=0.01) were associated with shock related anxiety in the univariate model, however female gender was the only variable significantly associated with shock related anxiety in the multivariate analysis (p=0.03). The risk of shock related anxiety was found to be four times (OR 3.8 [95% CI 1.1-13.3] p=0.03) in women compared to men. Furthermore, as in the multivariate analysis for depression and anxiety, NT-proBNP was not associated to shock-related anxiety and hence, the association between gender and shock-related anxiety was independent of NT-proBNP levels.

Table 4-7C: Presentation of the results from the univariate and multivariate analyzes in shock related anxiety.

	Shock related anxiety			
Covariates	**Unadjusted OR (95% CI)**	**p-value**	**Adjusted OR (95%CI)**	**p-value**
Previous shock, yes vs. no	1.5 (0.6-3.9)	0.31	1.3 (0.4-3.5)	0.60
Palpitations, yes vs. no	2.0 (1.0-3.7)	0.02	1.4 (0.7-3.0)	0.27
Gender	4.2 (1.4-12.5)	0.01	3.8 (1.1-13.3)	0.03
NTproBNP (ng/L)	1.0 (0.7-1.3)	0.77	1.0 (0.7-1.3	0.80

5.0 Discussion

5.1 Findings

5.1.1 Main findings

The main findings in the present study were that 1) concentrations of NT-proBNP, a surrogate for disease severity, were not associated with prevalent depression or anxiety in the study population, 2) among the covariates investigated we found palpitations and dyspnea to be independent predictors of depression, and female gender to be associated with shock related anxiety and 3) previous shock was not associated with the patient related outcomes.

5.1.2 Demographical findings

Among the participants included in the study, 190 (81%) completed the two individual questionnaires; HADS and FSAS. 12 participants had not complete information regarding the clinical variables (non-complete CRF), and these participants were consequently excluded, yielding a total of 178 participants in the present substudy. The mean age of the participants was 66.9±9.9 years, whereas the age was comparable to the mean age in previous studies (90, 108, 109). The current study population comprised of 89% men and 11% women, and the gender distribution was similar to previous patient-reported outcome studies of patients treated with ICD (90, 91, 108).

5.1.3 Prevalence of the patient related outcomes

Depression and anxiety, classified by HADS (sumscore ≥8), were identified in 10.1% and 12.9%, respectively. Shock related anxiety, assessed by FSAS (sumscore ≥12), was present in 38.8% of the study population. The proportion of anxiety and depression was lower in the current study compared to findings from a systematic review, which assessed 45 studies regarding anxiety and depression in the ICD population (87). The prevalence of depression and anxiety in the present study may have been increased with a higher percentage of participants, and if all of the submitted questionnaires were included in the statistical analysis. On the other hand, Bilge et al. concluded with high prevalence of depression (46%) and anxiety (41%) in participants treated with ICD, despite only 91 participants (110). These results indicate that higher amount of participants may not have changed the prevalence of the patient related outcomes in the current study. In addition, a higher proportion of participants may have identified a lower prevalence of depression and anxiety instead of a higher prevalence. Shock related anxiety was the most prevalent mental distress in the study

with a total of 38.8%. Female participants had higher proportion of shock related anxiety (70.6%) when compared to the male participants (32.0%, p=0.008), whereas this result was consistent with previous studies (93-95). On the other hand, higher percentage of women with shock related anxiety, compared to men, is seen to not be significant associated after statistical corrections (111). Male participants had higher prevalence of depression (8.4%) and anxiety (11.8%), although the results did not reach statistic significance. The proportion of men with depression and anxiety was comparable with findings from the general population in a small part of Norway, whereas the prevalence of mental distress was 10% and 9%, respectively (112). The low prevalence of depression and anxiety in the previous study may indicate that Norway is a country with low amount of mental distress. Further, the national distribution of depression and anxiety may support the low prevalence of depression and anxiety in the current substudy due to approximetly equal standard of living.

5.1.4 Concentrations of NT-proBNP

A numerical, although not significant, difference between the concentrations of NT-proBNP in participants with (median 698 [IQR 272-1828] ng/L) vs. without (median 478 [IQR 209-1162] ng/L) depression was found. Higher NT-proBNP concentrations were also seen in participants with (median 541 [IQR 203-1150] ng/L) anxiety vs. without anxiety (median 512 [IQR 211-1234] ng/L), and in participants with shock related anxiety (median 567 [IQR 203-1234] ng/L) vs. no shock related anxiety (median 448 [IQR 211-1116] ng/L), but the concentrations of NT-proBNP did not reach statistical significance.

No association between concentrations of NT-proBNP and depression, anxiety or shock related anxiety was found in the study population. A previous study presented an association between depression and higher levels of BNP in patients with HF (not treated with ICD) (113). The study suggested that participants with higher concentrations of BNP had up to 12-folds higher risk of having severe depression, when compared to participants with lower BNP levels (113). In contrast, another study in patients with HF found no significant association between concentrations of NT-proBNP and symptoms of depression (114). The association between natriuretic peptides and anxiety in patients with HF was studied by Herrmann-Lingen et al., who reported increased concentrations of ANP in patients with anxiety (115). Previous studies indicate that there may be an association between NT-proBNP and mental distress in patients with HF (113, 115). At the time of writing, no previous studies had

assessed the relationship between NT-proBNP and depression, anxiety and shock related anxiety in the ICD population.

5.1.5 Clinical determinants of patient related outcomes

5.1.5.1 Clinical determinants of depression

Participants with depression had high prevalence of dyspnea (NYHA class III or IV, 52.9%), and NYHA class III or IV was an independent determinant for depression in the ICD population after the multivariate regression (OR 10.8 [95% CI 2.3-50.5] p=0.002). The result was supported by previous studies that found a significant association between dyspnea and depression (116, 117). Further, 66.7% of the participants with depression had palpitations. In addition, the presence of palpitations was found to be associated with depression in our study population, and the association was still significant after multivariate adjustment (OR 4.5 [95% CI 1.2-16.9] p=0.02). Few previous studies have assessed the relation between palpitations and depression in the ICD population, but palpitations have been identified as one of the most frequent causes of hospitalization in the respective population (109). Due to the relation between palpitations and hospitalization, many of the participants in the current study may have been hospitalized as a consequence of the palpitations because of the pre-held beliefs on how a cardiac event evolves. As a consequence of recurrent hospitalizations, depression may have developed over time. Haworth et al. suggested that increased prevalence of depression could be explained by reduced activity, resulting time to reflect on the poor health status (118). Experienced palpitations during physical activity may have contributed to inactivity for many of the participants, and consequently depression. The same association may have been seen in the participants who had experienced syncope. 70.6% of the participants who had experienced syncope had depression, whereas 37.5% of the participants without depression had experienced syncope. However, syncope was not eligible for the regression analyzes of depression, indicating no significant association between depression and experienced syncope in the study population. History of HF was not different between participants with vs. without depression. Previous studies have presented HF as the predominantly determinant for development of depression and anxiety in participants treated with ICD whereas the patient measured outcomes were linked to symptoms of HF (93, 113, 118-120). According to these studies, the current prevalence of HF participants with depression (94.1%) and anxiety (95.5%) may have been seen due to HF symptoms and not as a consenquence of living with ICD.

5.1.5.2 Clinical determinants of anxiety

As for depression, HF is seen to be a determinant for anxiety in the ICD population, whereas the current result was surprising (93). No difference in NYHA class (p=0.75) was seen between the participants with anxiety vs. without anxiety. Lang et al. suggested that higher NYHA class, a score for dyspnea on exertion, was associated with anxiety in the ICD population, whereas the results differed from the current results (121). The distribution of diabetes was unequal between the participants with (26.1%) and without (19.4%) anxiety. Previous studies have discussed the relation between diabetes and anxiety, although without consensus between the results (111, 117, 122). The results in the present study regarding diabetes and anxiety, may have contributed to additional strengthening of the studies where no association between diabetes and anxiety in the ICD population has been seen. Heart rate (p=0.04) was found to be higher in participants with anxiety, however no association between heart rate and anxiety in the multivariate analysis was detected (OR 1.0 [95% CI 0.9-1.0] p=0.31). This result was consistent with a previous study that suggested low heart rate variability when having anxiety in the ICD population (122). A preset pacemaker rhythm from the ICD is often seen in ICD participants, and therefore should the relation between heart rate and anxiety in the present study, also depression and shock related anxiety, be interpreted in the light of no differentiation between participants with vs. without pacing in the study (123). LVEF was found to be lower for the participants with anxiety, compared to the participants without anxiety (p=0.01). This finding could indicate that reduced LVEF was a determinant for the participants with anxiety. However, this result was not consistent with previous studies whereas no relation between low LVEF and anxiety was detected (121). The deviation in the results between the studies may due to a higher prevalence of lower LVEF in the current study, indicating participants with increased severity in the current study. LVEF was not used in the regression analyzes for anxiety; consequently the variable was not associated with anxiety in the study population.

5.1.5.3 Clinical determinants of shock related anxiety

History of palpitations (OR 2.0 [95% CI 1.0-3.7] p=0.02) and female gender (OR 4.2 [95% CI 1.4-12.5] p=0.01) was significantly associated with shock related anxiety in the univariate models. However, only female gender was associated with shock related anxiety in the multivariate regression (p=0.03). Few studies have assessed palpitations in relation to shock related anxiety. In general, palpitations are normal symptoms of anxiety, where the unpleasant sensation of palpitations can increase the feeling of anxiety and panic (82).

Moreover, palpitations are typical symptoms in the cardiac population, whereas the participants in the study might not have been able to differentiate the palpitations as cardiac symptoms or anxiety symptoms (82). The participants with shock related anxiety might have associated palpitations with upcoming ICD shock, due to experienced previous shock or pre-held beliefs of how an ICD shock develops. As a consequence, the frequency of the palpitations may have increased due to shock related anxiety and not due to cardiac symptoms. As discussed for the association between depression and palpitations, palpitations are a frequent cause of hospitalization in the ICD population (109). Consequently, the participants with shock related anxiety might have developed anxiety related to shock due to hospitalization of palpitations, as a consequence of a previous cardiac event. Female gender is previously seen to be a determinant for development of shock related anxiety in the ICD population, whereas previous studies supported the significant association between female gender and shock related anxiety in the current study (93-95). Higher proportion of shock related anxiety in women could be explained by higher sensitivity and mental stress, compared to men (82).

5.1.6 Specific items from the questionnaires

5.1.6.1 Hospital Anxiety and Depression Scale for depression

The amount of participants that could laugh and see the funny in things "as much as I always could" (75.8%), was similar to the amount of participants that reported to have a good mood "most of the time" (74.1%). In addition, the high proportion of participants that answered "definitely as much" (59.6%) to the question regarding having enjoyment of things, corresponded with the percentage of participants who answered, "as much as I ever did" (65.3%) on the question regarding looking forward to things with enjoyment. When putting these results in relation, it is seen that a positive mindset in the ICD population contributes to a better a mental health and improved social functioning (124). The majority of the participants in the study population appeared to have a positive mindset, and consequently a good mental health. This suggestion is supported by the low percentage of depression in the current study.

The majority of the participants answered that they felt "slowed down" in different scales. Slow body movements are one of the typical symptoms of depression, whereas this symptom was expected to be seen in participants with depression (82). Although a substantial part of the study population experienced this feeling, the findings did not correspond to the

proportion of participants with depression (10.1%). Due to the mean age of 66.9±9.9 the population, the feeling of being slowed down may have been related to the age and not mental distress.

57.4% did care about their appearances in the same scale as before, 4.0% reported that they didn´t care about their appearance and 23.5% could have cared more. As for slow body movement, increased age may be the cause of reduced care of appearance, whereas the older population care more for their physical function (125).

The majority of the participants in the study reported enjoyment of a good book or a radio/TV-program, whereas only 2.2% could do this very rarely. The participants that had no or little enjoyment of a book or TV-show may not have enjoyed these situations despite having an ICD, whereas the results might not due to depression.

5.1.6.2 Hospital Anxiety and Depression Scale for anxiety

The same amount of participants that mostly felt tense or "wound-up" (1.1%) or were restless very often (1.7%,) could not sit down in ease and feel relaxed (1.1%). These results indicate that being nervous or "wound up" is associated with restlessness and the reduced ability to sit down in ease and feel relaxed. The low percentage of participants that were restless and could not sit down in ease can be discussed as a consequence of a potential low amount of very sick cardiac participants in the study.

10.2% of the study population answered "yes, but not too badly" on the question regarding having a frightened feeling of something terrible is going to happen, whereas 0.57% reported "very definitely, and quite badly". Thoughts of catastrophes are often seen in participants treated with ICD, and panic may be associated with these kinds of thoughts (126). When taking this in consideration, the proportion of the study population that reported frightened feeling "yes, but not too badly" corresponded with the percentage of participants that had the feeling of panic quite often (2.8%) and very often (1.1%), indicating that the participants with panic had thoughts of catastrophes.

5.1.6.3 Florida Shock Anxiety Scale

Fear of exercising due to risk of triggering the ICD was seen to be one of the dominant shock related concern in the study population. Concerns regarding exercising are seen to increase

inactivity in participants treated with ICD (127, 128). Regardless, exercising is not associated with increased number of ICD shock, in fact is exercising seen to befit cardiac rehabilitation and should not be avoided (129, 130).

Lack of control is a prevalent cause of anxiety in the ICD population, and no exceptions were discovered in the current study (88, 131). It concerned several of the participants that they didn´t knew when the ICD could fire. The participants reported that they had these thoughts occasionally (6.9%), often (2.8%) and all the time (2.8%). Other aspects of lack of control was the fear of being alone if the would ICD fire, a prevalent concern in the study population, and not knowing if the ICD would not fire if needed, whereas only a small amount of the participants reported this concern. Although the mentioned questions related to lack of control were only answered by a small amount of the current study population, the concerns may have contributed to avoidance behavior related to places or situations that the participants associated with potential ICD shock (89).

10.4% was concerned occasionally 2.3% often and 2.3% was concerned all the time of a potential ICD firing as a consequence of increased heart rate. Experienced shock may have been the cause of the fear, whereas previous studies have suggested that experienced tachycardia and AF could increase anxiety and concerns related to ICD firing (108, 126). According to Morken et al. “the experience of tachyarrhythmia, especially VT, may be a reminder of the underlying life-threatening disease and thereby increase psychological vulnerability, such as fear” (108). The concerns regarding shock from the ICD is suggested to be anchored to the conception of a failing health and further to death anxiety, whereas death anxiety is correlated to the amount of shocks (105, 126). Moreover, general anxiety and shock related anxiety is suggested to trigger the ICD to fire (124, 132). In addition, anger is seen to be a significant factor of ICD shock (133). The majority (77.9%) of the current study population reported no avoidance of getting angry, and the response may indicate reduced concerns of anger in relation to ICD shock.

Previous studies have suggested increased amount of concerns regarding being sexual active in the ICD population (134-136). In the current study 3.6% answered all the time, 1.8% often and 3.0% occasionally on the question regarding concerns of being sexual active. Although the majority (82.5%) of the participants didn’t have any sexual concerns, the percentage of participants with sexual concerns should be taken seriously. The results did not correspond

with previous studies, but as discussed earlier for prevalence of depression and anxiety, a higher percentage of participants may had identified a higher rate of sexual concerns (136). Sexual education after implantation of ICD is suggested in order to prevent sexual inactivity (134, 135).

Low prevalence of anxiety and depression in the study population may have indicated a relatively high rate of ICD acceptance, whereas most of the participants live a good life with the device. Compared to other studies, higher prevalence of anxiety and depression is associated with lack of device acceptance (137, 138). In order to emphasize the correlation between device acceptance and low prevalence of mental distress, the Florida Patient Acceptance Survey (FPAS) could have been used in addition to FSAS (139).

5.1.7 Patient related outcomes in relation to previous shock

8.7% of the participants with previous shock had depression, although no difference in history of previous shock was seen between the participants with vs. without depression (p=1.00). Further, the multivariate regression of depression did not expose any significant association between previous shock and depression in the study population (OR 1.4 [95% CI 0.2-7.7] p=0.68). Thylén et.al suggested that concerns regarding the ICD have a higher impact on depression in the ICD population than previous shock, whereas this may have been the cause of non-significant association between previous shock and depression in the current study (90).

Previous shock is previously seen to increase the risk of anxiety in patients treated with ICD (90, 140). 17.4% of the current participants with previous shock had anxiety, compared to the 10.6% with anxiety with no previous shock. As for depression, no difference in history of experienced ICD shock was seen between the participants with and without anxiety (p=0.30). Further, previous shock was not a significant determinant of anxiety in the study population (OR 1.5 [95% CI 0.3-6.7] p=0.59). Although previous studies did not support the current results, Jacq et al. could not conclude with a significant association between previous shock and anxiety in the ICD population (90,91,140). The results from the current and previous study indicate that the association between previous shock an anxiety should be investigated further due to conflicting results.

Results from previous studies have not been consistent regarding the association between previous shock and development of shock related anxiety (90, 108). 47.8% of the participants in the present study with shock related anxiety had experienced shock, whereas 38.0% with shock related anxiety had not experienced previous shock (p=0.35). As for depression and anxiety, previous shock was not significantly associated with shock related anxiety in the study population (OR 1.3 [95% CI 0.4-3.5] p=0.60). This result was supported by Thylen et.al (90).

5.1.8 Treatment

Although the majority of the study population did not experience depression or anxiety, the small percentage of participants with mental distresses needs to be focused on in order to increase the mental health. Attention on treatment of these patients is much needed. Several studies have shown reduced symptoms of anxiety and depression after systematic therapies, in addition to reduced avoidance behavior and increased acceptance of the ICD (98, 141, 142). A beneficial therapy should consist of ICD education, symptoms of cardiac events and cognitive behavioral therapy (98, 143). Increased knowledge regarding function of the ICD and cardiac events correspond with decreased anxiety and depression. It must be emphasized that therapy should also be given to patients with no symptoms of depression and/or anxiety, in order to prevent the prevalence of mental distress in the ICD population. It is also suggested that implementing strategies such as education, action plan and debriefing before and after an ICD-shock, have a positive impact on psychological concerns (144). In order to reduce anxiety and depression in the ICD population, it is necessary to design therapy programs for the individual patient and not for the entire population (145).

5.2 Methodical considerations

5.2.1 Recruitment and sampling

The participants in the present study were recruited from the ongoing SMASH-1 study at AUH. 236 of the 249 participants in the SMASH-study received questionnaires, consent forms and information regarding the study by mail or at their SMASH-1 visits at AUH. 81% of the 236 participants completed and submitted the questionnaires and 75% had their complete CRF registered, whereas data from these participants were used in the statistical analyzes. 89% of the participants were men. The higher amount of men may indicate lower amount of female cardiac participants treated with ICD at AUH. However, it must be discussed that more female patients could have been excluded or did not want to participate in the SMASH-1 study. Due to the unequal amount of men and women, it was difficult to determine significant results for the female participants.

The inclusion and exclusion criteria in the current study were the same as in the SMASH-1 study. Few inclusion criteria were implemented in the SMASH-1 study, resulting in many potential participants from the ICD population at AUH (99). The low minimum age contributed to a range of variation in age, and further to reduced chance of excluding potential participants. The exclusion criteria were related to factors that potentially could have interfered with the study results (99). In addition, exclusion of participants with terminal cancer and neurological conditions with short life expectancy contributed to inclusion of participants with higher chances of long-term survival and participation in the study. To maintain the proportion of participation, the SMASH-1 study excluded participants with lower chances of compliance, such as drug- or alcohol abusers. The inclusion of participants to the SMASH-1 study started approximately a year before the current study, without any records of excluded participants, and therefore was it impossible to track how many participants who were excluded from the main SMASH-1 study and consequently from the current study.

Standardized routines were established in order to have good routines for processing the transmission of the questionnaires and reminders, and the completed and submitted questionnaires with the signed consent forms (146). A register with the participants name, date of birth, study ID and date for received questionnaires was established. In addition, the consent forms and questionnaires were labeled with the participants study ID (the same number as in the SMASH-1 study) when received.

The questionnaires were distributed in two rounds, where the first distribution was completed October 2017. An inconvenience in the first distribution process occurred, which resulted in a delay for when the completed questionnaires were received at AUH. The cause of the delay was lack of decent marking of the submission address to the right division at AUH, on the stamped envelopes. As a consequence, some of the questionnaires may have disappeared in the mail. In addition, it took nearly a month before the first completed questionnaires with signed consent forms arrived. For some of the submitted questionnaires it took up to two or three months before they arrived at the right division. The delay was a setback for the progression in the study, consequently the predicted deadlines had to be altered. Normally, the reminders, with a new set of questionnaires and consent forms, should have been sent out a month after the first distribution to the participants who had not answered (146). Nevertheless, the reminders were sent out January 9th 2018 to the participants who had not answered and to the participants who only had submitted the questionnaires and not the signed consent forms, in order to decrease the risk of missing participants. In addition, questionnaires and consent forms were sent to the participants included in the SMASH-1 study between October 2017 and January 2018. The stamped envelopes were correctly marked with full address to AUH, division and contact person before the second transmission. In addition, a cover letter with information regarding why the participants received a reminder, was attached in order to solve any confusions (Appendix 8). The participants who received the questionnaires for the first time after the second transmission, received the original cover letter. The purpose of the reminder was to ensure a high percentage of participation (146). A second reminder is usually sent out 6-8 weeks after the first distribution, but only one reminder was sent out in the current study due to alterations in the timelines (146). The participants who received the questionnaire for the first time in January 2018, did consequently not receive a reminder. The inconvenience may have contributed to decreased amount of participants. On the other hand, the statistical analyses were postponed approximately a month in order to obtain a higher amount of completed questionnaires.

There was a difference in how and when the participants received the questionnaires. The majority received the questionnaires by mail between the inclusion consultation and the one-year follow-up by mail. The strengths by sending out the questionnaires by mail was that the questionnaires was sent out to participants who lived far away from AUH, in addition to

include the participants that didn't have annual or biannual check-ups at AUH at the time of inclusion. The remaining participants received the questionnaires at their baseline visit or at the one-year visit to the SMASH-1 study. In order to standardize the participants environment when answering the questionnaires, the participants at the SMASH-1 visit received the questionnaires to answer home instead of an interview. These participants answered the questionnaires in the same environment and with the same impact from others as the participants who received the questionnaires by mail.

15 of the 236 participants had not submitted the signed consent forms with the questionnaires after the first transmission. Lack of signed consent forms resulted in exclusion of these participants. It was not clearly explained that the consent forms had to be signed and submitted in order to participate in the study in the first cover letter. However, the importance of a signed consent form was described clearly in the cover letter to the reminder. The questionnaires and consent forms were not marked with the participants study ID before the first transmission, resulting in missing participants when the submitted questionnaires were received without ID. The only way to find the correct participants study ID after the first submission was to check with the names written on the consent forms and match the names up with the corresponding participants study ID in the register. Before the last submission, the participants study ID was written on the questionnaires to ensure that participants with and without signed consent forms were registered with completed questionnaires after the last submission. 2 participants with completed questionnaires were excluded from the current study due to an error made by the investigator. The participants study ID were written on the consent forms and the questionnaires when received at the department, before separated into different binders. The investigator wrote the same participant study ID on two questionnaires, resulting in exclusion of the participants whom had their participants study ID written on last. For example, patient study ID 1179 was written on two questionnaires, whereas the questionnaire that had 1179 written on last was excluded. This error would have been avoided if the investigator had written the participants study ID on the questionnaires before the first submission.

4 participants withdrew their consent from the SMASH-study, which resulted in exclusion of three participants in the current study. One of the participants had already answered the questionnaires when he/she withdrew the consent, however the investigator had the permission from the participant to use the data from the CRF and the completed

questionnaires in the present study. The relatives of two participants reported that the participants had to withdraw the consent due to severely poor health. The fourth patient withdrew his/hers consent without any explanation. It is widely known that participants don't complete their participation in a study if the study requires too much from the participants (146). The participants who withdrawn their consent may have felt strongly that the participation in the SMASH-1 study required too much with two consultations, complete and submit questionnaires to a substudy, in addition to a possible resubmission due to an error in the current study which was not the participants fault. 5 of the participants in the SMASH-1 study died after the current study started, whereas one of the participants completed and submitted the questionnaires before the death occurred. The data from this participant were included in the statistical analysis.

Questionnaires received after March 12th was not included in the study. 5 of the 236 distributed questionnaires were received after the deadline. The written consent form was missing to one of the questionnaires, and another questionnaire had already been submitted and registered on the respective participant after the first submission. Male participants with a mean age of 60.4 years completed all the questionnaires received after the deadline. The delayed questionnaires could not have altered the results significantly, due to low amount.

5.2.2 Questionnaires

A presentable questionnaire should consist of information regarding the study, guidance, questions and answer options (146). The questionnaires in the current study consisted of a cover letter, guidance to each section, questions and answer options. The cover letter contained information regarding the purpose of the study participation and questionnaires, information regarding the participants rights and contact information directly to the investigator. The cover letter to the reminder was more detailed due to the added information regarding the consent form and how to submit the questionnaire. The first cover letter contained the telephone number to the research group, whereas the participants that contacted the research group may have received wrong information from the person who answered with reduced knowledge regarding the substudy, or information from the participants may have stopped at the person who answered.

5.2.2.1 Hospital Anxiety and Depression Scale

Previous articles have assessed HADS as a questionnaire with high validity and reliability for measurement of anxiety and depression (147, 148). HADS is not only seen to assess severity and causality of anxiety and depression in hospitalized somatic and psychiatric patients, but also for patients in the general population (147). On the other hand, HADS was not constructed to assess anxiety and depression specific in the ICD-population (148).

HADS consisted of 14 questions, whereas it took about five minutes to complete the questionnaire. Seven of the questions concerned anxiety (HADS-A) and the last seven concerned depression (HADS-D) (104). The questions were formulated as statements where the participants ticked off the answer that corresponded with the participants subjective health status and concerns (104). The questions were short and addressed the essence of the questions in a simple matter. Good questions can only be interpreted in one matter because inexpedient words and formulations are removed (146). In addition, well-formulated questions are open and do not lead the participants in a desired direction (146). The HADS questions were open, clear and direct statements constructed to gather information regarding how often the participants experienced symptoms of anxiety and depression. Strength for the questions was the use of a participant friendly vocabulary (146). Questions where the participants have to remember long back in time in order to answer could result in answers with lack of trustworthiness due to difficulties of differentiating the actual event with other memories (146). HADS obtained information regarding the participants feelings the last week, consequently reducing the uncertainty in the answers. In order to ensure that the answers in HADS represented the participants mean general mental health, not only the last week, the guidance could have stated that the participants had to answer according to their subjective health in the every day life. However, this approach may have increased the uncertainty in the answers.

As for the questions, it's important that the answers options in a questionnaire are well formulated and easy to interpret (146). In addition, the answer options must be easy to differentiate from each other and concern a variety of options that covers the participants different meanings, feelings or emotions (146). Some of the answers in HADS may have been difficult to differentiate and interpret. The validated Norwegian version of HADS may have been the cause of the difficulties when differentiating the answer options, due to the Norwegian formulation. Examples of answer options that may have been difficult to

differentiate were “veldig ofte” and “ganske ofte”, whereas the answer options “helt sikkert, og veldig ille” and “ja, men ikke så veldig ille” may have been difficult to interpret due to the formulation. In addition, the answer options where “like mye som før” or “like mye som jeg alltid har gjort” were included, may have been difficult to interpret due to no clarification in the guidance on what time the participants had to compare with. Should the participants have answered according to the time before the ICD implantation or cardiac event?

How the participants interpreted the answer options are subjective, therefore may the answer options in the Norwegian version be reformulated so they could be interpreted in one way. The participants could have ticked off answer options that did not match with their thoughts and feelings, as a possible consequence of the current formulation of the answer options.

5.2.2.2 Florida Shock Anxiety Scale

FSAS has been assessed as a valid and reliable clinical tool used to measure shock related anxiety in the ICD population (149). The questionnaire consisted of 10 questions designed to obtain information regarding concerns related to the ICD and potential ICD shock (149). As for the question in HADS, the questions in FSAS were formulated as statements, where the participants circled around the answer options that represented their thoughts and feelings (105). The guidance was short and addressed the essence of the questionnaire and how to complete the questionnaire. It took approximately 5 minutes to complete FSAS.

The questions in FSAS were short, precise and easy to interpret. In addition, the questions were well formulated and open. The questionnaire used a simple and normal vocabulary, as the participants should have been able to understand without any difficulties. The term “ICD” is used by the physicians and other health care professionals at the clinic when communicating with the patients, whereas the majority of the participants in the study should haven been able to understand the use of “ICD” in the questionnaire. In order to generalize the questionnaires for all participants, its important to formulate the questions so all participants could recognize themselves in the question (146). Question #1, “jeg er redd for å trene fordi det kan øke pulsen min og føre til at min ICD gir støt”, should perhaps have included the term “mosjonere”. Many participants, especially older participants, may have interpreted “trening” as activities with high intensity and did consenquently not answer the question if they usually performed activities with low intensity, such as walking. On the other hand, the amount of non-responders to this question was not high when compared to the other

questions, with only six non-responders. Question #9 was formulated inaccurate, compared to the other questions in FSAS, by stating "jeg har uønskede tanker om at min ICD gir støt". As a consequence, this question was excessive and did not contribute with more information regarding ICD concerns. In addition, question #9 brought up an uncertainty for the investigator whether there were other aspects of the ICD concerns that should have been addressed, or if the participants had covered their concerns in the previous questions.

FSAS consisted of five answer options to each of the questions, whereas the grading of the answer options was easy to differentiate and interpret. Instead of collecting information on how many times or when was the last time the participants experienced concerns regarding the ICD, the answer options aimed for an overview of how often the concerns were applicable. In this way, the risk of having uncertain answers such as numbers (number of times or how long since) was reduced (146). Due to five well-formulated and scaled answer options, the participants could convey their level of concerns in an informative matter. Additional answer options for the questions regarding sexual activity and exercising should have been added. "I´m not sexual active" or " I don't exercise" should have been included as answers to ensure that all the participants answered all of the questions in FSAS. The amount of participants that didn't answer these questions may indicate that these participants were not sexual active or did not exercise. On the other hand, the additional answer options should have been added in order to reduce the risk of making assumptions about the non-responders.

5.2.2.3 Comparison of the questionnaires

HADS and FSAS complimented each other by assessing the participants level of anxiety, depression, and ICD concerns in the every day life. HADS was designed to assess the participants general mental state, whereas FSAS assessed the participants concerns related to the ICD (105, 147). Although the answer options in HADS were discussed as a potential cause of low proportion of answers, the amount of non-responders in HADS were lower than in FSAS. The amount of non-responders ranged from 2.3%-6.9% in the FSAS questions, whereas the amount of non-responders varied between 0.0%- 3.3% in the different questions in HADS.

Neither of the questionnaires addressed whether the anxiety and/or depression occurred before or after the participants was treated with ICD. In addition, none of the questionnaires included questions related to a potential history of mental disorders. This resulted in an

uncertainty in whether the mental disorder occurred before or after the implantation of ICD. A weakness with use of subjective measurements in the current study is that participants with mental distress may have transferred theirs worries, avoiding behavior and increased vulnerability, into their cardiac condition (146). Regardless cause of mental disorders, the use of HADS and FSAS exposed prevalence and associations of depression or anxiety in the study population.

FSAS included a question that might have been unpleasant or awkward to answer. It is shown that participants do not answer if a question is unpleasant (146). The question regarding sexual activity might have been difficult to answer for many of the participants due to increased age, relationship status (widow/widower) or the question regarding sex itself. With 12 (6.9%) non-responders, this question was the most common question the participants did not answer. Several of the participants who didn´t answer, commented the question with " I don´t have sex because I'm too old" or "I´m a widow/widower". On the other hand, it was necessary to include this question due to the younger participants in the study and in order to address possible concerns regarding sexual activity in relation to the fear of ICD shock.

It took approximately five minutes to complete the questionnaires, thus the short time of completion may have increased the percentage of participation (146). If longer questionnaires with many and perplexed questions were used, the amount of participants may have decreased due to time consuming participation (146).

5.2.3 Methods

The assessment of depression and anxiety in the study population could have been done as a clinical interview by a physiologist. However, the results from a clinical interview could have been affected by reduced psychological and physiological state the day of the interview, information bias, recall bias and/or lack of connection and trust between the participant and the psychologist (99). A higher amount of participation may have been seen in the current study because the participants answered the questionnaires when they had time, instead of taking up the participants time with a clinical interview. As a strength, the questionnaires was planned to be completed at home in order to avoid invasion of personal life and external influence from the interviewer (146).

When compared to blood samples and blood pressure, questionnaires are seen as a semi-quantitative measure (146). Thoughts and emotion are not a direct measurable size as for example to blood pressure or circulating biomarkers. In order to assess the participants subjective health as accurate and standardized as possible, questionnaires have been constructed as semi-quantitative tools (150). When transforming the participants subjective health status into numbers, the specific questionnaire depends on high validity and reliability in order to produce precise results (146). Although the questionnaires in the current study were used as intended, it was a residual uncertainty related to how the participants feelings and emotions in reality were. In order to narrow the uncertainty, we used validated questionnaires that previous articles have used (validity) and referred to correct use for the participants (reliability) (99).

Validity of a measurement tool shows how good the tool tested what was intended to test (150). Internal validity specifies to what extent the results are valid for the specific population being studied, where the definition includes collection and processing of the data in addition to interpretation of the results (150). High internal validity represents evidence for causality (151). Validity can be influenced by bias, errors in the collection or interpretation of epidemiologic data, where the results might deviate from the reality (150). Bias such as random errors related to coding and data entry, is hard to avoid and may have influenced the validity, and consequently the results in the current study (99). After the data entry was done, answers from the questionnaires were controlled by taking 10% of the questionnaires, whereas the answers were matched up with the answers registered in SPSS. In addition, the clinical data from the CRFs and questionnaires were double checked after they were typed into SPSS. Random errors such as no CRF occurred in the current study, whereas the validity may have been reduced. Missing variables from the laboratory measurements, not answered all the questions in the CRF or not yet validated CRF by the investigators of the SMASH-study, were the causes of missing CRFs. At the time of writing this thesis, not all of the participants who had submitted their questionnaires had their CRFs validated by the investigators. These participants were, as earlier mentioned, excluded from the current substudy.

External validity concerns the ability to generalize the results from a study to other study populations and situations (151, 152). The results from the current study are difficult to generalize to the general ICD population, mainly due to the small study population (153).

When compared to the 190 participants who completed the questionnaires, previous studies have had over thousand participants from the ICD population in each study, resulting in improved ability to generalize the results (90, 92, 95). Selection bias occurs when researchers select participants that will benefit the study, which influences the external validity (99). The participants in the current study were randomly recruited from the cardiology division at AUH, resulting in decreased risk of selection bias and participants representable for the general ICD population (99). On the other hand, many exclusion criteria were used in the present study in order to include the participants eligible for the study, whereas cxclusion of participants, that in reality was eligible for the study, may have occurred. Another aspect of generalization is whether the study population consists of participants included from a limited area or from various areas, such as different places in a country or several locations around the world (99). AUH is the central hospital for the population in Oslo and Akershus, and as a consequence the participants in the current study were from a limited area in Norway. In order to increase the ability to generalize the results from the study, the participants could have been recruited from several hospitals in Norway and/or from collaborative hospitals in Scandinavia. Generalization depends on the consistency of measurement tools used in a study, reliability, which is represented by the credibility of the measures by similar results if the methods are reproduced by other investigators (150). The high reliability in the current study was measured for both HADS (HADS-D Cronbach's α= 0.83, HADS-A Cronbach's α= 0.87) and FSAS (Cronbach's α= 0.90). The reliability for both questionnaires corresponded with previous studies (105, 147, 149).

Systematic errors, deviation between the average value from measurements performed under equivalent conditions and the actual values, may have occurred during the blood sampling procedures and the NT-proBNP analyzes in the current study (150, 154). During the storage of the equipment used for blood sampling, the racks with the labeled aliquots were covered with aluminum foil to prevent contamination. In addition, the labeling of the aliquots had to be done with gloves for the same purpose. If the study nurse forgot to wear gloves or if the aluminum foil was not properly packed around the racks, the blood samples may have been contaminated, whereas the concentration of the biological variables consequently may have been influenced. Information bias, also known as recall bias, occurs when the participants can't recall previous events or when the participants decorate the truth in order to appear better (99). Questions regarding cardiac events, the ICD or other relevant information may have been hard to recall, and the lack of precision may have resulted in insecure answers

(99). The investigators of the SMASH-1 study reviewed all of the data from the CRFs in order to reduce the risk of recall bias. The investigators matched the participants answers with the information from the digital journal system. Any discrepancies were corrected according to the participants journals.

5.2.3.1 Measurement of NT-proBNP

NT-proBNP is a widely used biomarker for HF due to high sensitivity, specificity and high analytical performances (71, 155). NT-proBNP is a more superior HF biomarker compared to BNP, due to higher stability and lager half-life, and prediction of mortality and morbidity (70, 156-158).

The concentrations of NT-proBNP were analyzed by the chemiluminescence immunoassay ECLIA on the immunologic analysis instrument Cobas e 801 (100). ECLIA has been shown to have high analytical precision (159, 160). The standardized NT-proBNP reference values in ECLIA are determined to be low in order to reduce the amount of false negative tests. Due to the use of an assay with high precision, accurate NT-proBNP concentrations are likely to be reported in the study. On the other hand, antibodies in the participants blood samples against the antibodies used in the analysis may have resulted in false increased NT-proBNP values (100).

The ECLIA analyzes in the present study used both monoclonal and polyclonal antibodies (100). A previous study suggested higher concentrations of NT-proBNP when using polyclonal antibodies, compared to the NT-proBNP concentrations where only monoclonal antibodies were used (161). Few studies have assessed the relation between use of both monoclonal and polyclonal antibodies, but one could only assume that use of monoclonal and polyclonal antibodies may give more accurate concentrations of NT-proBNP.

No discrepancies in the analysis of NT-proBNP occurred between the participants, despite different amount of completed SMASH-1 visits. The values from the NT-proBNP analyzes at the inclusion consultations were registered and analyzed in the present study. Consequently, the concentrations of NT-proBNP were collected at the same point (baseline visit) for all the participants.

5.2.4 Statistical methods

Although the low prevalence of female participants (11%), data from both genders were calculated and included in the statistical analyzes. The results from the female participants could have been excluded because the amount of male participants may have been satisfactory enough to present significant results alone. However, the results from the female participants were included due to the value of generating information from both men and women. The data from the female participants may have given significant results despite low percentage of the gender. On other hand, previous studies where significant associations between women and anxiety or depression have been presented comprised of a higher amount of women, compared to the present study (95, 162).

Socio-demographic variables, such as educational level and martial status (married/ not married), are widely used variables in statistical analyzes, in order to identify healthcare outcomes (153, 163). The statistical analyzes in the current study did not comprise educational level or martial status. However, patients with depression and/or anxiety are seen to have lower educational level and not being married compared to the general population (164, 165). Consequently, the mentioned variables should have been included in the statistical analyzes in order to establish a possible explanation model for the prevalence of anxiety and depression in the study population (164, 165).

Time since ICD implantation and time since previous shock, are two variables with valuable information, where the variables have been used in previous studies in an informative matter (90, 108). When assessing time since shock in relation to when symptoms of the patient measure outcomes first occurred, the variable could have indicated whether the shock was the cause of the depression and/or the anxiety or not. Time since ICD implantation could potentially have measured device acceptance and possible concerns regarding the device. For the mentioned reasons, time since ICD implantation and time since shock should have been included and analyzed in the study.

Increased number of previous shocks is seen to contribute to development of depression and affect the depression severity (91, 136). The current study did not assess whether the number of previous shock had any impact on the depression severity or not, only if experienced shock (yes vs. no) was significantly associated with depression in the ICD population. Although previous studies have assessed the number of previous ICD shock in relation to development

of depression, several studies have not (140, 166). This may indicate that amount of shock is an equally good variable to assess, whereas the results from the present study may not have been negatively influenced by only assessing shock/no shock.

Chest pain (angina pectoris) is seen to be a determinant for development for depression and/or anxiety (167, 168). In the statistical analyses, the variable “chest pain” was not included due to a methodical error in the CRF. Also, only five participants in the study population reported chest pain. Consequently an analysis error in the regression occurred and the variable was chosen away. With a higher amount of participants with chest pain, the symptom may have been seen as a significant determinant for the depression and/or anxiety in the study population (167, 168).

6.0 Strengths and limitations

6.1 Strengths

The use of two standardized, validated questionnaires, HADS and FSAS, contributed as a strength in the current study. HADS and FSAS have previously been assessed as questionnaires with high reliability. Another strength was the use of both clinical assessment tools (blood samples) and subjective measurements (questionnaires). By using two different measures, the results become more valid. A high amount of participants who completed and submitted the questionnaires, contributed to strengthening the results from the study.

6.2 Limitations

Compared to other studies investigating depression and anxiety in patients with ICD, the current study had a low amount of participants. Prevalence of depression, anxiety, shock related anxiety, in addition to the prevalence of the different symptoms, histories or concerns could have been different with a higher number of participants. In addition, higher percentage of participants may contribute to generalization of the study results. A higher amount of male participants, compared to female participants, was seen in the study. This unequal distribution may have contributed to no significant associations between NT-proBNP and depression or anxiety in the female participants. A higher percentage of female participants may have resulted in robust associations for the female subgroup. Another limitation in this study was that no clinical tools for assessment of mental diseases were used. In addition, the study did not assess if the depression or anxiety occurred before or after the implantation of the ICD. Without this vital information, it was difficult to distinguish the participants with mental distress due to the ICD and the participants with general depression or anxiety. 16 (8.9%) of the 178 participants didn´t have NT-proBNP values measured, but were still included in the statistical analysis. Participants with missing NT-proBNP concentrations may have contributed to the lack of significant association between the biomarker and depression or anxiety. An important consideration is survival bias: participants who died or did not answer the questionnaires may have amounted for the sickest part of the participants, whereas the participants who answered the questionnaires may have represented the group of participants with decreased prevalence of depression and or/ anxiety. Hence, if this was the case the results in the study may have only been representable for the ICD patients with low or moderate cardiac impairments. The FSAS cut-off value (≥12) was determined without any guidelines from previous studies, whereas the cut-off value may have been set to low.

Previous studies have shown the level of ICD acceptance as a predictor of patient related outcomes by the Florida Patient Acceptance Survey (FPAS), whereas the current should have included FPAS in order to assess for other explanation factors of anxiety and depression in the study population.

7.0 Conclusion

The current study demonstrates a low prevalence of depression and anxiety in the study population, and the majority of the participants had not experienced previous ICD shock. Concentrations of NT-proBNP were not associated with depression or anxiety in the participants treated with ICD. In regard to the specific objectives:

1. Depression was identified in 10.1% of the study participants, while 12.9% had anxiety. Shock related anxiety was most the most prevalent patient measured outcome in the study population, with a percentage of 38.8%.

2. Concentrations of NT-proBNP were not associated with depression or anxiety in the participants treated with ICD.

3. After adjusting for NT-proBNP, previous shock was not an independent determinant of the patient related outcomes in the study population. On the other hand, palpitations and dyspnea was seen as independent determinants of depression. None of the included variables in the study were associated with anxiety in the study population. Female gender was identified as an independent determinant for shock related anxiety.

The study contributes to existing literature by supporting results from previous studies, in addition to contribute with new knowledge. At the time of writing, no study had previously assessed a potential relation between concentrations of NT-proBNP and depression or anxiety in the ICD population. Although, the current study did not reveal any significant associations, the study contributed with new knowledge for future studies.

9.0 Future studies

There is a need for studies examining the relation between mental distress and circulating biomarkers in the ICD population, whereas future studies together with excising literature may contribute to increased focus on the ICD patients mental health. Future studies should include several research sites, a high percentage of participants will be included and more robust results may be seen as a concenquence. In addition, future studies should include participants from collaborative sites in different countries, both from nearby countries and around the world. This may result in an increased ability to generalize the results to the ICD population. Equal distribution of female and male participants will contribute to comparative results between the genders in future studies. Circulating biomarkers that are strongly associated with ventricular arrhythmias, for example secretoneurin, should be assessed. The value of detecting a potential association between biomarkers of cardiac conditions and mental distress is that increased focus of the relation will contribute to implementation of preventive psycological strategies in order to decrease the prevalence of mental distress in the ICD population. Future studies should also monitor the participants over a longer period of time in order to comprise outcomes such as death, ICD shock, cardiac events and clinical variables.

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APPENDIX 1 Protocol to SMASH-1 study

SMASH 1:
Scandinavian Multicenter study to Advance risk Stratification in Heart disease - ventricular arrhythmias

Protocol Identification Number: SMASH 1
EudraCT Number: n.a.
ClinicalTrials.gov Identifier: xx

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PROTOCOL VERSION NO. 1
Version #2

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Title	SMASH 1: Scandinavian Multicenter study to Advance risk Stratification in Heart disease-ventricular arrhythmias
Protocol ID no:	SMASH 1
ClinicalTrials.gov Identifier: :	Xx

Sponsor signatory approval
Hilde Lurås
Head of Research and Innovation
Akershus University Hospital

Signature *Date*

I hereby declare that this Protocol has been developed in compliance with ICH GCP and the applicable regulatory requirements:
Torbjørn Omland
PI/ MD PhD
University of Oslo and Akershus University Hospital

Signature *Date*

PI signatory approval
I hereby declare that I will conduct the study in compliance with the Protocol, ICH GCP and the applicable regulatory requirements:
Name:
Title:

PI signature *Date*

Intervention	None
Protocol no.	SMASH 1
Study phase	n.a.
Study title	SMASH 1: Scandinavian Multicenter study to Advance risk Stratification in Heart disease- ventricul arrhythmias
Sponsor	Akershus University Hospital, Norway
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Funding source(s)	Research Council of Norway

PROTOCOL SYNOPSIS

Study centers in Norway	Akershus University Hospital with possible additional sites Oslo University Hospital; Stavang University Hospital; Haukland University Hospital; St. Olav; and University Hospital of Northe Norway
Planned number of patients	>2000 patients
Timelines	Estimated study start (FPFV): Feb 1, 2016 Estimated recruitment end (LPFV): Feb 28, 2019 Follow-up period end date (LP off study): Sep 1, 2030 End of study: Sep 1, 2050
Background and rationale	Cardiovascular disease is the leading cause of morbidity and mortality in the world. The majority of

	deaths are caused by cardiac arrhythmias leading to sudden cardiac arrest. The introduction of treatment with ICD's in cardiovascular disease has proved lifesaving. However, current criteria lack the desired sensitivity and specificity for proper patient selection, as neither the electrocardiogram (ECG) nor any of the existing cardiac biomarkers are useful in this setting. We thus plan to perform an observational clinical study, recruiting patients with ICDs at Akershus University Hospital and possibly also other selected Norwegian university hospitals. All patients will be asked to donate blood speciments into a large biobank for the assessment of established and novel biomarkers for risk assessment in ICD patients. We will also be interested in the importance of patier history and clinical findings, ECG markers, and echocardiographic indices for risk assessment for incident ventricular arrhythmias and cardiovascular events.
Study objectives	To identify markers of increased risk for incident ventricular arrhythmias and cardiovascular events patients already being treated with an ICD by exploring patient history and clinical findings, biologic markers, ECG markers, and echocardiographic markers.
Study design	An observational trial recruiting from at least Akershus University Hospital, but possibly later al additional sites recruiting patients Screening phase: Patients treated with an ICD Study phase: Inclusion from outpatient clinic
Patient population	Inclusion Patients ≥ 18 years old Current treatment with an ICD Signed written informed consent before study commencement Exclusion Participation in other interventional clinical trial or previously included in the current study Patients not able to provide written informed consent Known or suspected, non-curable cancer, Neurological condition with short life expectancy; e.g. ALS Patients unwilling or unable to comply with the protocol History of non-compliance to medical management and patients who are considered potential unreliable by the Investigator History or evidence of alcohol or drug abuse with the last 12 months that may influence t participation of the patient in the study, as assessed by the Investigator during the screening phase Any surgical or medical condition, which in the option of the Investigator, will impair the ability of t patient to participate in the study
Visit schedule and assessments	We will recruit patients both being referred for ICD implantation and patients who already ha received an ICD and are being followed-up at the cardiology outpatient clinics of Akershus Universi Hospital and, given permission and interest, also from the other participating hospitals. Patients wi ICD will be screened by study personnel by reviewing the patient history to assess inclusion a exclusion criteria. The patient will be given oral and written information and all patients will provi written informed consent before study commencement. We will then perform biobanking of t participants that will enable later measurements of different classes of biological markers (e.g. DN RNA, protein, metabolites). We will also perform special ECG and echocardiographic analyses usi either the recordings at the inclusion visit or by re-analyzing previous recordings stored for off-li analyses. Patients will be followed for up to 34 years for incident ventricular arrhythmias a cardiovascular events (study ending year 2050). We will also perform blood sampling on later visi Registration of ventricular arrhythmias will be downloaded from the ICD at annual visits. Of note, t patient has already received the ICD based on clinical need, thus there is no new intervention to t participating patients. Downloading history of ventricular arrhythmias from the ICD is also standa clinical care for these patients and thus not different from regular visits in the outpatient clinic. W will obtain information on cardiovascular events during follow-up from national registries, includi disease registries for heart failure and myocardial infarction, and from the national death regristry. W will also validate cardiovascular events by an adjudication committee that will review relevant medic documents, including medical records from hospitals and other health professionals (GPs, nursi homes, etc).
Data management and statistical analysis	This is an observational study to obtain a large database of patients with ICD for the development risk markers for incident ventricular arrhythmias and cardiovascular events that will include patients Akershus University Hospital and, given permission and interest, also from the other participati hospitals. In addition to information from the baseline visit and future study visits (e.g. age, gend weight/height, heart rate, heart rhythm, blood pressure, clinical findings, nutrition, exercise status), v

	will also registrer information from the patients medicial records concerning comorbidities ar previous medical events. The data will be summarized with respect to demographic and baseline characteristics and ri markers/ measurements. Categorical data will be presented as absolute frequencies and percentage For continuous data, N, mean±SEM or median (quartile 1-3), and range may be presented. Diagnost and prognostic accuracy will be assessed by receiver operating statistical analysis and by calculati the area under the curve. Diagnostic and prognostic ability will also be assessed by calculating t category-free net reclassification index. Time to event variables and Kaplan-Meier product-lin estimates will be presented stratified according to biomarkers and other risk indices. The fin diagnosis of incident cardiovascular events will be established by an adjudication committee with tw senior physicians reviewing all information available on the patients, including information on t clinical outcome of the patient. The co-primary end-point of the study will be time to incide ventricular arrhythmias and cardiovascular events. We will use multivariate statistical models to asse the individual performance of biomarkers/ other tests.

Abbreviation or special term	Explanation
CVD	Cardiovascular disease
ICD	Implantable cardioverter-defibrillator
ECG	Electrocardiogram
LVEF	Left ventricular ejection fraction
Ca^{2+}	Calcium
RyR	Ryanodine receptor
CaMKIId	Ca^{2+}/calmodulin (CaM)-dependent protein kinase II d
NCX, SERCA	Ca^{2+} channels
EADs and DADs	Early and late afterdepolarizations
SN	Secretoneurin
DNA, RNA	Deoxyribonucleic acid, ribonucleic acid
ECG	Electrocardiogram
WGS	Whole genome sequencing
LVEF	Left ventricular ejection fraction
HFrEF/HFpEF	Heart failure with reduced/ preserved ejection fraction
TTE	Transthoracic echocardiogram
CV/CVD	Cardiovascular/ cardiovascular disease
RCT	Randomized controlled trial
ALS	Amyotrophic lateral sclerosis
AMI	Acute Myocardial Infarction
ACS	Acute coronary syndrome
CRF	Case report forms
SEM	Standard error of the mean
CRF	Case Report Forms
PI	Principal Investigator

Background and Status of Knowledge

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in the world. A substantial proportion of deaths are caused by cardiac arrhythmias leading to sudden cardiac arrest (Fig. 1).

Fig.1. *Left*; Aging is associated with structural heart disease, which increases the risk of ventricular arrhythmias and sudden cardiac death. *Right*; The burden of sudden cardiac death varies across different populations, but constitutes a major health burden as reported in different publications and here illustrated from the ESCAPE program.

Current cardiac rhythm management includes anti-arrhythmic drugs and the use of device-based therapy such as implantable cardioverter-defibrillators (ICDs). The introduction of treatment with ICD's in cardiovascular disease has proved lifesaving. However, current criteria lack the desired sensitivity and specificity for proper patient selection, as neither the standard electrocardiogram (ECG) nor any of the existing cardiac biomarkers have really been found useful in this setting. Thus, in approximately 70% of the patients who have an ICD implanted, the device is never activated. Given the high cost and potential serious complications of such devices, and recent policy changes that have tripled the number of eligible patients for such therapy, there is an urgent need to identify more specific and accurate prognostic tools to enhance the selection process.

Current Strategies Related to Ventricular Arrhythmias

Ventricular arrhythmias most commonly develop in subjects with structural heart disease or during acute myocardial ischemia (myocardial infarction). Subjects with morphologically normal hearts but with inherited Ca^{2+} channel mutations (channelopathies) can also develop ventricular arrhythmias, but this group constitutes <10% of all cases of cardiac arrest. Accordingly, current strategies focus on subjects considered high risk for incident ventricular arrhythmias (primary prevention) and subjects that have survived cardiac arrest (secondary prevention). Standard cardiac rhythm management includes anti-arrhythmic drugs and the use of device-based therapy such as pacemakers and implantable cardioverter-defibrillators (ICDs). However, with the exception of beta-blockers, anti-arrhythmic drug therapy has been a major disappointment with most drugs leading to increased risk of death. In contrast, the introduction of treatment with ICD's have proved lifesaving in high-risk groups such as patients with compromised cardiac function following acute myocardial infarction and patients with heart failure symptoms and reduced cardiac function. Furthermore, ICD therapy is expensive with costs for the device and expenditures associated with surgery and pre- and post-follow-up of the patients; thus, selecting the right patients for ICD therapy is crucial. Cardiac systolic function, commonly expressed as the left ventricular ejection fraction (LVEF), is the current main selection criterion for primary prevention, and guidelines recommend ICD implantation in all patients with post-infarction heart failure and LVEF<35%. Still, the current indices for classifying subjects as high risk for cardiac arrest lack the desired sensitivity and specificity, and a large proportion of patients that receive an ICD will never experience a ventricular arrhythmia. Vice versa; reviewing the status of patients who have suffered cardiac arrest suggest that over 65% of these patients would not have been identified as high risk subjects prior to the event. Identifying novel risk markers of incident ventricular arrhythmias would thus be of great clinical help.

CaMKIId and Ventricular Arrhythmias

Cardiomyocyte Ca^{2+} handling is at the core of all triggered arrhythmia; thus, accounting for a large proportion of all ventricular arrhythmias. Calcium-induced calcium release forms the basis for excitation-contraction coupling, but the fluxes of Ca^{2+} over membranes and across compartments makes the myocardium susceptible to disorganized Ca^{2+} handling (Fig. 2). The principal structures that control cardiomyocyte Ca^{2+} fluxes are different types of ion channels. One important channel is the ryanodine receptor (RyR), which regulates release of Ca^{2+} from the sarcoplasmic reticulum. The opening and closing probabilities of RyR and other Ca^{2+} channels are closely coordinated by intracellular kinases that regulate the channels by phosphorylating highly specific amino acids. One key intracellular kinase in cardiomyocytes is Ca^{2+}/calmodulin (CaM)-dependent protein kinase II d (CaMKIId), which is known to be hyperactive during myocardial ischemia and in patients with structural heart disease (Fig. 2). Accordingly, identifying a biomarker linked to CaMKIId activity could prove interesting to identify risk of incident ventricular arrhythmias

Secretoneurin: CV Biomarker and Ca^{2+} Regulator

Secretoneurin (SN) is a 33-amino acid peptide that belongs to the chromogranin-secretogranin (granin) protein family. The granin proteins are characterized by a high proportion of acidic amino acids and several dibasic

cleavage sites. Post-translational processing of the granin proteins produces multiple short ~30 amino acid peptides, including SN that is the functional peptide of secretogranin II. Our group is internationally leading in the exploration of the granin proteins in CVD and we have recently demonstrated the potential of SN as a CV biomarker and novel therapeutic strategy. We first demonstrated increased levels of short SN fragments in the myocardium and circulation in heart failure, and more recently we have been able to link SN levels directly to clinical outcomes in different CV cohorts. In addition, we have found SN to directly influence cardiomyocyte function. This work was recently published in an article in *JACC*, in which we demonstrated incremental prognostic information by SN to established risk indices and biomarkers in patients with (1) acute heart failure and (2) after ventricular arrhythmia-induced cardiac arrest. In addition, in a series of experiments ranging from molecular imaging to advanced molecular biology and electrophysiology, we were able to demonstrate the membrane-permeant properties of SN and the ability of SN to directly bind to and reduce CaMKIId activity. The potential of membrane-permeant peptides for pharmacological utility has recently also been explored outside of CVD.

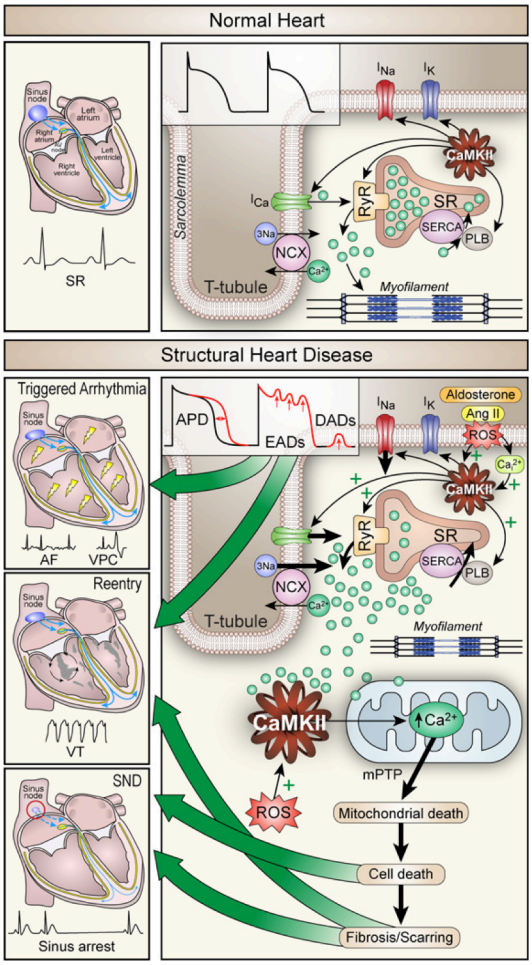
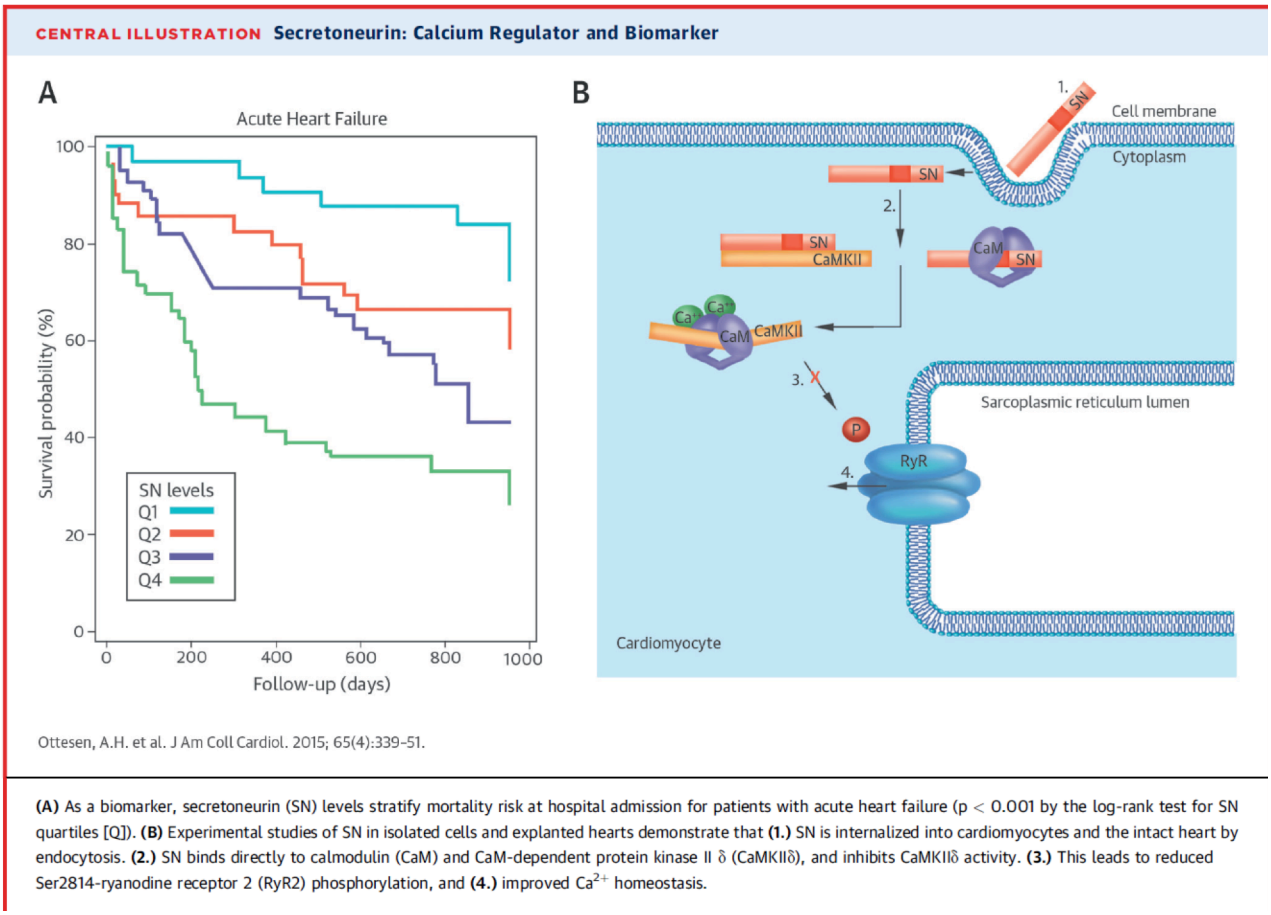


Fig.2. The role of CaMKII in normal heart (top) and CaMKII-linked pro-arrhythmic implications in structural heart disease (bottom). Normal excitation-contraction coupling (ECC) and conduction in the heart leads to sinus rhythm as detected by the surface ECG. CaMKII is an integral part of ECC as it regulates the function of several key components. On the single cardiomyocyte level, depolarization of the membrane trigger Ca^{2+} entry by the L-type Ca^{2+} channel that supports contraction by stimulating ryanodine receptors to release Ca^{2+} from the sarcoplasmic reticulum. Relaxation mainly occurs by Ca^{2+} uptake to the sarcoplasmic reticulum by phospholamban regulated SERCA and extrusion to the extracellular space by the NCX.
In structural heart disease, overexpressed and activated CaMKII disturbs Ca^{2+} homeostasis by hyperphosphorylating Ca^{2+} regulatory proteins leading to increased intracellular Ca^{2+} and increased rate of early and late afterdepolarizations (EADs, DADs). EADS and DADs can initiate and sustain arrhythmias, including atrial and ventricular premature complexes that may result in persistent atrial fibrillation and ventricular arrhythmias. *From Rokita AG, Anderson ME. Circulation. 2012;126:2125-39.*

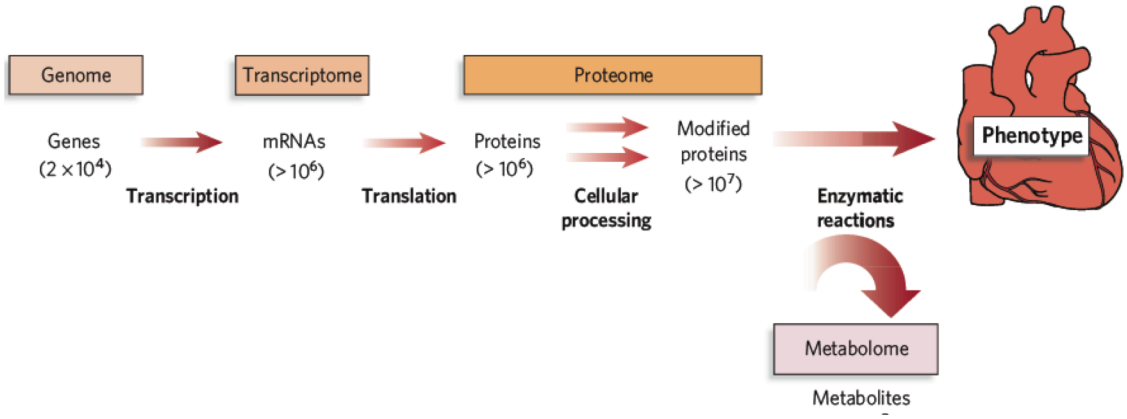


(A) As a biomarker, secretoneurin (SN) levels stratify mortality risk at hospital admission for patients with acute heart failure ($p < 0.001$ by the log-rank test for SN quartiles [Q]). **(B)** Experimental studies of SN in isolated cells and explanted hearts demonstrate that **(1.)** SN is internalized into cardiomyocytes and the intact heart by endocytosis. **(2.)** SN binds directly to calmodulin (CaM) and CaM-dependent protein kinase II δ (CaMKIIδ), and inhibits CaMKIIδ activity. **(3.)** This leads to reduced Ser2814-ryanodine receptor 2 (RyR2) phosphorylation, and **(4.)** improved Ca^{2+} homeostasis.

Fig.3. Central illustration of the work performed so far, which has identified SN as a novel CV biomarker and a direct Ca^{2+} regulator via CaMKIId inhibition. The model for SN as a CV biomarker and cardiomyocyte Ca^{2+} regulator was also supported in the editorial by Prof Anderson and in the podcast by Dr.Valentin Fuster, editor of JACC and Professor at Mount Sinai Hospital, NYC. Accordingly, analogous to the natriuretic peptides, SN levels seem to be associated with a poor outcome although the actions of the peptide itself seem to be protective. Hence, SN seems to represent a compensatory mechanism that is activated in the most severely ill patients. We also have additional, unpublished data demonstrating incremental prognostic information by SN to established risk indices in high-quality international clinical studies of patients with severe sepsis and in acute respiratory failure. Hence, SN seems to be an interesting prognostic biomarker in CVD that is functionally linked to cardiomyocyte Ca^{2+} handling. Whether SN may also be associated with cardiomyocyte Ca^{2+} handling and ventricular arrhythmias as a biomarker remain to be established and will be explored in this study,.

1.1 Spectrum of Biological Markers

Biological markers may come from the whole spectrum of biological substances; e.g. DNA, RNA, protein, and metabolites (Fig. 4):



Accordingly, in this study we plan to obtain biospeciments that enable us to test biological substances across the spectrum of potential biological markers.

1.2 Rationale for the Study

There is a lack of clinical useful risk markers in patients at high risk of ventricular arrhythmias. Accordingly, we aim to identify markers that can identify ICD patients at high risk for incident ventricular arrhythmias and cardiovascular events. To this end, we will explore patient history and clinical findings, the spectrum of biological markers, and ECG and echocardiographic indices as novel risk markers in patients with ICDs.

2 STUDY OBJECTIVES

The overarching aim of this multicenter observational study is to identify markers of increased risk for incident ventricular arrhythmias and cardiovascular events in patients already being treated with an ICD by exploring patient history and clinical findings, biological markers, ECG markers, and echocardiographic markers

2.1 Endpoints

Primary endpoints:

-To indentify markers of incident ventricular fibrilliation or tachycardia

-To identify markers of cardiovascular morbidity and mortality during follow-up, including hospitalizations for worsening heart failure and arrhythmias

Secondary endpoints:

To indentify markers of the combined endpoint of incident ventricular fibrilliation or tachycardia and cardiovascular morbidity and mortality during follow-up

To indentify markers of the total number of ventricular fibrilliation or tachycardia that requires cardioversion during follow-up

To indentify markers of the total number of hospitalizations for worsening heart failure and arrhythmias during follow-up

To identify markers of other cardiac arrhythmias during follow-up, including ventricular fibrilliation and tachycardia not requiring cardioversion, non-sustained ventricular arrhythmias, and atrial fibrilliation (paroxysmal, persistent, and chronic)

To indentify markers of the combined endpoint of cardiovascular morbidity and mortality and other cardiac arrhythmias, including ventricular fibrilliation and tachycardia not requiring cardioversion, non-sustained ventricular arrhythmias, and atrial fibrilliation (paroxysmal, persistent, and chronic), during follow-up

To indentify markers of the total number of other cardiac arrhythmias during follow-up, including ventricular fibrilliation and tachycardia not requiring cardioversion, non-sustained ventricular arrhythmias, and atrial fibrilliation (paroxysmal, persistent, and chronic)

2.2 Outcome measures

We will perform molecular characterization from DNA via RNA to protein and metabolites on inclusion and later during follow-up in the study, including by whole genome sequencing (WGS) and –omics based technology, with these aims:

Primary Outcome measures:

To identify genetic variants (DNA) and alterations in DNA (epigenentics) that are associated with the defined endpoints in this population

To explore RNA markers that are associated with the defined endpoints in this population

To assess the potential of novel and established protein markers, and especially secretoneurin, for the prediction of the defined endpoints in this population

To characterize the metabolome and to characterize substances that are associated with the defined endpoints in this population

To test whether change in biological markers during follow-up are associated with the defined endpoints in this population

We will also assess new and established ECG and echocardiological indices on inclusion and later during follow-up in the study with these aims:

To test whether established and novel ECG indices are associated with the defined endpoints in this population

To assess whether established and novel echocardiographic indices are associated with the defined endpoints in this population

To explore whether change in ECG and echocardiographic indices during follow-up are associated with the defined endpoints in this population

Secondary Outcome measures: The same risk markers/indices as for the primary outcome measures but in these pre-defined subgrops:

Patients stratified by age; e.g. 50 y

Patients stratified by gender

Patients stratified according to previous ventricular arrhythmia; e.g. patients with ICDs due to primary prevention and patients with ICDs due to secondary prevention

Patients stratified by LVEF 50%; e.g. HFrEF and HFpEF

3 STUDY POPULATION

3.1 Selection of Study Population

Over a period of approximately 3 years, we plan to enroll >2000 subjects already being treated with an ICD at at Akershus University Hospital and, given permission and interest, also from the other participating hospitals. The patients will primarily be recruited from the outpatient clinic.

All patients will be thoroughly informed about all aspects of the study and there will be no extra examinations compared to routine care for study participants. We will obtain written informed consent from all patients prior to study commencement. We will perform blood sampling by standard methods by drawing blood from venous or arterial access. We also want to have the possibility to assess ECG and echocardiographic indices associated with the outcomes in this study, including the possibility to re-analyzing previous examinations that have been stored for off-line analyses. At the request by the patient, all data collected in the study relating to the particular participant, and not already included in a publication, will be terminated. Whether the patients meet the inclusion and exclusion criteria will be assessed by direct dialogue with the patients and by accessing patient medical records. Blood samples for biobank will require signed written informed consent and collection of genetic samples will require a special consent.

Study personnel will not give any instructions directly related to the treatment of the patients. The study participants will receive all examinations that are considered appropriate by the treating physician. The decision of the patient to participate or to decline participation into the study will not influence the treatment that is offered to the patient at Akershus University Hospital or the other participating hospitals.

Inclusion Criteria

All of the following conditions must apply to the prospective patient at screening prior to inclusion in the study:

- Patients ≥ 18 years old
- Current treatment with an ICD
- Signed written informed consent before study commencement

Exclusion Criteria

Patients will be excluded from the study if they meet any of the following criteria:

Previously included into the study

Patients not able to provide written informed consent

Known or suspected, non-curable cancer

Neurological condition with short life expectancy; e.g. ALS

Patients unwilling or unable to comply with the protocol

History of non-compliance to medical management and patients who are considered potentially unreliable by the Investigator

History or evidence of alcohol or drug abuse with the last 12 months that may influence the participation of the patient in the study, as assessed by the Investigator during the screening phase

Any surgical or medical condition, which in the option of the Investigator, will impair the ability of the patient to participate in the study

3.2 Patient Registration

Each patient in the study will first receive a site-specific code and later be merged into the study database with a unique study specific code from 1 up to the last patient that is included in the study. Once assigned to a patient, a patient number will not be re-used. If the patient fails to start on study for any reason, the reason for not entering the study will be entered on the Screening Log. Each site will keep their separate files for matching identifiable information (e.g. name and 11-digit personal number) with the study specific code and only de-idenifiable data will be included into the study database. The file linking identifiable information with the study specific code will be protected from other people besides the local PIs by keeping the linkage document in a drawer that can be locked.

4 STUDY EXECUTION

4.1 Patient Screening and Inclusion

We will include ICD patients primarily from the outpatient clinic of Akershus University Hospital and, given permission and interest, also from the other participating hospitals. The identification of patients eligible for the study will either be from direct contact with physicians caring for ICD patients or by reviewing the program of the ICD outpatient clinic. After obtaining written informed consent study personnel will perform blood sampling and biobanking of biospeciments. Biospeciments will be stored at -80°C in research specific biobanks with labeling according to the study specific code. We will also analyze ECGs and echocardiographic reports, including re-analyzing previous echocardiographic measurements stored for off-line analyses. Clinical characteristics will be collected directly from the physician and from the medical records by a standardized protocol and plotted into the case reports forms (CRFs) of the study participants.

4.2 Patient Follow-Up and Data Storage

Study personnel will not give any instructions directly related to the treatment of the patients. Hence, there will be no restrictions to the diagnostic testing of our study participants. Study personnel will neither directly influence management nor therapy of the patient. The decision of the patient to participate or to decline participation into the study will not influence the treatment that is offered to the patient at the participating hospitals.

Patients will be followed for up to 10 years for incident ventricular arrhythmias and cardiovascular events. Registration of ventricular arrhythmias will be downloaded from the ICD at annual visits. Of note, the patient has already received the ICD based on clinical need, thus there is no new intervention to the participating patients. Downloading history of ventricular arrhythmias from the ICD is also standard clinical care for these patients and thus not different from regular visits in the outpatient clinic. We will also obtain new ECG and echocardiographic recordings and additional blood sampling at annual visits. Information about cardiovascular events during follow-up will also be recorded from national registries, including disease registries for heart failure and myocardial infarction, and from the national death regristry.

4.3 Adjudication of Clinical Events

We will adjudicate all clinical events by having two experts, whom will work independently, review all available data concerning the event. Discrepancy regarding the diagnosis will be resolved by consensus. We will use the same strategy to classify deaths as CV vs. non-CV mortality, and if possible; also to characterize the cause of CV or non-CV death (e.g. ventricular arrhythmia, decompensated HF, coronary artery event.). A diagnosis of acute myocardial infarction (AMI) will be based on the definition by the 3rd Universal Definition (if not updated by other, more recent globally accepted definitions); e.g. (1) Either patient history suggestive of AMI but sudden death before blood samples could be obtained OR (2) troponin rise and/or fall AND pluss one of the following: (i) Symptoms of ACS, (ii) ECG signs of AMI, (iii) transthoracic echocardiographic signs of AMI, or (iiii) obstructive coronary artery disease on angiogram. Ventricular arrhythmia as the cause for sudden death will be considered either in the case where there are documented ventricular arrhythmias on the ICD. In case the ICD is later discontinued in the patient after inclusion, we will also adjudicate ventricular arrhythmia as the cause for sudden death if there are no reports of pre-warning symptoms of other pathophysiological process (e.g. chest pain with AMI) or other suspected or known cause for acute death, and where the duration between start of symptoms and death is within minutes.

4.4 Deep Phenotyping

There is a need to understand more closely the pathophysiology and mechanisms underlying ventricular arrhythmias. Accordingly, we will establish a state-of-the-art biobank for extensive molecular phenotyping based on serial blood sampling (baseline and annual visits). Blood sampling will be performed by standard venous access or from indwelling arterial cannula if already present due to clinical need. We will obtain serum and citrate, heparin, and EFTA plasma. We will also collect special tubes for mRNA extraction (PAX tubes) and we will collect whole blood in EDTA plasma tubes for DNA extraction. We will also obtain lymphocytes according to special protocols (Lymphoprep).

We plan to measure established and novel markers across all classes of biomarkers (Fig. 4). Categories of biomarkers that will be measured relate to markers of hemodynamic stress, myocardial injury and function, neurohormones, cell necrosis, fibrosis, inflammation, renal disease, and pulmonary or other non-cardiac organ status. We will also perform specific analysis of individual genes and RNA classes related to the protein biomarkers. In addition, we ask permission to use –omics based methodology to perform unbiased analyses of DNA, RNA, protein, and metabolites. There will be a separate consent for genetic studies where we will also ask for permission to perform whole genome sequencing with filtering of genes and no information reported back to the participants except in the case that we find gene variants currently been examined in routine clinical care for patients with unexplained ventricular arrhythmias. In general, patients receiving an ICD after cardiac arrest of no obvious cause will already have been examined for these genes (routine clinical care). If novel methods for deep genetic phenotyping become available we ask permission to also perform these analyses. The protocol will be reviewed by the Regional Ethics Committee and other agencies prior to the start of the study, includining the section relating to biobanking and genetic samples. We also ask permission to send samples to collaborating researchers outside of Norway. Possible countries that may receive samples are all Western European countries, but especially Sweden, Denmark, Finland, Iceland, Germany, Great Britain, Switzerland, Italy, and Austria. We also ask permission to send samples outside of Europe, including to countries with different legislation compared to Norway for biological samples, and the main recipients are USA, Australia, China, and India. If samples are sent out from Akershus University Hospital the collaborating center will only receive de-identified samples; i.e. no samples will be sent out with linked personal information so that the material can be linked back to individual patients of the SMASH 1 Study.

We also ask permission to re-analyze inclusion ECGs and echocardiograms, or to re-analyze previous recordings stored for later off-line analyses. Possible traits related to the ECG recordings are morphology, PQ- and QT-intervals, QRS-width, etc. Also data from these recordings may be shared with national and

international collaborators analogous to the countries listed above for biological analysis. Only de-identified data will be sent out from Norway.
We will also aim to obtain information representative of a full transthoracic echocardiography examination in all subjects, but plan to use images obtained by clinicians and re-analyze previous recordings. We will assess LV dimension, septal and posterior wall thickness, and LV mass as recommended by American Society of Echocardiography. Left ventricular (LV) ejection fraction (EF) will be calculated using the modified Simpson's rule from biplane 4-chamber and long-axis views. LV diastolic function will be assessed by pulsed Doppler transmitral peak early (E), peak late (A) and E deceleration time. TVI-derived indices will be recorded at the base of the septal and lateral mitral annulus to determine peak systolic (S'), early diastolic (e') and late (a') diastolic velocities. Global and regional longitudinal strain will be analyzed by an offline semi-automated speckle tracking technique from the three apical views. The digital storage of echocardiographic images may also later permit analyses of novel imaging indices. The echocardiographic analyses will be performed by a limited number of researchers to ensure standardization of all recordings. Also data from these recordings may be shared with national and international collaborators analogous to the countries listed above for biological analysis. Only de-identified data will be sent out from Norway.

5 Data management and statistical analysis

5.1 Case Report Forms (CRFs)

Case report forms (CRF) will be provided for the recording of all data. Data will be recorded directly and legibly onto the record forms, in blue/black ink. The signature of the investigator will attest the accuracy of the data on each CRF. If any assessments are omitted, the reason for such omissions will be noted on the CRFs. Corrections, with the reason for the corrections if applicable, should be made legibly, dated and initialed. Correction fluid is not allowed. Data will be transferred to an electronic case report form (eCRF) and stored in a secure area of Akershus University Hospital research web. Given that additional study sites are included, data will also in these sites be stored according to local and national regulations in a secure area of the local research web. Study participants will only be identified by the study Id in the eCRF and the key to connect the eCRF data to the identity of the patients will be stored in a secure place with access control (only accessable to the PI and dedicated members of the study team).

5.2 Source Data

The medical records of each patient will be reviewed and we will also perform a structured interview of all patients included in the study. Data obtained during the inclusion visit and annual visits will be collected, de-identified, and stored in a secure web solution. Only de-identified data (marked with study code) will be shared with national and international collaborators as outlined in section #4.4.
We will ask permission to link our data to the hospital records and registries, including national morbidity and mortality registries. Morbidity and mortality data will be obtained from these sources, and for adjudication, we may also want to obtain information directly from physicians or other health personnel that have been involved in the treatment of the patient.

5.3 Source Data Verification

The investigator will be visited on a regular basis by a Clinical Study Monitor, who will check and collect completed CRFs, discuss the progress of the study and perform source data verification.
When the responsible study monitor has checked and verified the CRFs, the data will be entered into a computer database at the scientific server of the participating hospitals for further handling and statistical evaluation. Sponsor's representatives (e.g. monitors, auditors) and/or regulatory authorities will be allowed access to source data for source data verification in which case a review of those parts of the hospital records relevant to the study may be required.

5.4 Storage of Study Documentation

The investigator shall arrange for the retention of the patient identification and the code list. Patient files shall be kept for the maximum period of time permitted by each hospital. The study documentation (CRFs, Site File etc) shall be retained and stored during the study and for 15 years after study closure. All information concerning the study will be stored in a safe place inaccessible to unauthorized personnel.

5.5 Study Design

This is an observational study at Akershus University Hospital and, given permission and interest, also from the other participating hospitals.
The data will be summarized with respect to demographic and baseline characteristics and risk markers/ measurements. Categorical data will be presented as absolute frequencies and percentages. For continuous data, N, mean±SEM or median (quartile 1-3), and range may be presented. Diagnostic and prognostic accuracy will be assessed by receiver operating statistical analysis and by calculating the area under the curve. Diagnostic and prognostic ability will also be assessed by calculating the category-free net reclassification index. Time to event variables and Kaplan-Meier product-limit estimates will be presented stratified according to biomarkers and other risk indices. The final diagnosis of incident cardiovascular events will be established by an adjudication committee with two senior physicians reviewing all information available on the patients, including information

on the clinical outcome of the patient. The co-primary end-point of the study will be time to incident ventricular arrhythmias and cardiovascular events. We will use multivariate statistical models to assess the individual performance of biomarkers/ other tests.

5.6 Safety Analysis

Not applicable in this study.

5.7 Interim Analysis

The population will be stratified into a derivation (n=500) and validation cohort (n>1000) and we may perform analyses on the derivation cohort alone, both cohorts combined, or derivation cohort and later validation cohort (preferred strategy).

Ethical and regulatory requirements

5.8 Ethical Considerations

6.1.1 General Considerations

The responsible investigator will ensure that this study is conducted in agreement with the Declaration of Helsinki (Tokyo, Venice, Hong Kong, Somerset West and Edinburgh amendments) and the laws and regulations of the country where the trial is performed. The protocol has been written, and the study will be conducted according to the ICH Harmonized Tripartite Guideline for Good Clinical Practice (ref: http://www.ifpma.org/ethics/ifpma-code-of-practice/about-ifpma-code-of-practice.html). The study will be evaluated by the Regional Ethics Committee and other government agencies before initiation. The protocol will be registrated in www.clinicaltrials.gov before inclusion of the first patient.

6.1.2 Informed Consent

All patients will be thoroughly informed about all aspects of the study and provide written informed consent prior to study commencement. It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever he wants. This will not prejudice the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered for the study. This must be done in accordance with the national and local regulatory requirements.The written informed consent form should be signed and personally dated by the patient.

5.9 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with the Declaration of Helsinki and Good Clinical Practice (ICH-GCP). The Principal Investigator must assure that all study site personnel, including subinvestigators and other study staff members, adhere to the study protocol and all local and federal regulations and guidelines regarding clinical trials both during and after study completion. The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the CRFs. Periodic monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms may be reviewed by the Principal Investigator.

5.10 Record Retention

Study documentation includes all CRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms). Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. Study documents should be kept on file for 15 years after the completion and final study report.

5.11 Audits

To ensure the quality of data, study integrity, and compliance with the protocol and the various applicable regulations and guidelines, the sponsor may conduct site visits to institutions participating in this study. The investigator, by accepting to participate to this protocol, agrees to co-operate fully with any quality assurance visit undertaken by third parties, including representatives from the sponsor as well as to allow direct access to documentation pertaining to the clinical trial (including CRFs, source documents and other study files) to these authorized individuals. The investigator must inform the sponsor immediately in case of a scheduled inspection by a regulatory authority.

5.12 Publication Policy

The findings of this study will be published independent of its outcome. All personnel who have contributed significantly with the planning and performance of the study (Vancouver convention 1988) may be included in the list of authors. The position on the author list should be agreed on for all subprojects prior to the start of these projects.

6 STUDY MANAGEMENT

6.1 Investigator Delegation Procedure

The Principal Investigator is responsible for making and updating a "delegation of tasks" listing all the involved co-workers and their role in the project. He will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved

6.2 Study Amendments

If it is necessary for the study protocol to be amended, the amendment and/or a new version of the study protocol (Amended Protocol) must be notified to and approved by the Ethics Committee according to national regulations.

6.3 Audit and Inspections

Authorised representatives of a regulatory authority and Ethics Committee may visit the centre to perform inspections, including source data verification. Likewise the representatives from the sponsor may visit the center to perform an audit. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (ICH GCP), and any applicable regulatory requirements. The Principal Investigator will ensure that the inspectors and auditors will be provided with access to source data/documents.

7 Trial sponsorship and financing

The study is sponsored by the Research Council of Norway.

8 Trial insurance

This study is covered by the general insurance of the participating hospitals.

9 Acknowledgments

The first versin of this protocol was drafted by Assoc Prof Helge Røsjø. Prof. Torbjørn Omland conceived the idea of performing a multicenter observational study of ICD patients to assess the prognostic value of potential markers of incident ventricular arrhythmias. Drs Røsjø and Omland together finalized the initial protocol submitted to the Regional Ethics Committee October 27, 2015 and also performed the revision of the protocol according to the requests of the Regional Ethics Committee.

10 AMENDMENT 31.07.2017

As an addition to the original study, patient-reported outcomes (PROM) will be included in the data collection at the 1-year visit.

Purpose and background:

We aim to explore the association between psychological factors and cardiovascular biomarkers. Hence, an additional objective in the study will be to explore stress and anxiety as a marker of increased risk of incident ventricular arrhythmias and cardiovascular events in patients already being treated with an ICD.

PROM gains attention as secondary outcomes in interventional studies, particularly due to the use of quality-adjusted life years. Beyond PROM as outcomes, psychological distress has also been studied in relation to prevalence of shock therapy and mortality in ICD patients (Thylen, Europace 2016;18;828-835). Bidirectional mechanisms are likely exist; Anxiety, depression and distress are associated with increased sympathetic tone which may aggravate arrhythmias, but on the other hand, firing of ICD in a conscious patient is a traumatic event likely to initiate distress and anxiety. However, the relation between other biomarkers and psychosocial distress are not explored previously.

Methods:

Patients consenting to participate in this substudy will be asked to fill out three separate questionnaires at the 1-year visit, or these will be mailed to the participants. All the questionnaires are validated and extensively used in previous studies (Pedersen, Pace & Electrophysiology 2016;39;1261-1268)

Hospital Anxiety & Depression Scale (HADS), 14 items *(Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361-70). Commonly used instrument to assess symptoms of anxiety and depression in patients with somatic disease. The 14 items are scored 0-3, and subscales of anxiety (7 items) and depression (7 items) are calculated. A cut off ≥7 is commonly used to define clinical relevant anxiety or depression symptoms.*

EQ-5D, 6 items, *(EuroQol Group (1990-12-01). "EuroQol--a new facility for the measurement of health-related quality of life". Health Policy (Amsterdam, Netherlands). 16 (3): 199–208.) A generic instrument for assessing general health-related quality of life. The 6 answers will be scored according to a standard manual as a measure between 0 – 100.*Florica Shock Anxiety Scale (FSAS), 10 items ***(Kuhl et al. PACE 2006;29;614-8)***

The Florida Shock Anxiety

Scale (FSAS) is a brief tool designed to provide a quantitative measure of ICD shock-related anxiety. Each item is scored 1– 5, and a sum score will be calculated.

Statistics: The data will be included in the study database as described in the main protocol (above). For the purpose of this substudy we will explore the association between cardiovascular biomarkers and PROMs.

APPENDIX 2 Information and concent form to the SMASH-1 study

Forespørsel om deltakelse i forskningsprosjekt for å forstå og oppdage alvorlig hjerterytmeforstyrrelse

Bakgrunn og hensikt

Dette er et spørsmål til deg om å delta i et forskningsprosjekt der vi ønsker å utlede ny kunnskap om alvorlig hjerterytmeforstyrrelse (ventrikkelarytmi). Vi vil også undersøke metoder for tidlig å fange opp pasienter med høy risiko for slike hjerterytmeforstyrrelser. Du blir spurt om å delta i studien siden du allerede har implantert en defibrillator (ICD). Din ICD vil beskytte deg ved hjerterytmeforstyrrelse ved å gi elektrisk støt. Din ICD registrer også kontinuerlig om du har episoder med hjerterytmeforstyrrelser, noe som vanligvis leses av hver gang du er på sykehuset for ICD-kontroll. Vi ønsker å bruke denne informasjonen, som altså inngår i standardoppfølging av pasienter med ICD, til å øke vår forståelse av alvorlige hjerterytmeforstyrrelser. Gjennom dette prosjektet vil vi også teste om substanser i blodbanen (målt i vanlige blodprøver), analyser av hjertets elektrisk aktivitet (EKG) og ultralyd av hjertet (ekkokardiografi) kan identifisere pasienter som får fremtidig hjerterytmeforstyrrelse. Vi ønsker også å studere sammensetning og varianter av ulike gener med tanke på fremtidig risiko for alvorlig hjerterytmeforstyrrelse. Nye metoder for tidlig å diagnostisere alvorlig hjerterytmeforstyrrelse kan vise seg å være av betydning for store pasientgrupper. Studien planlegges gjennomført ved flere norsk universitetssykehus og med Akershus universitetssykehus som koordinator og ansvarlig institusjon.

Hva innebærer studien?

Studien vil ikke kreve tilleggsundersøkelser til det du normalt gjennomgår på kontroller for ICD bortsett fra samling av ekstra blodprøver til lagring i en forskningsbiobank (fryser). Disse prøvene vil senere bli analysert i forskningsøyemed. I dag finnes det ingen metode som sikkert kan hjelpe til med å identifisere høyrisikopasienter for hjerterytmeforstyrrelse utover noen etablerte genetiske varianter. Normalt er det hos ICD-pasienter under vanlig klinisk utredning allerede testet for slike sikre sykdomsgivende genetiske varianter. Det er således ikke aktuelt med direkte tilbakemelding til deltagerne på resultater i studien, inkludert genetiske analyser, bortsett fra i situasjoner der vi finner sikre sykdomsgivende genetiske varianter som vil bli meldt til studiedeltageren. De fleste pasienter med ICD etter tidligere rytmeforstyrrelse vil allerede være testet for slike varianter i forbindelse med den vanlige kliniske utredningen. Tilbakemelding om slike varianter vil håndteres av akkrediterte genetiske avdelinger i henhold til lovverket.

Vi ber også om tillatelse til å kunne re-analysere tidligere EKG- eller ultralydopptak slik at vi får enhetlig vurdering av disse opptakene. Det er også nye metoder som kan vise seg å være nyttige og vi ønsker tillatelse til også å analysere disse parameterne. Studien vil bli gjennomført i forbindelse med vanlig sykehuskontakt og etter at deltagerne har gitt muntlig og skriftlig samtykke til deltagelse. Ekstra blodprøvetaking vil kunne tilpasses andre undersøkelser som du skal gjennomgå ved din vanlige sykehuskontakt.

Mulige fordeler og ulemper

Studien medfører ingen risiko for deltageren utover fare for lokal infeksjon ved blodprøvetaking. Blodprøvetaking blir gjennomført etter standard metode og risiko for infeksjon må vurderes som lav. Det kan være litt ubehag ved sprøytestikket i forbindelse med blodprøvetaking. Gevinsten for pasienter som velger å delta i studien er bidrag til videre kunnskap innen feltet.

Hva skjer med prøvene og informasjonen om deg?

Informasjon som registreres, svar på blodprøver og EKG og ultralyd av hjertet skal kun brukes slik som beskrevet i hensikten med studien. En kode knytter deg til dine opplysninger og prøvesvar gjennom en navneliste, og denne navnelisten holdes nedlåst og adskilt fra andre opplysninger i studien. Således er det kun et fåtall autorisert personell tilknyttet prosjektet som har adgang til navnelisten og dermed kan finne tilbake til deg. I alle tilfeller vil det ikke være mulig å identifisere deg i resultatene av studien når disse publiseres.

Frivillig deltakelse

Det er frivillig å delta i studien. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke til å delta i studien. Dette vil ikke få konsekvenser for din videre behandling. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Om du nå sier ja til å delta, kan du senere trekke tilbake ditt samtykke uten at det påvirker din øvrige behandling. Dersom du senere ønsker å trekke deg eller har spørsmål til studien ved Akershus universitetssykehus, kan du kontakte Avdeling for medisinsk forskning v/Helge Røsjø på telefon 67 80 95 44.

Ytterligere informasjon om studien finnes i kapittel *A* – *utdypende forklaring av hva studien innebærer.*

Ytterligere informasjon om biobank, personvern og forsikring finnes i kapittel B – *Personvern, biobank, økonomi og forsikring.*

Samtykkeerklæring følger etter kapittel B.

Kapittel A- utdypende forklaring av hva studien innebærer

Kriterier for deltakelse

Forutsetningen for å delta i studien er at du er over 18 år, allerede har fått implantert en ICD og er i systemet for oppfølging ved de aktuelle universitetssykehusene som deltar i studien. Du må gi skriftlig samtykke til å delta i studien før du kan inkluderes.

Bakgrunnsinformasjon om studien

Alvorlig hjerterytmeforstyrrelse med påfølgende hjertestans er en viktig årsak til død ved hjerte-karsykdom. Vi ønsker nå å studere ICD-pasienter for bedre å forstå mekanismene for alvorlig hjerterytmeforstyrrelse og for bedre å finne pasientene med høyest risiko for fremtidig hjerterytmeforstyrrelse.

Undersøkelser på sykehuset
Deltagelse i studien innebærer ekstra blodprøvetaking i forbindelse ved vanlig sykehuskontakt. Dette gjelder både ved start av studien (første visitt) og også på senere kontrollbesøk på sykehuset for din ICD. Det meste av blodet vil bli frosset ned ved - 80 °C og tint opp på et senere tidspunkt for å gjennomgå spesialanalyser, der vi måler stoffer som eventuelt kan ha betydning for hjerte- og lungesykdom.

Videre vil det, dersom du gir eget samtykke til dette (se siste side), tas blodprøver som er egnet for undersøkelse av arvestoffet (DNA). Disse prøvene vil bli undersøkt med tanke på allerede kjente eller nye endringer i arvestoffet som kan ha betydning for forståelse av hjertesykdom (rytmeforstyrrelser ved hjertesvikt). Vi ønsker også mulighet til å undersøke hjertets arvestoff med nyere teknologi, såkalt helgenomsekvensering/dypsekvensering/ eventuelt ny teknologi som gir oss data på oppbygging og funksjon av arvestoffet. Vi vil filtrere resultatet i henhold til noen kjente varianter koblet til annen sykelighet da dette ikke er del av denne studien. I utgangspunktet vil ikke resultater bli meldt tilbake til deltagerne utover situasjonen der vi finner sikre sykdomsgivende genetiske varianter for hjerterytmeforstyrrelse. De fleste pasienter med ICD etter tidligere rytmeforstyrrelse vil allerede være testet for slike varianter i forbindelse med den vanlige kliniske utredningen. Vi vil så følge med på hvordan det går med deg og vi vil registrere funn ved ICD-avlesning av hjerterytmeforstyrrelse årlig i forbindelse med standard ICD-oppfølging.

Oppfølging videre
Etter at undersøkelsene som er beskrevet over er gjennomført, ønsker vi å kunne registrere opplysninger og funn senere fra kontroller og innleggelser som er relatert til denne innleggelsen. Det er mulig vi også ønsker å stille deg noen spørsmål om hvordan det er gått siden sist, og vi ønsker derfor å ha muligheten til å kontakte deg per telefon eller brev i tiden etter inklusjon i studien. Vi planlegger maksimal oppfølgingstid til år 2050, og mulige tidspunkter for kontakt er etter 3 og 6 måneder, 1 år og siden årlig, dog kan også andre tidspunkt bli aktuelle. Vi ønsker også å kunne undersøke pasientjournal for å kunne fastslå om det oppstår hendelser i løpet av oppfølgingstiden, og å kunne kontakte ulike registeret, inkludert (men ikke avgrenset til) Folkeregistret, Hjerte-karregisteret, Dødsårsaksregisteret, Medisinsk fødselsregister, Forsvarets helseregister og Helseundersøkelsen 40, for å registrere data om eventuelle dødsfall i løpet av oppfølgingstiden og sannsynlig dødsårsak. For å sikre at informasjon om sykelighet og mortalitet er korrekt så ber vi også om mulighet til å kontakte helsearbeidere ved andre behandlende institusjoner for å innhente og kontrollere opplysninger.

Mulige fordeler
Gjennom å delta i studien bidrar du til å bedre forståelse og kunnskap om alvorlig hjerterytmeforstyrrelse.

Mulige ulemper og bivirkninger
Studien innebærer *ikke* utprøving av medikamenter, og det er ikke knyttet noen risiko eller bivirkninger til noen av de undersøkelsene du vil få utført. Det er heller ikke noe ubehag, bortsett fra ordinær blodprøvetaking. Blodprøver tas på vanlig måte (venepunksjon i albuen). Venepunksjon medfører vanligvis ingen fare utover mulig lokal smerte, hevelse og lett ubehag. En sjelden gang kan det oppstå infeksjon.

Studiedeltakerens ansvar
Det er ikke noe særskilt ansvar knyttet til det å delta i studien.

Endringer underveis i studien
Studien vil pågå over mange år. Du vil bli informert skriftlig om eventuelle endringer som kan påvirke din villighet til å delta i studien. Du kan når som helst trekke deg fra studien hvis du ikke lenger ønsker å delta.

Kapittel B - Personvern, biobank, økonomi og forsikring

Personvern
Alle opplysninger som registreres om deg vil bli behandlet konfidensielt. Du og dine helseopplysninger er, som ellers i helsevesenet, beskyttet av Pasientrettighetsloven § 3-6 (rett til vern mot spredning av opplysninger), og helsepersonell er bundet av Helsepersonelloven § 21 om taushetsplikt. Det vil bli opprettet et notat i din journal, hvor din sykehistorie og resultater fra undersøkelsene vil fremgå. Disse opplysningene vil være tilgjengelig hvis du senere skulle bli behandlet ved sykehuset. Studien er godkjent av Regional komité for medisinsk og helsefaglig forskningsetikk (REK). Prosjektleder ved Akershus universitetssykehus er professor Torbjørn Omland, Medisinsk divisjon. Ved Akershus universitetssykehus ved administrerende direktør er databehandlingsansvarlig og studien er også godkjent av lokalt Personvernombud. Tilsvarende vil administrerende direktører ved de andre partnerne være databehandlingsansvarlig for lokal pasientkohort og studien vil også søke godkjenning av lokalt Personvernombud også ved de andre partnerne.

Biobank
Det vil bli opprettet en egen forskningsbiobank for studien. Dette betyr at dine blodprøver og informasjon utledet av dette materialet vil bli lagret separat og sikret med tilgangskontroll, adskilt fra andre blodprøver tatt ved sykehuset. Hvis du sier ja til å delta i studien, gir du også samtykke til at det biologiske materialet og analyseresultater inngår i forskningsbiobanken. Resultatene fra dine blodprøver vil kun bli brukt til denne studiens formål. Professor Torbjørn Omland er ansvarshavende for forskningsbiobanken. Biobanken planlegges å vare til år 2050. Etter dette vil materiale og opplysninger bli destruert og slettet etter interne retningslinjer. Biomarkørene vi primært vil undersøke reflektere prosesser som celledød, strekk av hjerteceller, fibrose i hjertet eller andre organer, inflammasjon, Ca2+ håndtering, nyrefunksjon, iskemi/hypoksi, trombose, samt andre patofysiologiske prosesser som kan være interessant mht hjerte-karfunksjon. Vi vil også analysere prøver med ulike metodologi for ikke-hypotese-basert undersøkelse der vi vil studere proteiner (eggehvitestoffer), metabolitter og andre stoffer som sirkulerer rundt i blodbanen. Alle blodprøver blir lagret avidentifisert, dvs. merket kun med kode og vi vil oppbevare koblingsnøkkel på et sikkert sted med adgangskontroll.

Utlevering av materiale og opplysninger til andre

Hvis du sier ja til å delta i studien, gir du også ditt samtykke til at prøver og avidentifiserte opplysninger kan utleveres til våre samarbeidsinstitusjoner. All slik overføring skjer avidentifisert, det vil si uten personlige kjennetegn, kun merket ved en kode. Blodprøver fra biobanken vil i hovedsak bli undersøkt ved deltagende universitetssykehus. Internasjonalt ledende forskning baserer seg imidlertid på samarbeid, og ved behov for spesialundersøkelser som ikke er tilgjengelige ved disse institusjoner, kan det bli aktuelt å sende enkelte blodprøver til analyse ved samarbeidsinstitusjoner i Norge eller i utlandet. For deltagere som har avgitt separat samtykke for dette, kan undersøkelse av arvematerialet bli utført ved universitetssykehusene som deltar i studien eller ved samarbeidsinstitusjoner i Norge eller i utlandet.
Våre europeiske samarbeidsinstitusjoner vil være bundet både av europeisk personvernlovgivning generelt og forhold knyttet til denne studien som beskrevet i dette kapittel spesielt. For å få utført spesielle analyser kan imidlertid prøveglass bli sendt til land som ikke tilfredsstiller europeisk personvernlovgivning. Personinformasjon vil ikke bli utlevert fra de norske universitetssykehusene, og prøveglass som sendes til samarbeidende institusjoner i Norge og i utlandet for analyser vil kun være merket med en kode. Vi ber også om mulighet til potensielt å sende avidentifiserte opplysninger om helse, altså opplysninger der navn, fødselsdato eller personnummer er fjernet, til samarbeidspartnere som ikke er bundet av europeisk personvernlovgivning.

Innhenting av opplysninger fra andre

For å sikre god kvalitet på data som samles inn, er det av og til behov for å innhente helseopplysninger fra andre sykehus eller fastlege. Hvis du sier ja til å delta i studien, gir du også ditt samtykke til at vi kan innhente opplysninger fra andre sykehus eller fastlege.

Rett til innsyn og sletting av opplysninger om deg og sletting av prøver

Hvis du sier ja til å delta i studien, har du rett til å få innsyn i hvilke opplysninger som er registrert om deg. Du har videre rett til å få korrigert eventuelle feil i de opplysningene vi har registrert. Dersom du trekker deg fra studien, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner.

Økonomi

Prosjektet er finansiert gjennom forskningsmidler fra Norges Forskningsråd. Ved senere behov vil det eventuelt kunne bli søkt om støtte fra andre private og offentlige fond.

Forsikring

Det er ikke tegnet noen spesiell forsikring for denne studien, men lov om erstatning ved pasientskader gjelder også for forskningsprosjekter.

Informasjon om utfallet av studien

Resultatene av studien vil bli sammenfattet i flere vitenskapelige artikler som sendes inn for publikasjon i internasjonale medisinske tidsskrifter. Forskningsgruppen vil også gjøre resultatene fra studien kjent i lokale og nasjonale medier. Du har som forsøksdeltaker rett til å få informasjon om utfallet. Etter at resultatene foreligger og er bearbeidet informeres deltakerne om resultatene for hele prosjektet, og hvordan vi tolker resultatene. Alle deltagere må være undersøkt før resultatene fremkommer, og dette skjer tidligst 2-3 år etter oppstart av prosjektet. Informasjonen vil bli gitt for prosjektet som helhet, og ikke i form av individuelle resultater for hver enkelt deltager.

Tilsvarende vil den enkelte deltager ikke få tilbakemelding om sine egne resultater av genetiske undersøkelser (undersøkelser av arvestoffet)**.**

Samtykke til deltakelse i studien

(fylles ut først når du kommer på sykehuset)

Jeg er villig til å delta i studien

(Dato, prosjektdeltakers navn med blokkbokstaver, signatur)

Jeg samtykker til at det tas blodprøver for analyse av arvestoffet, med tanke på variasjoner i arvestoffet som kan ha betydning for hjerte- og lungesykdommer. Jeg samtykker med dette til at blodprøver kan overføres til samarbeidsinstitusjoner i Norge eller i utlandet for slike analyser, og er kjent med at jeg ikke vil få informasjon om mine egne resultater.

(Dato, signatur):
Jeg (lege/sykepleier) bekrefter å ha gitt studiedeltaker informasjon om studien
---(Signert, rolle i studien, dato)

The patient file should include:

1. **Signed consent**
2. **Complete list of medications**
3. **Resting ECG**
4. **ICD-printout**
5. **CRF**
6. **Printout of blood samples: *Hb, LPK, TPK, MCV, Na, K, Creat, Glucose, NTproBNP***
7. **Printout of echo, CMR, angio, MUGA examination (if available)**
8. **Biobank confirmation sheet**

APPENDIX 3 Case report form-Visit 1

Patient ID: _____
Center: _____
(1=AHUS, 2=SUS etc.)
Date / time: _____
(dd/mm/yyyy, hh)

INFORMATION ON ICD / -CRT-D
ICD MANUFACTURER: _____ 1=Medtronic, 2=Boston Scientific, 3=St.Jude Medical, 4=Biotronik
HOME MONITORING: _____ 0=No, 1=Yes
ICD INDICATION: _____ 1=Primary prevention, 2=Secondary prevention
DATE OF IMPLANTAON:_____ (dd/mm/yyyy)

1. MEDICAL HISTORY:
HEART FAILURE: _____ 0=No, 1=HFpEF (LVEF≥50), 2=HFmrEF (LVEF 40-50%), 3=HFrEF (EF<40%)
CARDIOMYOPATHY _____0: No, 1-Ischemic, 2- non-ischemic
HOCM _____0=No, 1=Yes
CHANNELOPATHY: _____0=No, 1=Yes
ARVC _____0=No, 1=Yes
CHEMO/RADIATION HF:_____0=No, 1=Yes
VENTR. ARRHYT: _____ 0=No, 1=Non-sustained VT (<30 beats), 2=sustained-VT, 3=VF
SUPRAVENTR. ARRHYT:_____ 1=AFib, 2=AFlutter, 3=Other
AMI: _____ 0=No, 1=Yes
ANGINA PECTORIS/CAD:_____ 0=No, 1=Yes
CABG/PCI: _____ 0=No, 1=Yes
VALVULAR DISEASE: _____ 0=No, 1=Yes (excluding mild forms)
COPD: _____ 0=No, 1=Yes
DIABETES: _____ 0=No, 1=Type 1, 2= Type 2
RENAL FAILURE: _____ 0=No, 1=Yes (eGFR<30%)
➔ CREATININE: _____ (from the latest blood sample)
PERIPH. ARTERY DISEASE:_____ 0=No, 1=Yes
OBSTR. SLEEP APNEA: _____ 0=No, 1=Yes
CANCER: _____ 0=No, 1=Yes
➔ Year of diagnosis: _____ (yyyy)
FAMILY HISTORY: _____ 0=No, 1=SCD>50y, 2=SCD <50y

CARDIAC IMAGING / LEFT VENTRICULAR FUNCTION (leave blank if not available)
Most recent echo:_____(mm/yyyy)
➔ Echo LVEF: _____(%)
Most recent CMR: _____(mm/yyyy)
➔ CMR LVEF: _____(%) Scar Burden / Volume: _____(%) /_____(%)
Most recent angio: _____(mm/yyyy)
➔ Angio LVEF: _____(%)
➔ CAD (>70% stenosis):_____0=No, 1= 1 vessel, 2= 2 vessels, 3= 3 vessels
Most recent MUGA: _____(mm/yyyy)
➔ MUGA LVEF: _____(%)
2. SYMPTOMS/PREVIOUS EVENTS:
DYSPNEA (NYHA): _____ 1 / 2 / 3 / 4 (last month)
CHEST PAIN (CCS): _____ 1 / 2 / 3 / 4 (last month)
LIMITING SYMPTOM: _____ 1=Dyspnoe, 2=Chest Pain, 3=Other
ORTHOPNEA: _____ 0=No, 1=Yes
PALPITATIONS: _____ 0=No, 1=Yes, before ICD, 2=Yes, after ICD, 3=Both
PRESYNCOPE: _____ 0=No, 1=Yes, before ICD, 2=Yes, after ICD, 3=Both
SYNCOPE: _____ 0=No, 1=Yes, before ICD, 2=Yes, after ICD, 3=Both
ABORTED SCD: _____ 0=No, 1=Yes (before ICD)
ICD SHOCK: _____0=No, 1=Yes (appropriate therapy), 2=Yes (non-appropriate therapy)
3. CLINICAL STATUS

AGE: _____ (years)
GENDER: _____ 1=Male, 2=Female
HEIGHT: _____ (cm)
WEIGHT: _____ (kg)
SMOKING: _____ 0=Never, 1=Daily, 2=Sporadic, 3=Former (>3months)
HEART RATE: _____ (bpm)
SBP: _____(mmHg)
DBP: _____(mmHg)
RESP. FREQUENCY: _____ (/min)
4. ECG
RHYTHM: _____ 1=SR, 2=AFli/Aflu, 3=Atrial PM, 4=Ventricular PM, 5=A+V PM
FREQUENCY: _____ (bpm)
BLOCK: _____ 0=No, 1=LBBB, 2=RBBB, 3=AV-block 2/3, 4=not applicable (ventr.pace)
PQ-TIME: _____ (ms)
QRS-DURATION: _____ (ms)
cQT-TIME: _____ (ms)

ICD REGISTRATION
DATE: _____(leave blank if same as baseline visit)
TIME FROM LAST CONTROL:_____(months)
Detection
VT1: _____ /min
VT2: _____ /min
VF: _____ /min
Events
SVT:_____ 0=No, 1=1 episode, 2=2 episodes etc.
NSVT:_____0=No, 1=1 episode, 2=2 episodes etc.
VT1:_____0=No, 1=1 episode, 2=2 episodes etc.
VT2:_____0=No, 1=1 episode, 2=2 episodes etc.
VF:_____0=No, 1=1 episode, 2=2 episodes etc.
DELIVERED SHOCK:_____0=No, 1=Yes
DATE OF SHOCK:_____(dd/mm/yyyy)

INTRINSIC HEART RATE:_____(bpm, average)
PVC:_____% , _____ /hour , _____no. since last ctr.
VENTRICULAR PACING: _____%
ATRIAL PACING:_____%
ATRIAL FIBRILLATION: _____%

VISIT 2 should include:

9. **Resting ECG**
10. **ICD-printout**
11. **CRF**
12. **Printout of blood samples: *Hb, LPK, TPK, MCV, Na, K, Creat, Glucose, NTproBNP***
13. **Epicrisis if hospitalized**
14. **Biobank confirmation sheet**

APPENDIX 4 Case report form-Visit 2

Center: _____
(1=AHUS, 2=SUS etc.)
Patient ID: _____
(P1001, P1002 etc)
(P2001, P2002 etc)
Date / time: _____
(dd/mm/yyyy, hh)

5. EVENTS SINCE LAST VISIT
[DEAD: _____ 0=No, 1=Yes → Cause of death: _____]
MYOCARD. INFARCTION:_____ 0=No, 1=Type 1, 2=Type 2, 3=Type 4/5
CORONARY REVASC:_____ 0=No, 1=PCI 2=CABG
STROKE:_____ 0=No, 1=Ischemic 2=Hemorrhagic
HF HOSPITALISATION: _____ 0=No, 1=Yes (Heart failure as the primary ICD-diagnosis)
CARDIAC ABLATION: _____ 0=No, 1=Atrial, 2=Ventricular
ICD SHOCK: _____0=No, 1=Yes (appropriate therapy), 2=Yes (non-appropriate therapy)
DATE EVENT: _____ (dd/mm/yyyy)
6. SYMPTOMS SINCE LAST VISIT:
DYSPNEA (NYHA): _____ 1 / 2 / 3 / 4 (last month)
CHEST PAIN (CCS): _____ 1 / 2 / 3 / 4 (last month)
LIMITING SYMPTOM: _____ 0=No, 1=Dyspnoe, 2=Chest Pain, 3=Other
ORTHOPNEA: _____ 0=No, 1=Yes
PALPITATIONS: _____ 0=No, 1=Yes
PRESYNCOPE: _____ 0=No, 1=Yes
SYNCOPE: _____ 0=No, 1=Yes
7. CLINICAL STATUS
WEIGHT: _____ (kg)
SBP: _____(mmHg)
DBP: _____(mmHg)
RESP. FREQUENCY: _____ (/min)
8. ECG
RHYTHM: _____ 1=SR, 2=AFli/Aflu, 3=Atrial PM, 4=Ventricular PM, 5=A+V PM
FREQUENCY: _____ (bpm)
BLOCK: _____ 0=No, 1=LBBB, 2=RBBB, 3=AV-block 2/3, 4=not applicable (ventr.pace)
PQ-TIME: _____ (ms)
QRS-DURATION: _____ (ms)
cQT-TIME: _____ (ms)

ICD REGISTRATION
DATE:_____(leave blank if same as visit)
TIME FROM LAST CONTROL:_____(months)

Detection
VT1: _____ /min
VT2: _____ /min
VF: _____ /min

Events
SVT:_____ 0=No, 1=1 episode, 2=2 episodes etc.
NSVT:_____0=No, 1=1 episode, 2=2 episodes etc.
VT1:_____0=No, 1=1 episode, 2=2 episodes etc.
VT2:_____0=No, 1=1 episode, 2=2 episodes etc.
VF:_____0=No, 1=1 episode, 2=2 episodes etc.
DELIVERED SHOCK:_____0=No, 1=Yes
DELIVERED ATP:_____0=No, 1=Yes
DATE OF SHOCK:_____(dd/mm/yyyy)

PVC:_____% , _____ /hour , _____no. since last ctr.
RIGHT VENTRICULAR PACING: _____%
LEFT VENTRICULAR PACING: _____% (only for CRT-D)
ATRIAL PACING: _____%
ATRIEFLIMMER _____%

APPENDIX 5 Information and consent form to the substudy

FORESPØRSEL OM DELTAKELSE I DELSTUDIE AV FORSKNINGSPROSJEKTET:

NYE RISIKOMARKØRER FOR ALVORLIGE HJERTERYTMEFORSTYRRELSER

Viser til ditt tidligere samtykke om deltakelse i SMASH 1-studien. Som studiedeltager får du denne forespørselen om å delta i en delstudie som kartlegger livskvalitet og bekymringer relatert til å leve med ICD.

HVA INNEBÆRER DET NYE DELPROSJEKTET?

Du får utdelt tre spørreskjemaer ved 1-års kontroll eller per post; Et om angst generelt (HADS, 14 spørsmål), et skjema om bekymringer spesifikt for ICD-pasienter (FSAS, 10 spørsmål) og et skjema om generell livskvalitet og funksjonsnivå (EQ-5D, 6 spørsmål). Disse skal besvares ved avkrysning ved svaralternativer.

MULIGE FORDELER OG ULEMPER

Utfylling av spørreskjemaene innebærer ingen direkte risiko eller nytte for deg. En mulig ulempe er at 1-årskontrollen vil vare noe lengre enn opprinnelig planlagt. Denne delstudien vil potensielt gi prosjektet utdypende og verdifull kunnskap om pasientgruppen og mulighet til å utforske nye sammenhenger mellom psykiske faktorer ved behandling med ICD og kardiovaskulære biomarkører.

FRIVILLIG DELTAKELSE OG MULIGHET FOR Å TREKKE SITT SAMTYKKE

Det er frivillig å delta i denne delstudien. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke. Dette vil ikke få konsekvenser for din videre behandling eller for din deltagelse i hovedstudien. Dersom du trekker deg fra prosjektet, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner. Dersom du senere ønsker å trekke deg eller har spørsmål til prosjektet, kan du kontakte Avdeling for medisinsk forskning v/ professor Torbjørn Omland på telefon 67 96 47 71.

HVA SKJER MED INFORMASJONEN OM DEG?

Informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Du har rett til innsyn i hvilke opplysninger som er registrert om deg og rett til å få korrigert eventuelle feil i de opplysningene som er registrert. Alle opplysningene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger gjennom en navneliste.

Prosjektleder har ansvar for den daglige driften av forskningsprosjektet og at opplysninger om deg blir behandlet på en sikker måte. Informasjon om deg vil bli anonymisert og slettet etter prosjektslutt.

GODKJENNING

Prosjektet er godkjent av Regional komite for medisinsk og helsefaglig forskningsetikk.

SAMTYKKE TIL DELTAKELSE I PROSJEKTET

JEG ER VILLIG TIL Å DELTA I PROSJEKTET

Sted og dato	Deltakers signatur
	Deltakers navn med blokkbokstaver

APPENDIX 6 Questionnaires

Akershus universitetssykehus

Hospital Anxiety & Depression Scale
HADS

Dette spørreskjemaet er utformet for å hjelpe oss til å forstå hvordan du føler deg. For hvert utsagn sett **ett** kryss for det svaret som best beskriver dine følelser den siste uken.

1. Jeg er nervøs eller anspent
❑For det meste ❑Ofte ❑Noen ganger ❑Ikke i det hele tatt

2. Jeg gleder meg fremdeles over ting jeg pleide å glede meg over
❑Avgjort like mye som før ❑Ikke fullt så mye som før ❑Bare littegrann ❑Ikke det hele tatt

3. Jeg har en urolig følelse som om noe forferdelig kommer til å skje
❑Helt sikkert, og svært ille ❑Ja, men ikke så veldig ille ❑Litt ille, men det bekymrer meg lite ❑Ikke i det hele tatt

4. Jeg kan le og se det morsomme i situasjoner
❑Like mye som jeg alltid har gjort ❑Ikke like mye nå som før ❑Avgjort ikke like mye nå som før ❑Ikke i det hele tatt

5. Jeg har hodet fullt av bekymringer
❑Veldig ofte ❑Ganske ofte ❑Av og til ❑En gang i blant

6. Jeg er i godt humør
❑For det meste ❑Ganske ofte ❑Noen ganger ❑Aldri

Akershus universitetssykehus

7. Jeg kan sitte i fred og ro, og kjenne meg avslappet

- ❑Ja, helt klart
- ❑Vanligvis
- ❑Ikke så ofte
- ❑Ikke i det hele tatt

8. Jeg føler meg som alt går langsommere

- ❑Nesten hele tiden
- ❑Svært ofte
- ❑Fra tid til annen
- ❑Ikke i det hele tatt

9. Jeg føler meg urolig liksom jeg har sommerfugler i magen

- ❑Svært ofte
- ❑Ganske ofte
- ❑Fra tid til annen
- ❑Ikke i det hele tatt

10. Jeg har sluttet å bry meg om hvordan jeg ser ut

- ❑Ja, helt klart
- ❑Jeg bryr meg ikke så mye som jeg burde
- ❑Kan hende jeg ikke bryr meg nok
- ❑Jeg bryr meg like mye om utseendet som jeg alltid har gjort

11. Jeg føler meg rastløs som om jeg stadig må være i aktivitet

- ❑Uten tvil svært ofte
- ❑Ganske ofte
- ❑Ikke så veldig mye
- ❑Ikke i det hele tatt

12. Jeg ser med glede frem til hendelser og ting

- ❑Like mye som jeg alltid har gjort
- ❑Heller mindre enn jeg pleier
- ❑Avgjort mindre enn jeg pleier
- ❑Nesten ikke i det hele tatt

13. Jeg kan plutselig få en følelse av panikk

- ❑Uten tvil svært ofte
- ❑Svært ofte
- ❑Ikke så veldig ofte
- ❑Ikke i det hele tatt

14. Jeg kan glede meg over en god bok, eller et radio/TV-program

- ❑Ofte
- ❑Fra tid til annen
- ❑Ikke så ofte
- ❑Svært sjelden

Akershus universitetssykehus

Florida Shock Anxiety Scale
FSAS

Vi vil gjerne undersøke, hvordan det er for deg å leve med en ICD. Under finner du en del utsagn om dette. Ved å sette en sirkel rundt det tallet som passer best for deg, kan du angi hvor ofte du har disse tankene.

		Ikke i det hele tatt	Sjelden	Av og til	Ofte	Hele tiden
1.	Jeg er redd for å trene fordi det kan øke pulsen min og føre til at min ICD gir støt	1	2	3	4	5
2.	Jeg er redd for å være alene når min ICD gir støt og jeg trenger hjelp	1	2	3	4	5
3.	Jeg unngår å bli sint eller opprørt fordi det kan føre til at min ICD gir støt	1	2	3	4	5
4.	Det plager meg at jeg ikke vet når min ICD vil gi støt	1	2	3	4	5
5.	Jeg bekymrer meg over at min ICD noen ganger ikke gir støt når den skal	1	2	3	4	5
6.	Jeg er redd for å ta på andre av redsel for å gi dem støt hvis min ICD gir støt	1	2	3	4	5
7.	Jeg bekymrer meg for å tiltrekke oppmerksomhet på grunn av støt fra min ICD	1	2	3	4	5
8.	Når jeg merker at hjertet mitt banker raskt, bekymrer jeg meg over at min ICD skal gi støt	1	2	3	4	5
9.	Jeg har uønskede tanker om at min ICD gir et støt	1	2	3	4	5
10.	Jeg unngår å være seksuelt aktiv fordi det kan føre til at min ICD gir støt	1	2	3	4	5

Takk for at du tok deg tid til å svare på spørsmålene!

APPENDIX 7 Application for approval of the substudy

Prosjektendring Skjema for søknad om godkjenning av prosjektendringer i de regionale komiteer for medisinsk og helsefaglig forskningsetikk (REK)

Dokument-id: 923965 Dokument mottatt 10.10.2017

Nye risikomarkører for alvorlige hjerterytmeforstyrrelser (2015/2080)

1. Generelle opplysninger

a. Prosjektleder

Navn:	Torbjørn Omland
Akademisk grad:	dr med
Klinisk kompetanse:	Spesialist i indremedisin og hjertesykdommer
Stilling:	Professor
Hovedarbeidsgiver	Universitetet i Oslo
Arbeidsadresse:	Akershus Universitetssykehus
Postnummer	1478
Sted	Lørenskog
Telefon	40107050
E-post adresse	torbjorn.omland@medisin.uio.no

b. Prosjekt

Hvilket prosjekt skal endres?	Nye risikomarkører for alvorlige hjerterytmeforstyrrelser (2015/2080)

c. Ny Prosjektleder?

Skal prosjektet ha ny prosjektleder?	Nei

d. Forskningsansvarlig(e)

Forskningsansvarlig(e) som beholdes

Institusjon	Kontaktperson	Stilling	E-post adresse
Helse Stavanger HF - Stavanger universitetssjukehus	Alf Inge Larsen	Seksjonsleder	post@helse-stavanger.no
Akershus universitetssykehus HF			personvern@ahus.no

e. Prosjektmedarbeider(e)

Prosjektmedarbeider(e) som beholdes

Navn:	Stilling:	Institusjon:	Akademisk rolle:	Rolle:
Alf Inge Larsen	Seksjonsleder	Stavanger Universitetessykehus	MD, PhD	Daglig ansvarlig for studiesenteret på SUS
Helge Røsjø	Avdelingssjef	Akershus universitetssykehus	MD, PhD	Co-PI

2. Endring(er)

a. Endringen(e) innebærer

Annen prosjektendring

Redegjør for endringer

Vi ønsker å benytte Florida Shock Anxiety Scale (FSAS) i stedenfor implantable cardioverter defibrillator concerns (ICDC) i substudien med spørreskjemaer som nylig ble godkjent av REK. FSAS og ICDC er svært like og spørsmålene dreier seg om det samme, men FSAS har 2 fler spørsmål (10 vs 8). Det blir ingen endring på de andre to spørreskjemaene (HADS og EQ5D).

b. Begrunnelse for endringen(e)

Praktisk, faglig og vitenskapelig begrunnelse for endringen(e)

FSAS er allerede tatt i bruk i Norge og det finnes en etablert norsk oversettelse. Det er derfor fordelaktig at vi i Norge holder oss til én type spørreskjema når det gjelder angst og bekymringer hos pasienter med ICD.

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3. Avveining av nytte og risiko ved prosjektendringene

Hvorfor er det forsvarlig å gjennomføre endringene? Gi en begrunnet avveining av fordelene og ulempene ved prosjektendringene.

Det vil ikke få noen konsekvens for pasientene annet enn at de må fylle ut totalt 10 vs 8 spørsmål.

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4. Vedlegg

#	Type	Filnavn	Lagt inn dato
1.	Ny forskningsprotokoll	Protokoll_SMASH1_rev_amendment_FSAS_051017_PM.doc	05.10.17
2.	Øvrige vedlegg	Samtykke_substudie_spørreskjema_SMASH1_revFSAS_051017.docx	05.10.17
3.	Øvrige vedlegg	ICDC_norsk.pdf	05.10.17
4.	Øvrige vedlegg	FSAS_norsk.pdf	05.10.17

5. Ansvarserklæring

Jeg erklærer at prosjektet vil bli gjennomført
i henhold til gjeldende lover, forskrifter og retningslinjer
i samsvar med opplysninger gitt i denne søknaden
i samsvar med eventuelle vilkår for godkjenning gitt av REK

APPENDIX 8 Approval of the substudy from REK

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst	Anne S. Kavli	22845512	23.08.2017	2015/2080/REK sør-øst A
			Deres dato:	Deres referanse:
			08.08.2017	

Vår referanse må oppgis ved alle henvendelser

Torbjørn Omland
Akershus universitetssykehus HF

2015/2080 Nye risikomarkører for alvorlige hjerterytmeforstyrrelser

Forskningsansvarlig: Akershus universitetssykehus HF, Helse Stavanger HF - Stavanger universitetssjukehus
Prosjektleder: Torbjørn Omland

Vi viser til søknad om prosjektendring datert 08.08.2017 for ovennevnte forskningsprosjekt. Søknaden er behandlet av leder for REK sør-øst på fullmakt, med hjemmel i helseforskningsloven § 11.

Vurdering

REK har vurdert følgende endring i prosjektet:
-Innhenting av nye data fra samme utvalgsgrupper. Det søkes om å kartlegge psykologisk belastning og livskvalitet ved hjelp av HADS, et skjema om angst spesifikt for ICD-pasienter (ICD-concerns) og EQ-5D.

Komiteens leder har vurdert søknaden og har ingen innvendinger til endringen som er beskrevet.

Vedtak

Komiteen godkjenner med hjemmel i helseforskningsloven § 11 annet ledd at prosjektet videreføres i samsvar med det som fremgår av søknaden om prosjektendring og i samsvar med de bestemmelser som følger av helseforskningsloven med forskrifter.

Dersom det skal gjøres ytterligere endringer i prosjektet i forhold til de opplysninger som er gitt i søknaden, må prosjektleder sende ny endringsmelding til REK.

Av dokumentasjonshensyn skal opplysningene oppbevares i 5 år etter prosjektslutt. Opplysningene skal deretter slettes eller anonymiseres.

Opplysningene skal oppbevares avidentifisert, dvs. atskilt i en nøkkel- og en datafil. Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veileder for «Personvern og informasjonssikkerhet i forskningsprosjekter innenfor helse- og omsorgssektoren».

Prosjektet skal sende sluttmelding til REK, se helseforskningsloven § 12, senest 6 måneder etter at prosjektet er avsluttet.

Besøksadresse:
Gullhaugveien 1-3, 0484 Oslo

Telefon: 22845511
E-post: post@helseforskning.etikkom.no
Web: http://helseforskning.etikkom.no/

All post og e-post som inngår i saksbehandlingen, bes adressert til REK sør-øst og ikke til enkelte personer

Kindly address all mail and e-mails to the Regional Ethics Committee, REK sør-øst, not to individual staff

Klageadgang

Komiteens vedtak kan påklages til Den nasjonale forskningsetiske komité for medisin og helsefag, jf. helseforskningsloven § 10 tredje ledd og forvaltningsloven § 28. En eventuell klage sendes til REK sør-øst A. Klagefristen er tre uker fra mottak av dette brevet, jf. forvaltningsloven § 29.

Med vennlig hilsen

Knut Engedal
Professor dr. med.
Leder

Anne S. Kavli
Seniorkonsulent

Kopi til: Akershus universitetssykehus HF ved øverste administrative ledelse: personvern@ahus.no*; post@helse-stavanger.no;; forskning@sus.no*

APPENDIX 9 Cover letter to the reminder

Akershus universitetssykehus

Kjære deltaker i SMASH-1 studien.

Viser til tidligere utsendt spørreskjema relatert til angst, bekymringer og livskvalitet hos pasienter med ICD. Vi kan ikke se å ha mottatt spørreskjema og samtykke fra deg. Hvis du har fylt ut og sendt inn spørreskjema uten at vi har registrert dette, kan dette skyldes at samtykkeskjema ikke fulgte med eller var fylt ut, men det har også vist seg at vi dessverre har merket returkonvoluttene for dårlig i første utsendelse slik at de kan ha blitt borte i posten. Vi sender derfor ut skjemaene på nytt og håper du har mulighet til å fylle de ut igjen. Vennligst bruk den vedlagte returkonvolutten. Hvis du allerede har sendt inn beklager vi ekstraarbeidet det medfører å gjøre det på nytt.

Ved spørsmål ta kontakt på 41636059.

Med vennlig hilsen

Betina Cecilia Eide Blad
Masterstudent i Biomedisin

Peder L. Myhre
Lege og hjerteforsker